Universidade do Minho
Escola de Ciências da Saúde

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A ANALGESIA COMBINADA NA NEVRALGIA DO TRIGÉMIO:
associação de anticonvulsivante com o bloqueio periférico de Ropivacaina

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Maria Leonor Barbosa Gonçalves **Plasticity of the pain control system induced by neuropathic pain: the amygdala-medulla system**

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Tese de Doutoramento:
Ciências da Saúde – Medicina Clínica

Trabalho efectuado sob a orientação do
Professor Doutor Armando Almeida

Junho de 2009

DECLARAÇÃO

Nome: LAURINDA MARIA DA SILVA GUIMARÃES LEMOS

Endereço electrónico: laurindalemos2000ster@gmail.com Telefone: 253416698/933493439

Número do Bilhete de Identidade: 3567258

Título tese: A ANALGESIA COMBINADA NA NEVRALGIA DO TRIGÉMIO: associação de anticonvulsivante com o bloqueio periférico de Ropivacaina

Orientador: Professor Doutor Armando Almeida

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Man is a mystery. It must be solved,
and if you spend all your life trying to solve it,
you must not say the time was wasted.
I have chosen to occupy myself with the mystery

Fyodor Dostoevsky, 1839

À minha família:

à minha Mãe

ao meu Filho Luís Alberto

ao meu Marido Joaquim Alberto,

pelo amor, força, cooperação e infinita disponibilidade

À memória do meu Pai

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Resumo

A disfunção ou lesão de uma estrutura nervosa periférica ou central origina uma dor neuropática, de abordagem terapêutica difícil devido à má resposta no controlo da dor e à tendência para a cronicidade. Na nevralgia do Trigémio (NT), o utente caracteriza a sua dor como excruciante, fugaz e paroxística, localizada na região da face enervada pelo nervo Trigémio. O seu diagnóstico é basicamente clínico e o exame neurológico é, na maioria das vezes, normal. A abordagem terapêutica é planeada de modo individualizado, com o objectivo de se obter uma reabilitação funcional. É iniciada geralmente de um modo não invasivo, por monoterapia com anticonvulsivante (ex: carbamazepina, gabapentina), mas se os resultados não são satisfatórios pode-se progredir para a politerapia com a associação de anticonvulsivantes e antidepressivos (ex: amitriptilina), ou para planos terapêuticos mais invasivos (ex: descompressão microvascular cirúrgica). Em situações de agudização do quadro álgico, pode recorrer-se aos bloqueios analgésicos superficiais, técnicas não invasivas, simples de executar, que permitem bons resultados quando realizados com anestésicos locais de baixa toxicidade (ex: Ropivacaina). A prevalência da NT em idosos, com a correspondente maior incidência de patologias associadas, leva a ponderar a relação risco/benefício na utilização de técnicas invasivas elevado custo, às quais se podem associar défices ou sequelas sensoriais na face de gravidade variável, ou mesmo a situações de risco de vida que não devem ser ignoradas.

O conjunto de estudos que constituem esta tese teve como objectivo melhorar o uso de protocolos farmacológicos não invasivos no tratamento da NT, de modo a permitir resultados clínicos satisfatórios no controlo da dor com redução de efeitos adversos dos fármacos. Num primeiro trabalho, prospectivo e longitudinal, avaliamos a eficácia clínica de um protocolo combinado, não invasivo, que associa a Gabapentina oral (GBP; anticonvulsivante com baixa cardiotoxicidade e neurotoxicidade e reduzida incidência de efeitos adversos) com a administração periférica de Ropivacaina (ROP; anestésico local de baixa neurotoxicidade) nos pontos-gatilho ("trigger-points") indutores de dor na face (*Protocolo GBP+ROP*), em comparação com a administração de Gabapentina em monoterapia (*Protocolo GBP*). O Protocolo GBP+ROP demonstrou ser clinicamente eficaz, seguro, fácil de executar tecnicamente, não se tendo observado efeitos adversos. Em comparação com o protocolo GBP, a associação terapêutica GBP+ROP reduziu significativamente a intensidade de dor e o número de crises de dor/dia nos utentes, os quais necessitaram de doses de GBP (300 mg/dia) inferiores às descritas na literatura em monoterapia (900-1200 mg/dia), tendo os utentes no protocolo GBP+ROP

reportado ainda uma melhoria significativa na qualidade de vida, superior à dos utentes no protocolo GBP. Num segundo trabalho, com um desenho clínico semelhante ao anterior, foi avaliada a associação terapêutica de Carbamazepina (CBZ; anticonvulsivante considerado o fármaco de primeira linha no tratamento da NT, mas ao qual se associam mais efeitos adversos que a GBP) com o bloqueio periférico dos pontos-gatilho de dor facial com ROP (*Protocolo CBZ+ROP)*, por comparação com CBZ em monoterapia (*Protocolo CBZ*). O protocolo CBZ+ROP reforçou a eficácia clínica já referida na literatura em relação à CBZ em monoterapia, ao reduzir significativamente a intensidade da dor e o número de crises de dor/dia referidas pelos utentes ao fim de 6 meses, os quais necessitaram de doses de CBZ (600 mg/dia) inferiores às usadas em monoterapia (1200 mg/dia), o que permitiu reduzir a presença de efeitos adversos. Um terceiro estudo, retrospectivo, avaliou a relação custo/benefício de diferentes protocolos usados no tratamento da NT: um invasivo (cirúrgica de descompressão microvascular) e dois não invasivos (CBZ em monoterapia e a associação GBP+ROP); a análise da relação custo/benefício dos três protocolos demonstrou que a associação GBP+ROP apresenta maior benefício clínico e menor custo em Euros/dia em relação ao protocolo invasiso e ao outro protocolo farmacológco (*CBZ em monoterapia*). O benefício clínico dos três protocolos é equi-analgésico, mas a associação a efeitos adversos significativos na técnicas invasiva e na monoterapia da CBZ são de valorizar, ao contrário da associação GBP+ROP, na qual não se observaram efeitos secundários.

Os estudos que constituem esta tese permitem concluir que: (i) a associação de GBP oral e o bloqueio analgésico com a ROP abre uma nova perspectiva na abordagem da NT, permitindo aos utentes uma melhoria clínica rápida e isenta de efeitos secundários, associada à melhoria significativa da sua qualidade de vida; deste modo, o protocolo GBP+ROP constitui uma alternativa para os utentes que não obtiverem resultados terapêuticos satisfatórios com o protocolo típico de CBZ em monoterapia; (ii) a associação de CBZ oral e bloqueio analgésico com ROP permite reforçar a liderança e a eficácia deste anticonvulsivante no tratamento da NT, através da utilização de doses menores mas clinicamente eficazes de anticonvulsivante, com redução drástica dos seus efeitos adversos; (iii) a comparação entre diferentes protocolos comprovou a eficácia clínica e os efeitos adversos a eles associados; a análise dos custos económicos de três dos protocolos mais usados no tratamento da NT reforçou a importância da abordagem multidisciplinar dos utentes para, caso a caso, ponderar o risco/benefício dos protocolos invasivos versus não invasivos.

Abstract

A persistent noxious stimulation or a neural injury result in alterations of the nociceptive sensibility, and may induce a loss of ability to perceive pain (anesthesia) or cause spontaneous pain, alodinia (pain evoked by normally non painful stimuli) or hyperalgesia (exaggerated pain from normal stimulus). This condition is termed neuropathic pain, is normally severe and often resistant to treatment with current analgesic, thus tending to chronicity. Trigeminal neuralgia (TN) is considered to be a form of neuropathic pain and is defined as sudden, severe, brief, paroxistic, with pain free intervals, usually unilateral and limited to the distribution of one or more branches of the fifth cranial nerve. TN has a clinical diagnosis and usually presents a normal neurological examination. This condition remains incurable, although the symptoms can be well controlled. The aim of the analgesic protocol is to control the cause of this pain or reduce pain and improve the functionality of the patient. Therapy begins usually with a non-invasive procedure, like anticonvulsivant monotherapy (ex: Carbamazepin or Gabapentin), but if results are not satisfactory politherapy associating anticonvulsivants and antidepressants (ex: amitriptilina or fluoxetine) and a non invasive procedure using the analgesic block with Ropivacaine (local anesthetic with low toxicity) may be required. The first line treatment is conservative but, if the results are not satisfactory, the only possible treatment is an invasive produce (ex: surgical microvascular decompression). A large percentage of TN patients are elderly showing higher incidence of comorbidity. Thus, it is important to assess the costs and the ratio risk/benefice of the invasive technique, tacking into account the high incidence of neurological sequels and the prolonged recovery from pain.

The aim of this thesis is to improve non invasive pharmacological protocols for the management of TN, its clinical profile and effective control of pain, and correlate the ratio between risks / benefits and costs of non invasive versus invasive protocols. In a first prospective and longitudinal study, we evaluated the clinical outcome of a combined non invasive protocol, the association of oral Gabapentin (GBP; anticonvulsivant with low cardiotoxicity and neurotoxicity, and reduced incidence of side effects) with the peripheral analgesic block with Ropivacaine (ROP; a local anaesthetic of low neurotoxicity) at the trigger-points inducing pain (*GBP+ROP Protocol*); we compared this Protocol with Gabapentin in monotherapy (*GBP Protocol*). Patients under GBP+ROP Protocol referred an improved wellbeing and did not describe side effects or discomfort with the technique. In comparison with GBP Protocol, the therapeutical association GBP+ROP reduced significantly the pain intensity and the number of pain crises/day;

Additionally, patients needed lower doses of GBP (300mg/day) when compared with those described in the literature for GBP monotherapy (900-1200 mg/day); finally, GBP+ROP patients showed a significant improvement of their functionality, which was superior to patients submitted to GBP alone. In a second study, the same clinical design was used to evaluate the therapeutical association of the classic and first-line anticonvulsivant Carbamazepin (CBZ; however, it has more adverse effects than GBP) with the analgesic block of trigger-points with ROP (*Protocol CBZ+ROP*), in comparison with CBZ in monotherapy (*Protocol CBZ*). The Protocol CBZ+ROP reinforced the importance of the CBZ in the NT, by showing better results in clinical follow up, with a significant reduction in pain intensity and in the number of pain crises / day after 6 months; these patients used lowers doses (600mg/day) than in Protocol CBZ (1.200 mg/day) and, consequently, the side effects were reduced (dizziness and nauseas).

The third study was retrospective and transversal, and its aim was the analysis of the costs /risks ratio and benefits of three protocols used in the management of TN: one invasive (surgical microvascular decompression) and two non-invasive (CBZ in monotherapy and the association GBP+ROP). The results analysis of the cost / benefit ratio of the three protocols demonstrated that the association GBP+ROP present a higher clinical improvement at lower costs (Euros/day), when compared with the surgical and the other pharmacological protocols. The clinical wellbeing of the three protocols presented an equal analgesic result, but with different incidence of side effects: in the surgery they can be significant, in CBZ in monotherapy are reduced and in the Protocol GBP+ROP they are absent.

In the conclusion of this thesis we verify that: (i) the protocol GBP+ROP can constitute a new option in the management of TN, because it offers a rapid control of pain intensity and in the number of pain crises, associated with an improvement of patient functionality and absence of side effects; (ii) the protocol CBZ+ROP reinforce the first place of CBZ in the management of TN, because patients needed lower doses of CBZ and presented reduced side effects; (iii) the analysis of the three protocols confirmed the clinical efficacy and adverse effects associated and emphasized the importance of a multidisciplinary approach for a new patient or a patient insatisfyed with the classic treatment protocol, when deciding by an invasive or non invasive protocol.

ÍNDICE

LISTA DE ABREVIATURAS

5N - núcleo motor do Trigémio

AMPA – Amino-3-hidroxi-5-metal-4-isoxalona

CBZ - Carbamazepina

CBZ+ROP - Carbamazepina + Ropivacaina

CGRP - Peptídeo Relacionados com o Gene da Calcitonina

DMV - Cirurgia de Descompressão Microvascular

EVA - Escala Visual Analógica

GBP+ROP - Gabapentina + Ropivacaina

GBP - Gabapentina

HADS - *Hospital Anxiety and Depression Score*

LTP - Long Term Potentiation

Me5 - núcleo sensitivo mesencefálico do Trigémio

NMDA – N-metil-D-aspartato

NNT - *Number needed to treat*

NT - Nevralgia do Trigémio

PAG - Substância Cinzenta Peri-Aqueductal

Pr5 - núcleo sensitivo principal do trigémio

ROP - Ropivacaina

SIP - Sickness Impact Profile

SNC – Sistema nervoso central

SNP – Sistema nervoso periférico

Sp5 - núcleo sensitivo espinhal do trigémio

sp5 - tracto espinhal do trigémio

Sp5C - núcleo espinhal do trigémio, parte caudal

Sp5I - núcleo espinhal do trigémio, parte interpolar

Sp5O - núcleo espinhal do trigémio, parte oral

VPL - núcleo ventro-postero-lateral do tálamo

VPM - complexo ventro-postero-medial do tálamo

$\alpha 2\delta$ -sub-unidade alfa-2-delta (canais de cálcio)

Capítulo 1

INTRODUÇÃO

1.1. Enquadramento conceptual

A nevralgia do trigémio (NT) é uma situação clínica preocupante dado manifestar-se por uma dor intensa e paroxística, ser acompanhada por alterações psicoafectivas importantes que surgem com o prolongar da doença e apresentar uma prevalência nacional (e mundial) significativa. A NT não reverte em geral com analgésicos clássicos (anti-inflamatórios não esteróides, opióides) e apenas fármacos desenvolvidos primariamente para outras situações clínicas (antidepressivos, anticonvulsivantes) conseguem controlar a dor nesta patologia.

A etiologia da NT é na maioria das situações desconhecida, embora recentemente algumas teorias explicativas tenham sido avançadas. Em certos casos clínicos pode ocorrer uma compressão do nervo trigémio na sua saída do Sistema Nervoso Central (SNC), ao nível do Tronco Cerebral. Esta pode resultar de uma lesão tumoral (*Cheng et al 1993*) ou do contacto de um vaso arterial ou venoso (*Nurmikko, 2006*). A compressão poderá resultar em placas desmielinizadas na área afectada, onde as fibras perdem o isolamento eléctrico efectuado pela bainha de mielina, ocorrendo um aumento desregulado da actividade eléctrica das fibras sensitivas aferentes (*Devor, 2006*). Esta zona de sensibilização resultaria na produção de potenciais de acção ectópicos que resultam nos disparos de dor paroxísticos tipo choque eléctrico desencadeados pela estimulação de zonas indutoras de dor na face (pontos-gatilho – "trigger-points"). Actualmente, parece ser consensual que são necessários mecanismos de sensitização centrais e periféricos na indução da NT (*Calvin et al, 1977; Fromm et al, 1981*). Só uma hipótese mista é que poderá explicar muitos dos fenómenos observados na NT (*Loeser, 2001; Devor, 2006*).

1.2. Dor

A IASP (*International Association for the Study of Pain*) definiu a dor como "Uma experiência sensorial e emocional desagradável, associada a um dano tecidular actual ou potencial ou descrito em termos dessa lesão" (*Merskey, 1979; 1986; Turk e Okifuji, 2001*).

O reconhecimento internacional da dor crónica como um síndrome ou entidade patológica, permitiu desenvolver uma nova perspectiva do utente com dor - ao ser associada a dor crónica a alterações do humor (depressão e ansiedade), a alterações cognitivas e a

perturbações da personalidade, torna-se importante uma abordagem de tratamento bio-psicossocial do utente (*Turk e Okifuji, 2001*).

1.2.1. O conceito de Dor

A dor era, tradicionalmente, entendida como uma experiência puramente sensorial, mas actualmente é aceite como uma experiência multidimensional; se ignorámos as suas componentes emocional e afectiva poderemos falhar no processo de avaliação e tratamento do utente. A dor, como experiência subjectiva que é, é fortemente influenciada pelo estado emocional de cada indivíduo, pelos seus conhecimentos, cultura, memórias e experiências passadas e muitas outras variáveis afectivas e volitivas. A percepção da dor não pode ser definida simplesmente em termos de estímulos, mas sim como uma experiência única e pessoal, que depende em parte de factores psicológicos que variam ao longo de diferentes escalas temporais (*Loeser, 2006*).

Um estímulo nociceptivo (potencialmente lesivo e doloroso) origina um sinal eléctrico que irá activar o Sistema Nervoso Central (SNC) e será interpretado em função da experiência passada, do estado emocional e da cultura em que o indivíduo se insere. No SNC é feita a selecção e processamento da informação, já que a Dor é um processo dinâmico, que envolve uma interacção contínua entre o sistema nociceptivo ascendente e um sistema descendente de transmissão e modulação entre o encéfalo e a medula espinhal (ou equivalente para o processamento facial) (*Millan, 1999; 2002; Almeida et al 2006*). A informação interage em áreas do encéfalo onde a componente sensitiva-discriminativa é modulada pelas emoções e pela memória de experiências de vida processadas no sistema límbico. Desta interacção, forma-se a informação capaz de originar uma tendência volitiva ou um comportamento de fuga ou ataque, que ajudarão a planear diferentes estratégias ou respostas perante situações diversas (*McNally, 1999*).

Loeser classificou a Dor segundo outro modelo, que permite uma compreensão mais elaborada do fenómeno no Homem (*Loeser, 2006*) e considera quatro componentes importantes: a nocicepção, a dor, o sofrimento e o comportamento do utente com dor. O Sofrimento é a resposta afectiva negativa originada no cérebro pela dor ou por uma variedade de estados emocionais, como a depressão e a ansiedade. O sofrimento será o espelho da integridade psicológica e física do utente. O comportamento do utente com Dor traduz-se numa

expressão verbal e corporal, na apetência pelos serviços médicos e por terapêuticas medicamentosas, na abstenção ao trabalho e no isolamento. A análise do comportamento do utente com dor pode ser utilizada para avaliar a sua evolução ao longo dos tratamentos realizados, através da aplicação de instrumentos psicométricos pré e pós–tratamento. Assim, pela complexidade da avaliação da dor, torna-se necessária e fundamental uma avaliação e tratamento numa perspectiva multidisciplinar da dor como uma doença (*Loeser, 2006*).

1.2.2. Dor Aguda e Crónica

1.2.2.1. Dor Aguda

A dor aguda é a experiência imediata resultante de uma lesão ou agressão. Esse estímulo nóxico ocasiona a activação de nociceptores, (fibras sensitivas periféricas) que irão transduzir a energia (mecânica, térmica ou química) do estímulo lesivo num sinal eléctrico, que será posteriormente transmitido ao SNC e percepcionado pelo cérebro (*Millan, 1999*). A dor aguda está associada a uma reacção de *stress* fisiológico, com aumento da pressão arterial, da frequência cardíaca e respiratória e do afluxo sanguíneo aos músculos, proporcionando ao indivíduo a capacidade física de reacção / fuga. Apesar de ser uma experiência desagradável, a dor aguda, é na grande maioria das situações útil e essencial à sobrevivência do organismo, pois é o mecanismo pelo qual o indivíduo é informado de uma agressão tecidular (*McNally, 1999*). A dor aguda, no entanto, pode ser analisada numa outra perspectiva, em que não pode ser considerada útil, pelo menos aparentemente, como no caso das cefaleias, pois o sofrimento ocasionado e as interferências negativas na vida quotidiana são desproporcionais a um eventual benefício relativo desconhecido. Um aspecto curioso é o facto de só recentemente o tratamento da dor pós-operatória ter sido considerado vital e útil, em utentes de qualquer idade. Também a ideia passada do recém-nascido não necessitar de tratamento analgésico (que vigorou até aos anos 80 do século XX), pela sua imaturidade sensorial e consequente incapacidade de sofrer, só foi completamente ultrapassada à relativamente pouco tempo (*Fitzgerald e Walker, 2009; Lim et al, 2009*).

De um modo geral, a dor aguda é auto-limitada pela resolução da patologia subjacente ou pelo sucesso terapêutico atingido. A sua persistencia por alguns dias poderá ser útil, se for reversível, pois a imobilização pela dor irá proteger a zona lesada e contribuirá para a sua recuperação. A dor aguda é um dos principais motivos pela qual os utentes recorrem às

Unidades de Saúde, devido a processos infecciosos (de um órgão ou estrutura), processos inflamatórios ou traumatismos (*Galer et al, 2000*).

A dor aguda pode ser *somática*, com origem nas estruturas superficiais (*dor somática cutânea)* ou profundas (*dor somática profunda)* da parede do corpo e áreas controladas por movimentos voluntários, ou *visceral*. A *dor somática cutânea* caracteriza-se por um início brusco, é bem localizada, apresenta intensidade variável, associa-se a uma lesão na pele e nas estruturas subjacentes e resulta da estimulação nociceptores que terminam sob a forma de terminações nervosas não capsuladas na pele (base da epiderme e derme); a *dor somática profunda* caracteriza-se por uma localização mais alargada e imprecisa, de intensidade variável e associa-se à agressão das estruturas osteo-articulares, musculares e ligamentares, por estimulação de nociceptores específicos dessas áreas. A *dor visceral* é caracterizada por uma dor difusa, de localização imprecisa, com pontos de referência a zonas somáticas (dor referida), que resulta da estimulação de nociceptores localizado nos órgãos ocos e origina a activação do sistema nervoso autónomo (*Bielefeldt e Gebhart, 2006*).

Embora na maioria das situações a dor aguda se resolva espontaneamente, a dor que persiste para além de 3 meses tem uma perspectiva mais reduzida de se resolver sem a intervenção médica (*Macfarlane et al, 1998*). A análise da evolução da dor aguda em duas pessoas que sofrem uma agressão idêntica, pode apresentar uma evolução diversa, em que uma tem evolução favorável e se extingue e na outra a evolução caminha para a cronicidade (*Macfarlane, et al 1998*). Está demonstrado que a transição de uma dor nociceptiva aguda para crónica é complexa, verificando-se o envolvimento de multiplos mecanismos moleculares periféricos (sensitização periférica) e centrais (sensitização central), associados à plasticidade do sistema nociceptivo (*Coderre et al, 1993; Coderre e Katz, 1997; Zimmermann, 2001; Campbell e Meyer, 2006*).

1.2.2.2. Dor Crónica

A dor aguda e a dor crónica, embora apresentem características comuns por serem experiências sensoriais e emocionais desagradáveis, são clinicamente diferentes e, por isso, necessitam de uma abordagem específica individualizada. Uma dor persistente não tem uma função biológica útil e torna-se prejudicial pelo contínuo stress físico e emocional e pelas consequências psico-sociais. A dor crónica pode ser definida como a dor que persiste para além

do período definido arbitrariamente de três a seis meses ou, de modo mais objectivo, aquela que persiste para além do período de tempo previsto para resolução de uma patologia subjacente (*Turk e Okifuji, 2001*). Como tem um controlo difícil, origina o prolongamento da incapacidade funcional do utente, do qual pode resultar um comportamento alterado, influenciado por factores psicológicos e comportamentais (depressão, ansiedade e fadiga) (*Loeser, 2006*).

A classificação convencional da dor crónica, baseada em critérios anatómicos, funcionais e de duração no tempo, foi criticada por não permitir uma abordagem terapêutica eficaz (*Woolf et al, 1998*). Assim, uma nova classificação multidimensional ou multiaxial de dor crónica foi publicada pela *IASP,* com o objectivo de uniformizar as descrições dos vários síndromes álgicos e fornecer uma tabela de referência (*Turk e Okifuji, 2001*). A classificação taxonómica da dor crónica é aqui efectuada sobre 5 eixos: *eixo 1* - região do corpo; *eixo 2* - sistema envolvido e a função anormal correlacionada com a dor referida; *eixo 3* - características temporais da dor, padrão de ocorrência; *eixo 4* - intensidade da dor e o período de tempo que decorreu desde o seu início (duração); *eixo 5* - etiologia. Esta classificação permite a abordagem mais efectiva dos síndromes dolorosos, mas não inclui ainda os factores psicossociais. Assim, a utilidade das classificações multiaxiais na avaliação de um utente com dor crónica depende sempre do seu grau de aplicabilidade (*Turk e Okifuji, 2002*).

A dor crónica pode ser classificada, quanto à patogénese, em três categorias: nociceptiva, neuropática e psicogénica (*Turk e Rudy, 1987*). A *dor crónica* ***nociceptiva*** caracteriza-se pela activação prolongada dos nociceptores periféricos, sem lesão primária do tecido nervoso, sendo a informação nociceptiva transmitida através das fibras Aδ e C no sistema nervoso periférico (SNP) (ex: artrite reumatóide). A *dor* ***neuropática*** pode subdividir-se em Periférica (DNP) e Central (DNC): na DNP ocorre uma lesão do SNP (ex: nevralgia pós-Herpes Zoster, neuropatia diabética); na DNC a lesão nervosa localiza-se no SNC (ex: dor talámica após um acidente vascular cerebral, ou na tetraplegia ou paraplegia após lesão medular). Como possíveis mecanismos da DNP têm sido apontados: 1) a alteração do funcionamento do sistema do controlo do portão ("gate-control") que regula a transmissão nociceptiva a nível da medula espinhal (*Melzack e Wall, 1965*); 2) alterações do nervo que o tornam mecanicamente sensível, resultando em actividade eléctrica ectópica; 3) interligações anómalas entre as fibras finas e fibras grossas devido a fenómenos de desmielinização e falta de isolamento axonal; 4) alteração no processamento da informação a nível central resultante de plasticidade neuronal (*Devor, 2006*). *A dor* ***psicogénica*** inclui-se no vasto âmbito da dor crónica através de critérios de

exclusão clínicos de outros tipos de dor e associa-se frequentemente a patologias do foro psiquiátrico. No seu diagnóstico será fundamental a avaliação especializada pela Psiquiatria, pois embora na dor crónica possam estar associadas alterações do humor, afectivas e cognitivas, incluídas como co-morbilidade de uma dor neuropática ou nociceptiva crónica, na dor psicogénica não existe o componente orgânico objectivo.

1.2.3. Dor Neuropática

A Dor que se associa a uma lesão primária de um nervo ou à disfunção do processo nociceptivo do SN pode ser observada após uma lesão traumática (iatrogénica ou não), após a realização de protocolos farmacológicos terapêuticos específicos (tuberculostáticos, antibioterapia, quimioterapia, radioterapia), na sequência de um processo infeccioso (bacteriológico ou vírico), ou associada a diabetes ou a uma patologia arterial isquémica. No entanto, a caracterização da sintomatologia referida nas várias neuropatias é independente da natureza da lesão ou disfunção nervosa, já que o utente refere características transversais a todas elas, com maior ou menor exuberância: dor espontânea, alodínia e hiperalgesia (*Boreau et al, 1990; Bennett, 2001; Dworkin, 2002*). Na abordagem do utente com dor neuropática são fundamentais a etiologia e o resultado do exame neurológico sumário específico, o estado funcional do utente correlacionado com a intensidade dos sintomas e a avaliação do comportamento de adaptação à neuropatia. No exame neurológico podem observar-se alterações sensitivas, motoras e do sistema nervoso autónomo (*Galer et al, 2000*). As alterações sensitivas referidas são: alodínia (sensação dolorosa ocasionada por um estímulo que normalmente não é doloroso), hiperalgesia (sensação dolorosa exagerada a um estímulo nóxico) e dor espontânea isolada, desencadeada por estímulos cutâneos superficiais (*Treede, 2006*). As alterações motoras não específicas, que complementam o quadro clínico da neuropatia, podem ser a ataxia e a atrofia muscular (*Galer, 2000*). As alterações autonómicas são caracterizadas por variações de temperatura e por sudação.

A lesão neuropática a nível do SNP induz impulsos ectópicos persistentes nas fibras lesadas e adjacentes, mesmo na ausência de uma estimulação nóxica externa. Esses potenciais de acção ectópicos deslocam-se bidireccionalmente ao longo do axónio; os impulsos que caminham distalmente ao local da lesão irão ocasionar, à periferia, uma produção aumentada de neuropeptídeos, os quais irão ocasionar um aumento de descargas ectópicas – ***sensitização***

periférica; já a nível da extremidade central das fibras lesadas, no corno dorsal da medula espinhal, verifica-se uma reorganização dos contactos sinápticos, um aumento da actividade e do campo receptivo do neurónio de segunda ordem (espinhal) e o fenómeno de "windup", uma potenciação anormal dos impulsos gerados pelo SNP - ***sensitização central***. A nível do encéfalo, estas alterações podem ser evidenciadas por meios complementares de diagnóstico de neuroimagem, que evidenciam várias alterações na actividade de diferentes áreas (aumento ou diminuição), nomeadamente a nível do córtex sensorial e motor, do córtex pré-frontal, do tálamo, do hipotálamo e de outras estruturas sub-corticais (*Apkarian et al, 2005*).

Estudos animais demonstraram que as agressões traumáticas manifestam-se por perturbações no comportamenteo "doloroso", que se associam a alterações anatómicas e fisiológicas. Num estudo experimental em que se realizou a laqueação do nervo ciático no rato, por um período longo, foi evidenciado que o animal apresentava resposta alterada à estimulação nóxica, nomeadamente aumento da sensibilidade ao estímulo doloroso – hiperalgesia, e dor resultante de um estímulo não doloroso - alodínia (*Bennett e Xie, 1988; Seltzer et al, 1991; Decosterd e Woolf, 2000*). No exame pós-morte desses ratos observaram-se importantes alterações estruturais no SNC em áreas do encéfalo implicadas no processamento doloroso, emocional e cognitivo (amígdala) (*Gonçalves et al, 2008*). Estas alterações comportamentais e na estrutura do SNC são acompanhadas, a nível funcional da medula espinhal de animais submetidos a modelos de dor neuropática, pelo aumento da sensibilidade dos neurónios nociceptivos de segunda ordem, traduzida por incrementos (i) na actividade espontânea, (ii) na actividade em resposta à estimulação nóxica periférica e (III) no campo receptivo de activação neuronal (*Bennett e Xie, 1988; Seltzer et al, 1991; Decosterd e Wolff, 2000*). Finalmente, a nível do sistema endógeno de modulação da dor (*Almeida et al, 2006*) ocorrem também profundas alterações na actividade de neurónios de centros supraspinhais de controlo da dor, no sentido de reforçarem a transmissão nociceptiva e a dor (*Gonçalves et al, 2007; Ansah et al, 2009*).

1.2.3.1. Mecanismos periféricos

As lesões nervosas podem induzir dor neuropática por dois mecanismos à periferia: pela produção de descargas ectópicas ou pela modificação a nível celular e molecular dos gânglios raquidianos, conduzindo a uma ampliação da transmissão nociceptiva na medula espinhal (*Devor, 2006*). As descargas eléctricas ectópicas resultam da tradução de potenciais de acção

espontâneos, originados em zonas desmielinizadas do axónio. Os neurónios nestas placas de desmielinização apresentam um aumento excepcional na densidade de canais de sódio dependentes da voltagem (*Devor et al 2006*). Este facto aumenta a probabilidade da transmissão de potenciais de acção através dos segmentos desmielinizados devido à acumulação de iões ao longo destes. Este fenómeno aumenta a probabilidade de se desencadearem espontaneamente potenciais de acção nos locais desmielinizados. Adicionalmente, a pressão mecânica nas extremidades a níveis em que os nervos são normalmente insensíveis, é suficiente para ocasionar descargas de impulsos ectópicos (base funcional para explicar a alodínia). Do mesmo modo, podem gerar-se impulsos reverberativos em múltiplos segmentos desmielinizados da membrana axonal, entre os pontos desmielinizados. Assim, um só potencial de membrana, gerado pela estimulação do receptor distal, pode produzir um grande número de impulsos dando origem a potenciais sucessivos tipo "disparo de metralhadora" nos terminais sensoriais do corno posterior da medula (*Devor et al, 2006*).

1.2.3.2. Sensitização Central

Quando um impulso nociceptivo se repete de um modo contínuo no tempo (ex: um processo inflamatório crónico), podem observar-se alterações na espinal medula e nos gânglios raquidianos que conduzem ao aumento progressivo do impacto no influxo periférico sobre a transmissão nociceptiva central e nos neurónios que a medeiam. Com o prolongar da estimulação nociceptiva, os próprios estímulos inócuos inofensivos podem tornar-se dolorosos, por um fenómeno de sensibilização central (*Campbell e Meyer, 2006*). A transmissão nociceptiva para o SNC ocorre pela libertação de neurotransmissores como o Glutamato, Substância P e o peptídeo relacionados com o gene da calcitonina (CGRP), dos terminais centrais das fibras nociceptivas (*Woolf e Salter, 2000*). No caso da dor aguda, o glutamato activa receptores AMPA, permanecendo os receptores NMDA bloqueados por um ião de magnésio (Mg^{2+}) (*Antonov e Johnson, 1999*). Com o prolongar da estimulação nóxica, os receptores NMDA acabam por ser activados, originando um grande influxo de Ca^{++} e uma hiperdespolarização dos neurónios nociceptivos do SNC (*Willis, 2002*), que podem induzir alterações no genoma neuronal que conduzirão a um reforço das conexões entre as aferências nociceptivas e os neurónios do corno posterior da medula espinhal (*Woolf e Shortland, 1991*). O campo receptivo aumenta, podendo ocorrer respostas provocadas por estímulos provenientes de uma vasta área do corpo (*Boucher*

e McMahon 2001; Wu et al 2001); adicionalmente desenvolve-se o fenómeno de "wind up", (a estimulação repetida de fibras C resulta na descarga prolongada de neurónios nociceptivos espinhais) que conduz à hipersensibilidade a estímulos dolorosos (hiperalgesia) e à percepção dolorosa de um estímulo não nóxico (alodínia) (*Torebjork et al, 1992*). Apesar do "wind-up" ser uma mecanismo de curta duração, a sua repetição pode originar a "potenciação de longo prazo" (LTP – *long term potentiation*) que ocorre nos neurónios nociceptivos do corno dorsal da medula espinhal (*Rygh et al, 2005*) e envolve um aumento de longa duração da eficácia da transmissão sináptica (plasticidade sináptica) implicada na hiperalgesia e na alodínia. A hiperexcitabilidade dos neurónios nociceptivos está ainda dependente de mecanismos neuroimunológicos mediados pelas celulas gliais ou podem ser despoletados por esses mecanismos (*Tsuda et al, 2005*; *Moalem e Tracey, 2006*).

1.2.3.3. Bases terapêuticas da Dor Neuropática

A NT predomina no idoso e caracteriza-se por um quadro clínico de dor facial intensa, paroxística e persistente que parece estar relacionada com a produção de impulsos ectópicos na porção proximal do nervo trigémio, no tronco cerebral, imediatamente antes da entrada das suas raízes no SNC (*Cheshire, 2007*). Esta patologia é justificada pela desmielinização axonal localizada em resultado duma pressão excessiva causada por uma artéria mal formada ou tortuosa, geralmente a artéria cerebelosa superior, que pulsa contra a porção proximal do nervo trigémio. Nos indivíduos novos, a dor da NT pode estar associada a uma esclerose em placas (*Lazar e Kirckpatrick, 1979*), em que se observam placas desmielinizadas originadas por um processo inflamatório sobre o nervo. Nestas duas situações, os impulsos nervosos aferentes originados pela estimulação normal fisiológica dos receptores tecidulares são susceptíveis de gerar impulsos ao longo da região desmielinizada, mesmo na ausência de estimulação nóxica à periferia (*Devor, 2006*). Será provavelmente esta a razão do sucesso dos anticonvulsivantes no controlo da dor central; o bloqueio de canais de cálcio e sódio por fármacos como a gabapentina ou carbamazepina sugere que os impulsos ectópicos estão em grande parte na base do desencadear da dor neuropática (*Jensen, 2002; Attal et al, 2006; Cruccu et al, 2008*).

Para além do seu efeito conhecido sobre o humor, os antidepressivos têm um efeito analgésico significativo não só na dor crónica, após tratamento prolongado (*Benbouzid et al, 2008*), mas também após aplicação local, reduzindo sintomas de dor neuropática (hiperalgesia e

ansiedade) em estudos experimentais (*Haderer et al, 2003*). Dos antidepressivos destacam-se os tricíclicos, os inibidores da recaptação da serotonina e da noradrenalina e os inibidores selectivos da recaptação da serotonina (*Matsuzawa-Yanagida et al, 2008*), sendo que os antidepressivos tricíclicos são mais efectivos na dor neuropática periférica do que os outros tipos (*Mattia e Coluzzi, 2003*).

1.3. Anatomia do Nervo Trigémio e estruturas associadas

1.3.1. Nervo Trigémio

A sensibilidade da face depende dos ramos do nervo Trigémio e dos componentes do sistema trigeminal, que evidenciam um paralelismo quase exacto com o subsistema somestésico do resto do corpo. Os corpos celulares das fibras que compõem as três divisões do Nervo Trigémio estão localizados no gânglio de Gasser, o qual é equivalente ao gânglio raquidiano. O gânglio de Gasser está situado na fossa craniana média e na região posteromedial, no chão do seio cavernoso, na junção com o *sinus cavernosus*, que é anterior e situado à direita da região rochosa do osso temporal. O gânglio invagina-se na dura e fica subjacente á cavidade de Meckel, espaço que contacta com o líquido céfalo-raquidiano (*Nolte, 2002*).

A primeira divisão do Nervo Trigémio ou *Ramo Oftálmico* (*V1*), enerva a região frontal, englobando a região supraciliar que se prolonga para além da linha de implantação do cabelo e, no sentido inferior, a região peri-ocular e ocular, incluindo as córneas (Fig. 1). A segunda divisão ou *Ramo Maxilar* (*V2*), enerva a região central da face, incluindo o nariz, (a região interna e externa), o lábio superior na região externa e na face interna da boca (Fig. 1). A terceira divisão ou *Ramo Mandibular* (*V3*) enerva o mento, o lábio inferior, a margem inferior da mandíbula, o chão da boca e a língua (Fig. 1). O ramo *V1* e, em menor área, o *V2* enervam as meninges e a dura-máter, no interior do espaço sub-tentorial da cavidade craniana.

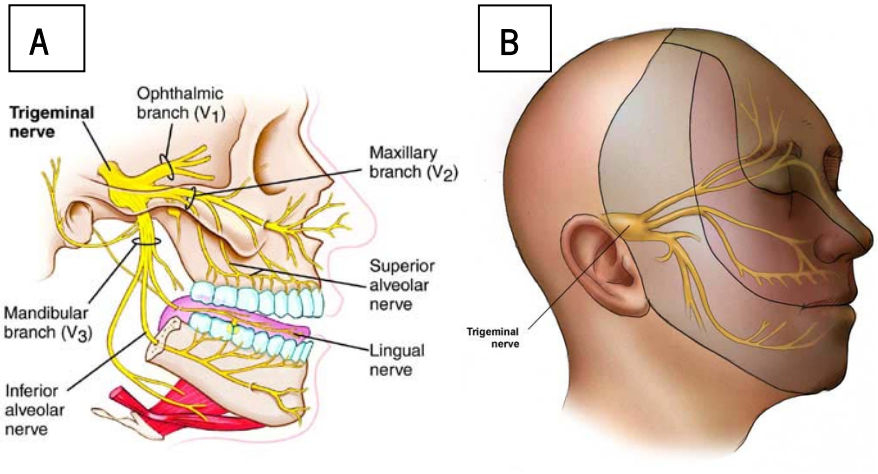

Figura 1. Nervo Trigémio. Representação dos ramos principais do nervo (A) e dos respectivos dermátomos (B).

A-Retirado de http://www.mayoclinic.org/trigeminal-neuralgia/enlargeimage2871.html; B-Retirado de http://medical-dictionary.thefreedictionary.com/trigeminal+nerve

1.3.2. Sistema sensitivo Trigeminal

Os estímulos nóxicos da cabeça são codificados por terminações sensoriais periféricas (aferentes primários) de quatro nervos cranianos, o V (Trigémio), o VII (Facial), o IX (Glossofaríngeo), o X (Vago) e ainda das terminações dos três nervos cervicais superiores (C1,C2 e C3). Os aferentes primários agrupam-se principalmente em três tipos de fibras sensitivas: Aβ (beta), Aδ (delta) e C. Os estímulos nóxicos geralmente associados à experiência dolorosa (estímulos nociceptivos) activam as fibras Aδ e C. Estas fibras (nociceptores), quando activadas, geram impulsos que são transmitidos até ao SNC e activam os neurónios do núcleo do Trigémio do tronco cerebral e do corno dorsal da medula espinhal, dependendo se o estímulo é aplicado na região da cabeça ou no resto do corpo. O nervo Trigémio tem três núcleos sensitivos, onde terminam as fibras sensitivas aferentes primárias (núcleos espinhal, principal e mesencefálico), e um núcleo motor (*Nolte, 2002*).

As fibras sensitivas do nervo trigémio originam-se, na sua maioria, a partir dos neurónios pseudo-unipolares do gânglio de Gasser (1° neurónio da via sensitiva). A maioria das fibras que transmitem informações ligadas ao tacto, vibração e às articulações (percepção espacial) (*sensibilidade epicrítica*), constituem as ramificações centrais dos axónios em T destes neurónios e terminam no ***núcleo principal do trigémio*** (Pr5); aquelas que transmitem informação nociceptiva (dor) e da temperatura (*sensibilidade protopática*) terminam principalmente no ***núcleo espinhal do trigémio*** (Sp5). Os segundos neurónios, localizados nos núcleos Sp5 e Pr5,

após processarem a informação das fibras nociceptivas dos primeiros neurónios, projectam através de axónios longos para o núcleo ventro-postero-medial (VPM) do tálamo (tálamo lateral). Este é o principal núcleo de processamento subcortical da informação sensorial proveniente da cabeça e é onde se encontra o terceiro neurónio da via nociceptiva. Estes terceiros neurónios projectam finalmente para o córtex somato-sensitivo, para o processamento cortical da informação. As fibras provenientes dos neurónios do núcleo VPM projectam através do joelho da cápsula interna e da coroa radiada e terminam somatotopicamente na porção lateral do gyrus pós-central, na zona do "*homúnculo sensitivo*" onde se encontram os neurónios que processam a representação da face. Ao contrário dos núcleos Sp5 e Pr5, os corpos celulares sensoriais dos neurónios primários do ***núcleo mesencefálico do Trigémio*** (Me5) localizam-se no mesencéfalo, mergulhados na substância cinzenta do SNC e estão ligados funcionalmente à proprionocicepção, isto é, à transdução de estímulos que nascem na membrana da mucosa oral, na articulação temporomandibular, nos músculos mastigadores e oculares e nos receptores ligamentares periodontais. Assim, os corpos celulares pseudo-unipolares dos núcleos mesencefálicos possuem ramificações periféricas (tracto mesencefálico) para os músculos e outras estruturas, enquanto as ramificações centrais projectam para o *núcleo motor do Trigémio* (5N), formando contacto mono-sináptico com neurónios somatomotores de modo a completar um arco reflexo de dois neurónios, análogo aos reflexos espinais.

O núcleo Sp5 está dividido em três subnúcleos: oral (Sp5O), interpolar (Sp5I) e caudal (Sp5C). As fibras nociceptivas Aδ e C ao entrarem no tronco cerebral percorrem o *tracto espinhal do trigémio* (sp5) em sentido descendente para terminarem principalmente no subnúcleo Sp5C. Pelo contrário, as fibras mielínicas grossas Aβ (epicríticas) dividem-se em ramos ascendentes curtos que terminam no núcleo Pr5 e em ramos descendentes longos, que passam pelo tracto sp5 e dão origem a colaterais para várias partes dos sub-núcleos espinhais. À medida que as fibras continuam caudalmente e colateralizam, ficam cada vez mais finas e têm uma condução cada vez mais lenta, até terminarem no sub núcleo Sp5C. A transmissão ascendente do núcleo Sp5 segue por um percurso multi-sináptico, terminando nos neurónios do núcleo Pr5; os axónios destes cruzam para o lado oposto do tronco cerebral e projectam em sentido ascendente. No percurso da parte caudal do tronco, as fibras associam-se para formar o *feixe trigémino-talámico,* que segue dorsalmente no *lemniscus mediano.* O feixe trigémino-talámico envia fibras terminais e colaterais para a formação reticular do tronco cerebral e para a

substância cinzenta periaqueductal (PAG), antes de terminar na região do complexo ventral posterior do tálamo, no VPM.

A enervação sensorial da face é uma das mais especializadas do corpo humano. O aspecto mais importante e clinicamente relevante é a organização somatotópica do sistema sensitivo do nervo Trigémio em diversas estruturas: no gânglio de Gasser, na raiz sensitiva, no tracto sp5 e no núcleo Sp5. No gânglio de Gasser, os corpos celulares dos mecanoreceptores e dos nociceptores aferentes do ramo oftálmico estão concentrados medialmente e anteriormente; os do ramo mandibular têm uma localização caudal e lateral e os corpos celulares dos neurónios do ramo maxilar encontram-se entre as camadas das outras duas divisões do nervo. Os corpos celulares dos neurónios que enervam a cavidade oral e peri-oral estão localizados mais cranialmente que as estruturas mais distais da boca. Nas raízes sensitivas, as aferências também apresentam uma organização somatotópica; a porção central da divisão mandibular está localizada postero–medialmente, a do ramo oftálmico está situada antero–lateralmente e a do ramo maxilar posiciona-se numa posição intermédia. Do mesmo modo, o tracto sp5 apresenta uma organização somatotópica, evidenciada em estudos clínicos e experimentais. Um dado somatotópico com importância clínica é demonstrado no eixo rostro-caudal do subnúcleo Sp5C, onde se observa uma distribuição tipo "cebola", com base no défice sensorial causado por lesões no tronco cerebral (*Nadeau et al, 2006*). A enervação sensorial perto da linha média da boca e do nariz está representada na porção mais anterior do sub–núcleo Sp5C, enquanto a enervação de áreas mais laterais da face terminam progressivamente em zonas mais caudais do núcleo Sp5C.

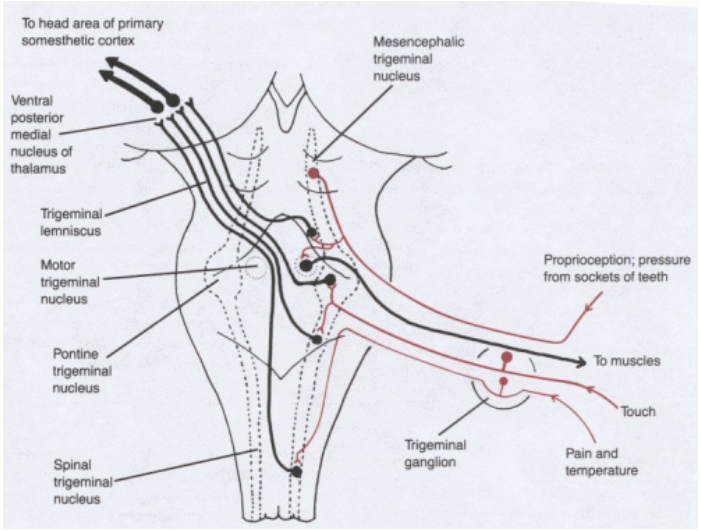

Figura 2. Nervo Trigémio. Representação das conexões entre as fibras sensitivas do 1º neurónio (aferentes primários) e os neurónios de 2ª ordem (espinhotalâmicos).

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http://instruct.uwo.ca/anatomy/530/530notes.htm

1.4. Nevralgia do Trigémio

O quadro clínico da NT é específico e ocasiona um impacto negativo intenso, dado que os períodos de dor paroxísticos e excruciantes típicos induzem alterações funcionais e psíco–afectivas importantes nos utentes (*Zakrzewska e Lopez, 2006*). O tratamento poderá envolver uma vasta gama de fármacos, mas estes apresentam uma eficácia incompleta e/ou conduzem a um efeito dose-limite (*Chong e Bajwa, 2003*). Se o protocolo terapêutico falha, será necessário planear técnicas progressivamente mais invasivas (*Merrison e Fuller, 2003*) e a cirurgia deverá ser a opção (*Chong e Bajwa, 2003*). O diagnóstico e estratégia terapêutica baseiam-se nos factores físicos e psicológicos que estão directamente relacionados com a dor (*Turk, 2002*). Nesse sentido, o plano interdisciplinar no utente que tem dor crónica neuropática, nomeadamente NT, tem uma perspectiva centralizada na reabilitação funcional e não na cura (*Turk, 2003*), devendo incluir abordagem farmacológica e não farmacológica e terapêuticas ocupacionais, comportamentais e cognitivas (*Turk, 2003*). A análise de trabalhos clínicos evidenciam que a abordagem multidisciplinar biopsicossocial conduz a uma melhoria do quadro clínico e funcional, enquanto as intervenções monodireccionais não evidenciam resultados ou prognósticos clínicos relevantes (*Guzmán et al, 2001*).

Embora o fármaco mais usado em estudos clínicos em grande escala da NT seja a carbamazepina em monoterapia ou em associação, há novos estudos com agentes do mesmo grupo, como a gabapentina e a lamotrigina (*Cheshire, 2002; 2007*) ou de outros grupos farmacológicos como os antidepressivos amitriptilina e clomipramina (*He et al, 2006*). No entanto, são necessários mais estudos que avaliem os benefícios clínicos da associação de diferentes fármacos (*Simpson, 2001; Gilron et al, 2005*), e o impacto psicossocial no paciente com TN (*Taylor, 2000*).

1.4.1. Epidemiologia

Em 2007 foi publicado um estudo epidemiológico para avaliar a prevalência da dor crónica neuropática na população Francesa (*Bouhassira et al, 2008*), tendo sido recolhida informação de 23712 utentes. Nesse estudo, a prevalência de dor crónica na população em geral foi de 31,7%, atingindo uma intensidade severa em 15,1%, moderada a severa em 18,8% e média em 46,5% dos utentes com dor; a prevalência de dor crónica com características de dor neuropática é de 6,9%, é mais frequente no sexo feminino (60,5%) e o pico de idade de

incidência é entre os 50-64 anos; a localização mais frequente é na região lombar (62,7%), seguida da região cefálica (8,9%). Existe um estudo português sobre a prevalência da dor crónica em Portugal, em adultos (maiores de 18 anos) numa amostra de 5100 pessoas, que refere a prevalência de dor crónica moderada a forte em 14% da população, com a dor crónica a ter uma incidência de 30% (*Castro-Lopes et al, 2007*). A NT é a dor facial mais frequente, com uma incidência de 4-5 pessoas por 100 mil de habitantes nos Estados Unidos da América (*Katusic et al, 1990*) e uma prevalência de cerca de 15,5 por 100 mil habitantes por ano (. No entanto, estudos no Reino Unido indicam que os valores podem atingir 27 casos de NT em 100000 habitantes por ano (*Hall et al, 2006*), com incidência mínima de 2.1-8 por 100 mil habitantes por ano (*Brewis et al., 1966; MacDonald et al., 2000*). É uma dor típica do indivíduo com idade superior a 65 anos e predomina nas mulheres (60% dos utentes). Não há evidência de existirem factores raciais ou étnicos que predominem na incidência da patologia NT (*Loeser, 2001*). Um estudo numa cidade francesa mostrou que 2.7% da população tinha dores da face e/ou da cabeça e, dentro deste grupo, 0.1% padecia de NT (*Munoz et al., 1988*). Estudos da incidência desta nevralgia indicou valores entre 3.4 e 7.2 casos por 100 mil habitantes, respectivamente em homens e mulheres (*Loeser 2001*; *Merrison e Fuller, 2003*). O pico de incidência é em adultos (mais de 90% destas nevralgias surgem depois dos 40 anos) (*Katusic et al., 1990*). A NT atípica (ver abaixo) parece ser mais comum em doentes com esclerose múltipla do que na população em geral (*Katusic et al., 1990*) e em doentes que fumavam menos, consumiam menos álcool e tinham sofrido menos amigdalectomias, além de ter menor probabilidade de ocorrer em judeus ou imigrantes (*Rothman e Monson, 1973*). São necessários mais estudos de casos populacionais para estimar a prevalência desta patologia, o seu impacto na qualidade de vida e os custos sociais resultantes (*Zakrzewska e Lopez, 2006*).

1.4.2. Etiologia e Patofisiologia

Actualmente, nem a etiologia nem a patofisiologia da NT são explicadas de modo satisfatório, embora muitos progressos tenham sido obtidos recentemente. Este tipo de dor neuropática pode estar associado à compressão do V nervo craniano aquando da sua entrada no SNC (ao nível da Ponte), devido a um meningioma ou neurinoma (*Cheng et al 1993*) ou pela compressão ou contacto de um vaso tortuoso, arterial ou venoso (*Nurmikko, 2003*).

As Nevralgias dividem-se em típicas e atípicas. As ***nevralgias típicas*** referem-se a síndromes dolorosos restritos aos dermátomos enervados por um nervo craniano específico ou por um dos seus ramos, podendo ocorrer em qualquer nervo craniano com fibras aferentes somáticas, nomeadamente nos nervos Trigémio, Facial, Glossofaríngeo e Vago. As ***nevralgias atípicas*** podem ocorrer também nos nervos cranianos, mas não se restringem à área específica enervada pelo nervo afectado; estão frequentemente associadas a um traumatismo ou a uma infecção crónica do nervo afectado.

A NT é um dos síndromes dolorosos mais intensos da face (*Cruccu et al, 1990; Rosen, 2001*). A **nevralgia primária, típica** ou ***idiopática*** rotulada de "***tique doloroso***" parece ser, na maioria dos casos documentados, causada por uma compressão vascular intra–craniana do nervo Trigémio. Assim, segundo a IASP a NT típica ou idiopática é uma situação clínica que se traduz por uma dor súbita, de grande intensidade [9-10 pontos no teste da Escala Visual Analógica (EVA), num máximo possível de 10 pontos], de curta duração, geralmente unilateral, recorrente e referida ao dermátomo correspondente (um ou mais ramos do nervo Trigémio), mas que apresenta *exame neurológico normal*. A **NT secundária, atípica** ou ***sintomática*** resulta de lesões estruturais identificáveis, estando associada a um tumor, aneurisma ou a situações de esclerose múltipla (*Zakrzewska, 2003*).

Avanços importantes na compreensão dos mecanismos dolorosos derivados da lesão de nervos periféricos foram obtidos com base em diversos modelos de dor crónica neuropática, incluíndo modelos de NT desenvolvidos no laboratório (*Liang et al, 2007; Shinoda et al, 2007*). No entanto, algumas características únicas da NT, como os episódios recorrentes de dores lancinantes de curta duração, não são reproduzíveis nesses modelos e constituem um "puzzle" difícil de explicar no actual estado da arte (*Devor, 2006*). Aparentemente, a maioria dos pacientes com NT primária apresentam uma compressão mecânica do nervo Trigémio, quando este sai da ponte do tronco cerebral e atravessa o espaço subaracnoideu, cavidade de Meckel e zona de entrada da raiz nervosa (*Dandy, 1934*; *Jannetta, 1975*). Este ponto do nervo corresponde também à transição entre mielina central (derivada dos oligodendrócitos) e mielina periférica (derivada das células de Schwann). É possível que esta zona, já de si menos estável, seja mais sensível à compressão vascular. Essa compressão poderá também estar relacionada com alterações vasculares resultantes de arteriosclerose e a hipertensão, o que poderá explicar a prevalência da NT em idades mais avançadas. A compressão ocorre geralmente por intermédio de uma artéria de grande calibre, como a cerebelar superior ou, mais raramente,

pela cerebelar inferior posterior (*Loeser, 2001*). O contacto ou compressão do nervo Trigémio terá como consequência uma perda da bainha mielínica que envolve o nervo, resultando em actividade ectópica das fibras nervosas que se traduzem nos disparos de dor paroxísticos tipo choque eléctrico a partir dos "pontos-gatilho" referidos à superfície (tique doloroso). Uma percentagem dos doentes com NT atípica apresenta uma situação subjacente de esclerose múltipla, tendo a autópsia mostrado a presença de uma placa desmielinizada na raiz posterior do Trigémio (*Lazar e Kirkpatrick, 1979*).

Não se sabe porque é que uma placa desmielinizante, uma infecção no maxilar ou uma compressão arterial ou neoplásica do nervo trigémio podem causar uma dor tão intensa como aquela que ocorre no "tique doloroso". Existem duas teorias que procuram explicar a NT: a **hipótese "centralista"** explora as semelhanças entre o "tique doloroso" e a hiperactividade neuronal focalizada que ocorre na epilepsia (*Anderson et al, 1971*). De facto, a injecção de agentes convulsivantes no núcleo do trigémio pode causar hiperactividade neuronal e um síndrome doloroso em gatos e macacos; por outro lado, diversos agentes anti-convulsivantes têm estado na base da obtenção dos melhores resultados analgésicos na dor provocada pela NT (*Chong e Smith, 2000*). A **hipótese "periférica"** propõe que alterações na mielina e axónios do nervo Trigémio possam alterar a sensibilidade deste a estímulos químicos e mecânicos, sugerindo assim que o síndrome doloroso da NT tenha origem numa "sensitização periférica" do nervo (*Kerr e Miller, 1966*). Actualmente, parece ser consensual que são necessários mecanismos centrais e periféricos na indução da nevralgia do trigémio (*Calvin et al., 1977*; *From et al., 1981*). Só uma hipótese mista poderá explicar os fenómenos observados na NT (*Loeser, 2001*), já que os mecanismos das duas teorias são necessários para o aparecimento da NT (*Love e Coakham, 2001; Devor, 2006*).

Recentemente, outra hipótese, a "**teoria de ignição**", foi avançada para explicar a NT. Esta sugere que a dor paroxística se inicia por "descargas" em locais específicos das fibras do nervo Trigémio, de forma espontânea ou após a estimulação dos pontos-gatilho. A conjugação cruzada de descargas nas raízes ou no gânglio do nervo Trigémio lesado, ocasionam a activação em cadeia de fibras adjacentes "silenciosas" e desencadeiam a activação sucessiva, em "onda", dos neurónios adjacentes, originando uma activação global por "ignição". O resultado será uma resposta dolorosa rápida e explosiva, originando uma sensação de choque eléctrico (*Rappaport e Devor, 1994; Devor, 2006*).

1.4.3. Sintomas e Diagnóstico

A *história clínica* tem um papel fundamental no diagnóstico de NT e, por isso, é essencial que seja obtida com cuidado e se acompanhe por uma observação do comportamento não verbal do utente; sugere-se ainda que estes devem ser encorajados a descrever por palavras suas "a sua doença" (*Zakrzewska, 2003*).

A NT é um síndrome doloroso referido na face (*Zakrzewska e Lopez, 2006*), que se caracteriza por: (a) uma dor fortíssima, semelhante a choques eléctricos; (b) dor geralmente unilateral; (c) dor com início e fim abruptos; (d) períodos sem dor entre os ataques; (e) desencadear dor no ponto-gatilho por estimulação inócua, o qual muitas vezes se localiza numa zona diferente da área estimulada; (f) ausência de perda sensorial na zona dolorosa; (g) dor restrita à área enervada pelo nervo trigémio; (h) dor controlada por certos fármacos anticonvulsivantes e antidepressivos e não por analgésicos clássicos.

Os estímulos que desencadeiam o "tique doloroso" são inócuos, nomeadamente tocar na face (65%), mastigar e falar (75%), engolir ou simples exposição ao frio (48%) (*Rasmussen 1991*), quando são aplicados na face, nas zonas enervadas pelo Trigémio; só 4% dos doentes com esta nevralgia não apresentam um factor desencadeador (*Rasmussen 1991*). A NT é geralmente uma doença periódica. Muitos pacientes referem intervalos de meses ou até anos entre as crises. É comum os intervalos entre as crises irem diminuindo, enquanto a intensidade de dor vai aumentando. Alguns utentes permanecem num estado álgico contínuo após o início dos ataques. O stress físico e emocional parece aumentar a possibilidade da ocorrência desses ataques de dor intensa em pacientes com história de NT (*Loeser, 2001*). Muitos doentes, na tentativa de evitar o factor desencadeador, evitam alimentar-se, perdendo peso, apresentando uma aparência pouco cuidada e higiene deficiente. Têm que ser acompanhados do ponto de vista psicológico e/ou psiquiátrico, devido às alterações psicoafectivas e à alteração significativa da auto-estima geralmente associada à NT.

O exame neurológico sumário é fundamental para a avaliação das alterações na face nas três regiões de distribuição do nervo Trigémio. A pesquisa da sensibilidade superficial pela resposta ao toque através dos filamentos de von Frey não é suficiente, sendo necessário complementar este exame com a pesquisa do reflexo da córnea e do componente motor do Trigémio, para exclusão de lesão do nervo Facial. É importante avaliar a sensibilidade mecânica pela aplicação de um estímulo não doloroso na pele, para determinar a presença de ***alodínia***. A pesquisa de sensibilidade térmica avalia a alodínia relacionada com o calor ou o frio. É também

importante avaliar a existência de *hiperalgesia*; esta resposta anormalmente intensa a uma estimulação nóxica (pode ser térmica ou mecânica) é pesquisada pelos mesmos meios técnicos usados para a alodínia. A aplicação tópica de capsaicina, poderá ser usada para desencadear descargas ectópicas em nociceptores "silenciosos" e simulará uma hipersensibilidade local (*Gottrup et al, 2000*).

Os exames complementares a optar no diagnóstico de NT deverão incidir no despiste da relação de proximidade de vasos arteriovenosos com o gânglio de Gasser ou com as raízes do nervo Trigémio. No entanto, o diagnóstico de NT será efectuado pela articulação de dados obtidos na história clínica, no exame neurológico sumário e nos resultados dos meios complementares de diagnóstico [potenciais evocados, Tomografia Axial Computorizada (TAC) da fossa posterior e Ressonância Magnética do crânio] (*Mursch et al, 2002; Cruccu et al, 2006; Erbay et al, 2006*). Os diagnósticos principais a excluir serão a esclerose múltipla, a artrite temporal homolateral e as lesões tumorais. O exame complementar mais indicado é a ressonância magnética angiográfica, dada a sua alta sensibilidade e especificidade (*Cruccu et al, 2006; Erbay et al, 2006*).

1.4.4. Tratamento

Apesar de existirem múltiplos protocolos para o tratamento da NT aprovados pela Organização Mundial de Saúde (OMS), a resposta clínica na grande maioria dos utentes é irregular e muitas vezes não satisfaz nem o utente nem a equipa médica. A abordagem terapêutica deve ser planeada de modo individualizado e no sentido de se obter uma reabilitação funcional e uma estabilidade psíco-afectiva. Apesar do avanço progressivo nos conhecimentos sobre a génese da NT, da disponibilidade de novos medicamentos e de procedimentos cirúrgicos, a eficácia dos tratamentos ainda não é satisfatória, havendo um longo caminho a percorrer para se obter um sucesso terapêutico completo na NT. Em 2008, a Academia Americana de Neurologia (AAN) e a Federação Europeia da Sociedade de Neurologia (EFNS) elaboraram as principais linhas de orientação para o diagnóstico e tratamento farmacológico e cirurgico da NT, no sentido de uniformizar a solicitação de meios complementares de diagnóstico, os fármacos de primeiraa e segunda linhas e a indicação para cirurgia a nível do gânglio de Gasser (*Cruccu et al, 2008*).

1.4.4.1. Abordagem farmacológica

A abordagem do utente com Dor Neuropática deverá ter uma vertente nociceptiva (a dor e a funcionalidade) e uma não nociceptiva (a ansiedade, depressão, o sono) (*Finnerup e Jensen, 2006*): (I) como na dor neuropática os analgésicos anti-inflamatórios não esteroídes clássicos e os opióides fracos e fortes não são geralmente eficazes, a opção terapêutica incide nos analgésicos coadjuvantes, nomeadamente os anticonvulsivantes; Estes tendem a reduzir a excitação dos nociceptores periféricos e dos neurónios nociceptivos espinhais, ao modularem a excitabilidade das fibras por bloqueio dos canais de sódio e/ou cálcio; (II) para combater a hiperalgesia opta-se pelos antidepressivos tricíclicos (ex: amitripilina), que reforçam o controlo inibitório descendente já que inibem a recaptação da serotonina e noradrenalina nas sinapses do SNC; quando a dor neuropática se associa a alterações importantes de humor, como a depressão ou a ansiedade será importante também a utilização de antidepressivos e ansiolíticos para diminuir a modulação facilitadora da percepção dolorosa com origem no encéfalo; (III) nas disestesias, os anestésicos locais como a lidocaina actuam de modo eficaz sobre as fibras nociceptivas Aδ e C durante a realização de bloqueios analgésicos do neuro-eixo ou de nervos periféricos, ou ainda após bloqueios simpáticos; actuam por inibição da actividade das fibras sensitivas em resultado do bloqueio dos canais de sódio e cálcio responsáveis pela progressão do potencial de acção pela membrana citoplasmática (*Yanagidate e Strichartz, 2007*).

Na Nevralgia do Trigémio a abordagem farmacológica visa reduzir a intensidade e a frequência das crises álgicas e reduzir os períodos de dor. Ao planear a decisão terapêutica é fundamental ter a plena consciência dos meios e da equipa disponíveis, da indicação específica de cada fármaco e da via de administração mais eficaz e com menor risco de sequelas. A abordagem inicial da NT é sempre não invasiva, farmacológica, geralmente sob a forma de monoterapia com anticonvulsivantes; no insucesso desta está indicada uma terapêutica combinando vários anticonvulsivantes, ou poderá ser planeada uma associação com outras classes de fármacos analgésicos (*Cheshire, 2007; Cruccu et al, 2008*). Em caso de insucesso terapêutico terá de ser planeada uma abordagem mais invasiva, como as infiltrações analgésicas ao longo do nervo Trigémio usando bloqueios periféricos ou a radiofrequência pulsátil. A opção por procedimentos cirúrgicos engloba cirurgias a nível periférico, com a secção de um ramo ou vários ramos do nervo Trigémio, a secção de um feixe espinhal a nível da medula (tractotomia), ou uma intervenção a nível central, nomeadamente Radiocirurgia (técnica clássica) ou a cirurgia de descompressão microvascular do gânglio de Gasser (*Lonser e Apfelbaum, 2005*).

Na dor Neuropática os fármacos de primeira linha são os analgésicos classificados como adjuvantes: os anticonvulsivantes e os antidepressivos apresentam resultados clínicos satisfatórios, dada a sua acção específica e mecanismo de acção (*Jensen et al, 2006*). Os anticonvulsivantes como a *carbamazepina* (CBZ) e, em menor grau, *fenitoína*, têm-se revelado como o modo mais eficaz de controlar a dor do "tique doloroso" (*Sindrup e Jensen, 2002*) (*Campbell et al, 1966*). A CBZ consegue controlar a dor em 50-75% dos doentes e é considerada como o primeiro tratamento farmacológico na NT (*Merrison & Fuller, 2003; Wiffen et al., 2005*; *Zakrzewska e Lopez, 2006*); apresenta um NNT (*Number Needed to Treat* – nº de utentes necessários tratar para conseguir um doente tratado) de 1.8, o que representa um valor de estabilidade clínica muito significativo (*Campbell et al, 1966*). A CBZ actua principalmente por bloqueio dos canais de sódio dependentes da voltagem (*Chong & Smith, 2000*). O disparo do potencial de acção no axónio necessita de passagem do sódio para o interior deste, através dos canais de Sódio dependentes de voltagem; depois da activação, os canais de sódio ficam inactivos por um certo período de tempo. Anticonvulsivantes como a CBZ e a oxicarbamazepina estabilizam os canais de sódio dependentes da voltagem na forma inactiva, impedindo que eles voltem ao seu estado activo e bloqueando a despolarização das fibras. No entanto, a CBZ induz efeitos secundários importantes a nível gastrointestinal e do sistema nervoso central em cerca de 1/3 dos doentes (*McQuai et al., 1995*); também pode provocar imuno-depressão, hemato-supressão e hepatotoxicidade (*Killian e Fromm, 1968; Loeser, 2001; Canavero e Bonicalzi, 2006*), e ainda pode ser teratogénica se tomada por grávidas (espinha bífida). A interacção com outros fármacos torna necessária a monitorização sérica regular durante a sua administração, para evitar os efeitos secundários inerentes ao aumento dos seus níveis sanguíneos.

A *lamotrigina é um* anticonvulsivante que bloqueia canais de sódio pré-sinápticos, e diminui a libertação de neurotransmissores (*Sang e Hayes, 2006*). Observaram-se resultados eficazes, mas estatisticamente não significativos quanto à redução das crises e da intensidade de dor na NT (*Zakrzewska et al, 1997*). A *Fenitoína* foi o primeiro anticonvulsivante a ser usado no tratamento da dor neuropática e na abordagem farmacológica da NT, com obtenção de resultados positivos, mas são necessários estudos mais alargados para confirmação destes dados (*Sindrup e Jensen, 2002*); a sua acção analgésica incide também no bloqueio dos canais de sódio (*England et al, 1996; Devor, 2006*), mas hoje é pouco utilizada devido às doses altas necessárias para se obter um efeito terapêutico, ocorrendo por isso numerosos casos de intolerância (*Canavero e Bonicalzi, 2006; Cheshire, 2007*). A *Oxicarbamazepina* é um derivado

da CBZ, com um mecanismo de acção similar a esta. Apesar dos poucos estudos sobre o seu efeito analgésico na NT, parece ser um fármaco promissor, quer pelas suas características farmococinéticas quer pelo seu principal metabolito, o 10-monohidroxi–carbamazepina, que não faz indução enzimática, além de apresentar menor incidência de reacções adversas (cutâneas, hepatotoxicidade, teratogénicas e a nível medular - anemia aplástica) do que a CBZ (*Gomez-Arquelles et al, 2008*).

A gabapentina (GBP) é um anticonvulsivante recente que revelou efeitos analgésicos superiores à CBZ na maior parte das patologias neuropáticas, apesar de ser um fármaco de segunda linha no tratamento da NT, tendo a vantagem de não ocasionar efeitos secundários de relevo (*Loeser, 2001*) e de não interagir com outros fármacos (*Chong & Smith, 2000*). A sua acção no controlo da NT foi descrita pela primeira vez em 1998 (*Carrazana & Schacter, 1998*) e tem sido alvo de alguns estudos (*Cheshire, 2002; 2007*). O efeito analgésico da GBP foi também descrito para a dor facial atípica (*Sist et al., 1997*), esclerose múltipla (*Khan, 1998*; *Solaro et al., 1998*), nevralgia pós-herpética (*Rowbotham et al., 1998*) e neuropatia diabética periférica (*Backonja et al., 1998*). A GBP tem uma composição molecular análoga ao GABA (ácido γ-aminobutírico), o principal neurotransmissor inibitório do sistema nervoso central. A sua acção analgésica parece resultar da acção conjunta da sua ligação com a subunidade alfa-2-delta ($\alpha 2\delta$) dos canais de cálcio dependentes da voltagem pré-sinápticos e da redução da libertação dos neurotransmissores pré-sinápticos (*Baillie e Power, 2006*).

O *baclofeno é* um agonista dos receptores $GABA_B$ que inibe os sintomas associados à dor neuropática (alodínia e espasmos musculares) e tem bons resultados clínicos, podendo ser administrado quer em monoterapia quer associado à CBZ ou fenitoína. No entanto, o efeito clínico deste fármaco tem curta duração, dado que o seu mecanismo de acção desenvolve rapidamente tolerância (*Herman et al, 1992*). Na NT, cerca de 70% dos pacientes incapazes de tolerar a CBZ mostraram redução da dor (*Fromm et al, 1984*).

A toxina botulina (*toxina botulínica tipo A, BTX-A*) tem um efeito analgésico na dor neuropática, correlacionado directamente com o bloqueio da libertação da acetilcolina na placa motora impedindo a contracção muscular e da libertação de neurotransmissores como a substância P, o peptídeo relacionado com o gene da calcitonina (CGRP) e glutamato. Apresenta um efeito dose-dependente, que se estende desde poucas horas até 6 meses. A acção da BTX-A nos pontos-gatilhos da NT resulta em melhoria clínica provavelmente devido ao relaxamento

muscular, que ocasiona uma diminuição do fluxo nociceptivo no nervo (*Borodic e Acquadro, 2002; Piovesan et al, 2005; Turk et al, 2005*).

A *prégabalina* apresenta com mecanismo de acção similar à GBP na modulação dos canais de cálcio dependentes da voltagem existentes nas membranas dos axónios com actividade anormal associada à dor Neuropática Periférica e Central; parece actuar pela ligação à sub-unidade $\alpha 2\delta$ dos canais de cálcio dependentes da voltagem pré-sinápticos, que resulta na redução da libertação de neurotransmissores (*Gajraj, 2007; Bauer et al, 2009*). Observam-se efeitos adversos como sedação, alterações do equilíbrio, ataxia e aumento de peso. Serão ainda necessários estudos clínicos alargados para complementar a avaliação da acção da prégabalina na dor neuropática (*Dworkin, et al 2003*) e na TN (*Obermann et al, 2007; Pérez et al, 2009*). Em estudos animais parece ter também um efeito central no alívio da dor neuropática, por activar o sistema noradrenérgico antinociceptivo descendente (*Takeuchi et al, 2007*).

Em resumo, na NT os tratamentos clínicos iniciados com protocolos farmacológicos continuam a centrar-se na CBZ, mas esta poderá ser progressivamente substituída por anticonvulsivantes com menor incidência de efeitos adversos, como a GBP, a prégabalina e a oxicarbamazepina, ou em casos de intolerância à CBZ.

1.4.4.2. Técnicas não invasivas

A opção por técnicas não invasivas na NT tem longa tradição, sendo múltiplas as técnicas que podem ser utilizadas. Estas têm tido cada vez maior aderência dos clínicos, quer como técnica terapêutica principal, quer como uma técnica complementar ao tratamento farmacológico. As técnicas mais usadas são: a estimulação eléctrica transcutânea, os bloqueios neurolíticos periféricos, a acupunctura e o bloqueio analgésico.

A estimulação eléctrica transcutânea (TENS) é utilizada desde a década de sessenta, após a publicação da Teoria do Portão de Controlo (Gate Control Theory) por Melzack e Wall (1965). Esta técnica tem indicações precisas na dor neuropática (*Chesterton et al, 2003; Nnoaham e Kumbang, 2008*) e quase não apresenta contra-indicações (excepto utentes com *pace-maker*), mas necessita de mais estudos para comprovar a extensão da sua eficácia. A estimulação percutânea do gânglio de Gasser para o tratamento da NT foi introduzido em 1980, com bons resultados clínicos, os quais foram também conseguidos no tratamento específico da NT (*Meyerson e Hakansson, 1986; Mehrkens e Steude, 2007*). O *Bloqueio neurolítico dos ramos do nervo Trigémio* foi largamente utilizado entre 1960 e 1990 para ao tratamento da NT; é injectado

no gânglio o agente neurolítico Fenol ou Álcool Etílico, que impedem de modo prolongado, quase irreversível a transmissão dos impulsos dolorosos da periferia para o SNC, ocasionando analgesia e uma melhoria clínica prolongada (*Wilkinson, 1999; Erdem e Alkan, 2001*). No entanto, este bloqueio poderá ocasionar anestesia ou hipostesia a nível sensitivo e paralisia ou parésia a nível motor. Com os bons resultados obtidos com a utilização dos anticonvulsivantes e o impacto promissor da cirurgia para descompressão microvascular, os bloqueios neurolíticos passaram a ser opção secundária. A *Acupuntura* tem visto reforçar, ao longo do tempo, a evidência científica da sua acção no tratamento da dor (*Knardahl et al, 1998; Zhao, 2008*). A nível periférico pode ocasionar o bloqueio da transmissão nervosa, enquanto a nível central terá uma acção inibitória pré-sináptica e pós-sináptica sobre a transmissão nociceptiva na medula espinhal e parece activar também o sistema supraspinhal antinociceptivo (*Zhao, 2008*). A sua aplicação na NT terá que ser avaliada por estudos rigorosos (*Costantini et al, 1995*).

O *Bloqueio Analgésico* no nervo Trigémio é efectuado com a aplicação de um anestésico local em concentrações baixas (analgésicas) nos pontos-gatilho periféricos da NT (*Hille, 1977; Butterworth e Strichartz, 1990; Ragsdale et al,1994*). Este bloqueio permite o alívio de dor e contribui, como adjuvante, para o plano terapêutico que não tenha obtido a analgesia pretendida da área envolvida (*Lerich, 1949; Bonica, 1984*). A anatomia da região craniana e cervical apresenta múltiplas interligações com estruturas nervosas e grandes vasos (arteriais e venosos), sendo necessária uma técnica meticulosa e doses correctas de anestésicos locais para se realizar uma técnica segura. O bloqueio analgésico periférico no nervo Trigémio é uma técnica simples, não invasiva, não onerosa e que pode ser de extrema utilidade na fase inicial do protocolo terapêutico. A administração do anestésico local tem um impacto clínico importante, pois impede transitória e reversivelmente a transmissão dos impulsos dolorosos da periferia (a nível dos canais de sódio e cálcio) para o sistema nervoso central, ocasionando analgesia e melhoria clínica (*Yanagidate e Strichartz, 2007*). Além disso, o bloqueio analgésico das zonas de indução de dor tem um papel fundamental e complementar do protocolo farmacológico, permitindo o uso de doses menores de analgésicos adjuvantes (*Attal et al, 2006*) e, consequentemente, diminuindo os efeitos adversos destes fármacos. A escolha do anestésico local é feita atendendo à sua farmacocinética e baixa cardio-toxicidade. A *Ropivacaina* (ROP) é um anestésico local recente que tem uma capacidade analgésica semelhante ao analgésico local clássico *Bupivacaina,* mas possui maior segurança na sua utilização clínica dada a menor cardiotoxicidade e menor incidência de efeitos secundários (*McClellan e Faulds, 2000*);

apresenta menor lipossolubilidade do que a Bupivacaina e, assim, afecta menos a actividade motora mediada pelas fibras mielínicas grossas dos motoneurónios (*Bader et al., 1989*). Tanto quanto a pesquisa bibliográfica nos permitiu ver, não existia à data de início desta tese nenhum estudo publicado em que a ROP tivesse sido utilizada na terapêutica da NT. Tal como outros analgésicos locais, a acção da ROP resulta no bloqueio dos impulsos nervosos induzida pela redução da permeabilidade da membrana axonal a iões sódio (*Markham e Faulds, 1996*); bloqueia os canais de sódio resistentes à tetrodotoxina, os quais prevalecem nos neurónios pequenos dos gânglios raquidianos (os que conduzem a nocicepção por darem origem a fibras C e Aδ) (*Oda et al., 2000*). De facto, a ROP é mais selectiva no bloqueio de fibras nociceptivas C e Aδ do que de fibras Aβ condutoras de informação inócua.

1.4.4.3. Técnicas Invasivas

Quando não é possível reverter farmacologicamente a dor da NT e/ou os efeitos adversos associados ao tratamento são intoleráveis, é necessário planear um protocolo terapêutico invasivo. Actualmente, os tratamentos invasivos mais usados na NT são: (I) O *Bloqueio neurolítico do gânglio de Gasser* (*Gangliólise*), que pode ter consequências neurológicas menores ou graves, dependendo da difusão do anestésico para os nervos cranianos adjacentes (abdutor, facial e glossofaríngeo). Loeser considera a NT uma indicação para gangliólise (*Loeser, 1988*). Será importante ter a noção que o volume da cavidade de Meckel é de aproximadamente 0.5 mL e que é mandatória a realização de cisternografia (administração de 0.25 mL de um produto de contraste rádio-opaco) para se obter a confirmação da correcta posição da agulha e do volume de área do gânglio de Gasser para, posteriormente, administrar doses sucessivas de fenol ou álcool (entre 0.25 e 0.5 mL) (*Mullan e Lichtor, 1983*). Os resultados terapêuticos não são satisfatórios e é uma técnica pouco usada, dada a recorrência de dor e a sua baixa selectividade (*Hâkanson, 1981; Linderoth e Hâkanson, 2005*). (II) A *Radiofrequência pelo calor e a pulsada* actuam no potencial de acção do nervo. O mecanismo neurofisiológico sugere que o calor e onda de pulso têm um efeito selectivo nas fibras finas mielinizadas e nas fibras não mielinizadas, com bloqueio da transmissão de nocicepção primeiro nas fibras C e Aδ e só depois das fibras Aβ (*Letcher e Goldring, 1968*). Esta técnica resulta numa melhoria temporária em cerca de 80% dos utentes (*Lopez et al, 2004*) mas, ao fim de algum tempo, uma percentagem elevada dos doentes referem novamente dor (*Zakrzewska e Lopez, 2006*). Além disso, esta técnica pode ocasionar sequelas neurológicas como disestesias e anestesia da hemiface

homolateral, flacidez dos músculos da face e alteração do reflexo córneano (*Zakrzewska et al, 1999*). (III) A *Compressão percutânea do gânglio de Gasser* é uma técnica cirúrgica que pode ser planeada para uma abordagem do nervo a nível periférico ou a nível central (no próprio tronco cerebral). Foi introduzida há 25 anos (*Mullan e Lichtor, 1983*) e induz analgesia através da compressão do gânglio de Gasser com um balão de Fogarty, introduzido através do forâmen oval. Ocorre diferente sensibilidade das diferentes fibras sensitivas à compressão, sendo menor a sensibilidade das fibras mielínicas grossas (inócuas) do que a das fibras nociceptivas; a analgesia induzida é explicada pelo mecanismo da "Teoria do Portão de Controlo", onde a activação de fibras grossas inibe parcialmente a transmissão nociceptiva (*Mullan e Lichtor, 1983; Urculo et al, 1995*). (IV) A *Estimulação Extradural do Cortex Motor* foi proposta para o tratamento da dor neuropática refractária e na dor após um acidente vascular cerebral *(Tsubokawa,1991; Meyerson, 2005*). O possível mecanismo de acção associa-se a uma activação antidrómica dos neurónios do cortex sensorial e das estruturas implicadas na nocicepção (córtex cingulado, tálamo, tronco cerebral,) cujo papel na modulação da dor estão bem estabelecidos (*Peyron et al, 2007*), podendo resultar num reforço dos controlos inibitórios descendentes da dor (*Garcia-Larrea et al, 1999; Drouot et al, 2002*). Bons resultados têm sido obtidos na utilização desta técnica para o alívio da dor na NT (*Rainov e Heidecke, 2003; Lefaucheur et al, 2009*). (V) A *Estimulação Cerebral Profunda* é um procedimento neurocirúrgico que consiste na colocação estereotáxica de um eléctrodo intracerebral nos núcleos sensitivos do tálamo, substância cinzenta periventricular / periaqueductal ou na cápsula interna (*Wallace et al, 2004*) e a estimulação resulta em analgesia (*Bittar et al, 2005; Owen et al, 2007*). Esta técnica já foi usada em diversas neuropatias, inluindo na NT (*Thomas et al, 2009*), nevralgias pós-herpes Zoster e pós-acidente vascular cerebral, mas com resultados pouco relevantes. (VI) A cirurgia mais comum (*Loeser 2001*; *Merrison & Fuller, 2003*) é a *Cirurgia de Descompressão Microvascular* do gânglio de Gasser por craniotomia suboccipital (*Apfelbaum, 1977; Burchiel et al., 1981*). Aqui a abordagem das raízes do Nervo Trigémio é realizada na zona onde este penetra na Ponte. É efectuada a individualização dos vasos que envolvem o nervo e colocada entre o nervo e a artéria uma lâmina de "teflon", efectuando-se em seguida a secção e electrocoagulação dos vasos (*Lonser e Apfelbaum, 2005*). O objectivo desta técnica é descomprimir o nervo Trigémio sem o traumatizar, para se obter o controlo da dor, mas preservando a sensibilidade da face. Nesta proposta cirúrgica é fundamental ponderar o risco anestésico-cirúrgico após a avaliação do estado clínico do utente e a idade (menor que 70 anos).

O sucesso clínico desta abordagem é superior a 70%, embora apresente um índice de mortalidade de 1% (*Piatt e Wilkins, 1984*). Esta técnica poderá associar-se a uma morbilidade alta (complicações neurológicas) (*Barker et al, 1996*), dada a proximidade aos nervos cranianos VIII e VII e ao Cerebelo.

1.5. Objectivos e Metodologia

No conjunto de estudos desta tese planeamos a avaliação clínica de protocolos terapêuticos com associação de diferentes fármacos, no sentido de melhorar a abordagem terapêutica da NT, sem recurso a técnicas invasivas. A constatação da prevalência da NT em utentes idosos e a maior incidência nestes de patologia associada (*Katusic et al., 1990*), leva-nos a ponderar o risco/benefício das técnicas invasivas, as quais não são isentas de efeitos adversos.

O primeiro estudo teve por finalidade avaliar a eficácia clínica de um protocolo analgésico na NT: a associação da toma oral de GBP com o bloqueio analgésico dos pontos-gatilho de dor facial com ROP. O sinergismo potencial da associação analgésica da GBP (anticonvulsivante) com a ROP (Anestésico Local) permitiria a melhoria clínica de utentes com NT que não possam, por motivos de risco anestésico-cirúrgico correlacionado com alguma patologia associada, submeter-se a cirurgia ou a terapias farmacológicas protocoladas com CBZ (fármaco de 1ª linha), por intolerância à CBZ ou pela impossibilidade de controlar a dor com CBZ.

O segundo estudo pretendeu melhorar o resultado clínico da CBZ, no sentido de reduzir a sua incidência de efeitos adversos, ao associar a sua toma oral com o bloqueio analgésico dos pontos-gatilho com ROP e compará-lo com a terapêutica de CBZ em monoterapia. Com esta associação farmacológica (CBZ + ROP) procurou-se reduzir a dose de anticonvulsivante necessária para controlar a dor e os efeitos adversos associados.

O terceiro estudo avaliou a relação custo/benefício de três protocolos usados frequentemente no tratamento da NT: um invasivo (a cirurgia de descompressão microvascular) e dois não invasivos (a CBZ em monoterapia e a GBP associada ao bloqueio analgésico com ROP). As técnicas invasivas, apesar de poderem resultar em melhorias muito significativas, não são isentas de sequelas, que se poderão manifestar por défices sensoriais faciais pouco acentuados ou por lesões neurológicas centrais ou periféricas mais graves. Além disso, os custos

dos tratamentos invasivos e não invasivos parecem ser diferentes, apesar dos resultados terapêuticos poderem ser muito idênticos e com franca melhoria clínica.

A metodologia seguida nos estudos clínicos foi planeada de modo diverso para os três estudos realizados. Planeamos dois estudos clínicos observacionais, prospectivos e longitudinais, e um estudo retrospectivo e transversal. Ao longo de quatro anos, avaliamos terapêuticas em 116 utentes com NT que estavam inscritos na Unidade de Dor Crónica da Unidade de Fafe (Centro Hospitalar Alto Ave – EPE - Guimarães) e nos Serviços de Neurologia e Neurocirurgia do Hospital de S. Marcos (Braga). Os utentes com NT foram alocados de modo aleatório aos protocolos terapêuticos (nos três estudos) e foi efectuada a monitorização de evolução dos tratamentos, em vários momentos pré–definidos. O resultado terapêutico foi avaliado através da evolução de diferentes parâmetros: (i) a intensidade de dor, através de um instrumento unidimensional que avalia a dor na sua grandeza - a Escala Visual Analógica (EVA), a qual, pela sua simplicidade, permite uma colheita de dados fácil e eficiente (*Chapman e Syrjala, 2001*); (ii) o número de crises de dor paroxística / dia; (iii) a dose (mg/dia) de GBP ou CBP administrada nos vários momentos de avaliação e a referência de efeitos adversos; (iv) o impacto psicossocial da NT na qualidade de vida do utente; este parâmetro incluiu a avaliação: (a) da funcionalidade geral do utente através da aplicação do inquérito SIP (*Sickness Impact Profile*; *Bergner et al, 1976; 1981; de Bruin et al, 1992*); (b) do seu estado de Humor (Depressão e Ansiedade), através da aplicação do inquérito HADS (*Hospital Anxiety and Depression Scale*; *Zigmond e Snaith, 1983; Snaith, 2003;* versão traduzida e adaptada por *McIntyre et al, 1999*); (c) o grau de satisfação do utente com o tratamento efectuado e com a equipa que o realizou, através de um inquérito elaborado de modo específico para este estudo (versão de *Lemos et al*, resultados não publicados).

1.6. Bibliografia

1. Almeida, A., Leite-Almeida, H., Tavares, I., 2006. Medullary control of nociceptive transmission: reciprocal dual communication with the spinal cord. *Drug Disc Today Disease Mech*, 3:305–312 (2006).
2. Anderson LS, Black RG, Abraham J, Ward AA Jr. Neuronal hyperactivity in experimental trigeminal deafferentation. *J Neurosurg*, 35:444-452 (1971).
3. Ansah OB, Goncalves L, Almeida A, Pertovaara A. Enhanced pronociception by amygdaloid group I metabotropic glutamate receptors in nerve-injured animals. *Exp Neurol*, 216:66-74 (2009).
4. Antonov SM, Johnson JW. Permeant ion regulation of N-methyl-D-aspartate receptor channel block by Mg(2+). *Proc Natl Acad Sci U S A*, 96:14571-14576 (1999).
5. Apfelbaum RI. A comparision of percutaneous radiofrequency trigeminal neurolysis and microvascular decompression of the trigeminal nerve for the treatment of tic douloureux. *Neurosurgery*, 1:16-21 (1977).
6. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain*, 9:463-484 (2005).
7. Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P. EFENS Guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol*, 13:1153-1169 (2006).
8. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: A randomized controlled trial. *JAMA*, 280:1831-1836 (1998).
9. Bader AM, Datta S, Flanagan H, Covino BG. Comparison of bupivacaine- and ropivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesth Analg*, 68:724-727 (1989).
10. Baillie JK, Power I. The mechanism of action of gabapentin in neuropathic pain. *Curr Opin Investig Drugs*, 7:33-39 (2006).
11. Barker FG 2nd, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome of microvascular decompression for trigeminal neuralgia. *N Engl J Med*, 334:1077-1083 (1996).
12. Bauer CS, Nieto-Rostro M, Rahman W, Tran-Van-Minh A, Ferron L, Douglas L, Kadurin I, Sri Ranjan Y, Fernandez-Alacid L, Millar NS, Dickenson AH, Lujan R, Dolphin AC. The increased trafficking of the calcium channel subunit alpha2delta-1 to presynaptic terminals in neuropathic pain is inhibited by the alpha2delta ligand pregabalin. *J Neurosci*, 29:4076-4088 (2009).
13. Benbouzid M, Choucair-Jaafar N, Yalcin I, Waltisperger E, Muller A, Freund-Mercier MJ, Barrot M. Chronic, but not acute, tricyclic antidepressant treatment alleviates neuropathic allodynia after sciatic nerve cuffing in mice. *Eur J Pain*, 12:1008-1017 (2008).
14. Bennett GJ, Xie YK A peripheral mononeuropathy in the rats that produces disorders of pain sensation like those seen in man. *Pain*, 33:87-107 (1988)

15. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain*, 92:147-157 (2001).

16. Bergner M, Bobbitt RA, Kressel S, Pollard WE, Gilson BS, Morris JR. The sickness impact profile: conceptual formulation and methodology for the development of a health status measure. *Int J Health Serv*, 6:393-415 (1976).

17. Bergner Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care*, 19:787-805 (1981).

18. Bielefeldt K, Gebhart GF. Visceral pain: basic mechanisms. In: "*Melzack´s Textbook of Pain*", 5th edition, McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 721-736 (2006).

19. Bittar RG, Kar-Purkayastha I, Owen SL, Bear RE, Green A, Wang S, Aziz TZ. Deep brain stimulation for pain relief: a meta-analysis. *J Clin Neurosci*, 12:515-519 (2005).

20. Bonica JJ Sympathetic Nerve Blocks of Pain Diagnosis and Therapy. Breon Laboratories, New York (1984).

21. Borodic GE, Acquadro MA. The use of botulinum toxin for the treatment of chronic facial pain. *J Pain*, 3:21-27 (2002).

22. Boucher TJ, McMahon SB. Neurotrophic factors and neuropathic pain. *Curr Opin Pharmacol*, 1:66-72 (2001).

23. Boureau F, Doubrere JF, Luu M. Study of verbal description in neuropathic pain. *Pain*, 42:145-152 (1990).

24. Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic with neurophatic characteristics in the general population. *Pain*, 136:380-387 (2008).

25. Bowsher D. Neurogenic pain syndromes and their management. *Br Med Bull*, 47:644-66 (1991).

26. Brewis M, Poskanzer DC, Rolland C, Miller H. Neurological disease in an English city. *Acta Neurol Scand*, 42 (Suppl 24):1-89 (1966).

27. Burchiel KJ, Steege TD, Howe JF, Loeser JD. Comparison of percutaneous radiofrequency gangliolysis and microvascular decompression for the surgical management of tic douloureux. *Neurosurgery*, 9:111-119 (1981).

28. Butterworth JF, Strichartz GR. Molecular mechanisms of local anesthesia: a review. *Anesthesiology*, 72:711-734 (1990).

29. Calvin WH, Loeser JD, Howe JF. A neurophysiological theory for the pain mechanism of tic douloureux. *Pain*, 3:147-154 (1977).

30. Campbell FG, Graham JG, Zilkha KJ. Clinical trial of carbamazepine (tegretol) in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry*, 29:265-267 (1966).

31. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. *Neuron*, 52:77-92 (2006).

32. Canavero S, Bonicalzi V. Drug therapy of trigeminal neuralgia. *Expert Rev Neurother*, 6:429-440 (2006).

33. Carrazana EJ, Schachter SC. Alternative uses of lamotrigine and gabapentin in the treatment of trigeminal neuralgia. *Neurology*, 50:1192 (1998).

34. Castro Lopes JM, Azevedo LF, Costa, Pereira A, Dias C, Agualusa L, Lemos L, Romão J, PatoT, Vaz Serra S, Abrunhosa R, Carvalho CJ, Cativo MC, Correia D, Correia J, Coucelo G, Craveiro Lopes B, Loureiro MC, Silva B. Tradução, adaptação cultural e estudo multicêntrico de validação de instrumentos para rastreio e avaliação do impacto da dor crónica. *Dor*, 15:6-56 (2007).

35. Chapman CR, Syrjala KL. Measurement of pain. In: "*Bonica´s Management of Pain*", 3rd Edition, Loeser JD, Butler SH, Chapman CR, Turk DC (Eds). Lippincott Williams & Williams, Philadelphia, pp 855-866 (2001).

36. Cheng TM, Cascino TL, Onofrio BM. Comprehensive study of diagnosis and treatment of trigeminal neuralgia secondary to tumors. *Neurology*, 43:2298-2302 (1993).

37. Cheshire WP. Defining the role for gabapentin in the treatment of trigeminal neuralgia: a retrospective study. *J Pain*, 3:137-142 (2002).

38. Cheshire WP. Trigeminal neuralgia: for one nerve a multitude of treatments. *Expert Rev Neurother*, 7:1565-1579 (2007).

39. Chesterton LS, Foster NE, Wright CC, Baxter GD, Barlas P. Effects of TENS frequency, intensity and stimulation site parameter manipulation on pressure pain thresholds in healthy human subjects. *Pain*, 106:73-80 (2003).

40. Chong MS, Bajwa ZH. Diagnosis and treatment of neuropathic pain. *J Pain Symptom Manage*, 25 (5 Suppl):S4-S11.

41. Chong MS, Smith TE. Anticonvulsivants for the management of pain. *Pain Rev*, 7:129-149 (2000)

42. Coderre TJ, Katz J.Peripheral and central hyperexcitability: differential signs and symptoms in persistent pain. *Behav Brain Sci*, 20:404-419 (1997).

43. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain*, 52:259-285 (1993).

44. Costantini D, Tomasello C, Buonopane CE, Sances D, Marandola M, Delogu G. Treatment of trigeminal neuralgia with electroacupuncture. Experience with 104 cases. *Ann Ital Chir*, 66:373-378 (1995).

45. Cruccu G, Biasitta A, Galeotti F, Iannetti GD, Truini A, Gronseth G.. Diagnostic accuracy of trigeminal reflex testing in trigeminal neuralgia. *Neurology*, 60:139-141 (2006).

46. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol*, 15:1013-1028 (2008).

47. Cruccu G, Leandri M, Feliciani M, Manfredi M. Idiophatic and syntomatic trigeminal pain. *J Neurosurg Psychiatry*, 53:1034-1042 (1990).

48. Dandy WE. Concerning the cause of trigeminal neuralgia. *Am J Surg*, 24:447-455 (1934).

49. de Bruin AF, de Witte LP, Stevens F, Diederiks JP. Sickness Impact Profile: the state of the art of a generic functional status measure. *Soc Sci Med*, 35:1003-10014 (1992).

50. Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. *Pain*, 87:149-158 (2000).

51. Devor M. Responses of nerves to injury in relation to neuropathic pain. In: "*Melzack´s Textbook of Pain*", 5th edition, McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 905-927 (2006).

52. Devor M. Sodium channels and mechanisms of neurophatic pain. *J Pain*, 7 (Suppl 1): S3-S12 (2006).

53. Drouot X, Nguyen JP, Peschanski M, Lefaucheur JP.The antalggic efficacy of chronic motor cortex stimulation is related to sensory changes in the painful zone. *Brain*, 125: 1660-1664 (2002).

54. Dworkin RH. An overview of neuropathic pain: syndromes, symptoms, signs, and several mechanisms. *Clin J Pain*, 18:343-349 (2002).

55. Dworkin RH, Corbin AE, Young JP Jr, Sharma U, LaMoreaux L, Bockbrader H, Garofalo EA, Poole RM. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology*, 60:1274-1283 (2003).

56. England JD, Happel LT, Kline DG, Gamboni F, Thouron CL, Liu ZP, Levinson SR. Sodium channel accumulation in human withpainful neuronas. *Neurology*, 47:272-6 (1996).

57. Erbay SH, Bhadelia RA, Riesenburger R, et al. Association between neurovascular contact on MRI and response to gamma knife radiosurgery in trigeminal neuralgia. *Neuroradiology*, 48:26-30 (2006).

58. Erdem E, Alkan A. Peripheral glycerol injections in the treatment of idiopathic trigeminal neuralgia: retrospective analysis of 157 cases. *J Oral Maxillofac Surg*, 59:1176-1180 (2001).

59. Finnerup NB, Jensen TS. Mechanisms of disease: mechanism-based classification of neuropathic pain-a critical analysis. *Nat Clin Pract Neurol*, 2:107-115 (2006).

60. Fromm GH, Chattha AS, Terrence CF Glass JD. Role of inhibitory mechanisms in trigeminal neuralgia. *Neurology*, 31:683-687 (1981).

61. Fromm GH, Terrence CF, Chattha AS. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. *Ann Neurol*, 15:240-244 (1984).

62. Gajraj NM. Pregabalin: its pharmacology and use in pain management. *Anesth Analg*, 105:1805-1815 (2007).

63. Galer BS, Henderson J, Perander J, Jensen MP. Course of symptms and quality of life measurement in Complex Regional Pain Symdrome: a pilot survey. *J Pain Symptom Manage*, 20: 286- 92 (2000).

64. García-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguière F, Sindou M, Laurent B. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. *Pain*, 83 :259-273 (1999).

65. Gilron I, Bailey JM, Dongsheng T, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Eng J Med*, 352:1324-1334 (2005).

66. Gomez-Arguelles JM, Dorado R, Sepulveda JM, Herrera A, Arrojo FG, Aragón E, Huete CR, Terrón C, Anciones B. Oxcarbazepine monotherapy in carbamazepine-unresponsive trigeminal neuralgia. *J Clin Neurosci*, 15:516-519 (2008).

67. Gonçalves L, Almeida A, Pertovaara A. Pronociceptive changes in response properties of rostroventromedial medullary neurons in a rat model of peripheral neuropathy. *Eur J Neurosci*, 26:2188-2195 (2007).

68. Gonçalves L, Silva R, Pinto-Ribeiro F, Bessa JM, Pertovaara A, Sousa N, Almeida A. Neuropathic pain is associated with depressive behaviour and induces neuroplasticity in the amygdala of the rat. *Exp Neurol*, 213:48-56 (2008).

69. Gottrup H, Bach FW, Arendt-Nielsen L, Jensen TS. Peripheral lidocaine but not ketamine inhibits capsaicin-induced hyperalgesia in humans. *Br J Anaesth*, 85:520-528 (2000).

70. Guzmán J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary rehabilitation for chronic low back pain: systematic review. *BMJ*, 322:1511-1516 (2001).

71. Haderer A, Gerner P, Kao G, Srinivasa V, Wang GK. Cutaneous analgesia after transdermal application of amitriptyline versus lidocaine in rats. *Anesth Analg*, 96:1707-1710 (2003).

72. Håkanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. *Neurosurgery*, 9:638-646 (1981).

73. Letcher FS, Goldring S. The effect of radiofrequency current and heat on peripheral nerve action potential in the cat. *J Neurosurg*, 29:42-47 (1968).

74. Linderoth B, Håkanson S. Retrogasserian glycerol rhizolysis in trigeminal neuralgia. In: "*Schmidek and Sweet's Operative Neurosurgical Techniques: Indications, Methods, and Results*", 5th Edition, Vol 2, Schmidek HH, Roberts DW (Eds), pp 1531-1543 (2005).

75. Hall GC, Carroll D, Parry D, McQuay HJ. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. *Pain*, 122:156-162 (2006).

76. He L, Wu B, Zhou M. Non-antiepileptic drugs for trigeminal neuralgia. *Cochrane Database Syst Rev*, 3:CD004029 (2006).

77. Herman RM, Uzanky SC, Ippolito R, Intratecal baclofeno supresses central Pain in patients with spinal lesions. A pilot study. *Clin J Pain*, 8: 338-345 (1992).

78. Hille B: Local anesthetics: hydrophilic and hydrophobic pathways for drug receptor reaction *J Gen Physiol*, 69:490-515 (1977).

79. Jannetta PJ. Trigeminal neuralgia and hemifacial spasm–etiology and definitive treatment. *Trans Am Neurol Assoc*, 100:89-91 (1975).

80. Jensen TS. Anticonvulsants in neuropathic pain: rationale and clinical evidence. *Eur J Pain*, 6 (Suppl A):61-68 (2002).

81. Jensen TS, Backonja MM, Jimenez SH ,Tesfay S Valensi P, Ziegler D. New perspectives on the management of diabetic peripheral neuropathic pain. *Diab Vascular Dia Manage*, 3:108-19 (2006).

82. Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal Neuralgia, Rochester, Minnesota, 1945-1984. *Ann Neurol*, 27:89-95(1990).

83. Kerr FW, Miller RH. The pathology of trigeminal neuralgia. Electron microscopic studies. *Arch Neurol*, 15:308-319 (1966).

84. Khan OA. Gabapentin relieves trigeminal neuralgia in multiple sclerosis patients. *Neurology*, 51:611-614 (1998).

85. Killian JM, Fromm GH. Carbamazepine in the treatment of neuralgia. Use of side effects. *Arch Neurol*, 19:129-136 (1968).

86. Knardahl S, Elam M, Olausson B, Wallin BG. Sympathetic nerve activity after acupuncture in humans. *Pain*, 75:19-25 (1998).

87. Lazar ML, Kirkpatrick JB. Trigeminal neuralgia and multiple sclerosis: demonstration of the plaque in an operative case. *Neurosurgery*, 5:711-717 (1979).

88. Lefaucheur JP, Drouot X, Cunin P, Bruckert R, Lepetit H, Créange A, Wolkenstein P, Maison P, Keravel Y, Nguyen JP. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. *Brain*, 132 :1463-1471 (2009).

89. Lerich R: La chirurgie de la douleur. Masson et Cie, Paris (1949).

90. Liang YC, Huang CC, Hsu KS. The synthetic cannabinoids attenuate allodynia and hyperalgesia in a rat model of trigeminal neuropathic pain. *Neuropharmacology*, 53:169-177 (2007).

91. Lim EJ, Back SK, Kim MA, Li C, Lee J, Jeong KY, Na HS. Long-lasting neonatal inflammation enhances pain responses to subsequent inflammation, but not peripheral nerve injury in adult rats. *Int J Dev Neurosci*, 27 :215-222 (2009).

92. Loeser JD. Cranial neuralgias. In: "*Bonica´s Management of Pain*", 3rd Edition, Loeser JD, Butler SH, Chapman CR, Turk DC (Eds). Lippincott Williams & Williams, Philadelphia, pp 855-866 (2001).

93. Loeser JD. Pain as a disease. In "*Handbook of Clinical Neurology – Pain*", Vol 81 (3rd series), Cervero F, Jensen TS (Eds). Elsevier, London, pp 11-20 (2006).

94. Lonser RR, Apfelbaum. Neurovascular decompression in surgical disorders of cranial nerves V, VII, IX, and X. In "*Schmidek and Sweet's Operative Neurosurgical Techniques: Indications, Methods, and Results*", 5th Edition, Vol 2, Schmidek HH, Roberts DW (Eds), pp 1531-1543 (2005).

95. Lopez BC, Hamlyn PJ, Zakrzewska JM. Stereotactic radiosurgery for primary trigeminal neuralgia: state of the evidence and recommendations for future reports. *J Neurol Neurosurg Psychiatry*, 75:1019-1024 (2004).

96. Love S, Coakham HB. Trigeminal neuralgia: pathology and pathogenesis. *Brain*, 124:2347-2360 (2001).

97. MacDonald BK, Cockerel OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain*, 123:665-676 (2000).

98. MacFarlene LL, Simmons MM, Hunter MH. The use of corticosteroids in the management of herpes zoster. *J Am Bard Fam Pract*, 11:224-228 (1998).

99. Markham A, Faulds D. Ropivacaine. A review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs*, 52:429-449 (1996).

100. Marchettini P, Lacerenza M, Marangoni C, Pellegata G, Sotgiu ML, Smirne S. Lidocaine test in neuralgia. *Pain*, 48:377-82 (1992).

101. Mattia C, Coluzzi F. Antidepressants in chronic neuropathic pain. *Mini Rev Med Chem*, 3:773-784 (2003).

102. Matsuzawa-Yanagida K, Narita M, Nakajima M, Kuzumaki N, Niikura K, Nozaki H, Takagi T, Tamai E, Hareyama N, Terada M, Yamazaki M, Suzuki T. Usefulness of antidepressants for improving the neuropathic pain-like state and pain-induced anxiety through actions at different brain sites. *Neuropsychopharmacology*, 33:1952-1965 (2008).

103. McClellan KJ, Faulds D. Ropivacaine: an update of its use in regional anaesthesia. *Drugs*, 60:1065-1093 (2000).

104. McNally GP. Pain facilitatory circuits in the mammalian central nervous system: their behavioral significance and role in morphine analgesic tolerance. *Neurosci Biobehav Rev*, 23:1059-1078 (1999).

105. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. *BMJ*, 311:1047-1052 (1995).

106. Mehrkens JH, Steude U. Chronic electrostimulation of the trigeminal ganglion in trigeminal neuropathy: current state and future prospects. *Acta Neurochir Suppl*, 97 (Pt 2):91-97 (2007).

107. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*, 150:971-979 (1965).

108. Merrison AFA, Fuller G. Treatment options in trigeminal neuralgia. *BMJ*, 327:1360-1361 (2003).

109. Merskey H. Pain terms: a list with definitions and notes on usage recommended by the IASP Subcommittee on Taxonomy. *Pain*, 6:249–252 (1979).

110. Merskey H. Classification of chronic pain.Descrition of chronic pain syndromes and definition of pain terms. Pain, Suppl 3:345-356 (1986).

111. Meyerson B. Motor cortex stimulation – effective for neurophatoic pain but the mode of action remains illusive. *Pain*, 118:6-7 (2005).

112. Millan MJ. The induction of pain: an integrative review. *Prog Neurobiol*, 57:1-164 (1999).

113. Millan MJ. *Descending control of pain*. Prog Neurobiol, 66:355-474 (2002).

114. Miller JP, Acar F, Hamilton BE, Burchiel KJ.Radiographic evaluation of trigeminal neurovascular compression in patients with and without trigeminal neuralgia. *J Neurosurg*, 110:627-32 (2009).

115. Moalem G, Tracey DJ. Immune and inflammatory mechanisms in neuropathic pain. *Brain Res Rev*, 51:240-264 (2006).

116. Mullan S, Lichtor T. Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. *J Neurosurg*, 59:1007-1012 (1983).

117. Munoz M, Dumas M, Boutros-Toni F, Coquelle D, Vallat JM, Jauberteau MO, Ndzanga E, Boa F, Ndo D. A neuro-epidemiologic survey in a Limousin town. *Rev Neurol (Paris)*, 144:266-271 (1988).

118. Mursch K, Schafer M, Steinhoff BJ, et al. Trigeminal evoked potentials ans sensory deficits in atypical facial pain – a comparison with results in trigeminal neuralgia. *Funct Neurol*, 17:133-136 (2002).

119. Nadeau SE, Ferguson TS, Valenstein E, Vierck CJ, Petruska JC, Streit WJ. Ritz LA. Neurosciences médicales. Tradução do inglês de Garcia-Larrea L, Bastuji H, Magnin M, Grosclaude M. Elsevier, London (2006).

120. Nnoaham KE, Kumbang J. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database Syst Rev*, (3):CD003222 (2008).

121. Nolte J. The human brain: an introduction to its functional anatomy. Mosby, London (2002).

122. Nurmikko TJ. Recent advances in the diagnosis and management of trigeminal neuralgia. *Int J Pain Pall Care*, 3:2-11 (2003).

123. Nurmikko TJ. Trigeminal neuralgia and other facial neuralgias. In "*Handbook of Clinical Neurology – Pain*", Vol 81 (3rd series), Cervero F, Jensen TS (Eds). Elsevier, London, pp 573-596 (2006).

124. Obermann M, Yoon MS, Sensen K, Maschke M, Diener HC, Katsarava Z. Efficacy of pregabalin in the treatment of trigeminal neuralgia. *Cephalalgia*, 28:174-181 (2007).

125. Oda A, Ohashi H, Komori S, Iida H, Dohi S. Characteristics of ropivacaine block of Na+ channels in rat dorsal root ganglion neurons. *Anesth Analg*, 91:1213-1220 (2000).

126. Owen SL, Green AL, Nandi DD, Bittar RG, Wang S, Aziz TZ. Deep brain stimulation for neuropathic pain. *Acta Neurochir Suppl*, 97:111-116 (2007).

127. Pérez C, Saldaña MT, Navarro A, Martínez S, Rejas J. Trigeminal neuralgia treated with pregabalin in family medicine settings: its effect on pain alleviation and cost reduction. *J Clin Pharmacol*, 49:582-590 (2009).

128. Peyron R, Faillenot I, Mertens P, Laurent B, Garcia-Larrea L. Motor cortex stimulation in neuropathic pain. Correlation between effect and hemodynamic changes in the brain. A PET Study. *Neuroimage*, 34:310-21 (2007).

129. Piatt JH Jr, Wilkins RH. Microvascular decompression for tic douloureux. *Neurosurgery*, 15:456 (1984).

130. Piovesan EJ MD, Teive MD, Kowacs PA; Della Coletta MV, Werneck LC, Silberstein, SD. An open study of botulium–A toxin treatment of Trigeminal Neuralgia. *Neurology*, 65:1306-1308 (2005).

131. Ragsdale DS, McPhee JC, Scheuer T, Catterall WA. Molecular determinansts of state–dependent block of Na^+ channels by local anesthetics. *Science*, 265:1724-1728 (1994).

132. Rainov NG, Heidecke V. Motor cortex stimulation for neuropathic facial pain. *Neurol Res*, 25:157-161 (2003).

133. Rappaport ZH, Devor M. Trigeminal neuralgia: The role of self-sustaining discharge in the trigeminal ganglion. *Pain*, 56:127-138 (1994).

134. Rasmussen P. Facial pain. IV. A prospective study of 1052 patients with a view of: precipitating factors, associated symptoms, objective psychiatric and neurological symptoms. *Acta Neurochir (Wien)*, 108:100-109 (1991).

135. Rygh LJ, Svendsen F, Fiskå A, Haugan F, Hole K, Tjølsen A. Long-term potentiation in spinal nociceptive systems–how acute pain may become chronic. *Psychoneuroendocrinology*, 30:959-964 (2005).

136. Rosen TD. Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia. *Headache*, 41 (Suppl 1):S25-S32 (2001).

137. Rothman KJ, Monson RR. Epidemiology of trigeminal neuralgia. *J Chronic Dis*, 26:3-12 (1973).

138. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*, 280:1837-1842 (1998).

139. Sang CN, Hayes KS. Anticonvulsivant medications in neuropathic pain. In: "*Melzack´s Textbook of Pain*", 5th edition, McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 499-506 (2006).

140. Seltzer Z, Bielin BZ ,Ginzberg Ret al: The role of injury discharge in the induction of neuropathic pain behaviour in rats. *Pain*, 46:327-336 (1991).

141. Shinoda M, Kawashima K, Ozaki N, Asai H, Nagamine K, Sugiura Y. P2X3 receptor mediates heat hyperalgesia in a rat model of trigeminal neuropathic pain. *J Pain*, 8:588-597 (2007).

142. Simpson DA. Gabapentin and Venlafaxine for the treatment of painful diabetic neuropathy. *J Clin Neuromus Dis*; 3; 53 -62 (2001).

143. Sindrup SH, Jensen TS .Pharmacotherapy of Trigeminal neuralgia. *Clin J Pain*, 18: 609-611 (2002).

144. Sist T, Filadora V, Miner M, Lema M. Gabapentin for idiopathic trigeminal neuralgia: report of two cases. *Neurology*, 48:1467 (1997).

145. Snaith, RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes, 1:29 (2003).

146. Solaro C, Lunardi GL, Capello E, Inglese M, Messmer Uccelli M, Uccelli A, Mancardi GL. An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. *Neurology*, 51:609-611 (1998).

147. Takeuchi Y, Takasu K, Ono H, Tanabe M. Pregabalin, S-(+)-3-isobutylgaba, activates the descending noradrenergic system to alleviate neuropathic pain in the mouse partial sciatic nerve ligation model. *Neuropharmacology*, 53:842-853 (2007).

148. Taylor ML. Psychological strategies for managing chronic pain. In: "*The Pain Clinic Manual*", 2nd Edition, Abram SE, Haddox JD (Eds). Lippincott Williams &Wilkins, Philadelphia, 103-107 (2000).

149. Thomas L, Bledsoe JM, Stead M, Sandroni P, Gorman D, Lee KH. Motor cortex and deep brain stimulation for the treatment of intractable neuropathic face pain. *Curr Neurol Neurosci Rep*, 9:120-126 (2009).

150. Torebjörk HE, Lundberg LE, LaMotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *J Physiol*, 448:765-780 (1992).

151. Treede RD. Pain and hyperalgesia:definitions and theories. In "*Handbook of Clinical Neurology – Pain*", Vol 81 (3rd series), Cervero F, Jensen TS (Eds). Elsevier, London, pp 3-10 (2006).

152. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. *J Neurochir Suppl (Wien)*, 52:137-139 (1991).

153. Tsuda M, Inoue K, Salter MW. Neurophatic pain and spinal microglia: a big problem from molecules in "small" glia. *TINS*, 28:101-107 (2005).

154. Turk DC, Rudy TE. IASP taxonomy of chronic pain syndromes: preliminary assessment of reliability. Pain, 30:177-189 (1987).

155. Turk DC. Cognitive-behavioral approach to the treatment of chronic pain patients. *Reg Anesth Pain Med*, 28:573-579 (2003).

156. Turk DC, Okifuji A. Pain terms and taxonomies of pain. In: "*Bonica´s Management of Pain*", 3rd Edition, Loeser JD, Butler SH, Chapman CR, Turk DC (Eds). Lippincott Williams & Williams, Philadelphia, pp 17-25 (2001).

157. Turk DC, Okifuji A. Psychological factors in chronic pain: evolution and revolution. *J Consult Clin Psychol*, 70:678-90 (2002).

158. Türk U, Ilhan S, Alp R, Sur H. Botulinum toxin and intractable trigeminal neuralgia. *Clin Neuropharmacol*, 28:161-162 (2005).

159. Urculo E, Martinez L, Arrazola M, Ramirez R. Macroscopic effects of percutaneous trigeminal ganglion compression (Mullan's technique): an anatomic study. *Neurosurgery*, 36:776-779 (1995).

160. Wallace BA, Ashkan K, Benabid AL. Deep brain stimulation for the treatment of chronic, intractable pain. *Neurosurg Clin N Am*, 15:343-357 (2004).

161. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. *Cochrane Database Syst Rev*, (3):CD001133 (2005).

162. Wilkinson HA. Trigeminal nerve peripheral branch phenol/glycerol injections for tic douloureux. *J Neurosurg*, 90:828-832 (1999).

163. Willis WD. Long-term potentiation in spinothalamic neurons. Brain Res Rev, 40:202-214 (2002).

164. Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain? *Pain*, 77:227-229 (1998).

165. Woolf CJ, Shortland SW. The induction and maintenance of central sensitization is dependent on N-methyl-D aspartic ac. receptors activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain*, 44:293-299 (1991).

166. Woolf CJ, Salter MW. Neuronal plasticity: incrising the gain in pain. *Science*, 288:1765-1769 (2000).

167. Wu G, Ringkamp M, Hartke TV, Murinson BB, Campbell JN, Griffin JW, Meyer RA. Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. *J Neurosci*, 21:RC140 (2001).

168. Yanagidate F, Strichartz GR. Local anesthetics. *Handb Exp Pharmacol*, (177):95-127 (2007).

169. Zakrzewska JM. Trigeminal, eye, and ear pain. In: "*Handbook of Pain Management – a clinical companion to Wall and Melzack´s Textbook of Pain*", Melzack R, Wall PD (Eds). Churchill-Livingstone, London, pp 199-215 (2003).

170. Zakrzewska JM, Lopez BC. Trigeminal and glossopharyngeal neuralgia. In: "*Melzack´s Textbook of Pain*", 5th edition ,McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 1001-1010 (2006).

171. Zakrzewska JM, Sawsan J, Bulman JS. A prospective, longitudinal study on patients with trigeminal neuralgia who underwent radiofrequency thermocoagulation of the Gasserian ganglion. *Pain*, 79:51-58 (1999).

172. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (lamicatal) in refractory trigeminal neuralgia: results from a double blind placebo controlled crossover trial. *Pain*, 73:223-230 (1997).

173. Zhao ZQ. Neural mechanism underlying acupuncture analgesia. *Prog Neurobiol*, 85:355-375 (2008).

174. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*, 67:361-370 (1983).

175. Zimmermann M. Pathobiology of neuropathic pain. *Eur J Pharmacol*, 429:23-37 (2001).

Capítulo 2

RESULTADOS

Capítulo 2.1

Publicação (I)

Lemos L, Flores S, Oliveira P, Almeida A.

"Gabapentin supplemented with Ropivacain block of trigger points improves pain control and quality of life in Trigeminal Neuralgia patients when compared with Gabapentin alone"

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Gabapentin Supplemented With Ropivacain Block of Trigger Points Improves Pain Control and Quality of Life in Trigeminal Neuralgia Patients When Compared With Gabapentin Alone

Laurinda Lemos, MD,† Sara Flores,† Pedro Oliveira, PhD,‡ and Armando Almeida, PhD**

Objective: Pain control in trigeminal neuralgia (TN) is achieved using anticonvulsivants, mainly carbamazepine. When this drug cannot be used, other drugs like gabapentin (GBP) have been used to provide adequate pain control. To improve the therapeutic effect of GBP, we evaluated the clinical efficacy of associating GBP with ropivacain (ROP) analgesic block of facial trigger points in TN patients.

Design: Thirty-six TN patients were randomly assigned during 4 weeks to 1 of the following protocols: Protocol I—daily oral GBP administered in a titrated dose; Protocol II—ROP applied as analgesic block to TN trigger points once a week; Protocol III—daily oral GBP plus ROP once a week. Protocol II had to be discontinued in 7/12 patients owing to insufficient pain control. Pain intensity was evaluated by the Visual Analog Scale (VAS) and disability was assessed by Sickness Impact Profile.

Results: When compared with Protocol I, Protocol III (GBP + ROP) patients showed (1) a reduction of VAS score after 7 and 28 days of treatment, an effect that was still present 6 and 12 months later; (2) a faster reduction of VAS score using a significantly lower dose of GBP; (3) a smaller total and daily GBP dose at the end of the treatment, which resulted in a total absence of adverse side effects; and (4) an improvement of the functional well-being measured by the Sickness Impact Profile. The number needed to treat (NNT) (GBP + ROP vs. GBP protocols) to obtain 1 GBP + ROP-treated patient with at least 50% pain relief was 1.71 (day 7) and 2.40 (day 28).

Conclusions: The association of GBP and ROP is safe, without side effects and results in an important clinical benefit associated to an improvement of the functional health status of TN patients when compared with GBP alone. This may constitute a therapeutic alternative for pain control in TN patients who cannot be treated with carbamazepine.

Key Words: trigeminal neuralgia, gabapentin, ropivacain, analgesic block, pain intensity, Quality of Life, SIP

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Trigeminal neuralgia (TN) has a strong clinical impact because its severe and unpredictable pain periods induce important functional and psychoaffective changes in patients.[1] Pain is described as burning or shooting and, is characterized by paroxysmal "electric shocklike" intense episodes, with an instantaneous progression from the onset to the peak. Pain lasts from several seconds to less than 2 minutes and is triggered by a non-noxious stimulus, usually when eating, speaking, or touching on the naso-labial fold or perioral region (trigger points).[2] Treatment options can include a variety of drug therapies, but progressively more invasive techniques may be needed.[3]

TN does not respond to primary analgesics and the solution is the use of adjuvant analgesics, mainly anticonvulsivants (ACs). Several ACs are known to stabilize plasma membrane of peripheral nerve fibers by inhibiting ectopic discharges in altered membranes.[4] Carbamazepine (CBZ) has been the most efficacious (beneficial in 70% of patients) and most used AC in the treatment of TN[1] and was the only drug evaluated in large placebo-controlled trials.[1,5] However, the main problem concerning the use of ACs is the tolerance to the drug doses controlling pain, owing to side effects (dizziness, somnolence, and ataxias).[4,6] The absence of CBZ efficacy in some patients, cases of intolerance,[7] hypersensitivity, fluid retention,[8] drug interactions, a narrower therapeutic index and a higher degree of adverse side effects than recent drugs like gabapentin (GBP) has led to a progressively increased use of the latter drug in several neuropathic pain syndromes.[9–12] GBP has been used alone[13] or in association with CBZ or iamotrigine[14] and results in pain reduction in at least 47% of TN patients. However, it should be noted that the effectiveness of GBP and other drugs like

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From the *Health and Life Sciences Research Institute (ICVS), School of Health Sciences; ‡Production and Systems Engineering, University of Minho, Braga; and †Hospital Center of Alto Ave, Unit of Fafe, Fafe, Portugal.

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Reprints: Prof Armando Almeida, PhD, Health and Life Sciences Research Institute, School of Health Sciences, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal (e-mail: aalmeida@ecsaude.uminho.pt).

phenytoin and topiramate in TN have not been evaluated in large scale trials,[1] probably because of the relatively rarity of this pathology.

Surprisingly, although the association of analgesics with different mechanisms of action may putatively result in analgesia potentiation and less adverse side effects, the possibility for associating drug therapies has been explored very little until present.[4] To the best of our knowledge, and excluding the association of different ACs,[14] no treatment associating different drug classes have been described and no multimodal prospective trials have been performed for TN. A potential adjunctive treatment that have not been explored, is the combination of an AC with an analgesic block of TN facial trigger points using a local anesthetic. These drugs have a complementary mechanism of action because local anesthetics at low doses block anomalous membrane excitability and ACs block also ectopic activity of peripheral fibers without abolishing sensory transmission.[15] Thus, their association may have improved control over the instability of membrane potential and thus reinforce the clinical improvement of TN patients.

The objective of the present study was to improve the clinical effect of GBP as an alternative protocol to CBZ, whenever this drug cannot be the first choice treatment. We evaluated the therapeutic efficacy of associating the oral administration of GBP with ropivacain (ROP) local analgesia of TN trigger points, in comparison with GBP monotherapy.[13] We selected the local anesthetic ROP which has a lower risk of cardiovascular and nervous toxicity and a higher affinity for Aδ-nociceptive and C-nociceptive fibers than Aβ-innocuous fibers when compared with bupivacain.[16] Additionally, ROP has a smaller risk in case of continuous or successive bolus administration than levobupivacain. The outcomes analyzed were (1) the degree of pain reduction, (2) the number of daily paroxysmal pain crises, (3) the time necessary to obtain satisfactory clinical results, (4) the degree of adverse side effects, and (5) the impact upon Quality of Life. Part of this study has been presented in abstract form.[17]

METHODS

The organization of the present study followed as possible the recommendations for improving the quality of reports of parallel-group randomized trials.[18]

Patients—Entry and Exclusion Criteria

Participants for this study were recruited from the Chronic Pain Unit of the Hospital Center of Alto Ave, Portugal during the years 2003 to 2006. Patients were eligible for the study if they had a pain intensity Visual Analog Scale (VAS) score (see below) ≥ 6 and met the consensus criteria for the diagnosis of primary (idiopathic) TN.[8] The inclusion criteria were:

- Occurrence of episodes of intense facial paroxysmal pain in territory innervated by the trigeminal nerve (VAS score ≥ 6)
- Presence of a normal neurologic examination
- Normal neuroimaging analysis

The following exclusion criteria were also considered:

- Patient refuse to participate
- Psychologic instability
- Atypical pain location (eg, no specific trigger points)
- Anticlotting therapy
- Secondary TN[2]
  - Multiple sclerosis
  - Temporomandibular joint disorders
  - Neoplasias
- Altered neurologic profile
  - Hypoesthesia
  - Dysesthesia
  - Anesthesia
  - Paresis
- Association with other cranial nerve neuralgias (eg, glossopharyngeal neuralgia)
- Imagiologic alterations
- Proposed surgical intervention
  - Compression of the Gasser ganglion
  - Preference of the patient

The treatment protocols used were accepted by the Hospital Ethical Committee and the patients were informed that (1) they would be submitted to 1 of 3 different protocols to solve their pain problem and (2) they could drop or change treatment if no pain control was achieved. All patients signed an informed consent.

Random Allocation

It has been recommended that a detailed description of the expanded criteria followed for adequate allocation of patients to treatment groups should prevail over minimal description.[19] The 36 TN patients defined to enter the study were the first 36 arriving to the chronic Pain Unit and fulfilling the inclusion criteria (Table 1; Fig. 1). The first patient was presented at the entrance of the study with a box containing 36 sealed code opaque envelops, where the treatment protocol to be followed was specified (12 envelops for each protocol, which was written in a cardboard inside) [method adapted from the unrestricted (simple) randomization described by Doig and Simpson[20]]. The random attribution of an envelope to the patient ended when he/she takes 1 from the box without looking inside. The second patient fulfilling the entry criteria to the study was presented to the box with the 35 envelopes left, which were mixed before the second patient took an envelope. The same sequence was followed to preserve the random allocation of the 34 other patients to the 34 envelopes left.

Treatment Protocols

Patients were allocated to one of the following treatment protocols (Fig. 1):

Protocol I

Protocol I—treatment using only GBP,[13] which was administered orally in progressively higher doses.[16] The first 2 days, patients were given 100 mg/d oral GBP at

TABLE 1. Baseline Characteristics of the Patients

	Protocol I (GBP) (n = 12)	Protocol II (ROP) (n = 12*)	Protocol III (GBP + ROP) (n = 12)	P**
Age (y, average and SD)	61 (10.8)	62 (7.7)	64 (19.2)	0.35
Sex (women/total)	5/12	6/12	9/12	0.23
Pain location (trigeminal branches)				
V1 or V2 or V3	2	4	3	
V1 + V2 or V2 + V3	7	6	8	
V1 + V2 + V3	3	2	1	
Facial side (right/total)	8/12	7/12	9/12	
Type of pain (electric shock)	12	12	12	
Pain duration at day 0				
1-2 y	7	8	4	
3-4 y	4	4	3	
5 and more	1	0	5	

*The 12 patients were included in the study on day 0 of the treatment, at days 7 and 30, only 5 patients showed adequate pain control.
**P values were obtained by Kruskal-Wallis test.

night by prescription from the hospital staff; from the third to the seventh day, they progressively received from 100 to 300 mg/d oral GBP to decrease pain intensity (until VAS < 6; see below VAS definition). From the seventh day to the end of the study (28th day), the dose taken by each patient could amount to 300 to 900 mg/d oral GBP if the pain intensity reached a VAS score ≥ 6 (see below). Each 7 days, during their visit to the Pain Unit, patients were evaluated, the VAS score was recorded, and GBP titration was verified. Patients were told that each increase in GBP daily dose should be restricted to 100 mg/d and taken when they felt worse. It is the experience of our Pain Unit that all TN patients with VAS scores of 9 to 10 felt much better and relieved when their VAS score dropped below 6. Because patients express their pain experience in this scale, the motivational-affective impact of being free from their excruciating pain made them feel well and helped them cope with some pain with all spectrum values of VAS scale below 6. Thus, we defined the VAS value of 6 as the threshold for increasing drug therapy. In practice, however, patients were free to increase their GBP dose by 100 mg/d whenever they felt the necessity for improving their pain control.

Protocol II

Protocol II—administration of a superficial analgesic block with ROP to the trigger point(s) inducing paroxysmal pain crises in TN patients. The injection was performed at the Pain Unit under sterile conditions, using a 27-gauge needle for administering subcutaneously 2 mL[21] of a 2 mg/mL ROP solution in each trigger point (Fig. 2). Each local block was performed once a week[22] during the 1-month treatment (days 0, 7, 14, 21, and 28). Patient usually reported immediate pain relief.

Protocol III

Protocol III—treatment using GBP plus ROP (GBP + ROP). The GBP and ROP were administered following the same rationale as for Protocols I and II, respectively. Thus, at day 0, a ROP analgesic block was performed on trigger points and 100 mg of GBP administered at night to each patient. On subsequent days, the increase in GBP daily administration followed the rationale described above for Protocol I and, each 7 days (days 7, 14, 21, and 28), a ROP block was performed as for Protocol II.

During the 28-day treatment, all patients were evaluated by the hospital staff at the first 2 days and periodically at days 7, 14, 21, and 28. During the periods between days 3 and 6, 8 and 13, 15 and 20, and 22 and 27, patients were at home and were requested to record their VAS pain intensity score in an individual Pain Diary provided by the hospital staff, the GBP dose (patients from Protocols I and III), and the hour when medication was taken.

Paracetamol 1000 mg was used in this study for breakthrough pain in those cases where patients needed pain control between GBP doses, or if the study medication was not having an analgesic effect. They were instructed to take it as needed every 8 hours with a maximum of 4000 mg/d. Patients were requested to keep a calendar of time and amount of rescue medication used.

After the 1-month period of protocol treatment, patients were requested to continue their treatment at home, using the same GBP dose used at day 28 (Protocols I and III). If Protocol II patients experienced a new pain episode they were instructed to return to the Pain Unit for evaluation and were provided the most adequate conventional treatment.

Experimental Sequence and Primary Outcome Measures

The application of each protocol treatment (Fig. 1) was performed by a first researcher (*Experimenter 1*; *Dr Laurinda Lemos*), who was blinded to the VAS scores of pain intensity and Sickness Impact Profile (SIP) scores of Quality of Life obtained by each patient. VAS and SIP before and along the 28 days of protocol treatment were evaluated by a second researcher (*Experimenter 2; Dr Sara Flores*), who was blinded to the protocol assigned to each patient. The statistical evaluation of the data was performed by a third researcher (*Experimenter 3; Dr Pedro Oliveira*). The mechanical procedures of mixing the envelopes for their random allocation were performed by a *fourth person* not belonging to the research staff of this study.

The predefined primary outcome measures were:

(1) Evaluation of pain intensity using the VAS.[23,24] Patients located their relative pain in a line marked in each extremity with 0 (0: no pain—on the left) and

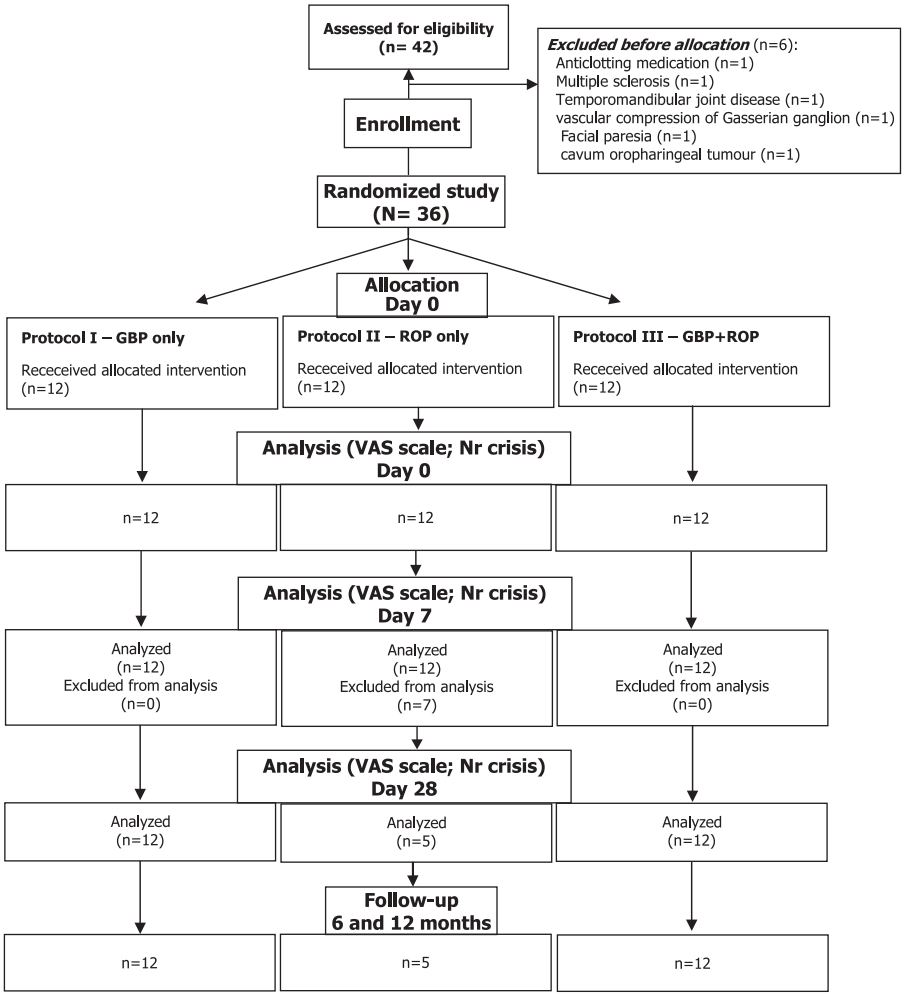

FIGURE 1. Consort flowchart of the steps followed by TN patients along the experimental design of the study. Note that from the 42 TN patients who were assessed to participate in this study, 12 were excluded before allocation owing to exclusion criteria and 7 following Protocol II had to leave the study at day 7 owing to insufficient pain control.

10 (10: the worst pain imaginable—on the right). Moderate pain was considered to be over 30 mm (VAS > 3) and severe pain over 60 mm (VAS $\geq$ 6).[25] A pain reduction of 2 points in the VAS scale on the 100-mm VAS from the baseline pain score was considered to be clinically significant.[26–28] Only VAS scores evaluated at the beginning of the treatment (day 0), the seventh day (day 7; just before ROP administration), and at the end of the treatment (day 28; 2 d after the last ROP administration) were used for statistical comparison between protocols. However, to increase GBP daily dose by 100 mg, the VAS score of the most intense pain period was determined everyday by the patient at night and recorded in the Pain Diary provided to each patient by the hospital staff.

(2) Daily number of paroxysmal pain episodes. This variable was evaluated everyday, but only values obtained at the end of the treatment period (day 28) and 5 and 11 months after the end of the treatment (follow-up) were used for statistical analysis. The follow-up evaluation was performed at the end of the day during a phone interview to each patient, who was asked (1) how many pain attacks suffered during that day or, in case of no pain, (2) how many pain attacks suffered in the worst day of the last week before interview. If no pain was felt during the last week before interview, the staff recorded 0 for the patient.

(3) NNT. Instead of comparing a drug treatment with a placebo group like the usual application of NNT formula to clinical studies,[29,30] we compare the therapeutic result between a new proposed therapy (GBP + ROP protocol) and a conventional treatment (GBP protocol), as suggested by Altman.[31] This allows a comparison of efficacy between the 2 clinical treatments.[31] Thus, in the present study, NNT is defined as 1/[the proportion of patients successfully treated with GBP + ROP (with at least 50% pain relief) – the proportion of patients successfully treated with the standard GBP monotherapy], as expressed in the equation below. The NNT of Protocol III over protocol I was determined for days 7 and 28. The 95% confidence

interval (CI) for each NNT value was obtained using the free calculator at the site of the University of Manchester www.phsim.man.ac.uk/nnt:

$$NNT = \frac{1}{\frac{\text{50\% VAS reduction GBP+ROP patients}}{\text{Total number of GBP+ROP patients}} - \frac{\text{50\% VAS reduction GBP−only patients}}{\text{Total number of GBP−only patients}}}$$

Evaluation of Patient Quality of Life—SIP

A secondary outcome measure of this study was the evaluation of the Quality of Life of patients using the SIP (''Sickness Impact Profile'')[32–34] adapted to the Portuguese population (McIntyre and Araújo-Soares, 1999 and personal communication). SIP evaluates the descriptive profile of the patients in terms of impact of the pathology analyzed upon specific day life behaviors. It is constituted by 136 questions divided along 11 categories. To analyze each patient in dimensions other than pain intensity, patients were requested by the staff to answer the SIP at the beginning (day 0) and end (day 28) of GBP + ROP and ROP protocols. We analyzed the answers obtained at day 0 and day 28 in the following categories: ''Domestic Work,'' ''Mobility,'' ''Communication,'' ''Locomotion,'' ''Eating,'' ''Recreation-Pastimes,'' ''Mobility,'' ''Emotion,'' ''Social Interaction,'' ''Alertness,'' and ''Rest.'' Additionally, the longitudinal evolution of the SIP total score was also evaluated between the beginning and end of each therapy. It should be noted that the score obtained in each category of the SIP is inversely proportional to the performing capacity of the patient.

Power of the Study

We previously determined that the number of patients allocated to each protocol should be 12, as a balance between the small incidence of TN patients in the population and a sufficient number of patients to avoid too small a sample. A total of 36 patients entered this 3 treatment parallel-designed randomized and blinded study, GBP (Protocol I), ROP (Protocol II), and GBP + ROP (Protocol III). In the context of 1-way analysis of variance (ANOVA) (single factor experiments allowing the comparison of more than 2 treatments), Montgomery[35] suggests an approach for determining the sample size according to the interest of the experimenter, bearing in mind that small effects requires replication. When the null hypothesis is rejected, the mean square of treatment/mean square error statistic is a noncentral F random variable (section 4.2 of Montgomery[35]). The probability of type II error can be expressed as a function of the difference of any 2 treatments (Appendix Chart V of Montgomery[28]). In the present case, we have considered that a difference of 2 VAS units was the minimum clinically relevant decrease in pain control measured by the VAS score when comparing 2 treatments, as sustained by others.[26–28] For different estimates of the standard deviation (SD) and for different number of patients, power was determined. For estimates of the SD ranging from 0.5 to 2 and number of patients ranging from 4 to 15, the power ranged from 0.9 to 0.97. The maximum power was observed for a SD of 1.75 and a number of patients of 12. In addition, we also determined the real observed power at days 7 and 28 with the patients who remained in the study, using SPSS 14.0 software for Windows.

Statistics

Data are presented as media ± SD along the several variables under study. Tacking into account that at days 0, 7, and 28, data were obtained from patients of the 3 protocols tested, mean values were compared by 1-way ANOVA followed by the Tukey post hoc test. Where the homogeneity of variances was not observed, the nonparametric test of Kruskal-Wallis was used. The χ^2 test was applied to compare the sex distribution among the 3 groups. On the other hand, because only 2 protocols were evaluated with the SIP at day 28 and at follow-ups after the end of treatments (5 and 11 mo), the mean values from both Protocols I and III were compared by the nonparametric Mann-Whitney test. The normal distribution of the results was verified using the Kolmogorov-Smirnov test, whereas the equality of variances was evaluated by the Levene test. The differences between means from the different protocols were considered significant when $P < 0.05$. All calculations were carried out using SPSS 14.0 for Windows.

RESULTS

Patient Baseline Characteristics

From the 42 TN patients assessed for eligibility, 36 patients were randomized (Fig. 1). Twelve assigned to each treatment protocol. From those 12 patients assigned to Protocol II (ROP), 7 had to abandon this therapy and were excluded from the study because local analgesia of trigger points with ROP each 7 days was insufficient to decrease pain below a VAS score of 6 for a long period. These patients were excluded from the study and moved to a conventional TN treatment after the ROP administration at day 7. Figure 1 summarizes the flow of patient in this study. The analysis of the patients in the three protocols showed no significant differences ($P = 0.35$ and 0.23, respectively) (Table 1) in demographic characteristics including sex and age. In each protocol, no differences were detected between patients with different TN trigger points owing to the rare incidence of this pathology in the population and the number of patients available for the study.

Effect of Different Protocols in Pain Control

No differences were found between patients from Protocols I (GBP; $VAS_0 = 8.5 \pm 1.3$), II (ROP; $VAS_0 = 9.2 \pm 0.9$), and III (GBP + ROP; $VAS_0 = 8.8 \pm 1.6$) ($P = 0.45$) (Fig. 3) in pain intensity at the beginning of the treatment (day 0). This result reinforces the homogeneity of the participants and the similarity between patients allocated to the 3 protocols. After 7 days of each

therapy (day 7), the 3 protocols reduced pain intensity (ANOVA, $P = 0.03$) but this reduction was significantly more pronounced in patients treated with GBP + ROP ($VAS_7 = 4.5 \pm 1.6$) compared with patients treated only with GBP ($VAS_7 = 6.8 \pm 1.2$; $P = 0.003$) or ROP ($VAS_7 = 6.3 \pm 1.8$; $P = 0.025$) (Fig. 3). No differences were observed between GBP and ROP groups ($P = 0.71$). However, it should be noted that these ROP values concerned only 5 of the 12 patients who have begun Protocol II therapy. The other 7 patients had to drop the study because VAS values reached 9.0 ± 0.8 after 5 to 6 days with complete pain control and before rescue medication that begun around day 6. When they arrived the Pain unit at the seventh day under rescue medication (paracetamol), they were given the expected ROP injection and moved immediately to conventional AC drug therapy (carbamazepine or GBP). At the end of the experimental period of treatment (day 28), both Protocols I and III were effective in controlling pain in all 12 patients who have begun the treatment. Although both protocols reduced pain intensity, this effect was more pronounced in patients treated with GBP + ROP ($VAS_{28} = 2.8 \pm 0.9$) than in those treated with GBP ($VAS_{28} = 4.9 \pm 1.6$; $P < 0.001$). Interestingly, no differences were observed between pain intensities of GBP + ROP and the 5 ROP patients reaching the end of the study ($VAS_{28} = 3.4 \pm 0.6$; $P = 0.56$) (Fig. 3).

It is important to note that, in terms of time to achieve a good improvement in pain, the drop in pain intensity between days 0 and 7 was significantly more evident ($P < 0.001$) in patients treated with GBP + ROP ($VAS_{dif\ 7-0} = 4.3 \pm 1.6$) than in patients treated only with GBP ($VAS_{dif\ 7-0} = 1.8 \pm 1.0$; $P < 0.01$), with the decrease being near significance when compared with the 5 ROP patients continuing the study ($VAS_{dif\ 7-0} = 2.9 \pm 1.4$; $P = 0.057$). Additionally, if we consider the decrease in pain intensity between days 0 and 28, significant differences were again observed between the different protocols (ANOVA, $P = 0.005$). The decrease in the GBP + ROP group reached 6.0 ± 1.7 points in the VAS scale ($VAS_{dif\ 28-0}$), which was significantly more expressive than the 3.6 ± 1.8 points ($VAS_{dif\ 28-0}$) decrease observed for GBP-treated patients ($P = 0.005$) (Fig. 3). Concerning the ROP-treated group, a significant decrease in pain intensity between days 0 and 28 ($VAS_{28} = 3.4 \pm 0.6$) was shown in the same 5 patients at the end of the treatment, which reached 5.4 ± 1.1 ($VAS_{dif\ 28-0}$) points (Fig. 3). No differences occurred in total pain decrease between days 0 and 28 when compared with GBP + ROP protocol ($P = 0.78$).

The baseline number of daily crises of paroxysmal sudden and intense pain was similar between patients of the 3 protocols (ANOVA, $P = 0.36$) [$n_{episodes} = 10.5 \pm 2.0$ (GBP), 9.2 ± 1.5 (ROP), and 9.8 ± 1.5 (GBP + ROP)]. A clear decrease was observed after 28 days of treatment (ANOVA, $P < 0.001$), with patients treated with

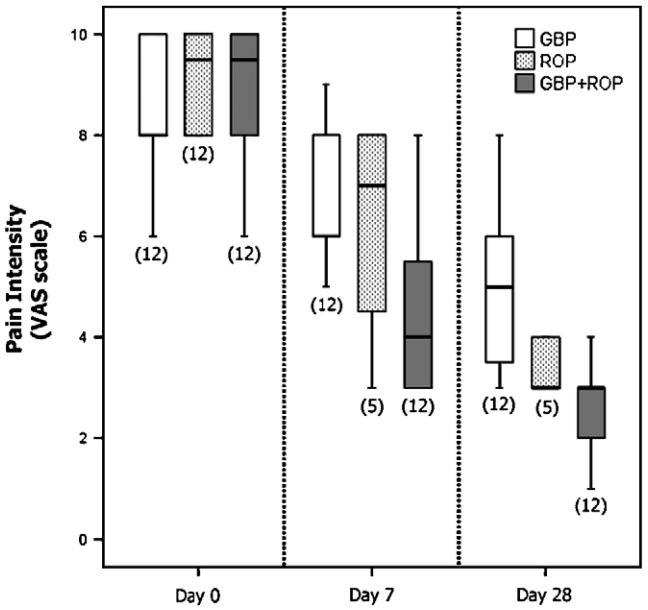

FIGURE 3. Effect of the 3 protocols (GBP, ROP, and GBP+ROP) on the Pain Intensity of TN patients along the treatment. Note the more intense and rapid reduction in pain scores following GBP+ROP treatment. Additionally, a significant inferior pain intensity was recorded by these patients at the end of the 28-day period when compared with those treated only with GBP. Note that patients evaluated in ROP group were 12 at day 0, but only 5 at days 7 and 28. The number of patients included in the mean (n) is present between brackets below the data bars. For statistical significances, see Results section.

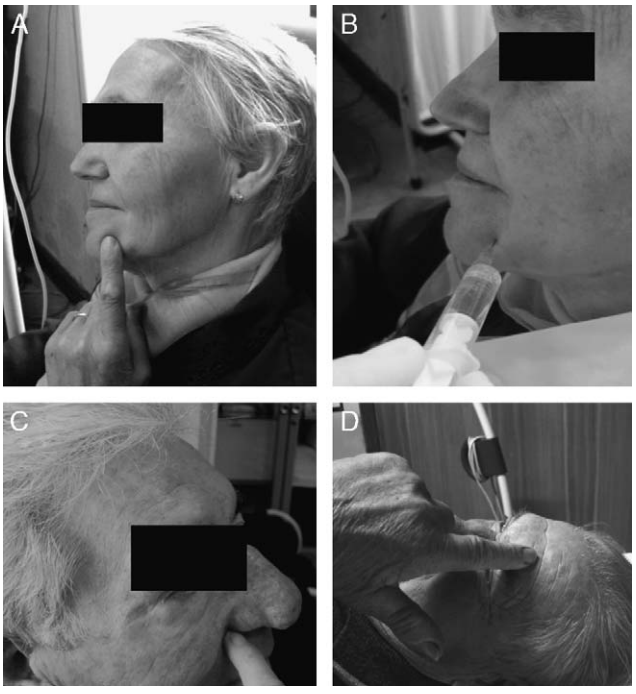

FIGURE 2. Location of trigger points in 2 TN patients. Note their location near the V3 (A), V2 (C), and V1 (D) branches of the trigeminal nerve. B, The administration of ROP was performed in the area pointed as a trigger point by the patient in (A).

GBP + ROP ($n_{episodes} = 2 \pm 1.0$) showing a significantly lower number of pain crises than those treated only with GBP ($n_{episodes} = 4.8 \pm 1.4$; $P < 0.001$) or ROP ($n_{crises} = 6.8 \pm 0.8$; $P < 0.001$) (Fig. 4). It should be recalled that at day 28, the number of patients in Protocol II (ROP) was 5, but in this case the improvement was far from being comparable with the GBP + ROP treatment.

Follow-up

Five months after the end of the 28 days of treatment, the number of daily pain episodes was significantly lower ($P < 0.001$) in the GBP + ROP group ($n_{episodes} = 1.6 \pm 1.4$) than in ROP group ($n_{episodes} = 4.2 \pm 0.8$; $P = 0.001$), whereas in the GBP-treated group the number of daily episodes has even raised again ($n_{episodes} = 6.3 \pm 1.1$; $P < 0.001$) (Fig. 4). Eleven months after the end of the treatment, the GBP + ROP group of patients presented a statistically significant lower number of daily pain episodes (1 ± 0.7) when compared with both GBP (2.3 ± 0.5; $P < 0.001$) and ROP (2.6 ± 0.6; $P < 0.001$) (Fig. 4). Note that only 5 patients were evaluated in Protocol II (ROP) at these 2 time points of follow-up. Again, the improvement in ROP patients was inferior to that obtained by GBP + ROP patients.

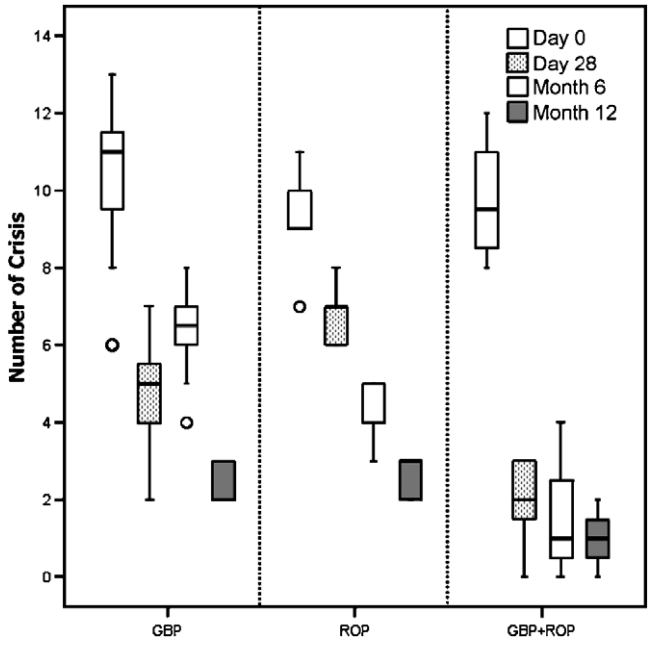

FIGURE 4. The number of daily episodes of paroxysmal pain at the end of the treatment protocols and 5 and 11 months later. It is evident a much more rapid and significant decrease in pain episodes induced by the application of the associative therapy GBP+ROP performed in Protocol III, especially in comparison with GBP monotherapy. It should be noted that following Protocol I (GBP only), the number of daily pain episodes even enhanced from the end of the treatment to 5 months later. Additionally, patients evaluated in ROP group were 12 at day 0, but only 5 at day 28 and after the follow-ups 5 and 11 months later. For statistical significances see Results section.

GBP Daily Dose

At days 1 and 2, all GBP and GBP + ROP patients took 100 mg/d GBP. At day 7, GBP and GBP + ROP patients were taken 200 or 300 mg/d (mean = 266.67 mg/d). Protocol III (GBP + ROP) resulted in a lower final daily dose of GBP (300 mg/d in all patients) at the end of the treatment (day 28) than in patients following Protocol I (mean = 525 mg/d; minimum = 300 mg/d, maximum = 600 mg/d) (Fig. 5). No GBP was administered to ROP-treated patients.

NNT

When comparing the clinical benefit obtained by GBP + ROP and ROP protocols, the NNT for the treatment associating GBP + ROP (Protocol III) over the GBP treatment (Protocol I) was 1.71 (95% CI: 1.23-3.67) at day 7 and 2.40 (95% CI: 1.46-8.49) at the end of the therapy (day 28).

Power of the Study

The observed power of the present study was, for 0.90 for day 7 and 0.98 for day 28, when the alternative hypothesis is set based on the observed values. For the power of the study calculated before the experimental period, see the Methods section.

Patient Quality of Life—SIP

For all categories studied, we analyzed only the evolution of the Quality of Life scores obtained between the beginning and the end of the treatment period (Table 2). Accordingly, between the beginning (day 0) and the end (day 28) of the treatment, it was observed that (Table 2) (1) Protocol III patients showed a significant improvement in all SIP categories ($P < 0.05$); (2) Protocol I patients improved significantly in 9 categories ($P < 0.05$) but failed to ameliorate in 2 categories, "Emotion" and "Alertness."

Patients treated with GBP + ROP showed a significant improvement in total SIP scores (Quality of Life) after the period of treatment (day 0: GBP, 687.8 ± 124.4; GBP + ROP, 676.7 ± 169.8; day 28: GBP, 543.2 ± 60.7; GBP + ROP, 476.3 ± 60.6; $P = 0.038$, Mann-Whitney, $U = 36.00$, $z = -2.078$; Fig. 6).

DISCUSSION

In the present study, we evaluated possible therapeutic alternatives for TN patients who cannot be treated with the main AC drug used for pain control (CBZ). The clinical efficacy of associating GBP and ROP for TN treatment was determined by measuring pain intensity, number of paroxysmal pain crises, NNT, and Quality of Life provided to the patients. GBP monotherapy (Protocol I), ROP administration to trigger points (Protocol II), and the proposed GBP + ROP association (Protocol III) have all resulted in a significant reduction of the initial pain intensity and number of crises. However, patients treated with the association of GBP + ROP presented (1) a faster clinical improvement, (2) a significantly higher reduction of pain (VAS and

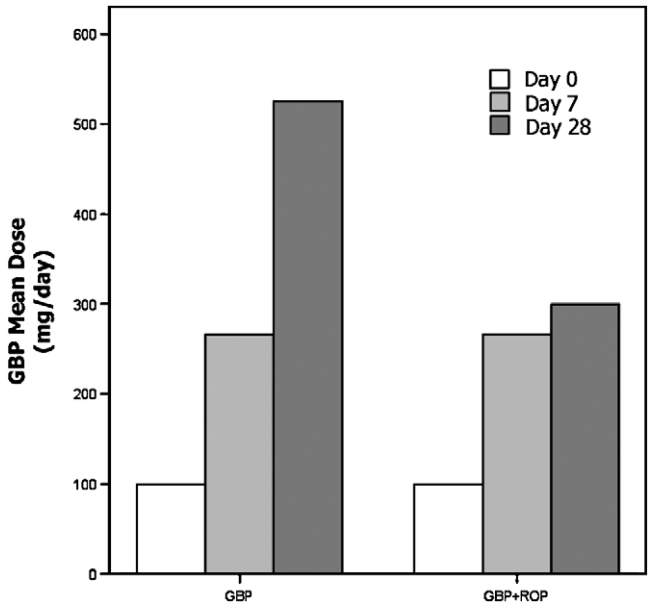

FIGURE 5. Longitudinal evolution of the daily dose of GBP administered during treatment Protocols I and III. Prolonged therapy with GBP+ROP needs significantly smaller doses of GBP than GBP-only protocol at the end of the 28-day treatment period.

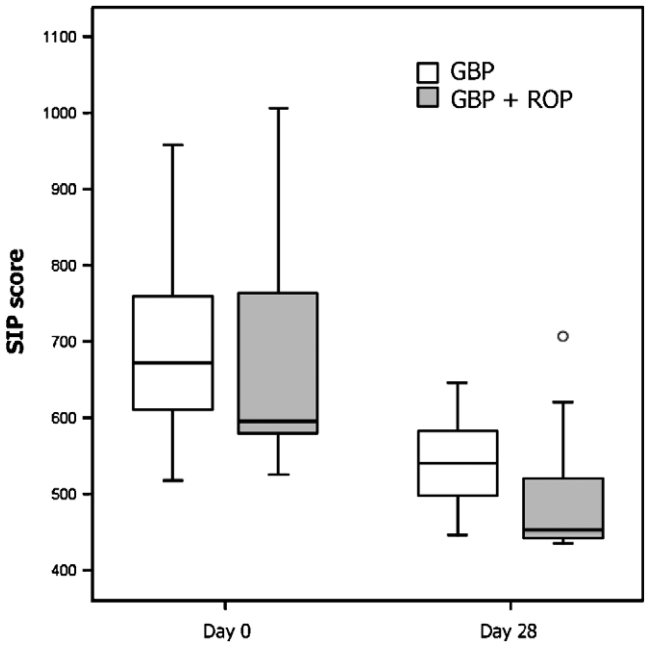

FIGURE 6. Effect of Protocols I and III (GBP and GBP+ROP) on the total SIP score of Quality of Life. Note that no differences were observed at the beginning of the treatment (day 0) between both patient groups. However, at the end of the treatment (day 28), Protocol III induced a significant decrease in the total SIP score, which indicates an improvement in the Quality of Life of TN patients.

NNT scores), (3) an inferior daily dose of GBP, and (4) a better Quality of Life than patients treated only with GBP. On the other hand, it was clear that ROP alone applied to TN trigger points (Protocol II) was sufficient for a reliable satisfactory pain control in some but not all patients.

Study Design and Methodologic Considerations

To perform this study, several aspects needed to be addressed owing to the specific nature of TN pain. First, the rationale was to increase the efficacy of GBP[13] in TN to provide an improved alternative to patients where the primary treatment with CBZ failed or cannot be applied; thus, it was not an objective of the study to evaluate an alternative to CBZ as a first choice drug treatment for TN pain. The possibility of associating GBP with a local anesthetic in analgesic concentration occurred when pilot studies of our group, using the administration of ROP as

TABLE 2. Scores of the Different Categories of the Quality of Life SIP Questionnaire Evaluated at the Beginning and End of TN Therapeutical Protocols I and III

	GBP (Protocol I)				GBP + ROP (Protocol III)			
	Day 0		Day 30		Day 0		Day 30	
SIP Categories	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Locomotion	50.00	21.68	40.01	20.78	*41.73*	*8.93*	*32.63*	*5.82*
Wellbeing	*81.11*	*28.49*	*34.28*	*3.76*	*52.55*	*26.82*	*33.20*	*2.85*
Mobility	*63.81*	*15.16*	*46.27*	*11.81*	*75.66*	*10.34*	*43.71*	*7.83*
Domestic Work	*71.95*	*21.78*	*55.56*	*17.58*	*68.61*	*22.15*	*53.61*	*8.58*
Eating	*40.85*	*17.75*	*25.35*	*4.39*	*53.38*	*24.86*	*29.95*	*12.50*
Communication	*53.15*	*18.30*	*38.32*	*5.45*	*65.49*	*19.32*	*42.19*	*8.67*
Emotion	46.39	10.46	45.33	11.01	*44.86*	*13.40*	*39.89*	*10.15*
Recreation and Pastime	*65.29*	*20.01*	*54.12*	*17.84*	*63.58*	*23.95*	*45.26*	*17.69*
Social Interaction	*80.09*	*25.47*	*74.63*	*24.45*	*86.02*	*19.14*	*66.11*	*23.59*
Alertness	60.73	10.58	58.48	9.48	*56.23*	*23.68*	*45.87*	*12.11*
Rest	*74.40*	*11.50*	*70.87*	*8.14*	*68.62*	*17.34*	*63.07*	*12.05*
Total SIP Score	*687.78*	*124.43*	*543.22*	*60.71*	*676.73*	*169.75*	*495.50*	*88.11*

Italics indicate that there was a significant improvement ($P < 0.05$) in that category between days 0 and 30 of treatment.
Note that GBP + ROP-treated patients showed improvement in all categories analyzed, whereas GBP patients did not improve in 2 categories of the SIP.

a rescue analgesic in TN paroxysmal pain crises, showed a prolonged pain free state that largely overcame the normal period of ROP local analgesia (72 h). Although pain relief outlasting by days, weeks, or months, the short duration of the pharmacologic action of local anesthetics like ROP has been documented, a clear explanation for this effect is not currently available.[21,22,36] It is possible that the prolonged effect is based not only on the pharmacologic effect of the drug but also on the physical action of local administration of the analgesic solution by clearing adhesions or inflammatory exudates from the vicinity of the nerve.[22] These mechanisms may explain the improvement observed in a set of TN patients entered into Protocol II (ROP only) treatment during this study. In fact, trigeminal nerve block analgesia is a procedure considered already as a TN treatment when pharmacologic approaches have failed.[22]

Although other possibilities have been raised, we decided that the third group of our study (in addition to GBP and GBP + ROP) should be ROP treatment alone. A second alternative could have been the administration of saline injections upon TN trigger points in a group of GBP patients; although protected by using GBP and acting as a placebo for ROP, this group would not rule out the physical effect of administering a volume of liquid to each trigger point. A third alternative, the possibility of having a study branch with just saline administration to the trigger points would be unethical and was not considered, because no pain control would be achieved and, on the contrary, it could induce paroxysmal pain crises. Thus, by using a third group of patients treated with ROP monotherapy, we evaluated the degree of pain control that can be achieved just by the local analgesia plus the physical effect of liquid administration to trigger points.

The frequency and number of ROP injections applied to TN patients followed the guidelines for the practice of interventional techniques described by Manchikanti et al.[22] It is advisable that in the stabilization phase, a patient should receive an injection at intervals not smaller than 1 week, which was the period chose to mediate between each ROP administration. The follow-up evaluation of patients treated with Protocols I and III, it was performed by phone interview; consequently, while the determination of the number of pain crises could be assessed 6 and 12 months after the beginning of the treatment, the pain intensity measured in a VAS scale was obviously not possible to perform.

Clinical Significance of the GBP+ROP Association

A 2-point decrease in the mean VAS scale (0 to 10 scale) has been considered the minimum clinical relevant difference in pain intensity when comparing the effect of 2 treatments.[26–28] Taking into account that GBP, ROP, and GBP + ROP treatments decreased pain intensity between 3.4 and 6.0 VAS points, all protocols were clinically effective in reducing pain after a 1-month therapy. When comparing with GBP protocol, it is relevant to note that GBP + ROP was not only more efficient in reducing pain intensity at the end of the treatment, but was the only protocol being clinically effective in reducing pain after 7 days of treatment. This suggests a potentiation or synergism between the AC and local analgesic effects when associated in the same protocol. Curiously, ROP administration alone resulted in a pain decrease at the end of 28-day treatment about as significant as the GBP + ROP association, but the follow-up evaluation was not so efficient. Although a careful systematic administration of ROP to TN trigger points has been performed in patients following Protocols II and III, further studies are needed to determine the causes for the great variability and unpredictability of pain control obtained in patients submitted only to local analgesic block.

GBP Dose and Quality of Life

TN treatment with titrated GBP was adapted from other studies[16] and is used in several pain units in Portugal. It started with a 100-mg daily administration that is gradually increased by 100 to 300 mg each 3 to 5 days until patients refer a satisfactory pain relief (VAS < 6) or intolerable side effects[16] (but see, initial dose 300 to 900 mg/d[9,10,37]). Clinically effective GBP doses given monotherapeutically are usually placed between 900 and 1200 mg/d but may reach concentrations as high as 3600 mg/d.[16,37,38] To evaluate the best GBP dose to be administered to each patient, the GBP dose in our study started at 100 mg/d in all protocols. At the end of the treatment (day 28), the mean GBP daily administration in patients treated with GBP + ROP was 300 mg/d, just a little higher that the dose at the seventh day. On the contrary, patients treated with GBP monotherapy needed significantly higher doses of GBP (525 mg/d) with the mean dose on day 28 being the double of that recorded at day 7. These data show that the clinical result of NT treatment with GBP + ROP is superior to GBP monotherapy, because the low dose of GBP needed along Protocol III did not result in a single patient showing the usual side effects associated with GBP, sedation, ataxias, and dizziness.[39] The possibility of GBP subtherapeutic treatment was excluded, as shown by the significant pain decrease and improvement of Quality of Life.

The evaluation of Quality of Life in TN patients revealed a clear beneficial effect in 9 of the 11 categories analyzed with SIP[32,33] in patients treated with GBP + ROP, whereas GBP-only treated patients showed improvement in 9 categories. Thus, the general functional well-being of TN patients improved significantly in more SIP categories following the GBP + ROP protocol. Accordingly, the longitudinal analysis of the SIP total score showed a significant improvement in the functional status of GBP + ROP patients.

Potential Mechanisms Mediating GBP+ROP Therapeutic Association

To the best of our knowledge, no studies have evaluated the clinical effect of associating an AC with

another drug therapy for treating TN.[1,2,37] This fact is intriguing because pain reduction with ACs seems to decrease pain only about 30% owing to incomplete efficiency, adverse side effects, or both.[40–42] Even for treating neuropathic pain in general, only a recent study associating GBP and morphine applied to patients with diabetic neuropathy and postherpetic neuralgia is worth mentioning owing to the significant reduction of daily pain intensity measured by the VAS scale and McGill Pain Questionnaire.[40]

Complementary mechanisms associated with the local analgesic action of ROP and GBP may be at the basis for the strong pain reduction resulting from the association of both therapies in Protocol III. Low-dose ROP has an analgesic action similar to CBZ, because both drugs act on voltage-gated sodium channels,[11,43,44] reducing the membrane potential oscillations and membrane excitability associated to neuropathic pain[45] but not blocking nerve conduction.[15,44] GBP also suppresses ectopic afferent discharge activity generated by injured peripheral fibers,[10,46] without blocking nerve conduction.[15,40] The analgesic action of GBP is not based on blocking sodium channels along nerve fibers[47,48] but on voltage-gated calcium channels containing the α2δ subunit.[49,50] Calcium channels are essential for modulation of cell-membrane excitability and thus are implicated in neuropathic pain,[51] with the expression of the α2δ subunit being increased in some neuropathic models.[52] These channels are also essential for the release of central neurotransmitters from axonal terminal boutons to the synaptic gap[51] and pregabalin (a close structural relative of GBP) binding to the α2δ subunit reduces their presynaptic liberation.[53] The importance of this effect in GBP action is not known as ACs that act synaptically (eg, barbiturates) are largely ineffective as analgesics.[15] According to the "ignition hypothesis" of TN,[15,54,55] pain paroxysms begin with discharges in a small set of trigeminal primary afferents resulting from spontaneous activation or after cutaneous trigger point stimulation. Crossed-afterdischarge then excites nonstimulated neighbor fibers through a "windup" mechanism that self-sustains fiber activity beyond the original focal fiber discharge. It should also be pointed that a central effect of ROP may exist owing to some degree of systemic circulation.[15] Thus, it is possible that the therapeutic value of the present GBP + ROP association may result from the synergistic/additive control of (1) fiber depolarization at trigger points (by ROP), (2) crossed-afterdischarge of passive neighboring neurons at the trigeminal ganglion (by GBP and ROP), and (3) central neurotransmitter release from primary afferents (GBP).

Limitations of the Study

There are 4 main limitations to the present study. First, the generalization of the findings to all patients who do not tolerate drug therapy after CBZ should be made with caution because no comparisons were made with other ACs that can be alternative to the main treatment. The exclusion criteria were extensive and 14% of TN patients arriving to the Pain Unit were withdrawn from the study, which indicates that the data need to be confirmed in a less homogenous population. Second, although all effort has been made to avoid patients meeting with each another within and between protocols and all patients from the 3 protocols have been evaluated by the hospital staff, it was not possible to blind patients to therapeutic group (ROP injection vs. no injection). Thus, the study was blinded only to the research staff. Third, it was only possible to perform the follow-up by phone interview, which precluded the possibility of evaluating the Quality of Live in patients since the SIP has 136 questions. Consequently, patients' VAS pain was used as a surrogate measure. Patients were also trained to count their number of daily pain periods and this measure was also obtained at the follow-up. Finally, although the therapeutic effect on the number of crises was still significantly different after a year of treatment with GBP + ROP and ROP, the follow-up period may not have been sufficient to determine the long-term effect of the proposed treatment.

CONCLUSIONS

GBP is already the first choice drug therapy for all types of neuropathic chronic pain in several international pain control centers, owing to the facility of monitoring, relatively low incidence of adverse side effects, lack of interaction with other drugs acting on the nervous system, and evident perception of its efficacy.[10,11,56,57] However, concerning TN, CBZ has been the most widely used drug therapy, with significant results on pain relief obtained in large scale placebo studies.[5,8] On the other hand, whenever CBZ fails to control TN pain, GBP is an alternative for reducing its intensity.[13,14] The present study indicates that the association of oral GBP and peripheral analgesic block with low-dose ROP results in a clinical pain control of TN with a rapidity, a decrease in pain intensity and a long-term action that is superior to GBP monotherapy. This is reinforced by complete lack of adverse side effects and the global improvement of the functional Life Quality of TN patients submitted to GBP + ROP therapeutic association. However, large-scale GBP studies are needed to place more accurately GBP in the spectrum of drugs that can be used in TN pain control.

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REFERENCES

1. Zakrzewska JM, Lopez BC. Trigeminal and glossopharyngeal neuralgia. In: McMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Churchill Livingstone: Elsevier; 2006:1001–1010.
2. Loeser JD. Cranial neuralgias. In: Loeser JD, Butler SH, Chapman CR, et al, eds. *Bonica's Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams & Williams; 2001:855–866.

3. Merrison AFA, Fuller G. Treatment options in trigeminal neuralgia. *BMJ*. 2003;327:1360–1361.
4. Chong MS, Bajwa ZH. Diagnosis and treatment of neuropathic pain. *J Pain Sympt Manag*. 2003;25(5S):S4–S11.
5. Wiffen PJ, McQuay HJ, Moore RA. Carbamazepine for acute and chronic pain. *Cochrane Database Syst Rev*. 2005;20:CD005451.
6. Jensen TS. Anticonvulsants in neuropathic pain: rationale and clinical evidence. *Eur J Pain*. 2002;6:61–68.
7. Taylor JC, Brauer S, Espir MLE. Long-term treatment of trigeminal neuralgia with carbamazepine. *Postgrad Med J*. 1981;57:16–18.
8. Zakrzewska JM. Trigeminal, eye, and ear pain. In: Melzack R, Wall PD, eds. *Handbook of Pain Management—A Clinical Companion to Wall and Melzack's Textbook of Pain*. London: Churchill Livingstone; 2003:199–215.
9. Khan AO. Gabapentin relieves trigeminal neuralgia in multiple sclerosis patients. *Neurology*. 1998; 51:611–614.
10. Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsivants for neuropathic pain syndromes: mechanisms of action and place in therapy. *Drugs*. 2000;60:1029–1052.
11. Rowbotham MC, Petersen KL. Anticonvulsants and local anesthetic drugs. In: Loeser JD, Butler SH, Chapman CR, eds. *Bonica's Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams & Williams; 2001:1727–1735.
12. Wiffen PJ, Collins S, McQuay H, et al. Gabapentin for acute and chronic pain. *Cochrane Database Syst Rev*. 2005;20:CD005452.
13. Cheshire WP Jr. Defining the role for gabapentin in the treatment of trigeminal neuralgia: a retrospective study. *J Pain*. 2002;3: 137–142.
14. Solaro C, Messmer Uccelli M, Uccelli A, et al. Low-dose gabapentin combined with either iamotrigine or carbamazepine can be useful therapies for trigeminal neuralgia in multiple sclerosis. *Eur Neurol*. 2000;44:45–48.
15. Devor M. Responses of nerves to injury in relation to neuropathic pain. In: McMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Churchill Livingstone: Elsevier; 2006: 905–927.
16. Ahmad M, Goucke CR. Management strategies for the treatment of neuropathic pain in the elderly. *Drugs Aging*. 2002;19: 929–945.
17. Lemos L, Macedo G, Flores S, et al. Gabapentine plus ropivacain: a significant improvement in the treatment of trigeminal neuralgia. 4th FENS Meeting. 2004;121.10.
18. Moher D, Schulz KF, Altman DG, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001;357:1191–1194.
19. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet*. 2002;359:614–618.
20. Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care*. 2005;20: 187–193.
21. Breivik H. Local anesthetic blocks and epidurals. In: McMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Churchill Livingstone: Elsevier; 2006:903–925.
22. Manchikanti L, Singh V, Trescot AM, et al. Guidelines for the practice of interventional techniques. In: Boswell MV, Cole BE, eds. *Weiner's Pain Management: A Practical Guide for Clinicians*. 7th ed. CRS Press; 2006:847–878.
23. McCoffery M, Pasero C. Assessment—underlying complexities, misconceptions and practical tools. In: Bowlus B, ed. *Pain Clinical Manual*. St Louis: Mosby Inc; 1999:35–99.
24. Chapman CR, Syrjala KL. Measurement of pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. *Bonica's Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams & Williams; 2001: 310–328.
25. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimeters? *Pain*. 1997; 72:95–97.
26. Farrar JT, Portenoy RK, Berlin JA, et al. Defining the clinically important difference in pain outcome measures. *Pain*. 2000;88: 287–294.
27. Finnerup NB, Sindrup SH, Bach FW, et al. Lamotrigine in spinal cord injury pain: a randomized controlled trial. *Pain*. 2002;96: 375–383.
28. Salaffi F, Stancati A, Silvestri CA, et al. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain*. 2004;8: 283–291.
29. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ*. 1995;310:452–454.
30. McQuay HJ, Moore A. Methods of therapeutic trials. In: McMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Churchill Livingstone: Elsevier; 2006:415–425.
31. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998;317:1309–1312.
32. Bergner M, Bobbitt RA, Carter WB, et al. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care*. 1981;19:787–805.
33. Turner JA, Romano JM. Psychological and psychosocial evaluation. In: Loeser JD, Butler SH, Chapman CR, et al, eds. *Bonica's Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams & Williams; 2001:329–341.
34. Jamison RN. The role of psychological testing and diagnosis in patients with pain. In: Dworkin RH, Breitbart WS, eds. *Psychological Aspects of Pain: A Handbook for Health Care Providers. Progress in Pain Research and Management*. Vol 27. Seattle: IASP Press; 2004:117–137.
35. Montgomery DC. *Design and Analysis of Experiments*. 3rd ed. New York: John Wiley & Sons; 1991.
36. Arnér A, Lindblom U, Meyerson BA, et al. Prolongad relief of neuralgia alter regional anesthetic blocas. A call for further experimental and systematic clinical studies. *Pain*. 1990;43:287–297.
37. Nurmikko TJ. Trigeminal neuralgia and other facial neuralgias. In: Cervero F, Jensen TS, eds. *Handbook of Clinical Neurology—Pain, Vol 81 (3rd series)*. London: Elsevier; 2006:574–596.
38. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther*. 2003;25:81–104.
39. Marson AG, Kadir ZA, Hutton JL, et al. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia*. 1997;38:859–880.
40. Gilron I, Bailey JM, Dongsheng T, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Eng J Med*. 2005;352: 1324–1334.
41. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280:1837–1842.
42. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280: 1831–1836.
43. Burchiel KJ. Carbamazepine inhibits spontaneous activity in experimental neuromas. *Exper Neurol*. 1988;102:249–253.
44. Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain*. 1992;48:261–268.
45. Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. *J Neurosci*. 1999;19:8589–8596.
46. Pan H-L, Eisenach JC, Chen S-R. Gabapentin suppresses ectopic discharge and reverses allodynia in neuropathic rats. *J Pharmacol Expl Ther*. 1999;288:1026–1030.
47. Sang CN, Hayes KS. Anticonvulsant medications in neuropathic pain. In: McMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Churchill Livingstone: Elsevier; 2006: 499–506.
48. Roza C, Laird JMA, Souslova V, et al. The tetrodoxin-resistant Na+ channel Nav1.8 is essential for the expression of spontaneous activity in damaged sensory axons of mice. *J Physiol*. 2003;550: 921–926.
49. Sills G. The mechanism of action of gabapentin and pregabalin. *Curr Opin Pharmacol*. 2006;6:108–113.

50. Gee NS, Brown JP, Dissanayake VU. The novel anti-convulsant drug gabapentin (Neurontin) binds to the alpha-2 delta subunit of calcium channel. *J Bio Chem*. 1996;271: 5786–5776.
51. Gribkoff VK. The role of voltage-gated calcium channels in pain and nociception. *Sem Cell Devel Biol*. 2006;17:555–564.
52. Luo ZD, Chaplan SR, Higuera ES, et al. Upregulation of dorsal root ganglion α2δ calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. *J Neurosci*. 2001;21: 1868–1875.
53. Joshi I, Taylor CP. Pregabalin action at a model synapse: binding to presynaptic calcium channel alpha2-delta subunit reduces neurotransmission in mice. *Eur J Pharmacol*. 2006;553: 82–88.
54. Rappaport ZH, Devor M. Trigeminal neuralgia: the role of self-sustaining discharge in the trigeminal ganglion. *Pain*. 1994;56: 127–138.
55. Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: the ignition hypothesis. *Clin J Pain*. 2002;18:4–13.
56. Backonja MM. Anticonvulsivants (antineuropathics) for neuropathic pain syndromes. *Clin J Pain*. 2000;16(suppl 2):S67–S72.
57. Rosen TD. Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia. *Headache*. 2001;41(suppl 1): S25–S32.

Capítulo 2.2

Artigo (II)

Lemos L, Flores S, Oliveira P, Almeida A.

"Clinical evaluation of the association between Carbamazepin and peripheral analgesic block with Ropivacain for the treatment of Trigeminal Neuralgia"

Submetido

Clinical evaluation of the association between Carbamazepin and peripheral analgesic block with Ropivacain for the treatment of Trigeminal Neuralgia

By

Laurinda Lemos, MD,*[Δ] Ramalho Fontes, MD,[Σ] Sara Flores,[Δ] Pedro Oliveira, Ph.D,[#] Armando Almeida, Ph.D*

*Life and Health Sciences Research Institute (ICVS), School of Health Sciences, Campus de Gualtar, University of Minho, Braga, Portugal; [Δ]Hospital Center of Alto Ave, Unit of Fafe, Fafe, Portugal; [Σ]Department of Neurology, Hospital São Marcos; [#]Products and Systems Engineering, Campus de Azurém, University of Minho, Guimarães, Portugal

Key-Words: trigeminal neuralgia, carbamazepin, ropivacain, therapeutical association, pain intensity, daily dose

Corresponding Author:
Prof. Armando Almeida
Life and Health Sciences Research Institute (ICVS)
School of Health Sciences, Campus de Gualtar
University of Minho
4710-057 Braga – Portugal
Phone: +351-253-604808; Fax: +351-253-604809
E-mail: aalmeida@ecsaude.uminho.pt

ABSTRACT

Trigeminal neuralgia (TN) is characterized by periods of intense paroxistic pain periods, with a large number of patients showing no structural nerve lesion and a normal neurological evaluation. Treatment is achieved by using adjuvant analgesics like anticonvulsivants (ACs). The AC carbamazepin (CBZ) is still considered the first-line pharmacological approach for TN patients, although several side effects are usually present. Recently, other approaches using ACs like gabapentin (GBP), but especially GBP associated to the peripheral analgesic block of TN trigger-points with the local anesthetic ropivacaine (ROP), resulted in decreased pain and daily drug administration and, consequently, in a strong reduction of adverse side effects. The objective of the present study is to evaluate if the association between CBZ and the peripheral block of TN trigger-points with ROP reinforces the clinical value of CBZ as major therapy for TN.

Fourty-four patients with idiopathic TN were randomly treated during 4 weeks with the traditional approach of CBZ in monotherapy (CBZ Protocol; n=21;) or with CBZ associated with the peripheral analgesic block of trigger-points with ROP (CBZ+ROP Protocol; n=23). Pain intensity was evaluated using the Visual Analog Scale (VAS) and the number of daily paroxysmal pain crises. Statistical evaluation points were at the arrival to the Pain Unit (day 1), the end of the treatment (day 30) and after a follow-up of five months (month 6). Both protocols resulted in a decrease of pain intensity and in the number of pain crisis, but only the association CBZ+ROP showed a significant stronger reduction in pain intensity at month 6, and allowed a significant decrease in the daily dose of CBZ given to patients (both at day 29 and month 6); in contrast, the daily dose in CBZ-only patients remained constant or even increased. The Number Needed to Treat (NNT) of the new treatment CBZ+ROP over the classic CBZ approach was 5 at the end of the treatment (day 29), but improved to 3 at month 6.

These data contribute to reinforce the use of CBZ as a primary pharmacological tool to control pain in TN patients, as the association of this AC with the peripheral block of trigger-points (1) further improves the clinical qualities of this approach, (2) strongly reduces the daily dose of CBZ and (3) reduces the important side effects attributed to CBZ in monotherapy.

INTRODUCTION

Neuropathic pain (NP) is a form of pain caused by a lesion of the peripheral or central nervous system (*Hansson, 2002; Cruccu et al, 2004*). It is a challenging condition to treat due to (i) the heterogeneity of etiologies, symptoms and underlying mechanisms, (ii) the poorly response to conventional analgesics and (iii) the tendency for treatment being performed in a uniform fashion across the patient population (*Vadalouca et al, 2006*). First-line treatment recommendations for neuropathic pain include the anticonvulsivant (AC) gabapentin (GBP) (*Dworkin et al, 2003*), which significantly reduced pain compared to placebo in clinical trials for a large number of conditions: postherpetic neuralgia (*Rowbotham et al, 1998; Rice et al, 2001*), painful diabetic neuropathy (*Backonja et al, 1998; Gorson et al, 1999*), phantom limb pain (*Bone et al, 2002*), Guillain-Barré syndrome (*Pandey et al, 2002*), spinal cord injury (*Tai et al, 2002*), complex regional pain syndrome (*Van de Busse et al, 2004*), neuropathic cancer pain (*Caraceni et al, 2004*), post-stroke pain, postoperative pain, multiple sclerosis (*Vadalouca et al, 2006*) and mixed neuropathic pain (*Sang and Hayes, 2006*). When patient fail to have a satisfactory response to treatment with GBP or one of the other four first-line medications (5% lidocaine patch, opioid analgesics, tramadol and two tricyclic antidepressants), several drugs can be considered second-line approaches (*Dworkin et al, 2003*); these include other ACs, like lamotrigine (the first second-line pharmacological therapy in most neuropaties) and carbamazepine (CBZ), the latter being a second-line approach for almost all neuropathic pain syndromes, when there is no response to GBP (*Vadalouca et al, 2006*).

Trigeminal neuralgia (TN), the most common neuralgia (annual incidence of 4-5/100000; *Katusic et al, 1991*) is a type of neuropathic pain characterized by periods of intense paroxistic pain, usually of short duration and triggered by innocuous stimuli, although resulting in excruciating pain (*Loeser, 2001; Nurmikko, 2006*). A large number of cases of TN are idiopathic (primary or asymptomatic TN), with no detectable structural nerve lesion in most cases (includes the potential vascular compression of the fifth nerve in 15% of these patients) and a normal neurological evaluation (*Cruccu et al, 2008; Gronseth et al, 2008*). Like in all above referred neuropathies, classic analgesics most frequently have no beneficial effects in controlling TN pain, even in secondary (symptomatic) TN, when it is associated to identifiable structural lesions, like a tumor or multiple sclerosis. Treatment is achieved by using adjuvant analgesics like anticonvulsivants (AC) and antidepressives. However, contrary to the other neuropathies referred above, the AC carbamazepin (CBZ) has been for long and still is considered the first-line

pharmacological approach for TN patients (reviews by *Jorns and Zakrzewska, 2007; Nurmikko, 2006; Cheshire, 2007; Cruccu et al, 2008*), although several drawbacks are associated to CBZ intake; it produces a toxic epoxide metabolite and regular blood tests are thus recommended, it is associate with 10% incidence of rashes and has a negative effect on bone density, as well as significant interactions with other drug classes (*Killian, 1969; Loeser et al, 2001; Vadalouca et al, 2006; Cheshire, 2007*). As second-line drugs, baclofen, lamotrigine (*Gronseth et al, 2008*) and GBP (*Sist et al, 1997;* Khan, 1998; *Solaro et al, 2000; Chesire, 2002; 2007; Lemos et al, 2008; Pandey et al, 2008*) are at frontline. For patients with TN refractory to medical therapy, Gasserian ganglion percutaneous techniques, gamma knife and microvascular decompression may be considered. However, the role of surgery versus pharmacotherapy in the management of TN in old patients remains uncertain (*Cruccu et al, 2008; Gronseth et al, 2008*).

In cases of CBZ intolerance, hypersensitivity or drug interactions, or due to a narrower therapeutic index and a higher degree of adverse side effects, GBP can be used as a second-line treatment (*Solaro et al, 2000; Loeser, 2001; Chesire, 2002; Lemos et al, 2008*). Recently, the association of different drugs has been used to treat TN, and especially when GBP is associated to the peripheral analgesic block of TN trigger-points with the local anesthetic ropivacaine (ROP), the result is a significant decrease of the pain intensity scores, the number of paroxistic pain crises and the daily drug intake (*Lemos et al, 2008*). As a consequence of smaller GBP doses of the association GBP+ROP, a reduction of adverse side effects is obtained when compared with GBP in monotherapy, which presents already a much lighter pattern of side effects than CBZ in monotherapy. Finally, one of the main objectives of the clinical approach to TN, the functional capacity of the patients, is significantly improved when associating the peripheral block of TN trigger-points with ROP to the GBP oral intake (*Lemos et al, 2008*).

The objective of the present study is to evaluate if a similar association between CBZ and the peripheral analgesia of TN trigger-points with ROP reinforces the clinical value of CBZ as major therapy for TN, by reducing pain intensity scores, daily drug doses and adverse side effects.

METHODS

The methodology followed in the present study is reported as possible to the recommendations of the CONSORT group for improving the quality of reports of parallel-group randomized trials (*Moher et al, 2001*).

Patients – Entry and Exclusion Criteria

Fourty-four patients from the Fafe Pain Unit of the Hospital Center of Alto Ave with idiopathic TN were randomly treated during 4 weeks with the traditional approach of CBZ in monotherapy (CBZ Protocol; n=21) or with CBZ associated with the peripheral analgesic block of trigger-points with ROP (CBZ+ROP Protocol; n=23). Patients were eligible for the study if they presented a pain intensity measured by the Visual Analog Scale (VAS) with a score ≥ 6 and met the consensus criteria for the diagnosis of primary (idiopathic) TN (*Zakrzewska, 2003*). The inclusion criteria were:

- Occurrence of episodes of facial paroxysmal pain in territory innervated by a branch of the trigeminal nerve (VAS score ≥ 6);
- Normal neurologic examination;
- Normal neuroimaging analysis

On the other hand, the following exclusion criteria were also considered:

- Patient refuse to participate
- Psychological instability (clinical depressive condition)
- Atypical pain location (e.g., no specific trigger-points)
- Anticlotting therapy
- Secondary (symptomatic) TN (*Loeser, 2001*)
    - Multiple sclerosis
    - Temporomandibular joint disorders
    - neoplasias
- Altered neurologic profile
    - Hypoesthesia
    - Dysesthesia
    - Anesthesia
    - paresis

- Association with other cranial nerve neuralgias (eg, glossopharyngeal neuralgia)
- Imagiological alterations
- Proposed surgical intervention
    - Compression of the Trigeminal nerve confirmed by imagiology
    - Preference of the patient in cases of uncontrolled pain and adverse side effects

The therapeutic protocols used were accepted by the Hospital Ethical Committee and the patients were informed that (1) they were going to be submitted to one of two different treatment protocols to solve their pain problem and (2) they could drop or change treatment if no pain control was achieved. All patients signed an informed consent.

Random Allocation and Treatment Protocols

The 44 TN patients entering the study were the first arriving to the Chronic Pain Unit and fulfilling the inclusion criteria. There were two days in the week (Monday and Thursday) for pain consult at the unit, with those patients arriving in the first day being assigned to one treatment group and those arriving in the second day of the week being attributed with the second therapeutic protocol of the study. Thus, there was no sequential attribution of protocols CBZ or CBZ+ROP, but patient allocation was solely dependent on the day of presentation at the Pain Unit. Patients were recruited between January 2006 and October 2008. Patients were allocated to one of the following treatment protocols (**Fig. 1**):

Protocol CBZ+ROP – treatment using CBZ given orally plus ROP administered superficially at TN facial trigger-points. The peripheral analgesic block with ROP was performed at the Pain Unit under sterile conditions, using a 27-gauge needle for administering subcutaneously 2mL of a 2 mg/mL ROP solution (*Breivik, 2006; Lemos et al, 2008*) in each trigger-point. Each local block was performed once a week (*Manchikanti et al, 2006; Lemos et al, 2008*) during the 1-month treatment (days 1, 8, 15, 22 and 29). When patients arrive to the Pain Unit (day 1) referred from other Health Institutions, they have uncontrolled pain under a CBZ dose of already 400-1000 mg/day. From the first day, the CBZ dose taken by each patient could increase gradually until 1200 mg/day if the pain intensity reached or kept a VAS score ≥ 6, or gradually reduced if pain control was regained. Each 7 days, during their visit to the pain Unit, the VAS score of the patients was recorded and CBZ dose adjusted if necessary, being each alteration performed in steps of 200 mg/day.

Protocol CBZ – treatment using only CBZ in monotherapy; patients entering this protocol received additionally a control injection of saline (the vehicle of ROP administered in the other protocol, CBZ+ROP) at facial trigger-points each 7 days of treatment (days 1, 8, 15, 29). The usual effective dosage ranges between 400 and 1000 mg/day (*Ahmad and Goucke, 2002*). Since patients with uncontrolled pain were referred from other Health Institutions, when they arrived at the Fafe Pain Unit (day 1) their CBZ dose (whatever it was) was increased by 200 mg/day; thus, no titulation of the drug was needed. Each 7 days, during their visit to the Pain Unit, the VAS score of the patients was recorded and CBZ dose adjusted if necessary.

Experimental Sequence

During the 28-day treatment (*Lemos et al, 2008*), all patients were evaluated by the hospital staff at day 1 and then periodically at days 8, 15, 22 and 29 (1 month treatment). During the periods between days 2 and 7, 9 and 14, 16 and 21, and 23 and 28, patients were at home and were requested to record their VAS pain intensity score in an individual Pain Diary provided by the staff, plus the CBZ dose, the hour when medication was taken and side effects observed.

Paracetamol was used in this study for breakthrough pain in those cases where patients needed pain control between CBZ doses, or if the medication prescribed in the protocol was not having an analgesic effect. They were instructed to take it as needed every 8 hours with a maximum of 3000 mg/day, in order to avoid a potentiation of the toxic effect of CBZ at the hepatic level.

After the 1-month period of treatment, patients from both protocols were requested to continue their treatment at home, using the same CBZ dose used at day 29. If patients during the 5-month follow-up experienced a new pain episode they were instructed to return to the Pain Unit for evaluation and readjustment of the treatment or for administration of the most adequate conventional treatment.

Double-Blinded Study

The application of each protocol treatment to the patients was performed by a researcher who was blinded to the VAS scores evaluation of pain intensity and to the number of daily pain crisis of each patient. VAS and number of pain crisis were evaluated by a second researcher, who was blinded to the protocol assigned to each patient. The statistical evaluation of the data was

performed by a third researcher who was not an Health Service professional and was not aware of the clinical implications of protocols CBZ and CBZ+ROP. These precautions resulted in a study blinded to the authors. As already stated for the informed consent of the patients, they were not aware of which protocol was being applied to them. Contrary to an earlier study (*Lemos et al, 2008*), where a control group has been submitted to a protocol of ROP-only (which implied absence of a blinded study to the patients) in addition to a GBP-monotherapy group and a GBP+ROP protocol, the clinical insecurity of a ROP-only protocol (*Lemos et al, 2008*) resulted in a present study with only two protocols; these allowed a study blinded also to the patients.

Primary Outcome Measures

The predefined primary outcome measures were:

(1) Evaluation of pain intensity using the VAS scale. Evaluation points were the arrival to the Pain Unit (day 1), the end of the treatment (day 29) and after a follow-up of five months (month 6). Patients located their relative pain in a line marked in each extremity with 0 (no pain) on the left and 10 (the worst pain imaginable) on the right. Moderate pain was considered to be over 30 mm (VAS > 3) and severe pain over 60 mm (VAS ≥ 6) (*Collins et al, 1997*). A pain reduction of 2 points in the VAS scale on the 100 mm VAS from the baseline pain score (day 1) was considered to be clinically significant (*Farrar et al, 2000; Finnerup et al, 2002; Salaffi et al, 2004*).

(2) Daily number of paroxysmal pain episodes. This variable was evaluated every day, but only data obtained at day 1 and 5 months after the end of the treatment (follow-up; month 6) were used for statistical analysis. The follow-up evaluation was performed at the end of the day performing month 6, during a phone interview to each patient, who was asked (1) how many pain attacks suffered during that day or, in case of no pain, (2) how many pain crisis suffered in the worst day of the last week before interview. If no pain was recorded following these two questions, the staff recorded 0 (zero) crisis for the patient.

(3) Number Needed to Treat (NNT). The NNT is an estimate of the number of patients that would need to be given a treatment for one of them to achieve a desired outcome (*McQuay and Moore, 2006*). Following the rationale of a previous study (*Lemos et al, 2008*), we compare the therapeutic result between a new proposed therapy (GBP+ROP protocol) and a conventional treatment (CBZ protocol), as

suggested by Altman (*1998*). This allows a comparison of efficacy between the two clinical treatments (*Altman, 1998*). Accordingly, in the present study, NNT is defined as 1/[the proportion of patient successfully treated with CBZ+ROP (with at least 50% pain relief) – the proportion of patients successfully treated with the standard CBZ monotherapy], as expressed in the equation below. The NNT of Protocol CBZ+ROP over Protocol CBZ was determined for days 29 (comparing with the baseline values at day 1) and month 6 comparing with baseline values at day 29). The 95% confidence interval (CI) for each NNT result was obtained using the free calculator at the site of the University of Manchester, www. phsim.man.ac.uk/nnt.

$$NNT = \frac{1}{\frac{\text{50\% VAS reduction CBZ+ROP patients}}{\text{Total number of CBZ+ROP patients}} - \frac{\text{50\% VAS reduction CBZ-only patients}}{\text{Total number of CBZ-only patients}}}$$

Secondary Outcome Measure

A secondary outcome measure of this study was the evolution of daily dosage of CBZ following the 1 month treatment under protocols CBZ+ROP and CBZ (day 1 and day 29) and after a follow-up of 5 months (month 6). Taking into account the numerous and sometimes severe adverse side effects of CBZ, changes in the daily dose of CBZ would be reflected in the pattern of side effects associated.

Statistics

Data are presented as media ± Standard Deviation (SD) along the several variables under study. The normal distribution of the results was verified using the Kolmogorov-Smirnov test, whereas the equality of variances was evaluated by the Levene test. A comparison of the VAS, Number of Pain crisis and CBZ dosage means of protocols CBZ+ROP and CBZ was performed at each statistical evaluation point (day 1, day 29, month 6 for EVA and CBZ dosage data; day 1 and month 6 for Number of Pain Crisis results) using the Student's *t*–test for Equality of Means.

RESULTS

Patient Baseline Characteristics

From the 47 patients assessed for eligibility, 44 patients were randomly allocated to one of the two therapeutical protocols (**Fig. 1**). Twenty-three were assigned to Protocol CBZ+ROP and 21 to Protocol CBZ. Figure 1 summarizes the flow of patients throughout the experimental protocol in this study. The baseline data for the demographic characteristics of patients selected for both protocols are expressed in **Table 1**.

Effect of CBZ+ROP and CBZ Protocols in Pain Control

No differences were found between patients from Protocol CBZ+ROP (VAS_1 = 9.1 ± 1.1) and Protocol CBZ (VAS_1 = 9.1 ± 1.4) (p=0.887, *t*-test) (**Fig. 2**) in pain intensity at the beginning of the treatment (day 1). This result demonstrates the homogeneity of the participants and the similarity between patients allocated to the two protocols. At the end of the treatment (day 29), both protocols significantly reduced pain intensity, but CBZ+ROP therapy resulted in a significantly stronger pain reduction than patients following CBZ protocol (CBZ+ROP, VAS_{29} = 2.8 ± 0.88; CBZ, VAS_{29} = 3.8 ± 1.0; p=0.001, *t*-test) (**Fig. 2**). After 5 months, significant differences were observed again between the two protocols, with CBZ+ROP inducing a significantly stronger reduction in pain intensity than CBZ alone (CBZ+ROP, VAS_{6m} = 2.0 ± 0.7; CBZ, VAS_{6m} = 3.9 ± 1.4; p<0.0001, *t*-test) (**Fig. 2**).

The baseline number of daily crises of paroxysmal sudden and intense pain was similar between patients of both protocols (day 1: CBZ+ROP, n_{crises} = 9.6 ± 2.3; CBZ, n_{crises} = 10.65 ± 2.2; p=0.131, *t*-test) (**Fig. 3**). No data were obtained at the end of the treatment (day 29) but, after a follow-up of 5 months, both protocols have reduced the number of daily crisis with patients treated with CBZ+ROP protocol showing a significantly stronger reduction than those under CBZ monotherapy (month 6: CBZ+ROP, n_{crises} = 2.5 ± 0.5; CBZ, n_{crises} = 4.1 ± 1.7; p<0,0001, *t*-test) (**Fig. 3**).

NNT

When comparing the clinical benefit obtained by CBZ+ROP, the NNT for the treatment associating CBZ+ROP over the CBZ protocol was 5.25 (95% CI: 2.48 - 27.95) at the end of the 4-week period of treatment (day 29), but reduced to 3.11 (5% CI: 1.84 – 15.33) after a follow-up of

5 months (month 6). Thus, 5 and 3 are the estimated number of patients (at day 29 and at month 6, respectively) who need to be treated with the new treatment (CBZ+ROP protocol) rather than the standard treatment (CBZ protocol) for one additional patient to benefit (*Altman, 1998*).

CBZ Daily Dose

When arriving to the Pain Unit from other Health Center Institutions (day 1), patients beginning the CBZ+ROP protocol were taking 836 ± 253 mg/day of CBZ and patients initiating the CBZ protocol were tacking 626 ± 163 mg/day of CBZ (**Fig. 4**). At the end of the treatment, the CBZ daily dose has been reduced significantly in patients with CBZ+ROP protocol, while CBZ intake even increased in patients submitted to CBZ monotherapy (day 29: $CBZ+ROP_{dose}$ = 525 ± 165 mg/day; CBZ_{dose} = 757 ± 200 mg/day; $p<0.0001$, *t*-test) (**Fig. 4**). Finally, after the follow-up period, CBZ intake further reduced in CBZ+ROP protocol and resulted in a significantly lower final daily dose of CBZ than in patients following CBZ protocol (again, in this case, CBZ intake further increased) (month 6: $CBZ+ROP_{dose}$ = 367 ± 183 mg/day; CBZ_{dose} = 826 ± 291 mg/day; $p<0,0001$) (**Fig. 4**).

DISCUSSION

Carbamazepin has been for long and is still considered the first-line pharmacological option for controlling pain in TN. However, CBZ treatment often results in adverse side effects and intolerance, with these cases being solved by second-line AC or antidepressant drugs or, in case of prolonged intolerance, a surgical option may be needed. In order to improve the clinical outcome of CBZ therapy and reduce its unwanted effects, the present study evaluated the association of CBZ with the peripheral analgesic block of TN trigger-points with the local anesthetic ROP. A similar approach has resulted in improved efficacy when using GBP in the treatment of TN (*Lemos et al, 2008*). The protocol associating CBZ+ROP resulted in a significant reduction (1) in pain intensity, (2) in the number of daily pain crises and (3) in the daily dose of CBZ intake, when compared with the traditional CBZ protocol in monotherapy.

Methodological Considerations

The rationale of the present study was to further increase the efficacy of first-line drug CBZ in controlling TN pain and, not less important, to reduce the impact of the severe adverse side effects associated with this drug (*Zakrzewska and Lopez, 2006; Canavero and Bonicalzi,*

2006; Cheshire, 2007). In order to eliminate the possibility that any beneficial effect could depend on the physical action of local administration of the analgesic ROP solution by clearing adhesions or inflammatory molecules from the vicinity of the nerve (*Manchikanti et al, 2006*), the protocol CBZ-only was accompanied by injection of saline to TN trigger-points. Thus, the improvements observed in the different outcomes analyzed resulted exclusively from the pharmacological action of CBZ+ROP and CBZ and not by the manipulation and liquid introduction at trigger-points.

The frequency of ROP injections applied subcutaneously to TN patients respected the guidelines for the practice of interventional techniques (*Manchikanti et al, 2006*); a patient should receive an injection at intervals not smaller than 1 week, which was the period chose to mediate between each ROP (or saline) administration. The follow-up evaluation of patients treated with both protocols was performed by phone interview.

Clinical Impact of the CBZ+ROP Association

Since a 2-point decrease in the mean VAS scale (0-10 scale) is considered the minimum clinical relevant difference in pain intensity when comparing the effect of two treatments (*Farrar et al, 2000; Finnerup et al, 2002; Salaffi et al, 2004*), the CBZ+ROP and CBZ protocols, by decreasing pain intensity between 6.3 and 5.3 (respectively), were clinically effective in reducing pain after a 4-week therapy. At the end of the treatment, the pain reduction obtained by CBZ+ROP was significantly stronger than that obtained by CBZ. However, since the VAS mean was only 1-point smaller after CBZ+ROP than CBZ (2.8 versus 3.8), it is questionable if the significant improvement of CBZ+ROP protocol reaches a real clinical importance. After a 5-month follow-up, however, the significant reduction in pain intensity obtained by CBZ+ROP patients reached the 2-point difference of clinical significance when compared with the reduction obtained by CBZ patients (2.0 versus 3.9). Two aspects must be considered when approaching the discussion of these data. Firstly, from the end of the treatment to five months later, the pain intensity in CBZ+ROP patients showed a further decrease (2.8 $\rightarrow$ 2.0), whereas no changes were observed in CBZ-treated patients (3.8 $\rightarrow$ 3.9); secondly, the same authors claiming that a 2-point scale decrease is the minimum clinical benefit following a pain treatment for a “much better improvement”, also considered that a 1-point reduction in the VAS pain scale was felt as “slightly better” (*Salaffi et al, 2004*), which can also be considered an improvement. In fact, a 1-point reduction in pain intensity represented the minimally clinically important difference, as

defended by the same authors. These data indicate that both at the end of the 4-week treatment (day 29) and after a follow-up 5 months later (month 6), the CBZ+ROP protocol reinforced the pain reduction resulting from the traditional CBZ-only protocol. This suggests that, like previously demonstrated for the GBP+ROP association (*Lemos et al, 2008*), a potentiation or synergism between the AC and local analgesic effects occurs when CBZ and ROP are associated in the same protocol. Previous studies indicated also TN pain control in associations as CBZ+GBP or GBP associated with lamotrigine (*Solaro et al, 2000*).

When comparing CBZ+ROP protocol with the standard CBZ protocol, another indication of improvement in the clinical outcome is the NNT, which was 5 after the 4-week treatment (day 29) and reduced even to 3 after a 5-month follow-up (month 6). Again, this indicates that data 5 months after the treatment are more robust in indicating an advantage of the association CBZ+ROP upon CBZ, than immediately after the end of the treatment.

Another important therapeutical improvement in the association CBZ+ROP is the demonstration of a large decrease in the daily dose of CBZ intake, both at the end of the treatment (day 29) and, even further, after the 5-month follow-up. On the contrary, CBZ monotherapy observed a progressive increment in the daily CBZ dosage. The CBZ+ROP proportioned pain control with a medium daily dose of 367 mg/day, which points clearly to the lower bottom of the usual clinical interval of typical maintenance CBZ doses applied to TN patients seen in the literature, which range between 300-800 mg/day (*Cheshire, 2007*), 600-800 mg/day (*Canavero and Bonicalzi, 2006*), 200-1200 mg/day (*Cruccu et al, 2008*) or 400-1200 mg/day (*Jorns and Zakrzewska, 2007*). On the contrary, in our study, the CBZ monotherapy protocol resulted in a daily CBZ intake of around 800 mg/day, which is located in the upper third of the above typical range doses of CBZ applied to TN patients. These data show that the clinical result of NT treatment with CBZ+ROP is superior to CBZ monotherapy, because the much lower dose of CBZ needed along CBZ+ROP protocol strongly decreased the presence / intensity of adverse side effects. The possibility of CBZ subtherapeutic treatment in the CBZ+ROP protocol was excluded, as shown by the significant pain decrease associated to this therapeutical approach.

Potential Mechanisms Underlying the Effect of CBZ+ROP Association

CBZ is involved in (1) the recruitment of endogenous descending nociceptive inhibitory mechanisms by inhibiting noradrenaline uptake (a mechanism in part related with the action of

some antidepressants), and (2) in the suppression of spontaneous neuronal activity and stabilization of hyperexited neural membranes, inhibition of repetitive firing and/or reduction of propagation of synaptic impulses, due to its modulation of voltage-gated sodium channels in a voltage- and frequency-dependent manner (*Sang and Hayes, 2006; Cheshire, 2007*). Importantly, low-dose ROP has an analgesic action based, at least partially, in common mechanisms, because both drugs act on voltage-gated sodium channels (*Burchiel, 1988; Devor et al, 1992; Liu et al, 2000; Rowbotham and Petersen, 2001*) and reduce ectopic neuronal activity without blocking nerve condution. Major causes of ectopic firing includes patches of demyelination, which can be present in TN at the trigeminal root entry zone or in focal areas resulting from microvascular nerve compression of the trigeminal nerve (*Love and Coakham, 2001; Cheshire, 2007; Arrese et al, 2008; Prasad and Galetta, 2009*); the cellular mechanism that appears to underlie ectopic neuronal hyperexcitability is the remodeling of voltage-sensitive ion channels (including sodium channels), which are present at very low densities in the axonal membrane under myelin (*Waxman et al, 1995*), but largely accumulate at sites of nerve injury and demyelination (*Devor, 2006*). Consequently, the "ignition hypothesis" of TN (*Rappaport and Devor, 1994*) postulates that pain paroxysms begin with discharge in a small cluster of trigeminal nerve afferents upon cutaneous trigger-point stimulation, which by crossed after-discharge "ignites" activity and the recruitment of passive uninjured neigbouring neurons; the augmented activity ignites additional passive neuronal fibers and the resulting positive feed-back chain reaction triggers a paroxysmal pain crisis (*Devor, 2006*). Thus, it is possible that the therapeutical value of the present CBZ+ROP association upon CBZ in monotherapy may result from additive (and synergistic?) (1) control upon peripheral fiber depolarization at trigger-points, (2) stabilization of uninjured passive neighboring neurons at the trigeminal ganglion/nerve (by both CBZ and ROP) and (3) increased action of noradrenaline at the synaptic cleft in the central nervous system (CBZ only).

Limitations of the Study

Some important limitations can be appointed to the present study. First, the generalization of findings to all patients who do not tolerate drug therapy after CBZ should be made with caution because no comparisons were made with other ACs that can be alternative to the main classic treatment. The exclusion criteria were extensive and 8.4% of TN patients arriving to the Pain Unit were withdrawn from the study, which indicates that the study should be

confirmed in larger scale (less homogenous) studies. Secondly, although the effect of treatment on pain intensity and number of paroxysmal crises was still significantly different after 6 months of treatment with CBZ+ROP and CBZ, the follow-up period may not have been sufficient to determine the potential long-term effects of the proposed treatment.

Conclusions

CBZ is known for long and still is recognized as the first-line drug choice for pain control in TN. However, when CBZ fails to reduce pain intensity or the important adverse side effects do not allow increasing CBZ dosage, second-line drugs like GBP may solve the problem. Recently, an improvement of this second alternative has been achieved by the association of GBP with the peripheral analgesic block of TN trigger-points with ROP (*Lemos et al, 2008*). The same approach has been the objective of the present study, in order to improve the clinical outcome of the CBZ therapy. We demonstrate that the association of CBZ and peripheral administration of ROP (CBZ+ROP protocol) resulted in a clinically significant further improvement in the decrease of pain intensity already achieved by CBZ in monotherapy (CBZ protocol), accompanied also by a clear decrease in the daily CBZ dosage needed for TN pain control, with a consequent reduction in the adverse side effects associated. Additionally, an NNT of 5 at the end of the treatment that reduces to 3 after a follow-up of 5 months indicates that in long-lasting treatments with CBZ, the advantages of associating the peripheral block with ROP increase with time. However, large-scale CBZ+ROP studies are needed to evaluate the dimension of the improvement obtained by the association CBZ+ROP.

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REFERENCES

1. Ahmad M, Goucke CR. Management strategies for the treatment of neuropathic pain in the elderly. *Drugs Aging*, 19:929-945 (2002).
2. Altman DG. Confidence intervals for the number needed to treat. *BMJ*, 317:1309-1312 (1998).
3. Arrese I, Lagares A, Alday R, Ramos A, Rivas JJ, Lobato RD. Typical trigeminal neuralgia associated with brainstem white matter lesions on MRI in patients without criteria of multiple sclerosis. *Acta Neurochir (Wien)*, 150:1157-1161 (2008).
4. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*, 280:1831-1836 (1998).
5. Bone M, Critchley P, Buggy DJ. Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study. *Reg Anesth Pain Med*, 27:481-486 (2002).
6. Breivik H. Local anesthetic blocks and epidurals In: "*Melzack´s Textbook of Pain*", 5th edition, McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 903-925 (2006).
7. Burchiel KJ. Carbamazepine inhibits spontaneous activity in experimental neuromas. Exp Neurol, 102:249-253 (1988).
8. Canavero S, Bonicalzi V. Drug therapy of trigeminal neuralgia. *Expert Rev Neurother*, 6:429-440 (2006).
9. Caraceni A, Zecca E, Bonezzi C, Arcuri E, Yaya Tur R, Maltoni M, Visentin M, Gorni G, Martini C, Tirelli W, Barbieri M, De Conno F. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. *J Clin Oncol*, 22:2909-2917 (2004).
10. Cheshire WP. Defining the role for gabapentin in the treatment of trigeminal neuralgia: a retrospective study. *J Pain*, 3:137-142 (2002).
11. Cheshire WP. Trigeminal neuralgia: for one nerve a multitude of treatments. *Expert Rev Neurother*, 7:1565-1579 (2007).
12. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimeters? *Pain*, 72:95-97 (1997).
13. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jørum E, Serra J, Jensen TS.

EFNS guidelines on neuropathic pain assessment. *Eur J Neurol*, 11:153-162 (2004).

14. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol*, 15:1013-1028 (2008).
15. Devor M. Responses of nerves to injury in relation to neuropathic pain. In: "*Melzack´s Textbook of Pain*", 5th edition, McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 905-927 (2006).
16. Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain*, 48:261-268 (1992).
17. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol*, 60:1524-1534 (2003).
18. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain*, 88:287-294 (2000).
19. Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. Lamotrigine in spinal cord injury pain: a randomized controlled trial. *Pain*, 96:375-383 (2002).
20. Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. *J Neurol Neurosurg Psychiatry*, 66:251-252 (1999).
21. Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology, 71:1183-1190 (2008).
22. Hansson P. Neuropathic pain: clinical characteristics and diagnostic workup. *Eur J Pain*, 6 (Suppl. A):47-50 (2002).
23. Jorns TP, Zakrzewska JM. Evidence-based approach to the medical management of trigeminal neuralgia. *Br J Neurosurg*, 21:253-261 (2007).
24. Katusic S, Williams DB, Beard CM, Bergstralh EJ, Kurland LT. Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and

differences, Rochester, Minnesota, 1945-1984. *Neuroepidemiology*, 10:276-281 (1991).

25. Khan OA. Gabapentin relieves trigeminal neuralgia in multiple sclerosis patients. *Neurology*, 51:611-614 (1998).
26. Killian JM. Tegretol in trigeminal neuralgia with special reference to hematopoietic side effects. *Headache*, 9:58-63 (1969).
27. Lemos L, Flores S, Oliveira P, Almeida A. Gabapentin supplemented with ropivacain block of trigger points improves pain control and quality of life in trigeminal neuralgia patients when compared with gabapentin alone. *Clin J Pain*, 24:64-75 (2008).
28. Loeser JD. Cranial neuralgias. In "*Bonica's Management of Pain*", 3rd Edition, Loeser JD, Butler SH, Chapman CR, Turk DC (Eds). Lippincott Williams & Wilkins, London, pp 855-866 (2001).
29. Liu BG, Zhuang XL, Li ST, Xu GH. The effects of ropivacaine on sodium currents in dorsal horn neurons of neonatal rats. *Anesth Analg*, 90:1034-1038 (2000).
30. Love S, Coakham HB. Trigeminal neuralgia: pathology and pathogenesis. *Brain*, 124:2347-2360 (2001).
31. Manchikanti L, Singh V, Trescot AM, Deer TR, Boswell MV. Guidelines for the Practice of Interventional Techniques. In: "*Weiner´s Pain Management: a practical guide for clinicians*", 7th Edition, Boswell MV, Cole BE (Eds). CRS Press, London, pp 847-878 (2006).
32. McQuay HJ, Moore A. Methods of therapeutic trials. In: "*Melzack´s Textbook of Pain*", 5th edition,.McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 415-425 (2006).
33. Moher D, Shulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*, 357:1191-1194 (2001).
34. Nurmikko TJ. Trigeminal neuralgia and other facial neuralgias. In: "*Handbook of Clinical Neurology – Pain*", Vol 81 (3rd serie). Cervero F, Jensen TS (Eds) Elsevier, London, pp 574-596 (2006).
35. Pandey CK, Bose N, Garg G, Singh N, Baronia A, Agarwal A, Singh PK, Singh U. Gabapentin for the treatment of pain in guillain-barré syndrome: a double-blinded, placebo-controlled, crossover study. *Anesth Analg*, 95:1719-1723 (2002).
36. Pandey CK, Singh N, Singh PK. Gabapentin for refractory idiopathic trigeminal neuralgia. *J Indian Med Assoc*, 106:124-125 (2008).

37. Prasad S, Galetta S. Trigeminal neuralgia: historical notes and current concepts. *Neurologist*, 15:87-94 (2009).
38. Rappaport ZH, Devor M. Trigeminal neuralgia: The role of self-sustaining discharge in the trigeminal ganglion. *Pain*, 56:127-138 (1994).
39. Rice AS, Maton S; Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain*, 94:215-224 (2001).
40. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*, 280:1837-1842 (1998).
41. Rowbotham MC, Petersen KL. Anticonvulsants and local anesthetic drugs. In: "*Bonica´s Management of Pain*", 3rd Edition, Loeser JD, Butler SH, Chapman CR, Turk DC (Eds). Lippincott Williams & Williams, London, pp 329-341 (2001).
42. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain*, 8:283-291 (2004).
43. Sang CN, Hayes KS. Anticonvulsivant medications in neuropathic pain In "*Wall e Melzack´s Textbook of Pain*", 5th Edition, McMahon S, Koltzenburg M (Eds). Elsevier, London, pp 964-976 (2006).
44. Sist T, Filadora V, Miner M, Lema M. Gabapentin for idiopathic trigeminal neuralgia: report of two cases. *Neurology*, 48:1467 (1997).
45. Solaro C, Messmer Uccelli M, Uccelli A, Leandri M, Mancardi GL. Low-dose gabapentin combined with either lamotrigine or carbamazepine can be useful therapies for trigeminal neuralgia in multiple sclerosis. *Eur Neurol*, 44:45-48 (2000).
46. Tai Q, Kirshblum S, Chen B, Millis S, Johnston M, DeLisa JA. Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial. *J Spinal Cord Med*, 25:100-105 (2002).
47. Vadalouca A, Siafaka I, Argyra E, Vrachnou E, Moka E. Therapeutic management of chronic neuropathic pain: an examination of pharmacologic treatment. *Ann N Y Acad Sci*, 1088:164-186 (2006).
48. van de Vusse AC, Stomp-van den Berg SG, Kessels AH, Weber WE. Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1. *BMC Neurol*, 4:13.
49. Waxman S L, Kocsis J, Stys P K (eds) The axon. Oxford University Press, London (1995).

50. Zakrzewska JM. Trigeminal, eye, and ear pain. In: Melzack R, Wall PD, eds. Handbook of Pain Management – a clinical companion to Wall and Melzack´s Textbook of Pain. London: Churchill Livingstone, pp 199-215 (2003).
51. Zakrzewska JM, Lopez BC. Trigeminal and glossopharyngeal neuralgia. In: "*Melzack´s Textbook of Pain*", 5th edition, McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 1001-1010 (2006).

FIGURE LEGENDS

Figure 1. Flowchart of the steps followed by TN patients along the experimental design of the study. Note that from the 47 TN patients who were assessed to participate in this study, 3 were excluded before allocation owing to exclusion criteria.

Figure 2. Effect of the 2 protocols (CBZ+ROP and CBZ) on the pain intensity of TN patients at the end of the 4-week treatment (day 29) and after a 5-month follow-up (month 6). For significant effects see the Results section.

Figure 3. The number of daily episodes of pain before (day 1) and after a 5-month follow-up (month 6). For significances see the Results section.

Figure 4. Longitudinal evolution of the daily dose of CBZ taken during treatment (4-week period) protocols CBZ+ROP and CBZ. Therapy with CBZ+ROP clearly reduced successively the intake of CBZ from day 1 to day 29 and from the end of the treatment to month 6, whereas CBZ monotherapy resulted in a progressive increase of the daily dose of this anticonvulsivant.

TABLE 1. Baseline characteristics of the patients

	Protocol (GBP+ROP) (n=23)	Protocol (CBZ) (n=21)
Age (years, average and SD)	64 (12.5)	68 (10.7)
Gender (women/total)	15 / 24	18 / 21
Pain location (nerve branches)		
V1 or V2 or V3	11	12
V1 + V2 or V2 + V3	9	6
V1 + V2 + V3	4	3
Facial side (right/total)	15 / 24	10/21
Pain duration at day 1		
1-5 years	8	9
6-10 years	12	4
11 and more	4	8

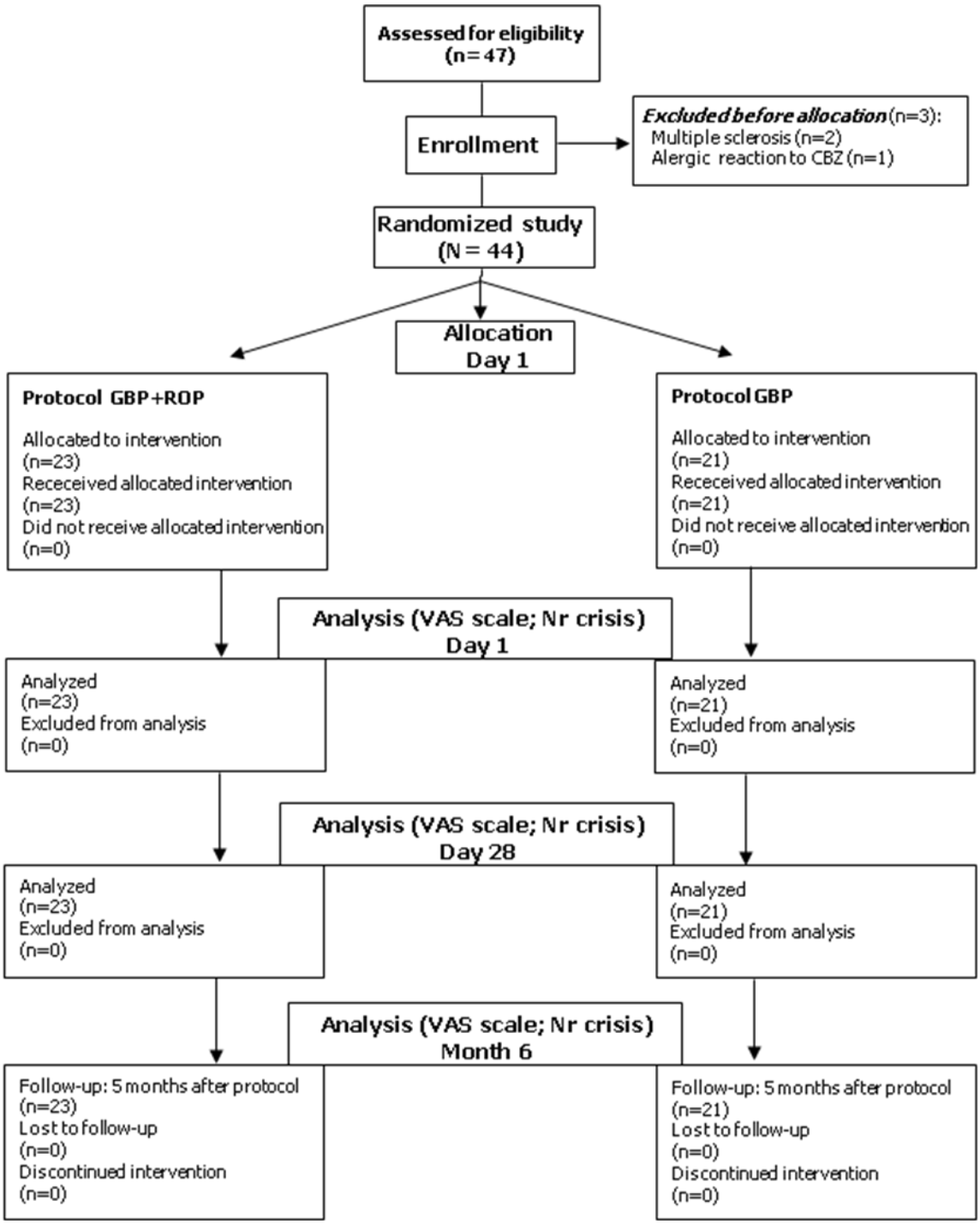
Assessed for eligibility
(n=47)
Enrollment
Excluded before allocation (n=3):
Multiple sclerosis (n=2)
Alergic reaction to CBZ (n=1)
Randomized study
(N=44)
Allocation
Day 1
Protocol GBP+ROP
Allocated to intervention
(n=23)
Receceived allocated intervention
(n=23)
Did not receive allocated intervention
(n=0)
Protocol GBP
Allocated to intervention
(n=21)
Receceived allocated intervention
(n=21)
Did not receive allocated intervention
(n=0)
Analysis (VAS scale; Nr crisis)
Day 1
Analyzed
(n=23)
Excluded from analysis
(n=0)
Analyzed
(n=21)
Excluded from analysis
(n=0)
Analysis (VAS scale; Nr crisis)
Day 28
Analyzed
(n=23)
Excluded from analysis
(n=0)
Analyzed
(n=21)
Excluded from analysis
(n=0)
Analysis (VAS scale; Nr crisis)
Month 6
Follow-up: 5 months after protocol
(n=23)
Lost to follow-up
(n=0)
Discontinued intervention
(n=0)
Follow-up: 5 months after protocol
(n=21)
Lost to follow-up
(n=0)
Discontinued intervention
(n=0)

FIGURE 1

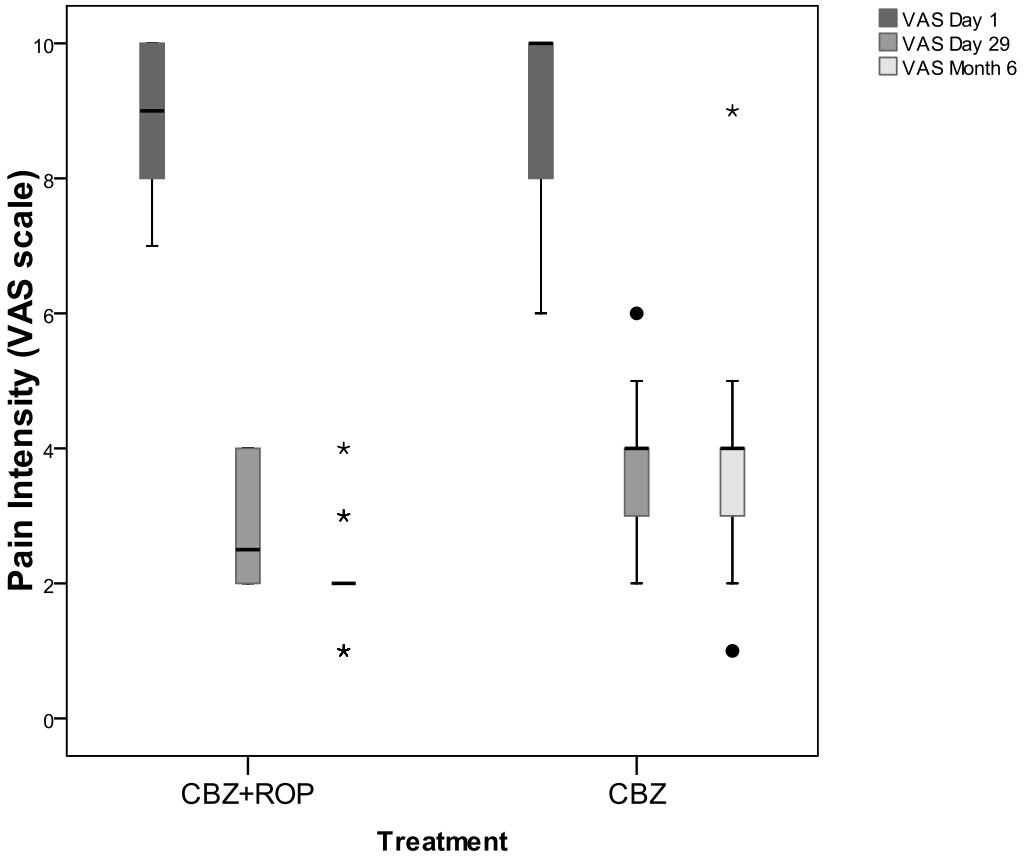
VAS Day 1
VAS Day 29
VAS Month 6
Pain Intensity (VAS scale)
10
8
6
4
2
0
CBZ+ROP
CBZ
Treatment

FIGURE 2

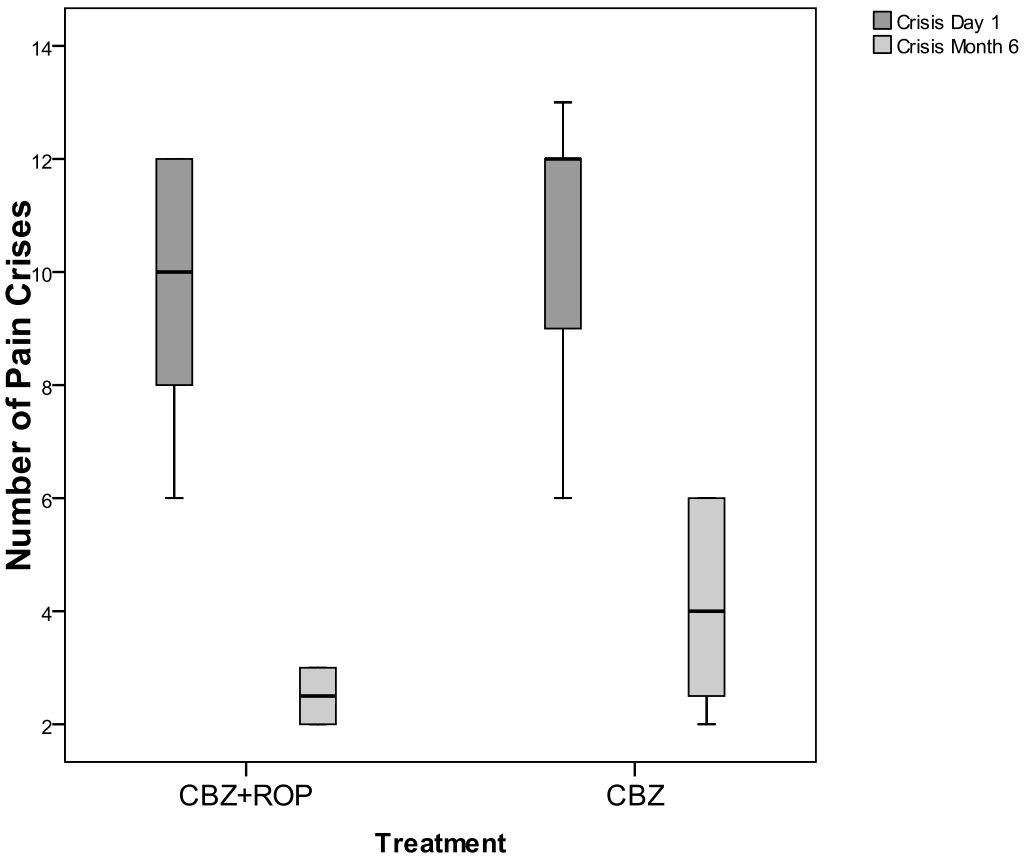
Crisis Day 1
Crisis Month 6
Number of Pain Crises
14
12
10
8
6
4
2
CBZ+ROP
CBZ
Treatment

FIGURE 3

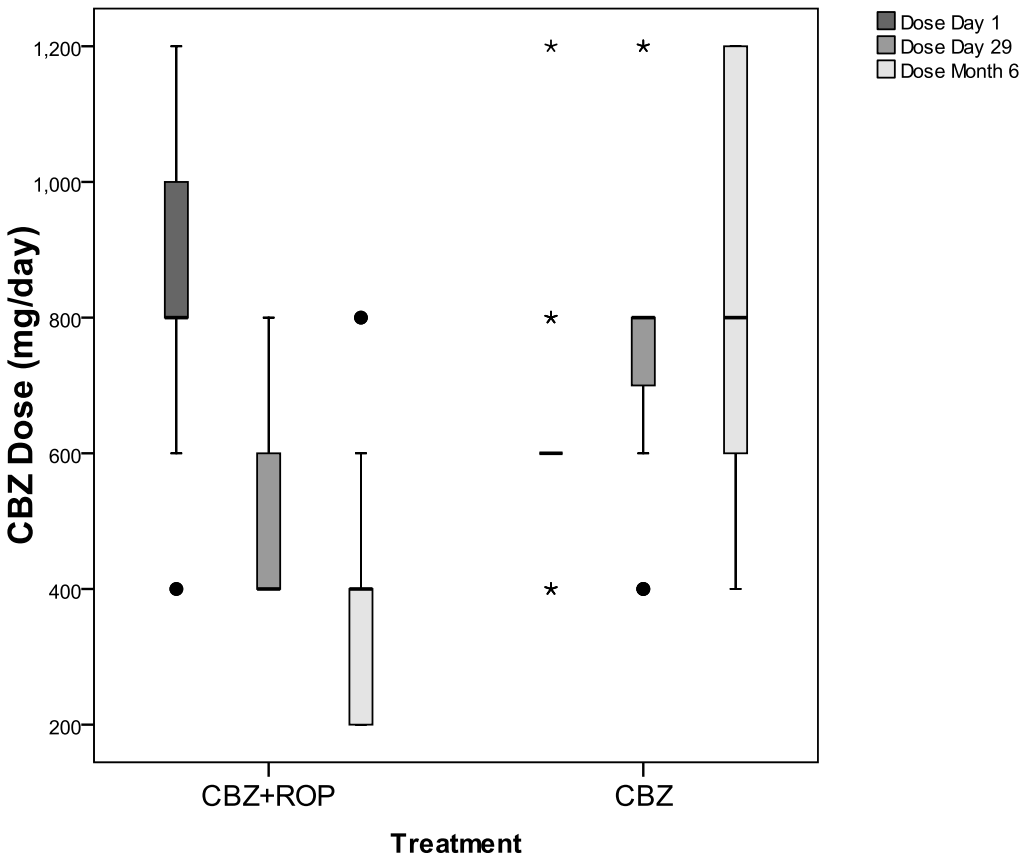
Dose Day 1
Dose Day 29
Dose Month 6
1,200
1,000
800
600
400
200
CBZ Dose (mg/day)
CBZ+ROP
CBZ
Treatment

FIGURE 4

Capítulo 2.3

Artigo (III)

Lemos L, Flores S, Fontes R., Alegria C, Oliveira P, Almeida A.

"Pharmacological Approach versus Microvascular Decompression for the Treatment of Trigeminal Neuralgia: clinical outcomes and effective costs"

Submetido

Pharmacological versus Microvascular Decompression Approaches for the Treatment of Trigeminal Neuralgia: clinical outcomes and direct costs

By

Laurinda Lemos, MD,*[Δ] Carlos Alegria, MD,[Σ] Joana Oliveira, MD,[Σ] Ana Machado,[Δ]

Pedro Oliveira, Ph.D,[#] Armando Almeida, Ph.D*

*Life and Health Sciences Research Institute (ICVS), School of Health Sciences, Campus de Gualtar, University of Minho, Braga, Portugal; [Δ]Hospital Center of Alto Ave, Unit of Fafe, Fafe, Portugal; [Σ]Department of Neurosurgery, Hospital São Marcos; [#]Products and Systems Engineering, Campus de Azurém, University of Minho, Guimarães, Portugal

Key-Words: trigeminal neuralgia, carbamazepin, gabapentin associated with ropivacain, microvascular decompression, clinical outcomes, direct costs

Corresponding Author:

Prof. Armando Almeida

Life and Health Sciences Research Institute (ICVS)

School of Health Sciences, Campus de Gualtar

University of Minho

4710-057 Braga – Portugal

Phone: +351-253-604808; Fax: +351-253-604809

E-mail: aalmeida@ecsaude.uminho.pt

ABSTRACT

Trigeminal neuralgia (TN) has a challenging management since classic analgesics are not effective. Since TN is one of the most painful conditions known, multiple drug and surgical approaches have been developed. In many cases of idiopathic TN the neurological imagiological evaluation is normal, while in other cases a vascular compression of trigeminal nerve root is present. Although the latter cases may be directly referred to surgery, several pharmacological options are usually the first approach to control TN pain. The objective of the present study was to compare the clinical outcome and direct costs of (1) a traditional pharmacological treatment (carbamazepine (CBZ) in monotherapy – CBZ Protocol], (2) the therapeutical association of gabapentin (GBP) and analgesic block of TN trigger-points with Ropivacain (ROP) (GBP+ROP Protocol) and (3) the most common TN surgery, the Microvascular Decompression of the trigeminal nerve (MVD Protocol).

Sixty-two TN patients were randomly treated during 4 weeks [CBZ (n=23) and GBP+ROP (n=17) protocols] from cases of idiopathic TN, or selected for MDV surgery (n=22) due to intractable pain. Direct medical costs estimates were determined by the price of drugs in 2008 from the National Therapeutic Index and the hospital cost accounting data. Pain intensity was evaluated using the Visual Analog Scale (VAS) and the number of daily paroxysmal pain crisis; the Hospital Anxiety and Depression Scale (HADS), the Sickness Impact Profile (SIP) and satisfaction with treatment and hospital team were evaluated by specific questionnaires. Assessments were performed at day 0 (arriving to the Hospital Unit) and 6 months after the beginning of treatment. All protocols showed a clinical improvement of pain control at month 6 (decrease in pain intensity and number of crisis). The GBP+ROP protocol was clearly the less expensive treatment, whereas surgery was, by far, the most expensive protocol. With time, however, GBP+ ROP tended to be the most expensive. No sequels resulted in any patient after CBZ+ROP and CBZ therapies, while after MDV surgery 10 out of 22 patients showed facial sensory deficits and one patient died.

Data reinforce the consensus that a (1) careful evaluation of the patient should be made before choosing the methodological therapy for pain control in TN, (2) different pharmacological approaches are available to initiate pain control in TN with low costs and (3) specific criteria for surgical interventions in TN should be clearly defined due to important adverse side effects and higher costs.

INTRODUCTION

Trigeminal neuralgia (TN) is a neuropathic pathology considered one of the most painful experiences patients can report, and no universal treatment is capable of reverting completely and definitely its intermittent paroxysmal excruciating pain crises (*Cheshire, 2007*). TN is associated with impairment of daily functionality, reduced quality of life (*Tölle et al, 2006; Lemos et al, 2008*) and depression (*Marbach and Lund, 1981*), to which contributes the overwhelming fear that pain can suddenly return again. Athough the huge impact of pain in TN, an incidence of 4-5 per 100000 (*Katusic et al, 1990*) or even higher (*MacDonald et al, 2000*), and a high prevalence in older patients should have been capable of resulting in clinical standards for TN treatment, this pathology is far from being well known and well treated. In most cases the pathophysiology underlying most TN cases in unknown or incompletely understood. Classical or idiopathic TN includes all cases without an established etiology (most of them) as well as those with potential vascular compression of the trigeminal nerve, whereas symptomatic TN results secondarily to cases like tumors or multiple sclerosis (*International Headache Society, 2004*).

TN is not controlled by classical analgesics, but the first-line therapy is still pharmacological, being based on anticonvulsivants (ACs), usually considered adjuvant analgesics in other pathologies but essential for neuropathic pain. Phenytoin in the past (*Cheshire, 1997; Sindrup and Jensen, 2002*) and now carbamazepin (CBZ) (*Campbell et al, 1966; Cheshire, 2007; Jorns and Zakrzewska, 2007; Cruccu et al, 2008*) are first-line drugs in NT, followed by several second-line ACs like lamotrigine (*Zakrzewska et al, 1997*), oxcarbamazepin (*Royal et al, 2001*), gabapentin (GBP) (*Cheshire, 2007*) and GBP associated with peripheral block of trigger-points with the local anaesthetic ropivacain (ROP) (*Lemos et al, 2008*); these treatments changed the management of TN, as previously it was almost exclusively surgical. Surprisingly, combination therapies, although common in epilepsy, have not been explored for TN management (*Solaro et al, 2000; Lemos et al, 2008*).

Surgical intervention for TN is usually reserved for patients with intractable pain refractory to an adequate trial of at least three drugs including CBZ (*Cheshire et al, 2007*). The decision to perform a surgical approach should be based on the clinical presentation (including co-morbilities) of the patient and not primarily or exclusively on neuroimaging (*Cheshire et al, 2007*), as craniotomy is not without risks and fine detail alone at actual MRI spatial resolution cannot distinguish the pathological from the incidental when a vessel course along the trigeminal

nerve root (*Cheshire, 2005a; Lang et al, 2005*). However, some patients may request surgical treatment due to intractable pain or strong adverse side effects (*Cheshire, 2007*). Microvascular decompression (MVD) of the trigeminal nerve root is a well established and superior method of choice among neurosurgical procedures in immediate (91-97%) and the long-term (53-70%) relief of TN (*Cheshire, 2005b; Cruccu et al, 2008*), but is associated several risks, including different degrees of facial sensory loss as well as a small risk of mortality (*Cheshire, 2007*). Other surgical options include Gasser ganglion compression, glycerol gangliolysis and radiofrequency thermocoagulation of the nerve, with the latter producing initial pain relief in more than 90% and a complete pain relief after 5 years reaching 57% of patients (*Kanpolat et al, 2001*); however, these cases are associated with a risk of anesthesia dolorosa (0.6-6%) and cases of transient or permanent cranial nerve palsies (*Kanpolat et al, 2001; Cheshire, 2007*). Gamma knife radiosurgery is less invasive, the onset of pain relief following procedure may require 1-2 months to occur but then 30-80% of cases report complete absence of pain (*Fountas et al, 2006; Dhople et al, 2009; Knafo et al, 2009*); however, again, frequency of paresthesia and dysesthesia range from 3-54% (*Gorgulho et al, 2006*) and there is a steady rate of late failure (*Dhople et al, 2009*).

From the revision above, we should consider that the choice of drug and whether or not to operate and which procedure to choose should be individualized to the particular needs and conditions of each patient (*Cheshire, 2007*). The role of surgery versus pharmacotherapy in TN management remains incertain as there are no studies dealing specifically for example with the issue of "when should surgery be offered?" (*Cruccu et al, 2008*). Additionally, only a few studies have evaluated the impact of TN costs to the patients, and compared only the cost-effectiveness of different surgical procedures. At longer follow-up intervals, MVD is predicted to be the most cost-effective surgery and should be considered the preferred operation for patients, when compared with glycerol rhizotomy and stereotactic radiosurgery (*Pollock and Ecker, 2005*), whereas cyberknife radiosurgery is a cost-saving alternative compared with MVD (*Tarricone et al, 2008*). However, no studies have evaluated the costs associated with different drug treatments when compared with surgery. The objective of the present study was to compare the clinical outcome and direct costs of (1) a first-line pharmacological treatment (CBZ), (2) the therapeutical association of GBP and the peripheral analgesic block of TN trigger-points with ROP (GBP+ROP) and (3) MVD, the most common TN surgery.

METHODS

Patients – Inclusion and Exclusion Criteria

This retrospective study includes a total of 62 patients from the Hospital Center of Alto Ave - Fafe Pain Unit and the Hospital São Marcos in Braga, whom were selected by different clinical teams as following: patients under the traditional approach to TN, were given CBZ in monotherapy (CBZ Protocol; n=23) and were randomly selected in the continuation of a previous study of our group (*Lemos et al*, unpublished data); patients submitted to an alternative TN approach were given GBP associated with the peripheral analgesic block of trigger-points with ROP (GBP+ROP Protocol; n=17) and were randomly selected in the continuation of another previous study of our group (*Lemos et al, 2008*); patients submitted to microvascular decompression of the Trigeminal nerve (MVD Protocol; n=22) were all those arriving to the Neurosurgery Department of Hospital São Marcos between 2004 and 2007 and indicated for surgery by this Hospital team (**Table 1**).

Patients from Protocols CBZ and GBP+ROP were eligible for the study if they presented a pain intensity with a score ≥ 6 measured by the Visual Analog Scale (VAS), and met the consensus criteria for the diagnosis of primary (idiopathic) TN (*Zakrzewska, 2003*). The inclusion criteria were (1) the occurrence of episodes of facial paroxysmal pain in territory innervated by a branch of the trigeminal nerve (VAS score ≥ 6), (2) presence of a normal neurological profile, and (3) presence of normal neuroimaging analysis. On the other hand, several exclusion criteria were also considered (see *Lemos et al, 2008*), including patient refuse to participate, clinical depressive condition, anticlotting therapy, secondary (symptomatic) TN, altered neurological profile, imagiological alterations, association with other cranial nerve neuralgias and proposed surgical intervention.

Patients following the surgical protocol (MVD) were selected by their intense intractable pain refractory to pharmacological therapy, or intolerable side effects of drugs (*Lonser and Apfelbaum, 2005*). When arriving at the Neurosurgery Department of Hospital São Marcos (day 0), 21 of 22 patients showed EVA = 10 and all were being medicated (12 patients were taken 600 mg/day of CBZ and 10 were taken 600 mg/day of CBZ plus 600 mg/day of GBP).

The therapeutical protocols used were accepted by the Hospital Ethical Committees (all three are actual therapies for TN pain control) and the patients were informed by the different clinical teams that: (1) they were going to be submitted to one of three (GBP+ROP; see *Lemos et al, 2008*) or one of two (CBZ; *Lemos et al, unpublished data*) pharmacological therapies, or to

surgery (MVD protocol); (2) they could drop or change treatment if no pain control was achieved (CBZ and GBP+ROP protocols) or that they would be continuing to take pharmacological agents if needed (MDV protocol). Patients signed and informed consent.

Treatment Protocols

Patients were submitted to one of the following treatment protocols:

CBZ Protocol – treatment using only oral CBZ in monotherapy; patients entering this protocol received additionally a control injection of saline [the vehicle of ROP administered to the other protocol, CBZ+ROP applied in another study (Lemos et al, unpublished data)] at facial trigger-points each 7 days of treatment (days 0, 7, 14, 28). The usual effective CBZ dosage ranges between 400-1000 mg/day (*Ahmad and Goucke, 2002*). Since these patients arrived to the Fafe Pain Unit from other Health Institutions with uncontrolled pain (day 0), their CBZ dose (whatever it was) was increased by 200 mg/day; thus, no CBZ titulation was performed. Each 7 days, during their visit to the Unit, the VAS score of the patients was recorded and CBZ dose adjusted if necessary. For statistical purpose the evaluation of patients was performed at day 0 (day before surgery) and after a follow-up of six months (month 6).

GBP+ROP Protocol – treatment using oral GBP plus administration of a superficial analgesic block with ROP to facial trigger-points, as described elsewhere (*Lemos et al, 2008*). The peripheral block with ROP was performed at the Pain Unit under sterile conditions, using a 27-gauge needle for administering subcutaneously 2 mL of a 2 mg/mL ROP solution (*Breivik, 2006; Lemos et al, 2008*). Each local block was peformed once a week (*Manchikanti et al, 2006; Lemos et al, 2008*) during the 1-month therapy (days 0, 7, 14, 21 and 28, when patient was received by the Unit staff). At day 0, a ROP block was performed and 100 mg GBP administered at night to each patient. On subsequent days, daily GBP increase followed the rationale described in *Lemos et al* (2008). For statistical purpose the evaluation of patients was performed at day 0 (day before surgery) and after a follow-up of six months (month 6).

MVD Protocol –This technique is thoroughly described elsewhere (*Lonser and Apfelbaum,* 2005). During pre-surgery, MVD patients undergo tests (blood, electrocardiogram, chest X-ray, TAC) several days before surgery. During surgery, patients are put to sleep using always the same protocol (endovenous general anesthesia) and are positioned on their back with their head turned or on their side with the symptomatic side facing up. A vertical incision is made behind the ear, 3-5 mm medial to the mastoid notch and extending about the length of the ear. A

circular portion of the skull is removed exposing the underlying dura, which is opened to expose the cerebellum and reach the posterior fossa. The cerebellum is allowed to fall out of the way exposing the side of the brainstem. By advancing over the superior surface of the cerebellum, the VII and VIII cranial nerves are avoided. The arachnoid membrane is dissected allowing visualization of the VII, VIII and finally the Trigeminal nerve. The offending loop of blood vessel is then mobilized. Venous vessels above or below the nerve are dissected away from the nerve and are coagulated and divided if needed. A sponge-like material (Teflon) is inserted between the vessel in contact with the nerve (usually the superior cerebellar artery). Frequently a groove or indentation is seen in the nerve where the offending vessel was in contact with the nerve. The sponge-like material is placed between the nerve and the offending blood vessel to prevent the vessel from returning to its native position. If venous vessels alone are in contact with the nerve, no prosthesis is required as they are coagulated and divided (*Lonser and Apfelbaum, 2005*). After the decompression is complete, the wound is flushed clean with saline solution. The dura is sewn closed. The skull is reconstructed and the overlying tissues are closed in multiple layers. The patient is allowed to wake up and is taken to an intensive care unit or other close observation unit for 3-5 days before returning home. For statistical purpose the evaluation of patients was performed at day 0 (day before surgery) and after a follow-up of six months (month 6).

Clinical outcome

The predefine outcome measures were:

(1) Evaluation of pain intensity using the VAS scale. Evaluation points were at the arrival to the Pain Unit or the day before surgery at the Neurosurgical Department (day 0) and 6 months later (month 6). Patients were told to locate their relative pain in a line marked in each extremity with 0 (no pain) on the left and 10 (the worst pain imaginable) on the right. Moderate pain was considered to be over 30 mm (VAS > 3) and severe pain over 60 mm (VAS > 6) (*Collins et al, 1997*). A pain reduction of 2 points in the VAS scale on the 100 mm VAS from the baseline pain score (day 0) was considered to be clinically significant (*Farrar et al, 2000; Finnerup et al, 2002; Salaffi et al, 2004*).

(2) Daily number or paroxysmal pain episodes. Although this variable was evaluated everyday, only data obtained at day 0 and month 6 were used for statistical analysis. The follow-up evaluation was obtained at the end of the day performing month 6,

during a phone interview at night to each patient, who was asked (1) how many pain crisis suffered during that day or, in case of no pain, (2) how many pain attacks suffered in the worst day of last week before the interview. If no pain was recorded following these two questions, the staff recorded 0 (zero) crisis for the patient.

(3) Adverse side effects, especially those involving sensory alterations. For each patient of the protocols evaluated, the types of sensory deficits were recorded before (day 0) and 6 months after the beginning of therapeutical intervention.

(4) the Hospital Anxiety and Depression Scale (HADS) questionnaire (*Zigmond and Snaith, 1983; Bjelland et al, 2002*) is a self-screening evaluation for depression and anxiety. It consists of 14 questions, seven for anxiety and seven for depression, which were presented to patients of the three protocols at day 0 and month 6.

(5) Evaluation of the life quality using the Sickness Impact Profile (SIP) (*Bergner et al, 1981; Turner and Romano, 2001; Jamison, 2004*). This questionnaire, adapted to the Portuguese population (*McIntyre and Araújo-Soares, 1999*), evaluated the evolution of the quality of life of patients submitted to the three protocols, from day 0 to month 6. SIP evaluates the descriptive profile of patients in terms of impact of the pathology analyzed upon specific day life behaviors. We analyzed the answers obtained at day 0 and day 28 to 136 questions distributed along the following categories: “Domestic Work”, “Mobility”, “Communication”, “Locomotion”, “Eating”, “Recreation-Pastimes”, “Emotion”, “Social Interaction”, “Alertness” and “Rest”.

(6) Questionnaire on the satisfaction with the treatment and medical team (QUASU). It contains 47 items that evaluate the patient satisfaction at different levels: Access, Expenses, Technical Quality, Communication/Information, Interpersonal Relations, team Coordination and Global Evaluation (created by *McIntyre et al*, based in Portuguese population).

The follow-up evaluation was performed at the end of the day performing month 6, during a phone interview to each patient. For VAS evaluation the patient was asked to reveal the pain felt at that moment as a number of the VAS scale with which they were used to deal with. With respect to the number of pain crisis, each patient was asked (1) how many pain attacks suffered during that day or, in case of no pain, (2) how many pain crisis suffered in the worst day of the last week before interview. If no pain was recorded following these two questions, the staff recorded 0 (zero) crisis for the patient. The adverse side effects were also recorded from and

questionnaires were performed to the patients.

Direct cost analysis: pharmacological and hospital costs

Concerning patients submitted to pharmacological (CBZ and GBP+ROP protocols) or surgical surgery (MVD protocol) therapies, direct medical cost estimates were determined using hospital cost accounting data (Published in Diário da República, article 132/2008), the "Simposium Terapêutico 2008" and the price lists included in the latter. Medical costs were calculated using the patient-reported dosage and number of doses taken daily and Hospital internment, which were converted to the cost between day 0 and 1 month (according to the 4-week treatment in protocols GBP+ROP and CBZ) and between day month 2 and month 6 (follow-up for the three protocols) (**Table 2**).

Statistics

Data are presented as media ± Standard Deviation (SD) along the several variables under study. The normal distribution of the results was verified using the Kolmogorov-Smirnov test, whereas the equality of variances was evaluated by the Levene test. A logarithmical transformation of data has been used whenever the homogeneity of variances was not verified. Mean comparisons of VAS scores, number of pain crisis, direct costs, SIP and HADS between values at day 0 and month 6 (or only at month 6 for costs data) were performed using paired-samples Student's *t*-test whenever possible, or the one-sample *t*-test when one of the means showed absence of variation (see Results Section). A mean comparison of the VAS scores following protocols CBZ, GBP+ROP and MVD was performed at month 6 using an one-way analysis of variance (ANOVA).

RESULTS

Patient Baseline Characteristics

The baseline data for the demographic characteristics of patients selected for the three protocols are expressed in **Table 1**.

Effect of CBZ, GBP+ROP and MVD Protocols in Pain Control

No differences were found between patients from Protocol GBP+ROP (VAS_0 = 8.8 ± 1.4)

and Protocol CBZ (VAS_0 = 9.1 ± 1.4) (p=0.41, *t*-test) (**Fig. 1**) in pain intensity at the beginning of the treatment (day 0), whereas 21 of 22 MVD patients presented EVA =10, the most painful condition imaginable (VAS_0 = 9.9 ± 0.4). Five months after the 4-week treatment followed in CBZ and GBP+ROP protocols (month 6), both pharmacological approaches have decreased significantly pain measured by EVA scores ($GBP+ROP_0$ x $GBP+ROP_{6m}$, p<0.0001; CBZ_0 x CBZ_{6m}, p<0.0001, paired-samples *t*-tests), while 6 months after MVD surgery EVA scores were also significantly reduced (MDV_0 x MDV_{6m}, p<0.001, one-sample *t*-test). Although the 3 protocols reduced pain intensity, GBP+ROP therapy resulted in a significantly lower EVA score than patients following CBZ or MVD protocols (GBP+ROP, VAS_{6m} = 2.6 ± 1,00; CBZ, VAS_{6m} = 3.9 ± 1.5; MVD, VAS_{6m} = 4.2 ± 1.7 - one-way ANOVA, p=0.002; GBP+ ROP_{6m} x CBZ_{6m}, p=0.011, $GBP+ROP_{6m}$ x MVD_{6m}, p=0.002, Tukey tests) (**Fig. 1**). With respect to VAS observed at month 6 for MVD patients, it can be concluded by a one-sample t-test that the VAS value is significantly different from 10 (p<0.001), the value observed before surgery (day 0).

The baseline number of daily crises of paroxysmal sudden and intense pain was similar between patients of both pharmacological protocols (day 0: GBP+ROP, n_{crises} = 9.6 ± 1.5; CBZ, n_{crises} = 10.7 ± 2.2; p=0.114, *t*-test), whereas 21 of 22 MVD patients presented 12 pain crises per day (MVD, n_{crisis} = 11.8 ± 0.6) (**Fig. 2**). Five months after the 4-week treatment followed in CBZ and GBP+ROP protocols (month 6), all three protocols have decreased significantly the number of daily pain crisis (month 6: GBZ+ROP, n_{crises} = 2.0 ± 1.6; CBZ, n_{crises} = 4.1 ± 1.7; MVD, n_{crisis} = 2.6 ± 0.6 - $GBP+ROP_0$ x $GBP+ROP_{6m}$, p<0.0001; CBZ_0 x CBZ_{6m}, p<0.0001, paired samples *t*-tests; MDV_0 x MDV_{6m}, p<0.001, one-sample *t*-test) (**Fig. 2**). Again, with respect to the number of daily pain crisis observed at month 6 in MVD patients, it can be concluded by a one-sample t-test, that the number of crisis is significantly different from 12 (p<0.001), the value observed before surgery (day 0).

Daily Dose of Anticonvulsivants

The three protocols showed a different evolution in the consumption of anticonvulsivants CBZ or GBP. At day 0 and 1 GBP+ROP patients took 100 mg/day of GBP; at day 7, these patients were taken 200 or 300 mg/day (mean = 266,67 mg/day); at the end of the 4-week treatment patients were tacking 300 mg/day of GBP, which was kept during the next 5 months, until the moment month 6 (*Lemos et al, 2008*). Patients following CBZ protocol arrived to the Hospital and began tacking 626 ± 163 mg/day of CBZ; at the end of the 4-week treatment, CBZ

intake increased to 757 ± 200 mg/day, which was even increased at month 6 to 826 ± 291 mg/day (see *Lemos et al*, unpublished data). Finally, patients for MVD protocol were taken 600 mg/day of CBZ in monotherapy (12 of the 22 patients) or CBZ+GBP (600 + 600 mg/day); However, at the end of the follow-up (month 6), MVD patients were still assisted by drugs, although at lower doses, namely 200 mg/day of CBZ or 300 mg/day of GBP, both in monotherapy.

Adverse Side Effects

The GBP+ROP protocol resulted in no significant side effects and no sensory deficits. Patients following the CBZ protocol showed no sensory deficits, but 7 of the 21 patients presented adverse side effects (dizziness). On the contrary, 5 of the 22 patients submitted to MVD protocol presented hypoesthesia of the hemiface affected, 3 were anesthetized in the hemiface, 1 showed paresthesias and 1 patient died in the immediate post-operative period due to brain hemorrhage, with a total of 10 in 22 patients with sensory sequelae; additionally, 5 of the 22 patients presented dizziness as adverse side effect and 7 in 22 showed a complete absence of side effects or sequelae.

Direct Costs

In what concerns direct costs of resources consumption, data show that MVD full cost was 1,056.78 ± 22.5 Euro per patient while, on the contrary, CBZ (384.2 ± 1.5 Euros) and especially GBP+ROP (252.47 Euros) were far less expensive between day 0 (before treatment/surgery) and the end of the first month 6 ($GBP+ROP_{euro}$ x CBZ_{euro}, $p<0.0001$; $GBP+ROP_{euro}$ x MVD_{euro}, $p<0.0001$, one-sample *t*-tests; CBZ_{euro} x MVD_{euro}, $p<0.0001$, paired-samples *t*-test) (**Table 2**; **Fig. 3**). With respect to the total direct cost per patient submitted to CBZ or MVD protocols, it can be concluded by one-sample *t*-tests, that the cost in Euros during the period day 0 → month 1 is significantly different from 252 ($p<0.001$), the average total cost value observed for each GBP+ROP patient. The difference is mostly explained by two factors: the cost of the surgical procedure and the cost of hospital stay for MVD patients. However, during months 2-5, the financial situation alters: GBP+ROP protocol turns to be the most expensive treatment ($GBP+ROP_{months\ 2\text{-}5}$ = 314.3 Euro), as GBP is more expensive than CBZ ($CBZ_{months\ 2\text{-}6}$ = 255.0 ± 6.3) and MVD patients take low dosage of anticonvulsivants ($MVD_{months\ 2\text{-}6}$ = 254.7 ± 40.9 Euro) (**Table 2**; **Fig. 3**).

Functional Quality of Life and Patient Satisfaction

In what concerns the quality of life, measured by the scores obtained through the SIP questionnaire, patients from both GBP+ROP and CBZ protocols showed a significant improvement in functionality ($GBP+ROP_0$ x $GBP+ROP_{6m}$, $p<0.0001$), which was not achieved by MVD patients (MVD_0 x MVD_{6m}, p=0.086, paired-samples *t*-tests) (**Fig. 4.1**). Interestingly, however, both anxiety and depression scores were significantly improved in MVD patients from day 0 to month 6, as measured by HADS questionnaire (MVD_{ANX0} x MVD_{ANX6m}, $p<0.001$; MVD_{DEP0} x MVD_{DEP6m}, $p<0.0001$, paired-samples *t*-test) (**Figs. 4.2 and 4.3**), whereas CBZ patients showed a significant improvement only in anxiety scores (CBZ_{ANX0} x CBZ_{ANX6m}, p=0.036, paired-samples *t*-test) and GBP+ROP patients did not improve any of the dimensions evaluated by the HADS questionnaire (**Figs. 4.2 and 4.3**).

The satisfaction of the patients with the treatment and with the clinical team, measured by the QUASU questionnaire, revealed a complete or high level of satisfaction of patients (**Fig. 5**). While all patients allocated to protocols GBP+ROP and CBZ were totally satisfied with the treatment and clinical team, 5 out of 22 MVD patients were acceptably or unsatisfied with the treatment (**Fig. 5.1**) due to sensory adverse side effects, and 2 / 22 MVD patients were just acceptably satisfied with the team (**Fig. 5.2**).

DISCUSSION

Economic evaluations of different therapeutical approaches are intended to support health-related decision-making process by informing clinical decision-makers of estimates of costs and benefits of surgery and comparing them to the prevalent pharmacological intervention. Although the three branches of the present study were randomly obtained at three different times, the clinical outcomes obtained and the direct costs associated reinforce the necessity of careful evaluation of the patient before decision to make an invasive surgical intervention. All protocols, GBP+ROP, CBZ and MVD, decreased significantly pain behavior in TN patients, as measured by the VAS scale and number of daily pain crises, and a total or large satisfaction with both the treatment and clinical team were achieved. However, the degree of adverse side effects was different between protocols, with GBP+ROP showing no side effects and MVD presenting facial sensorial deficits, with different levels of severity. Additionally, during the first month of treatment, a much higher cost was attributed to MDV protocol due to surgical procedures,

hospital stay and maintenance of drug therapy, whereas pharmacotherapy costs were concentrated on drug costs. On the contrary, during the follow-up the surgical protocol is the less costly protocol and GBP+ROP is the most expensive treatment.

Methodological Considerations

The rationale of the present study was to compare the efficacy of different therapeutical approaches to TN and evaluate the direct costs associated with each one. The protocol GBP+ROP was chosen due to its improved efficacy as an association of an anticonvulsivant and the analgesic block of TN trigger-points (*Lemos et al, 2008*), which can constitute a valid alternative whenever the classic first-choice pharmacological treatment, CBZ in monotherapy (*Cheshire, 2007*), cannot be used. The protocol CBZ is still considered the first-line choice for TN treatment (*Zakrzewska and Lopez, 2006; Canavero and Bonicalzi, 2006; Cheshire, 2007*). In order to eliminate the possibility that any beneficial effect could depend on the physical action of local administration of the analgesic ROP solution by clearing adhesions or inflammatory molecules from the vicinity of the nerve (*Manchikanti et al, 2006*), the protocol CBZ-only was accompanied by injection of saline to TN trigger-points. Thus, the improvements observed in the different outcomes analyzed resulted exclusively from the pharmacological action of GBP+ ROP and CBZ and not from the manipulation and liquid introduction at trigger-points (*Lemos et al, 2008*; *Lemos et al, unpublished data*). The frequency of ROP analgesic block applied subcutaneously to TN patients respected the guidelines for the practice of interventional techniques (*Manchikanti et al, 2006*). A patient should receive an injection at intervals not smaller than 1 week, which was the period chose to mediate between each ROP (or saline) administration. The protocol MVD is still considered the first-line surgical treatment for medical unresponsive TN (*Fujimaki et al, 1990; Lee et al, 1997; Apfelbaum et al, 2000*)

Clinical Impact of the Three TN Treatment Protocols

Since a 2-point decrease in the mean VAS scale (0-10 scale) is considered the minimum clinical relevant difference in pain intensity when comparing the effect of two treatments (*Farrar et al, 2000; Finnerup et al, 2002; Salaffi et al, 2004*), the GBP+ROP, CBZ and MVD protocols, by decreasing pain intensity 6.1, 5.3 and 5.7 (respectively), were clinically effective in reducing pain at the 6th month of follow-up; additionally, all protocols also reduced significantly the number of daily pain crisis. These results are in accordance with the literature in terms of efficacy in

controlling pain in TN (*Lemos et al, 2008, Cheshire, 2007; Lonser and Apfelbaum, 2005*). Since this study is a retrospective and observational evaluation of 3 sets of patients whom were randomly allocated in 3 different studies, no comparisons between the degrees of reduction of pain values between protocols can be performed (both EVA scale values and number of daily pain crisis). Another study has compared outcomes in a group of patients who have had both pharmacological and surgical TN treatments. Patients treated with oxcarbamazepine and different surgeries (MVD and Gasser ganglion surgery) were compared and patients would prefer to have had surgery before (*Zakrzewska and Patsalos, 2002*). Although sensory deficits and necessity for repeating surgery have occurred, pain relief was significantly longer after surgery than pharmacological treatment, with pain recurrence being 10 months after oxcarbamazepine and 28 months after surgery. As these data cannot be extrapolated to other antineuralgic drugs, other similar comparative studies would be appropriate.

When comparing the effect of GBP+ROP, CBZ and MVD protocols between baseline (day 0) and month 6, other indications of the clinical outcome can be performed using specific questionnaires. The functional analysis of quality of life measured by the SIP indicated that functional improvement was significant after pharmacological protocols but not after MVD. This may result from the large number of patients with sensory deficits occurring in the latter case, which may counteract the functional improvement resulting from pain control. This study shows that, in addition to GBP+ROP protocol (*Lemos et al, 2008*), CBZ improves functionality. Only one paper evaluated SIP in a surgical context (*Lefaucheur et al, 2009*), indicating improvement in TN patients after epidural motor cortex stimulation. Concerning HADS, only patients submitted to MVD showed a significant improvement in both anxiety and depression scores, probably because patients who are hospitalized for surgery have a very high degree of anxiety and expectation (*Castro et al, 2009*). On the contrary, all GBP+ROP and CBZ patients were completely satisfied with the treatment protocol and the clinical team, whereas some MVD patients were unsatisfied or acceptably satisfied with the treatment protocol. This may result from the sequelae that are present in a significant number of MVD patients, whereas CBZ protocol results only in dizziness in some patients and GBP+ROP patients showed virtually no adverse side effects.

Another important therapeutical improvement of GBP+ROP and MVD protocols is the demonstration of a large decrease in the daily dose of anticonvulsivant drug intake from baseline (day 0), both at the end of the treatment (day 29, GBP+ROP protocol) and, even further, after the 5-month follow-up (*Lemos et al, 2008*). On the contrary, CBZ monotherapy observed a

progressive increment in the daily CBZ dosage. These data show that the clinical results of NT treatment with GBZ+ROP and MVD are superior to CBZ monotherapy, because the significantly lower dose of CBZ and / or GBP protocols strongly decreased the presence / intensity of adverse side effects due to pharmacotherapy.

Direct Costs

The data presented in this study point to a much higher cost of the surgical approach to TN treatment than the other two pharmacological protocols. This results directly from the high costs of surgical intervention and Hospital stay pre-, during and after the MVD. However, during follow-up, the maintenance of pain control in TN patients submitted to surgery requires less medical therapy than the other two protocols. Although clearly the less expensive treatment during the first 4-week treatment period, the GBP+ROP protocol tends to be the most expensive therapy after stabilization of TN pain control (follow-up) due to the higher cost of GBP drug (Neurontin® or Gabamox®) versus CBZ pharmacological presentation (Tegretol®). Only a few studies have evaluated the effects of drugs in the reduction of costs in TN (*Pérez et al, 2009*) or have compared the cost of different TN surgical protocols (*Pollock and Ecker, 2005; Tarricone et al, 2008*). In accordance with a less expensive experience resulting from MVD surgery, in a comparison between this surgery, glycerol rhizotomy and stereotactic radiosurgery, it was shown that in longer follow-up intervals MVD is predicted to be the most cost-effective surgery and should be considered the preferred operation for patients (*Pollock and Ecker, 2005*). However, recent data point to cyberknife radiosurgery resulting to be a cost-saving alternative compared with MVD (*Tarricone et al, 2008*). The only study showing cost-saving using drug therapy in TN point to the use of pregabalin (*Pérez et al, 2009*). Finally, to the best of our knowledge, the present paper is the first attempt to compare clinical outcomes and costs between pharmacological protocols and the most common surgical approach in TN.

Limitations of the Study

This study has some limitations. First, the three groups of patients are not directly comparable; although they were randomly selected, data from patients allocated to the CBZ and GBP+ ROP branches were recruited for two different studies (*Lemos et al, 2008*; *Lemos et al, unpublished results*) and only the MVD patients were retrospectively selected for this specific study. Second, patients from MVD protocol had pain scores in the VAS scales significantly higher

at baseline (day 0) then patients from protocols CBZ and GBP+ROP; the difference in patients' characteristics is explained by the fact that MVD is usually not seen as an alternative to pharmacological protocols but, rather, as a second-line strategy whenever first-line or second-line drugs cause intolerable side effects or cannot control TN pain. Third, the cost analysis does not include those associated with loss of productivity by patients during the admission and evaluation periods at the Hospital / Pain Unit and insurance contributions (indirect costs). Fourth, although the effect of treatment on pain intensity and number of paroxysmal crises was still significantly different after 6 months of treatment with CBZ+ROP, CBZ and MVD protocols, the follow-up period may not have been sufficient to determine the potential long-term effects of the treatments; larger samples, sequential allocation of patients for surgical and pharmacological branches and longer follow-ups should verify data obtained.

Conclusions

CBZ is known for long and still is recognized as the first-line drug choice for pain control in TN, an improvement of second-line drug therapy has been achieved by the associating GBP intake with the peripheral analgesic block of TN trigger-points with ROP (GBP+ROP), and whenever pharmacological approaches fails, microvascular decompression is a surgical method of choice (MVD). We show that all three protocols resulted in a clinically significant improvement in pain, as shown by the VAS scale and number of paroxysmal pain crisis, which were accompanied by a clear decrease in the daily CBZ/GBP dosage needed for TN pain control, with a consequent reduction in the adverse side effects associated. The cost analysis indicates that the first 4-week period of treatment (or admission, surgery and treatment in MVD patients) results in GBP+ROP being by far the less expensive protocol and MVD the most expensive approach. However, with time course (follow-up), GBP+ROP protocol tended to be the most costly treatment and MVD the less expensive (very similar to CBZ protocol).

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REFERENCES

1. Ahmad M, Goucke CR. Management strategies for the treatment of neuropathic pain in the elderly. *Drugs Aging*, 19:929-945 (2002).
2. Apfelbaum RI. Neurovascular decompression: the procedure of choice? Clin Neurosurg, 46:473-498 (2000).
3. Bergner M, Bobbitt RA, Carter WB et al. The sickness impact profile: development and final revision of a health status measure. *Med Care*, 19:787-805 (1981).
4. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*, 52:69-77 (2002).
5. Breivik H. Local anesthetic blocks and epidurals In: "*Melzack´s Textbook of Pain*", 5th edition, McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 903-925 (2006).
6. Campbell FG, Graham JG, Zilkha KJ. Clinical trial of carbazepine (tegretol) in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry*, 29:265-267 (1966).
7. Canavero S, Bonicalzi V. Drug therapy of trigeminal neuralgia. *Expert Rev Neurother*, 6:429-440 (2006).
8. Castro AR, Siqueira SR, Perissinotti DM, Teixeira MJ, Siqueira JT. Emotional aspects of chronic orofacial pain and surgical treatment. *Int J Surg*, in press.
9. Cheshire WP. Can MRI distinguish injurious from innocuous trigeminal neurovascular contact? *J Neurol Neurosurg Psychiatry*, 76:1470-1471 (2005a).
10. Cheshire WP. Trigeminal neuralgia: diagnosis and treatment. *Curr Neurol Neurosci Rep*, 5:79-85 (2005b).
11. Cheshire WP. Trigeminal neuralgia: for one nerve a multitude of treatments. *Expert Rev Neurother*, 7:1565-1579 (2007).
12. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimeters? *Pain*, 72:95-97 (1997).
13. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jørum E, Serra J, Jensen TS. EFNS guidelines on neuropathic pain assessment. *Eur J Neurol*, 11:153-162 (2004).
14. Dhople AA, Adams JR, Maggio WW, Naqvi SA, Regine WF, Kwok Y. Long-term outcomes of Gamma Knife radiosurgery for classic trigeminal neuralgia: implications of treatment and critical review of the literature. *J Neurosurg*, *in press*.

15. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain*, 88:287-294 (2000).
16. Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. Lamotrigine in spinal cord injury pain: a randomized controlled trial. *Pain*, 96:375-383 (2002).
17. Fountas KN, Lee GP, Smith JR. Outcome of patients undergoing gamma knife stereotactic radiosurgery for medically refractory idiopathic trigeminal neuralgia: Medical College of Georgia's experience. *Stereotact Funct Neurosurg*, 84:88-96 (2006).
18. Fujimaki T, Fukushima T, Miyazaki S. Percutaneous retrogasserian glycerol injection in the management of trigeminal neuralgia: long-term follow-up results. *J Neurosurg*, 73:212-216 (1990).
19. Gorgulho A, De Salles AA, McArthur D, Agazaryan N, Medin P, Solberg T, Mattozo C, Ford J, Lee S, Selch MT. Brainstem and trigeminal nerve changes after radiosurgery for trigeminal pain. *Surg Neurol*, 66:127-135 (2006).
20. Jamison RN. The role of psychological testing and diagnosis in patients with pain. In: "*Psychological Aspects of Pain: a handbook for health care providers*", Dworkin RH, Breitbart WS (Eds). Progress in Pain Research and Management, Vol 27. IASP Press, Seattle, pp 117-137 (2004).
21. Jorns TP, Zakrzewska JM. Evidence-based approach to the medical management of trigeminal neuralgia. *Br J Neurosurg*, 21:253-261 (2007).
22. Kanpolat Y, Savas A, Bekar A, Berk C. Percutaneous controlled radiofrequency trigeminal rhizotomy for the treatment of idiopathic trigeminal neuralgia: 25-year experience with 1,600 patients. *Neurosurgery*, 48:524-532 (2001).
23. Katusic S, Williams DB, Beard CM, Bergstralh EJ, Kurland LT. Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences, Rochester, Minnesota, 1945-1984. *Neuroepidemiology*, 10:276-281 (1991).
24. Knafo H, Kenny B, Mathieu D. Trigeminal neuralgia: outcomes after gamma knife radiosurgery. *Can J Neurol Sci*, 36:78-82 (2009).
25. Lang E, Naraghi R, Tanrikulu L, Hastreiter P, Fahlbusch R, Neundörfer B, Tröscher-Weber R. Neurovascular relationship at the trigeminal root entry zone in persistent idiopathic facial pain: findings from MRI 3D visualisation. *J Neurol Neurosurg Psychiatry*, 76:1506-1509 (2005).

26. Lee KH, Chang JW, Park YG, Chung SS. Microvascular decompression and percutaneous rhizotomy in trigeminal neuralgia. *Stereotact Funct Neurosurg*, 68:196-199 (1997).
27. Lefaucheur JP, Drouot X, Cunin P, Bruckert R, Lepetit H, Créange A, Wolkenstein P, Maison P, Keravel Y, Nguyen JP. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. *Brain*, 132:1463-1471 (2009).
28. Lonser RR, Apfelbaum. Neurovascular decompression in surgical disorders of cranial nerves V, VII, IX, and X. In "*Schmidek and Sweet's Operative Neurosurgical Techniques: Indications, Methods, and Results*", 5th Edition, Vol 2, Schmidek HH, Roberts DW (Eds), pp 1531-1543 (2005).
29. Lonser RR, Apfelbaum. Neurovascular decompression in surgical disorders of cranial nerves V, VII, IX, and X. In "*Schmidek and Sweet's Operative Neurosurgical Techniques: Indications, Methods, and Results*", 5th Edition, Vol 2, Schmidek HH, Roberts DW (Eds), pp 1531-1543 (2005).
30. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain*, 123:665-676 (2000).
31. Manchikanti L, Singh V, Trescot AM, Deer TR, Boswell MV. Guidelines for the Practice of Interventional Techniques. In: "*Weiner´s Pain Management: a practical guide for clinicians*", 7th Edition, Boswell MV, Cole BE (Eds). CRS Press, London, pp 847-878 (2006).
32. Marbach JJ, Lund P. Depression, anhedonia and anxiety in temporomandibular joint and other facial pain syndromes. *Pain*, 11:73-84 (1981).
33. Pérez C, Saldaña MT, Navarro A, Martínez S, Rejas J. Trigeminal neuralgia treated with pregabalin in family medicine settings: its effect on pain alleviation and cost reduction. *J Clin Pharmacol*, 49:582-590 (2009).
34. Pollock BE, Ecker RD. A prospective cost-effectiveness study of trigeminal neuralgia surgery. *Clin J Pain*, 21:317-322 (2005).
35. Royal M, Wienecke G, Movva V Ward S, Bhakta B, Jensen M and Gunyea. Open label trial of oxcarbamazepin in neuropathic pain. Pain Med, 2:250-151 (2001).
36. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain*, 8:283-291 (2004).

37. Sindrup SH, Jensen TS. Pharmacotherapy of trigeminal neuralgia. *Clin J Pain*, 18:22-27 (2002).
38. Solaro C, Messmer Uccelli M, Uccelli A, Leandri M, Mancardi GL. Low-dose gabapentin combined with either lamotrigine or carbamazepine can be useful therapies for trigeminal neuralgia in multiple sclerosis. *Eur Neurol*, 44:45-48 (2000).
39. Tarricone R, Aguzzi G, Musi F, Fariselli L, Casasco A. Cost-effectiveness analysis for trigeminal neuralgia: Cyberknife vs microvascular decompression. *Neuropsychiatr Dis Treat*, 4:647-652 (2008).
40. Tölle T, Dukes E, Sadosky A. Patient burden of trigeminal neuralgia: results from a cross-sectional survey of health state impairment and treatment patterns in six European countries. *Pain Pract*, 6:153-160 (2006).
41. Turner JA, Romano JM. Psychological and psychosocial evaluation. In: "*Bonica´s Management of Pain*", 3rd Edition, Loeser JD, Butler SH, Chapman CR, Turk DC (Eds). Lippincott Williams & Williams, Philadelphia, pp 329-341 (2001).
42. Zakrzewska JM. Trigeminal, eye, and ear pain. In: "*Handbook of Pain Management – a clinical companion to Wall and Melzack´s Textbook of Pain*", Melzack R, Wall PD (Eds). Churchill Livingstone, London, pp 199-215 (2003).
43. Zakrzewska JM, Lopez BC. Trigeminal and glossopharyngeal neuralgia. In: "*Melzack´s Textbook of Pain*", 5th edition, McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 1001-1010 (2006).
44. Zakrzewska JM, Patsalos PN. Long-term cohort study comparing medical (oxcarbazepine) and surgical management of intractable trigeminal neuralgia. *Pain*, 95:259-266 (2002).
45. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. *Pain*, 73:223-230 (1997).
46. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*, 67:361-370 (1983).

FIGURE LEGENDS:

Figure 1. Effect of the 3 protocols (GBP+ROP, CBZ and MVD) on the pain intensity of patients 6 months after day 0. For significant effects see the Results section.

Figure 2. Number of daily episodes of pain before (day 0) and after a 5-month follow-up (month 6). For significances see the Results section.

Figure 3. Direct costs of the 3 protocols analyzed, evaluated after the first month of treatment and during the period 2-6 months.

Figure 4. Effect of Protocols GBP+ROP, CBZ and MVD on the Total SIP score of quality of life (**A**) and on the anxiety (**B**) and depression (**C**) scores measured by the HADS questionnaire. For significant differences see the Results section.

Figure 5. Satisfaction of patients submitted to GBP+ROP, CBZ and MVD with the treatment (**A**) and the clinical team (**B**).

TABLE 1. Baseline characteristics of the patients

	Protocol GBP+ROP (n=17)	Protocol CBZ (n=23)	Protocol MVD Surgery (n=22)
Age (years, average and SD)	63 (16.3)	66 (10.8)	66 (9.3)
Gender (women/total)	12 / 17	19 / 23	15/22
Pain location (trigeminal branches)			
V1 or V2 or V3	7	13	6
V1 + V2 or V2 + V3	6	7	9
V1 + V2 + V3	4	3	7
Facial side (right/total)	12 / 17	10 / 23	11 / 22
Pain duration at day 0			
1-5 years	13	9	4
6-10 years	4	5	14
11 and more	0	9	4

TABLE 2. Average direct healthcare cost per patient

PROTOCOL	COST CATEGORY	1st MONTH (€)	2-6 MONTH (€)*
GBP+ROP	GBP	7.29	109.2
	1st Consultation	71.42	
	Other Consultations		205.1
	3 Sessions	75.81	
	Imaging tests	79.55	
	Laboratory tests	18.40	
	TOTAL	**252.47** (0)	**314.3** (0)
CBZ	CBZ	9.69	49.9
	1st Consultation	71.42	
	Other Consultations	205.10	205.1
	Imaging tests	79.55	
	Laboratory tests	18.40	
	TOTAL	**384.2** (1.5)	**255.0** (6.3)
MVD	CBZ - GBP	30.39	49.6
	Surgery	719.90	
	1st Consultation	71.42	
	Other Consultations	137.12	205.1
	Imaging tests	79.55	
	Laboratory tests		
	TOTAL	**1,056.78** (22.3)	**254.7** (40.9)

* - Sum of costs along five months (months 2-6)
Numbers between brackets – Standard Deviation

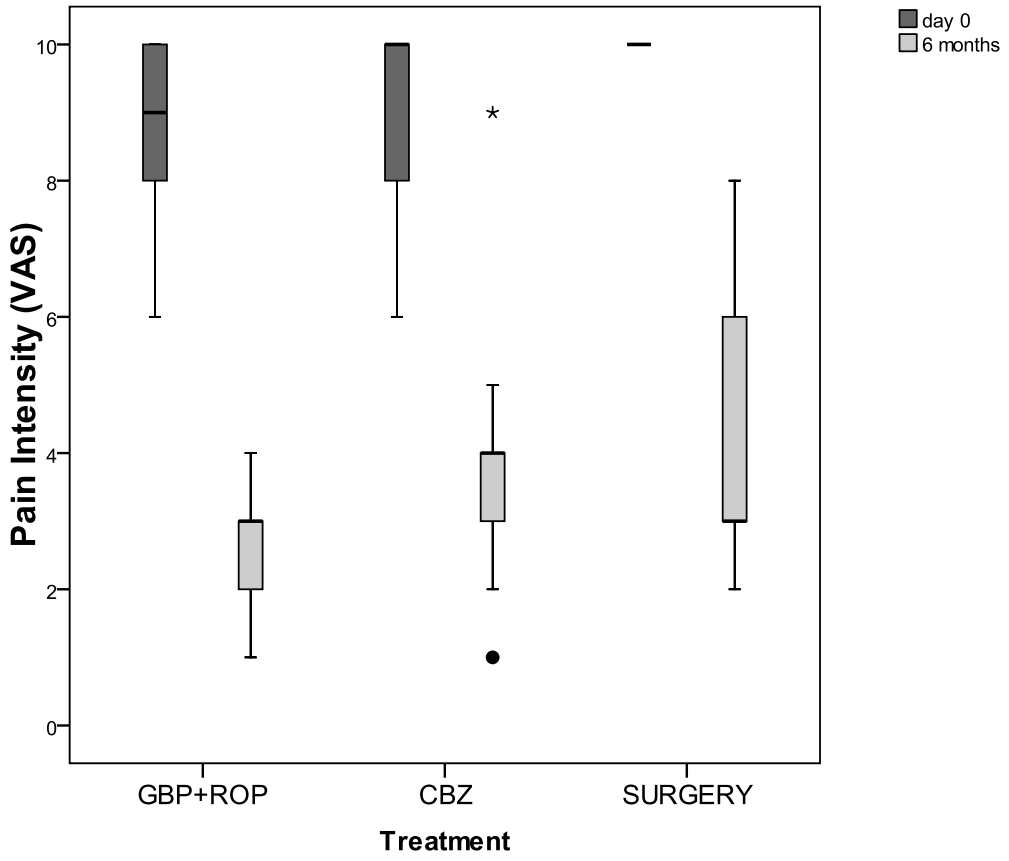

day 0
6 months
Pain Intensity (VAS)
10
8
6
4
2
0
GBP+ROP
CBZ
SURGERY
Treatment

FIGURE 1

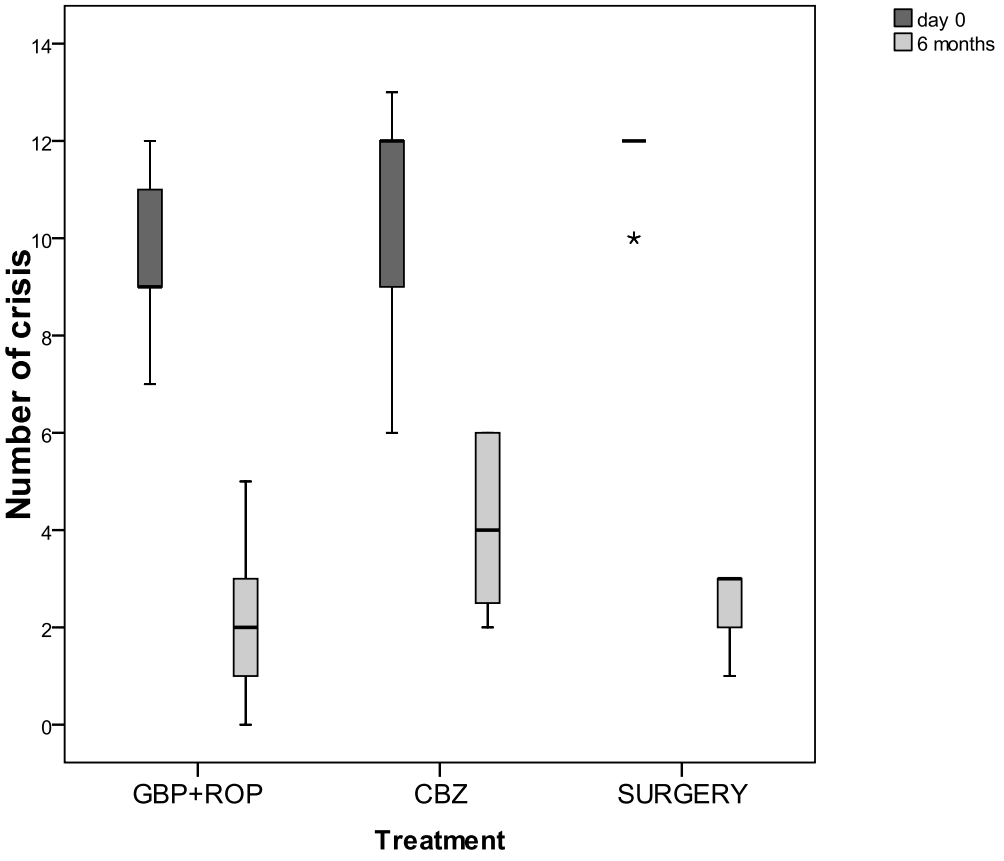

day 0
6 months
Number of crisis
14
12
10
8
6
4
2
0
GBP+ROP
CBZ
SURGERY
Treatment

FIGURE 2

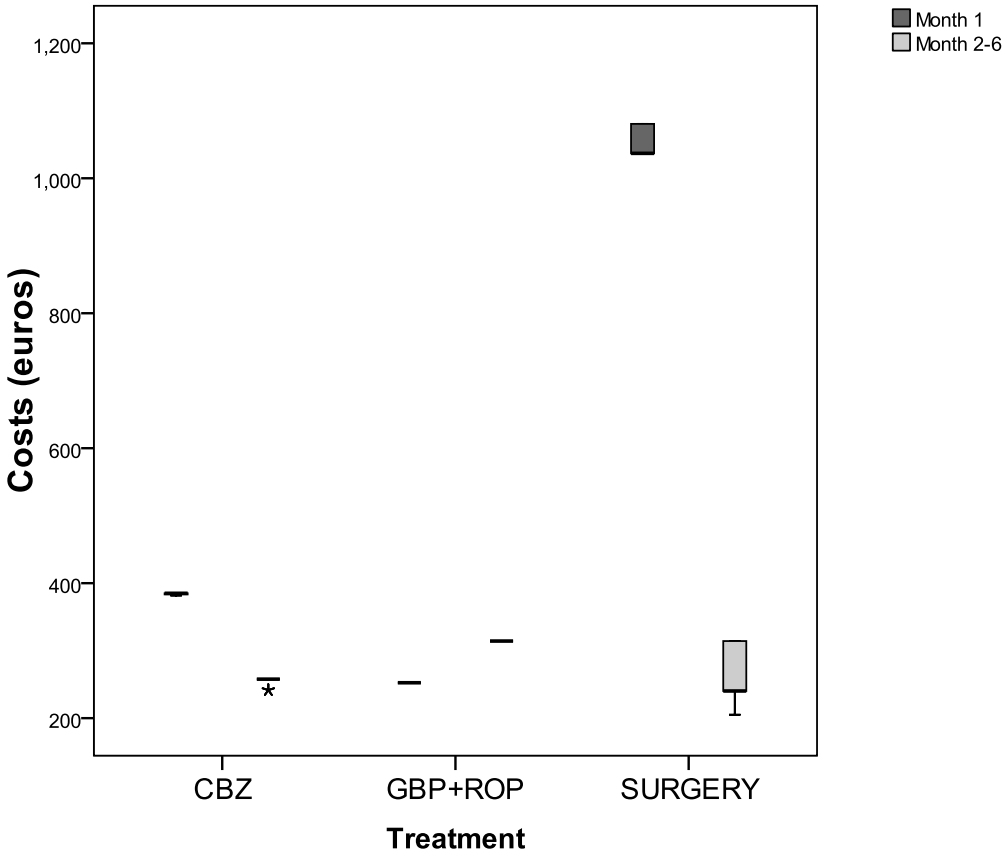
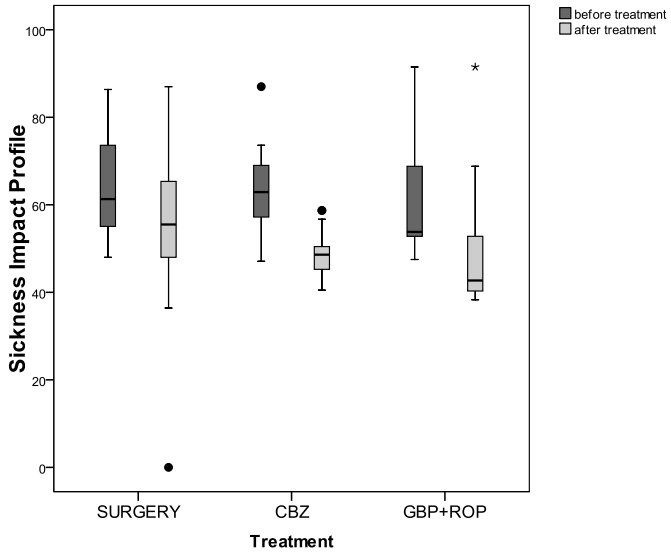
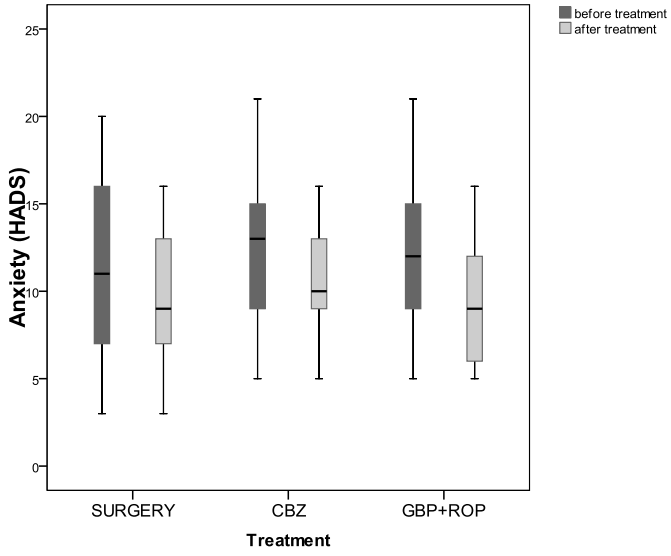

Month 1
Month 2-6
1,200
1,000
800
600
400
200
Costs (euros)
CBZ
GBP+ROP
SURGERY
Treatment

FIGURE 3


before treatment
after treatment
Sickness Impact Profile
100
80
60
40
20
0
SURGERY
CBZ
GBP+ROP
Treatment


before treatment
after treatment
Anxiety (HADS)
25
20
15
10
5
0
SURGERY
CBZ
GBP+ROP
Treatment

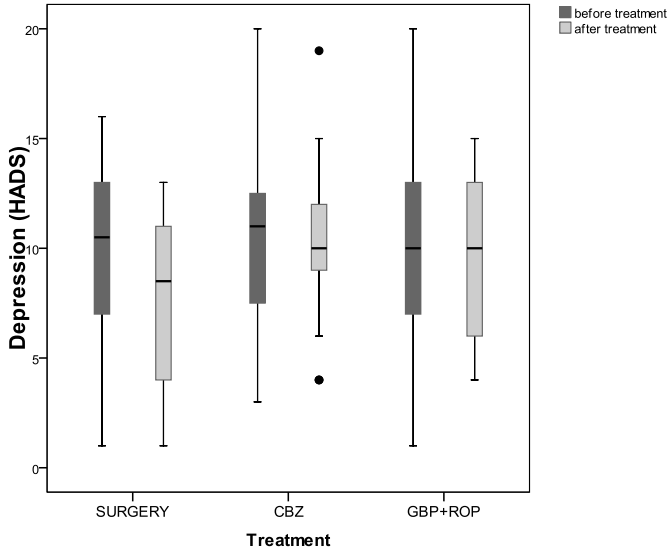
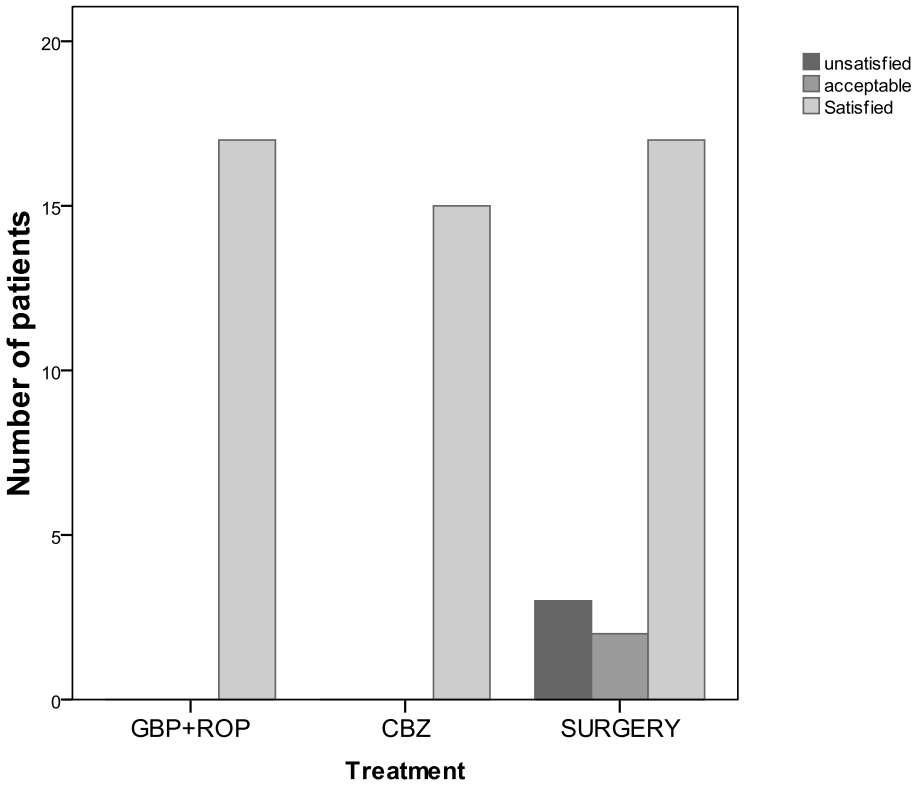

before treatment
after treatment
Depression (HADS)
20
15
10
5
0
SURGERY
CBZ
GBP+ROP
Treatment

FIGURE 4


20
15
10
5
0
Number of patients
GBP+ROP
CBZ
SURGERY
Treatment
unsatisfied
acceptable
Satisfied

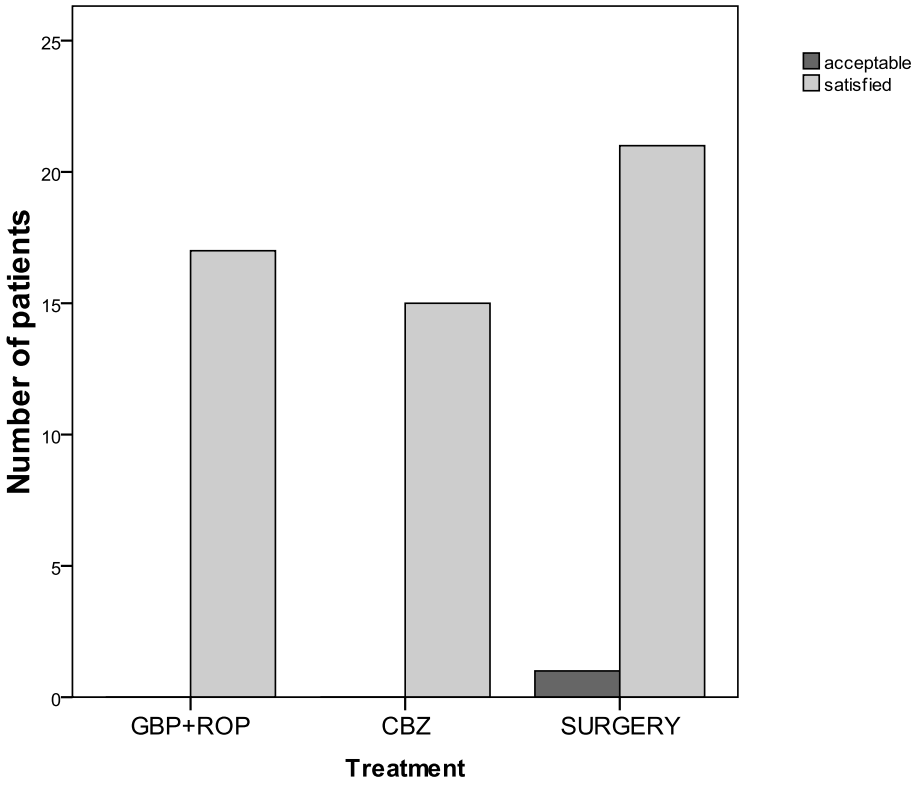

25
20
15
10
5
0
Number of patients
GBP+ROP
CBZ
SURGERY
Treatment
acceptable
satisfied

FIGURE 5

Capítulo 3

CONSIDERAÇÕES FINAIS

A análise global dos utentes avaliados nos 3 estudos que constituem esta tese envolveu um total de 99 utentes. A análise sócio-demográfica permitiu confirmar que a maioria dos utentes com Nevralgia do Trigémio (NT) se encontram acima dos 50 anos (90%), predominando no sexo feminino (67%) (Tabela 1); nos utentes com NT a dor predominava do lado direito da face (56 %), apresentavam um número de crises diário de 11-20 (58%) e todos referiam uma dor tipo choque eléctrico (99%) com uma intensidade superior a 7 medida pela escala visual analógica (EVA) (95%) (Tabela 1). Os utentes apresentavam patologia associada significativa (ex: hipertensão, diabetes), sendo por isso de prever uma maior incidência de efeitos adversos iatrogénicos após a aplicação de protocolos invasivos.

Tabela 1. Análise sócio-demográfica global

Número Total de Pacientes = *99*			
Idade	Grupos	n=99	Percentagem
	<25	**1**	**1.0**
	26-34	**0**	**0**
	35-49	**9**	**9.1**
	50-64	**37**	**37.4**
	65-74	**36**	**36.4**
	>75	**16**	**16.2**
Género (masculino/feminino)		**66 / 33**	**66.7 / 33.3**
Lado da face (direito/esquerdo)		**56 / 43**	**56.6 / 43.4**
Tipo de dor (choque eléctrico)		**99**	**99**
Duração da dor	*<2 years*	**21**	**21.2**
	3-5 years	**25**	**25.3**
	6-11 years	**40**	**40.4**
	> = 12 years	**13**	**13.1**
Crises (número)	*5 a 10*	**41**	**41.4**
	11 a 20	**58**	**58.6**
Intensidade (escala EVA)	*<3*	**0**	**0**
	4 a 6	**5**	**5.1**
	> 7	**94**	**94.9**

Ao longo dos vários estudos que constituem esta tese verificamos que, de um modo geral, todos os tratamentos não invasivos e invasivos permitem em maior ou menor grau, a estabilização clínica dos utentes com NT. No entanto, há diferenças fundamentais entre protocolos não invasivos e invasivos quanto: (1) aos resultados clínicos [redução da dor medida pela Escala Visual Analógica (EVA) e do número de crises]; (2) às sequelas iatrogénicas observadas (anestesia e hipostesia na face; tonturas); (3) aos custos económicos (comparação dos gastos/tratamento em igual período de tempo); (4) à reabilitação funcional, avaliada pelo questionário SIP (*Sickness Impact Profile*); (5) ao estado de ansiedade e depressão, avaliado pelo questionário HADS (Hospital Anxiety and Depression (HADS); (6) ao grau de satisfação com a Equipa e com o Protocolo efectuado, avaliado através de um inquérito especifico especialmente desenvolvido para os trabalhos incluídos na presente tese (Lemos e McIntryre, resultados não publicados).

Para se optar por um protocolo terapêutico é importante ponderar: (a) a segurança e eficácia clínicas; (b) a facilidade de execução e a necessidade de recurso a técnicas anestésicas (sedação ou analgesia) para a sua realização; (c) a recuperação e reabilitação rápida da funcionalidade e reintegração familiar e profissional; (d) os custos económicos, dada a política economicista dos Gestores das Unidades de Saúde Hospitalares; (e) o benefício clínico do protocolo, sendo este o ponto mais importante para a opção por determinado tratamento. A NT é uma dor facial em que se planeia numa fase inicial um tratamento farmacológico em monoterapia, geralmente com um anticonvulsivante; não havendo efeitos clínicos satisfatórios poderá ser planeado um protocolo em politerapia, no qual que associam vários anticonvulsivantes. Se continua a não haver resultados satisfatórios, terá de ser aplicado um tratamento invasivo como a cirurgia (*Steege, 2007*). Vários estudos clínicos apontam para a melhoria franca da intensidade de dor após tratamento com anticonvulsivante em monoterapia, em associação com outros fármacos, ou após a realização de uma intervenção cirúrgica, nomeadamente a descompressão microvascular do nervo Trigémio (*Zakrzewska e Lopez, 2006; Cheshire, 2007; Cruccu et al, 2008*).

3.1. Benefícios clínicos da associação anticonvulsivante e bloqueio analgésico

Na análise dos nossos estudos verificamos que nos protocolos em que se associou um anticonvulsivante [gabapentina (GBP) ou carbamazepina (CBZ)] com o bloqueio analgésico dos

pontos indutores de dor na face com Ropivacaina (ROP), se observou um controlo significativo da dor em associação com uma maior estabilização clínica (EVA < 3 e Nº Crises < 2), em comparação com os protocolos de GBP ou CBZ em regime de monoterapia. Verificamos ainda que a redução da intensidade de dor e do número de crises/dia dos utentes se traduziu numa maior funcionalidade e bem-estar do utente. Além disso, com a redução das doses eficazes de anticonvulsivantes, foi conseguida uma redução ou mesmo a abolição dos efeitos adversos típicos destes fármacos.

A análise específica do protocolo que combina gabapentina e o Bloqueio analgésico com Anestésico Local (*Protocolo GBP+ROP*) permitiu demonstrar a maior eficácia clínica da terapêutica GBP+ROP nos utentes com NT, em comparação com a administração de GBP em monoterapia (*Protocolo GBP*), devido: (i) à necessidade de doses menores, mas terapêuticamente eficazes de GBP; (ii) à ausência completa de efeitos adversos; (iii) à redução significativa da intensidade da dor e do número de crises dolorosas paroxísticas; (iv) ao baixo custo económico relativo; (v) à melhoria significativa na funcionalidade do utente; (vi) à completa satisfação com a equipa clínica e com o protocolo. Assim, este protocolo analgésico apresenta uma perspectiva futura de utilização importante, porque demonstrou ser clinicamente eficaz, seguro, de fácil execução técnica e com fácil adaptação terapêutica aos utentes com idade superior a 65 anos. A associação da acção analgésica da GBP com o bloqueio analgésico com ROP dos pontos gatilho na NT deverá estar na base desta redução significativa da intensidade de dor, quando comparada com a administração de GBP em regime de monoterapia. A GBP deverá ter o seu mecanismo de acção analgésica baseado na ligação à subunidade a2δ1 dos canais de sódio dependentes da voltagem (*Baillie e Power, 2006; Yaksh, 2006*). A ROP tem uma acção analgésica similar à CBZ, pois os dois fármacos actuam a nível dos canais de sódio dependentes da voltagem, bloqueando a entrada de sódio e impedindo a propagação de potenciais de acção (*Worley e Baraban, 1987; Zimányi et al, 1989; Liu et al, 2000; Oda et al, 2000*). No caso da NT, a activação espontânea das fibras nervosas é provavelmente devida a um excesso de acumulação de canais de sódio e cálcio dependentes da voltagem nos terminais nervosos, nas áreas de nervos lesados ou em placas desmielinizadas onde as fibras perdem o isolante eléctrico efectuado pela bainha de mielina (*Devor, 2006; Yaksh, 2006*). O bloqueio analgésico dos pontos-gatilho com ROP na NT constitui assim uma alternativa à administração de lidocaina endovenosa (*Edwards et al, 1985; Rowbothan and Petersen, 2001*), da qual resulta um efeito terapêutico satisfatório.

O protocolo que combina o anticonvulsivante (CBZ) e o Bloqueio analgésico com Anestésico Local (ROP) demonstrou uma eficácia clínica significativa, ao permitir o uso de menores doses terapêuticas eficazes de CBZ, reduzir a incidência dos efeitos adversos e resultar num custo económico intermédio e satisfação significativa do utente com a equipa e com o protocolo terapêutico. Ao analisarmos os múltiplos estudos clínicos realizados sobre a NT verificamos que esta é refractária aos fármacos tradicionalmente usados no controlo da dor, como os anti-inflamatórios não esteróides e os opióides (*Cheshire, 2007*), mas responde ao tratamento com anticonvulsivantes. Entre estes, a CBZ é considerada a terapia de 1ª linha, apresentando um NNT (*number needed to treat*) de 1.7. O seu efeito analgésico está associado a uma diminuição da condução nos canais de sódio e à inibição das descargas ectópicas (*Tremont-Lukats et al, 2000*). De um modo simples, o resultado deste protocolo reforça a liderança deste anticonvulsivante clássico no tratamento efectivo da NT, ao confirmar a eficácia clínica referida na literatura e, adicionalmente, permitir o uso de menores doses terapêuticas eficazes, conseguindo desse modo uma reduzida (ou mesmo ausência) incidência dos conhecidos efeitos adversos da CBZ.

Verificamos que a maioria dos utentes com Nevralgia do Trigémio são idosos, com patologia associada significativa, sendo importante a elaboração de protocolos com baixa incidência de efeitos secundários, com baixo impacto na sensibilidade da face e de fácil realização, mantendo o utente colaborante e sem recorrer a sedação anestésica. O bloqueio analgésico periférico é uma técnica não invasiva útil que se adapta a este grupo de utentes e ao seu risco clínico, com reduzida interferência com a utilização de outros fármacos. Para obter um bom prognóstico, a abordagem terapêutica deverá ser planeada não só a nível da intervenção farmacológica específica da dor, mas deverá considerar também a intervenção psicológica e sócio–familiar (terapia muktidisciplinar).

3.2. Benefícios clínicos de protocolos farmacológicos versus cirurgia

A escolha do tratamento da NT deve centrar-se não só na sua eficácia relativa, mas também na comparação da eficácia / tolerância / efeitos secundários. Na NT, tal como em qualquer dor neuropática, são considerados fármacos de primeira linha os anticonvulsivantes e os antidepressivos, não só em monoterapia como em associação com outros anticonvulsivantes (*Solaro et al, 2000*), antidepressivos ou outros fármacos (*Gilron et al, 2005*). Não havendo

melhoria clínica terapêutica, deve ser ponderada a opção por técnicas mais invasivas, incluíndo a cirurgia. A técnica cirúrgica mais utilizada e com melhores resultados é a Descompressão microvascular do nervo Trigémio; no entanto, embora os resultados sejam bons, esta abordagem não é isenta de riscos (*Lonser e Apfelbaum, 2005*). O benefício clínico e o custo efectivo de cada protocolo terapêutico devem ter em conta: (i) as variáveis que informam a evolução da melhoria clínica, funcional e psíco–afectiva do utente; (ii) os vários tratamentos que cada utente com NT pode realizar; (iii) o custo económico efectivo, o benefício clínico e o grau de satisfação do utente com a equipa clínica e com o tipo de protocolo realizado.

A cirurgia de descompressão microvascular (DMV) foi o protocolo invasivo da NT analisado e demonstrou uma eficácia clínica significativa, com alguns utentes a registar o alívio completo da dor, algo nunca conseguido por qualquer dos protocolos farmacológicos. Os utentes referem ainda uma satisfação significativa com a equipa e com o resultado do protocolo realizado, comparável àquela referida pelas duas terapias farmacológicas. No entanto, os efeitos adversos registados não são de minimizar, dado que se observaram sequelas neurológicas centrais "minor" (tonturas, vertigens, náuseas), alterações sensoriais da face (hipostesia, anestesia, alodínia e hiperalgesia) e, pontualmente, sequelas cerebrais "major" (lesão isquémica cerebral e mesmo a morte de um utente); adicionalmente, a cirurgia apresenta um custo económico significativamente mais elevado que os outros protocolos estudados. Por fim, é de salientar que perante uma dor incontrolável, no utente jovem ou na ausência de resposta a tratamentos farmacológicos prévios, a opção por este protocolo invasivo pode ser essencial para controlo da dor na NT.

A análise de três protocolos, gabapentina associada com o bloqueio analgésico com ropivacaina (GBP+ROP), carbamazepina em monoterapia (CBZ) e a cirurgia (DMV), demonstrou diferenças importantes entre os tratamentos. O *protocolo GBP+ROP* apresenta um benefício clínico significativo, ausência de efeitos adversos, o menor custo em Euros/dia e todos utentes referem grande satisfação com a Equipa (100%) e com o protocolo realizado (100%). A *CBZ em monoterapia* resultou numa melhoria clínica significativa, o custo económico foi intermédio (entre os 3 protocolos) e a satisfação com a Equipa (100%) e com o protocolo realizado de (100%) foi também total. A DMV apresentou também um benefício clínico marcado, mas também um custo económico claramente mais elevado (apesar de claramente competitiva entre os modelos cirurgicos; *Pollock e Ecker, 2005*) e com incidência de efeitos adversos "major" e outros; a satisfação com a Equipa (100%).e com o protocolo realizado foi também muito significativa

(95.5%); estes resultados sugerem que a opção por técnicas mais ou menos invasivas deverá ser feita sempre após se ter ponderado o risco / benefício, caso a caso e sempre após o consenso de Equipas Multidisciplinares especializadas em Dor Neuropática. Após a conclusão dos estudos deste trabalho, consideramos importante a opção por técnicas não invasivas, com tratamento planeado ao longo do tempo e com a sua manutenção a ocorrer em regime de ambulatório. A elaboração de um plano terapêutico analgésico combinado é a opção lógica, já que a associação de fármacos de diferentes grupos terapêuticos com pontos de acção diversos permite uma acção analgésica sinérgica mais eficaz do que o regime de monoterapia, além de resultar na utilização de menores doses de cada um dos fármacos, com a consequente redução ou eliminação de efeitos adversos inerentes ao seu uso. Quando a dor se torna intolerável ou intratável, quer pelo agravamento clínico, quer pela insuficiente resposta ao protocolo terapêutico instituído, há uma série de propostas terapêuticas progressivamente invasivas que poderão ser planeadas. Na abordagem terapêutica de jovens utentes a proposta invasiva poderá ser planeada mais precocemente, pois os factores médicos a ponderar, como a patologia associada e o risco anestésico - cirúrgico apresentam menores contra-indicações. Nos utentes que recusam a opção cirúrgica, ou que apresentam um risco anestésico – cirúrgico não aceitável, poderemos optar por técnicas menos invasivas, dado que os resultados clínicos actuais têm demonstrado um valor clínico significativo. É de notar no entanto que, em várias situações ou por opção do utente, a cirurgia é aconselhada e é mesmo a opção, nomeadamente quando (i) os outros protocolos não permitiram respostas terapêuticas satisfatórias e a dor se mantém intolerável e (ii) quando existe um diagnóstico de conflito vascular-nervoso confirmado em neuro-imagiologia.

3.3. Importância de uma equipa multidisciplinar na avaliação e tratamento da NT

Na abordagem dos utentes com NT é necessário reforçar a importância da complementaridade da Psicologia com a equipa clínica. A intervenção da Psicologia complementa e contribui para o aumento da efectividade dos protocolos terapêuticos instituídos. A intervenção multidisciplinar da equipa da Unidade de Dor Crónica de Fafe demonstrou a utilidade da participação da Psicologia na estabilização do humor dos utentes, na verifição da evolução dos níveis de ansiedade e depressão e na avaliação do impacto negativo significativo da dor na NT, na qualidade de vida do utente e no seu comportamento emocional.

A avaliação da funcionalidade ao longo do tratamento foi efectuado com um instrumento psicométrico específico (Sickness Impact Profile – SIP), que demonstrou de modo objectivo e significativo a recuperação da autonomia e da funcionalidade dos utentes correlacionada com a redução da intensidade de dor e do número de crises depois do tratamento farmacológico. Enfatizamos que o objectivo prioritário na abordagem farmacológica na NT é conseguir que o utente esteja clinicamente controlado, sem necessitar de doses de fármacos elevadas e regulares, referindo um sono descansado e sem manifestar sinais ou sintomas de ansiedade e/ou depressão.

Na Dor Crónica Neuropática e de modo especifico na NT, onde está presente uma dor imprevisível associada a altos níveis de ansiedade, constatamos um ciclo vicioso entre a Dor - Ansiedade e Ansiedade - Dor. A depressão é muito prevalente em doentes com dor crónica (*Remick et al, 1983*), incluíndo nos utentes com dor crónica facial e cefaleias (*Remick et al, 1983; Dworkin e Gitlin, 1991*). A avaliação dos níveis de ansiedade e depressão ao longo do tratamento farmacológico foi realizado aplicando um outro inquérito psicométrico (Hospital Anxiety and Depression Scale – HADS), que demonstrou nos três protocolo avaliados, CBZ+ROP, CBZ e DMV (i) uma correlação positiva entre a ansiedade e a depressão, (ii) uma redução dos níveis de ansiedade nos protocolos farmacológicos e (iii) uma redução significativa no nível de depressão no protocolo cirúrgico.

Capítulo 4

CONCLUSÕES E PERSPECTIVAS FUTURAS

O conjunto dos estudos incluídos nesta tese, teve como finalidade: (i) avaliar a eficácia clínica de novos protocolos analgésicos, combinando fármacos de vários grupos terapêuticos e optando por técnicas não invasivas em utentes com Nevralgia do Trigémio (NT) não estabilizada; (ii) avaliar, comparativamente, o impacto clínico e económico de diferentes protocolos farmacológicos e de um protocolo cirúrgico.

1. Nos estudos descritos verificou-se que, de um modo geral, todos os tratamentos não invasivos e invasivos contribuem para a estabilização clínica dos utentes com NT. No entanto, há diferenças fundamentais entre protocolos não invasivos e invasivos quanto: (1) aos resultados clínicos (redução da dor e do número de crises); (2) às sequelas iatrogénicas observadas (anestesia e hipostesia na face, tonturas e até morte); (3) aos custos económicos (comparação dos gastos/tratamento em igual período de tempo); (4) à reabilitação funcional conseguida; (5) ao estado de humor e níveis de ansiedade e depressão; (6) ao grau de satisfação com a equipa clínica e com o protocolo efectuado.

2. A associação de um anticonvulsivante oral [(gabapentina (GBP) ou carbamazepina (CBZ)] com o bloqueio analgésico dos pontos-gatilho indutores de dor na face após injecção do anestésico local Ropivacaina (ROP), resultou no controlo significativo da dor (intensidade de dor e número de crises) associado com uma maior estabilização clínica e uma maior funcionalidade do que no protocolo de GBP ou CBZ em monoterapia. Além disso, foi obtida a redução da dose diária eficaz de anticonvulsivante, que resultou na redução drástica, ou mesmo ausência, de efeitos secundários adversos.

3. A análise do protocolo que combina o anticonvulsivante GBP e o Bloqueio analgésico com ROP (protocolo GBP+ROP) permite ter uma perspectiva de utilização futura importante, dado ser clinicamente eficaz, seguro, de fácil execução técnica, adaptando-se aos utentes com idade superior a 65 anos e com patologia associada significativa. Permitiu demonstrar a associação da eficácia clínica a um baixo custo económico e os utentes referiram um grau de satisfação completo com a equipa e com o protocolo utilizado. Os utentes adaptaram-se a doses de GBP claramente inferiores e mostraram uma melhoria significativa da

funcionalidade e da qualidade de vida em comparação com os utentes submetidos a GBP em monoterapia (protocolo GBP). Muito importante foi o facto de os utentes do protocolo GBP+ROP não apresentarem efeitos secundários adversos, ao contrário dos outros pacientes.

4. O protocolo que combina o anticonvulsivante CBZ e o Bloqueio analgésico com ROP (protocolo CBZ+ROP) permitiu reforçar a liderança clínica da CBZ no tratamento da NT, ao reduzir as doses terapêuticas eficazes de CBZ e reduzir a incidência dos efeitos adversos característicos da CBZ em monoterapia (protocolo CBZ). Além disso, o protocolo CBZ+ROP reduziu significativamente a intensidade de dor e o número de crises paroxísticas.

5. A Cirurgia da Descompressão Microvascular (DMV) para controlo da dor na NT foi o protocolo invasivo analisado nesta tese. Este protocolo confirmou a eficácia clínica descrita em vários estudos, mas os efeitos adversos registados são importantes, tendo-se verificado em diversos utentes sequelas neurológicas centrais "minor" (tonturas, vertigens, náuseas), alterações sensoriais da face (hipostesia, anestesia, alodínia e hiperalgesia) e, ocasionalmente, sequelas cerebrais "major". Apresenta custos económicos significativos, implicando a necessidade de intervenção cirúrgica e internamento. Os utentes referem uma satisfação com a equipa e com o resultado do protocolo realizado significativa. No entanto, perante uma dor incontrolável no utente jovem ou na ausência de resposta aos tratamentos aplicados, a opção por este protocolo invasivo torna-se relevante no controlo da NT.

6. A análise conjunta de três protocolos avaliados, GBP+ROP, CBZ e DMV demonstrou que o protocolo GBP+ROP apresenta um benefício clínico significativo, ausência de efeitos adversos, o menor custo em Euros/dia de entre os 3 protocolos e os utentes referiram satisfação completa com a equipa e o protocolo realizado. O protocolo CBZ confirmou o seu efeito benéfico na NT, mas os efeitos adversos observados não são de minorar (tonturas e cefaleias); o seu custo económico foi intermédio e a satisfação com a equipa e com o protocolo realizado foi completa. A cirurgia DMV apresentou um alto benefício clínico, mas também um alto custo económico e incidência de efeitos adversos valorizáveis, incluindo alguns casos graves; a satisfação com a equipa e com o protocolo realizado foi muito significativa.

Ao longo da realização destes estudos, concluímos que: (i) o ponto fundamental na abordagem do utente com NT é a realização de uma avaliação clínica e analítica especifica paa cada paciente, de modo a obter-se um diagnóstico correcto e planear um protocolo individualizado, com fármacos sinérgicos e de baixa invasibilidade; (ii) a avaliação regular do utente pela equipa multidisciplinar é essencial para verificar a evolução da NT, titular a dose efectiva dos fármacos a administrar, registar a resposta clínica efectiva, efectuar o despiste precoce e controlar os efeitos adversos iatrogénicos; (iii) é imperativo que a equipa multidisciplinar que acompanha o utente planeie e prepare o utente para situações de novas crises álgicas de modo a efectuar o controlo global do seu quadro nociceptivo e não nociceptivo (emocional, afectivo e cognitivo).

Em termos de investigação futura, será planeada a aplicação de novos protocolos analgésicos para controlo da NT: (a) um anticonvulsivante oral associado a um anestésico local aplicado por via transdêrmica (ex: *selo dérmico* de lidocaína) (*Dobecki et al, 2006*); (b) um anticonvulsivante oral associado ao bloqueio com toxina botulínica dos pontos indutores de dor (*Borodic e Acquadro, 2002*); (c) um anticonvulsivante oral associado a radiofrequência pulsada dos pontos-gatilho (*Letcher e Goldring, 1968*).

Numa perspectiva mais alargada, a nível mundial, a investigação clínica e animal sobre NT deverá incidir sobre:

a) Fármacos que apresentem alta selectividade sobre os canais de sódio dependentes de voltagem activados na patologia neuropática periférica, mas que não ultrapassem a barreira hemato-encefálica, evitando os efeitos adversos centrais (*Bennett, 2004*);

b) Estudos em larga escala com oxicarbamazepina (e outros fármacos que representem potenciais melhorias da CBZ), dada a sua menor incidência de efeitos adversos em comparação com a CBZ e a presença de um efeito analgésico clínico provável, com potencialidades de utilização em utentes com NT (*Gomez-Arguelles et al, 2008*);

c) Anestésicos locais com semi-vida mais longa e ausência de cardiotoxicidade ou neurotoxicidade, que permitam um efeito analgésico mais duradouro após a realização de bloqueio dos pontos indutores de dor na NT (*Arner et al, 1990*);

d) A patofisiologia da NT, utilizando modelos animais de neuropatia do trigémio, aproveitando o desenvolvimento de modelos que mimetizam alguns aspectos que se pensam estar na génese da NT (ex: compressão do nervo) (*Xu et al, 2008*).

Bibliografia dos Capítulos 3 e 4

1. Arner S,Lindblom U, Meyerson BA ,Molander C. Prolonged relief of neuralgia after regional anessthetic blocks. A call for further experimental and sistematic clinical studies. *Pain*, 43:287-97 (1990).
2. Baillie JK, Power I. The mechanism of action of gabapentin in neuropathic pain. *Curr Opin Investig Drugs*, 7:33-39 (2006).
3. Bennett GJ. Neuropathic pain in the orofacial region: clinical and research challenges. *J Orofac Pain*, 18:281-286 (2004).
4. Cheshire WP. Trigeminal neuralgia: for one nerve a multitude of treatments. *Expert Rev Neurother*, 7:1565-1579 (2007).
5. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol*, 15:1013-1028 (2008).
6. Dobecki DA, Schocket SM, Wallace MS. ate on pharmacotherapy guidelines for the treatment of neuropathic pain. *Curr Pain Headache Rep*, 10:185-190 (2006).
7. Dworkin RH, Gitlin MJ. Clinical aspects of depression in chronic pain patients. *Clin J Pain*, 7:79-94 (1991).
8. Edwards WT, Habib F, Burney RG, et al. Intravenous lidocaine in the management of various chronic pain states – a review of 211 cases. *Reg Anesth*, 10:1-6 (1985).
9. Gilron I, Bailey JM, Dongsheng T, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Eng J Med*, 352:1324-1334 (2005).
10. Gomez-Arguelles JM, Dorado R, Sepulveda JM, Herrera A, Arrojo FG, Aragón E, Huete CR, Terrón C, Anciones B. Oxcarbazepine monotherapy in carbamazepine-unresponsive trigeminal neuralgia. *J Clin Neurosci*, 15:516-519 (2008).
11. Letcher S, Goldring S. The effect of radiofrequency current and heat on peripheral nerve action potential in the cat. *J Neurosurg*, 29:42-47 (1968).
12. Lonser RR, Apfelbaum. Neurovascular decompression in surgical disorders of cranial nerves V, VII, IX, and X. In "*Schmidek and Sweet's Operative Neurosurgical Techniques: Indications, Methods, and Results*", 5th Edition, Vol 2, Schmidek HH, Roberts DW (Eds), pp 1531-1543 (2005).
13. Liu BG, Zhuang XL, Li ST, Xu GH. The effects of ropivacaine on sodium currents in dorsal

horn neurons of neonatal rats. *Anesth Analg*, 90:1034-1038 (2000).

14. Oda A, Ohashi H, Komori S, Iida H, Dohi S. Characteristics of ropivacaine block of Na+ channels in rat dorsal root ganglion neurons. *Anesth Analg*, 91:1213-1220 (2000).
15. Pollock BE, Ecker RD. A prospective cost-effectiveness study of trigeminal neuralgia surgery. Clin J Pain, 21:317-322 (2005).
16. Remick RA, Blasberg B, Campos PE, Miles JE. Psychiatric disorders associated with atypical facial pain. *Can J Psychiatry*, 28:178-181 (1983).
17. Rowbotham MC, Petersen KL. Anticonvulsivants and local anesthetic drugs. In: "*Bonica´s Management of Pain*", 3rd Edition, Loeser JD, Butler SH, Chapman CR, Turk DC (Eds). Lippincott Williams & Williams, Philadelphia, pp 1727-1735 (2001).
18. Solaro C, Messmer Uccelli M, Uccelli A, Leandri M, Mancardi GL. Low-dose gabapentin combined with either lamotrigine or carbamazepine can be useful therapies for trigeminal neuralgia in multiple sclerosis. *Eur Neurol*, 44:45-48 (2000).
19. Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. *Drugs*, 60:1029-1052 (2000).
20. Worley PF, Baraban JM. Site of anticonvulsant action on sodium channels: autoradiographic and electrophysiological studies in rat brain. *Proc Natl Acad Sci USA*, 84:3051-3055 (1987).
21. Yaksh TL. Calcium channels as therapeutic targets in neuropathic pain. *J Pain*, 7 (Suppl 1):S13-S30.
22. Xu M, Aita M, Chavkin C. Partial infraorbital nerve ligation as a model of trigeminal nerve injury in the mouse: behavioral, neural, and glial reactions. *J Pain*, 9:1036-1048 (2008).
23. Zakrzewska JM, Lopez BC. Trigeminal and glossopharyngeal neuralgia. In: "*Melzack´s Textbook of Pain*", 5th edition ,McMahon SB, Koltzenburg M (Eds). Elsevier-Churchill Livingstone, London, pp 1001-1010 (2006).
24. Zimányi I, Weiss SR, Lajtha A, Post RM, Reith ME. Evidence for a common site of action of lidocaine and carbamazepine in voltage-dependent sodium channels. *Eur J Pharmacol*, 167:419-422 (1989).