I SIMPÓSIO INTERNACIONAL EM PLACEBO

12-14 FEVEREIRO / 2009

INSTITUTO SCALA
UNIVERSIDADE PRESBITERIANA MACKENZIE

RESUMOS DOS TRABALHOS APRESENTADOS

SHAM X REAL SHOCKWAVE THERAPY

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Introduction: Many studies have been made involving extracorporeal shock wave therapy (ESWT), but lack of an efficient placebo has been a limiting factor. **Purpose:** To compare the ability of subjects to perceive treatment differences between a placebo shockwave applicator and a real one. **Material and Methods:** Thirty (19 female) healthy adult volunteers (mean age 34.1±11.3 years) received 200 impulses of sham radial ESWT (Electro Medical Systems, Swiss), at a frequency of 15 Hz and 2.0 MPa of pressure over the origin of the plantar fascia at the medial tubercle of the calcaneus of one foot. The same 30 subjects received 200 impulses of real ESWT on the other foot. After each procedure, volunteers were asked to identify whether the device was an active and efficacious or an inactive and inefficacious intervention to treat pain. The McNemar test was used to verify the percentage of agreement between both interventions. **Results:** Of all 30 subjects, only 8 subjects provided the correct answer for the placebo intervention. The agreement rate for the placebo device was 53.33% and 51.11% (n=23 correct answers) for the real device. Total percentage of correct answers was 51.67%. There was no agreement between the placebo and the real devices (p=0.008). **Conclusion:** The placebo shockwave applicator seems to be an efficient placebo method in single blind or double blind trials, although further studies should be performed to test the effectiveness of this method.

A NOVEL *SHAM* LASER DEVICE: IS IT EFFECTIVE AS A *SHAM* INTERVENTION?

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Introduction: A major challenge in Physical and Rehabilitation Medicine research is lack of proper placebo controlled clinical trials. Most commonly used control interventions include waiting lists, other sham interventions obviously different from the intervention itself or non active treatments, which may carry non specific physiological effects. **Objectives:** To evaluate the efficacy of a *sham* laser device that could be used as a placebo intervention, we tested the agreement rate of the response of healthy volunteers receiving both placebo and real laser interventions. **Materials and methods:** Sixty-four (37 women) healthy laser naïve adult volunteers (age=38.8±11.6years) received both a placebo: 650nm wavelength 200mW laser without power source and an active intervention: 632nm wavelength Helium Neon 100mW (2 J/cm²), on the same day, in a randomly allocated order. In both real and *sham* laser applications, the upper trapezius muscles were stimulated. Each subject randomly received a stimulus for 10 seconds over the upper trapezius. After each procedure, volunteers were asked to identify whether the device was an active and efficacious or inactive and inefficacious to treat pain. McNemar test was used to verify the percentage of agreement between both interventions. **Results:** Of all 64 subjects, 24 subjects provided the correct answer for the placebo intervention. The agreement rate for the placebo device was 52.17% and 51.22% (n=42 correct answers) for the real device. Total percentage of correct answers was 51.56%. There was no agreement between the placebo and the real devices (p=0.03). **Conclusion:** The modified *sham* laser stimulator may be an effective placebo tool to be used in the control arm of PRM clinical trials.

A NOVEL TECHNOLOGY FOR ACUPUNCTURE PLACEBO NEEDLING

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Objectives: To present a new technology and design for the production of placebo acupuncture needles used in clinical research. **Introduction:** Many placebo needles have been described, but all present some level of limitation. The only double blind placebo needle described until now requires several modifications in the morphology of the real needle which limit its use in clinical trials. We have devised a placebo needle to address previous limiting factors and provide a true double blind capability for clinical research. **Materials and Methods:** Our device for placebo acupuncture needling consists of a silicon device, telescopic needle, acupuncture chuck and an adhesive disc. The silicon device was made with elastomer medical-grade silicone and adhesive silicone medical-grade silastic ®. Both the placebo and real acupuncture needles are similar to each other, but with small changes that prevent the acupuncturist from knowing the difference between real and placebo. The real acupuncture needle passes freely through the silicon disc, while the "placebo" needle is blocked. Telescopic movement, though, is still perceived by the acupuncturist when using the “placebo” needle. Both devices are stuck in the skin of the patient through a hypoallergenic polyester adhesive product. **Conclusions:** This novel design requires clinical trials to prove its effectiveness as a placebo device, with measures of specificity and sensitivity compared to conventional acupuncture needles for both the applicator and for the patients as well.

A PLACEBO DEVICE TO MIMIC RADIAL EXTRACORPOREAL SHOCKWAVE THERAPY: A NOVEL SOLUTION FOR DOUBLE BLIND TRIALS IN PHYSICAL AND REHABILITATION MEDICINE

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Introduction: One major challenge concerning the development and conduction of double blind clinical research involving radial extracorporeal shockwave therapy (RESWT) is the use of an effective placebo method. **Purpose:** The aim of this poster is to evaluate the ability of a newly designed placebo radial shockwave applicator device to effectively mask patients to the intervention using RESWT. **Material and Methods:** Fifty-eight healthy (33 women, mean age 38.7±11.6) adult volunteers received 200 impulses of a *sham* application of RESWT (Electro Medical Systems, Swiss), at a frequency of 15 and pressure of 2.0 MPa over the origin of the plantar fascia at the medial tubercle of the calcaneus. Patients were lying prone and the gel was applied to the skin where the application took place; following the same methodology to mimic the real intervention. **Results:** Of the total of 58 subjects, only 13.80% of the volunteers (n=8) considered the device as a *sham* device. **Conclusion:** Subjects were masked to the placebo radial ESWT device and provided a low percentage of agreement. This might be a useful tool to be employed in the control arm of randomized clinical trials of radial ESWT.

A PLACEBO DEVICE FOR RADIAL SHOCKWAVE THERAPY DOUBLE BLIND STUDIES: A NOVEL SOLUTION FOR DOUBLE BLIND TRIALS IN PHYSICAL AND REHABILITATION MEDICINE

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Introduction: Extracorporeal shock wave therapy (ESWT) is currently being studied as a treatment for several disease conditions including plantar fasciitis, tennis elbow, pseudoarthrosis, bursitis and tendonitis. The therapy consists of applying shockwaves (high intensity sound waves) through the device applicator point of contact at the skin surface to the area being treated. The device works by converting pneumatic energy into shockwave energy via a handpiece where the compressed air accelerates a projectile into an applicator tip, producing the shockwave. A major challenge concerning the development and conduction of double blind clinical research involving radial ESWT is the use of an effective placebo method. **Purpose:** The aim of this poster is to present a new technology device: a placebo shockwave applicator specifically designed for double blind placebo controlled trials. **Material and Methods:** Developed by EMS (Electro Medical Systems, Swiss), the placebo applicator of radial ESWT uses a shortening of the mechanical system inside the applicator, producing a free space between the applicator and the mechanical system that generates the shock waves. Therefore, the shockwaves can be normally heard, but they are not transmitted to the tip of the applicator in contact with the patient. A gel is applied to the skin where the application will take place; following the same methodology to mimic the real intervention. **Conclusions:** This novel radial ESWT placebo device may be useful in future double-blind clinical trials and its validity should be tested in future trials.

LACK OF PLACEBO EFFICACY OF SHAM EXTRACORPOREAL SHOCKWAVE THERAPY FOR REFRACTORY KNEE OSTEOARTHIRTIS PAIN

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Aim: To determine the efficacy of radial extracorporeal shockwave therapy (RESWT) for refractory knee osteoarthritis pain which failed to respond to other treatment modalities. **Material and Methods:** Nineteen women, with mean age of 72.7±7.2, range 61 to 84 years, scheduled for a total knee replacement due to refractory pain were randomly assigned to receive either *verum* or *sham* RESWT (*Swiss DolorClast* RESWT, Swiss). Weekly applications of 2000 shocks, at a frequency of 8 Hz, 2.5 to 3.5 MPa over the medial aspect of the knee joint were performed for three consecutive weeks. Pain intensity was assessed using a visual analogue scale before and after the end of the last treatment. *Sham* interventions were performed to mimic the *verum* application in all matters. **Results:** Patients were similar at baseline demographics and mean VAS scores. After the end of the treatment, statistically significant differences were observed between the two groups (2.94±1.7, 95%CI 1.37-4.52; 7.10±1.72, 95%CI 6.01-8.19; $p<0.0001$). Significant reduction on pain intensity occurred after treatment ($p<0.002$) in the *verum* RESWT group, but not in the *sham* group ($p=0.7$). Hematoma at the application site was observed in both groups and resolved spontaneously. There was no anesthetic requirement during the procedure. **Conclusion:** RESWT is an effective method for treating refractory knee osteoarthritis pain in patients scheduled for a total knee replacement. The *sham* device employed in the study did not provide pain relief in this population and one of the reasons might be due to refractoriness of pain in this population of patients.

RELIABILITY OF A SHAM DEVICE (RYODORAKU DEVICE) IN PHYSICAL MEDICINE AND REHABILITATION: RESULTS FROM A CROSS SECTIONAL CONTROLLED TRIAL

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Objectives: To evaluate a modified electro stimulator device used as a *sham* device compared to a real and effective electro stimulator. **Materials and methods:** We used a modified Ryodoraku device, a real HANS® device and 67 healthy volunteers as the objects of our investigation. In the Ryodoraku group, we did a circuit shortcut before the electrode tip isolating and deviating the electric current. When the shortcut was closed by a hidden button triggered by the doctor or therapist in point LI 4, the short circuit triggered the galvanometer display giving the false impression of a real stimulus. Real HANS® was also applied with a 15Hz frequency and 2-3mA perceivable intensity. In order to evaluate its efficacy as a placebo we collected the impression of 67 healthy adult volunteers with respect to the apparatus. Each subject randomly received each stimulus for 10 seconds in the acupoint Large Intestine number 4 (LI 4). After each procedure the volunteers were asked to identify whether the device was an active and efficacious or inactive and inefficacious to treat pain. McNemar test was used to verify the percentage of agreement between both interventions. **Results:** Of all 67 subjects, 28 subjects provided the correct answer for the placebo intervention. The agreement rate for the placebo device was 47.46% and 40.57% (n=43 correct answers) for the real device. Total percentage of correct answers was 43.03%. There was no agreement between the placebo and the real devices (p=0.001).**Conclusion:** The modified Ryodoraku stimulator may be an effective *sham* tool to be used in Physical and Rehabilitation Medicine clinical trials.

TESTING THE EFFICACY OF A MODIFIED ELECTRO STIMULATOR PLACEBO DEVICE FOR PHYSICAL MEDICINE AND REHABILITATION CLINICAL TRIALS: A CROSS SECTIONAL CONTROLLED STUDY

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Introduction: A major challenge in Physical and Rehabilitation Medicine research is lack of proper placebo controlled clinical trials. Most commonly used control interventions include waiting lists, other sham interventions obviously different from the intervention itself or non active treatments, which may carry non specific physiological effects. **Objectives:** To evaluate the efficacy of a modified electro stimulator device as a placebo intervention, we tested the agreement rate between the placebo and real interventions. **Materials and methods:** We used a modified Pointer Excel® stimulator (placebo intervention), a HANS® device (active intervention) and 67 healthy adult volunteers as the objects of our investigation. In the Pointer Excel®, the electrical circuit of the electrode tip was isolated and deviated direct to the horn. When the trigger stimulus button was triggered by the doctor or therapist in point LI 4, the short circuit triggered the buzzer giving the false impression of a real stimulus. Real HANS® was applied for 10 seconds with a 15Hz frequency and 2-3mA perceivable intensity. In order to evaluate the efficacy of the modified Pointer Excel® stimulator as a placebo device, we collected the impression of the 67 volunteers with respect to the apparatus. Each subject randomly received each stimulus for 10 seconds in the acupoint Large Intestine number 4 (LI 4). After each procedure, volunteers were asked to identify whether the device was an active and efficacious or an inactive and inefficacious intervention to treat pain. McNemar test was used to verify the percentage of agreement between both interventions. **Results:** Of all 67 subjects, 32 subjects provided the correct answer for the placebo intervention. The agreement rate for the placebo device was 51.61% and 39.78% (n=37 correct answers) for the real device. Total percentage of correct answers was 44.52%. There was no agreement between the placebo and the real devices (p=0.007). **Conclusion:** The modified Point Excel® stimulator may be an effective placebo tool to be used in the control arm of PRM clinical trials.

THE EFFICACY OF A PORTABLE ELECTRICAL DEVICE AS A *SHAM* INTERVENTION: BLINDING THE CARE PROVIDER

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Introduction: Blindness is an important issue in methodological quality assessment accounting for three out of eleven criteria to define a high quality clinical trial. Patients, care providers, outcome assessors and data analysts can be masked to the intervention. The most commonly used primary outcome in chronic pain studies is the visual analogue scale and the patients self rates their scores and are the outcome assessors. Therefore there is the need for the development of inert *sham* devices which are indistinguishable from the active ones and are capable of masking care providers for double blind controlled clinical trials in Physical and Rehabilitation Medicine. **Objectives:** To test whether care providers can be masked for a *sham* portable electro stimulator device. **Material and Methods:** Sixty-two physicians and therapists were asked to use a *sham* Pointer Excel® stimulator for 10 consecutive seconds over the acupoint Large Intestine number 4 (LI 4) of healthy adult volunteers. The electrical circuit of the electrode tip was isolated and deviated direct to the horn. In order to mimic a real stimulation, when the trigger stimulus button was triggered by the care provider over the acupoint LI 4, the short circuit triggered the buzzer giving the false impression of a real stimulus. Also, the intensity of the electric current appeared on the digital display as the short circuit spared the galvanometer of the device. Immediately after the procedure was performed, care providers were asked to identify whether the device was an active and efficacious or inactive and inefficacious to treat pain. **Results:** Only 27.40% of the care providers (n=17) considered the device as a *sham* device. **Conclusion:** Care providers were masked to the *sham* portable electro stimulator device and provided a low percentage of agreement. Further studies should evaluate the validity of this *sham* device to be used in the control arm of randomized clinical trials.

PLACEBO RESPONSE OF NON-PHARMACOLOGICAL AND PHARMACOLOGICAL TRIALS IN MAJOR DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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Background: Although meta-analyses have shown that placebo responses are large in Major Depressive Disorder (MDD) trials; the placebo response of devices such as repetitive transcranial magnetic stimulation (rTMS) has not been systematically assessed. We proposed to compare the placebo effects in MDD trials using sham rTMS with those of inert pill in pharmacological trials. **Methodology/Principal Findings: We** performed a systematic review and meta-analysis of the literature from April 2002 to April 2008, searching MEDLINE, Cochrane, Scielo and CRISP electronic databases and reference lists from retrieved studies and conference abstracts. We used the keywords placebo and depression and escitalopram for pharmacological studies; and transcranial magnetic stimulation and depression and sham for non-pharmacological studies. All randomized, double-blinded, placebo-controlled, parallel articles on major depressive disorder were included. Forty-one studies met our inclusion criteria – 29 in the rTMS arm and 12 in the escitalopram arm. We extracted the mean and standard values of depression scores in the placebo group of each study. Then, we calculated the pooled effect size for escitalopram and rTMS arm separately, using Cohen's d as the measure of effect size. We found that placebo response are large for both escitalopram (Cohen's d – random-effects model - 1.48; 95%C.I. 1.26 to 1.6) and rTMS studies (0.82; 95%C.I. 0.63 to 1). Exploratory analyses show that sham response is associated with refractoriness and with the use of rTMS as an add-on therapy, but not with age, gender and sham method utilized. **Conclusions/Significance:** We confirmed that placebo response in MDD is large regardless of the intervention and is associated with depression refractoriness and treatment combination (add-on rTMS studies). The magnitude of the placebo response seems to be related with study population and study design rather than the intervention itself.

LACK OF CLINICAL AND SCINTILOGRAPHIC PLACEBO EFFECTS IN CHRONIC ISCHEMIC STROKE PATIENTS TREATED WITH SUBCUTANEOUS ELECTRICAL STIMULATION.

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Objective: To evaluate the efficacy of subcutaneous electrical stimulation of the scalp in functional recovery of chronic ischemic stroke patients, with more than 18 months of evolution, associating clinical, neurological and functional findings to the changes in cold areas measured by cerebral perfusion scintilography. Casuistic and Methods: Sixty two patients with definite diagnosis of ischemic stroke with at least 18 months of history, from 24 to 65 years old were prospectively randomized in a control double blind clinical trial. Thirty four patients received ten sessions of low frequency electrical stimulation (2/100 Hz) applied through subcutaneous needles at the projection of the motor, sensory, frontal and temporal associative areas of Penfield homunculus in the scalp, for 30 minutes, twice a week. Twenty eight patients received ten sessions of placebo electrical stimulation, through disconnected electrical cables applied to the scalp, during seven seconds for each representative functional brain involved areas at the scalp, namely: sensitive and motor areas of the face, lower and upper limbs, as well as the supplementary motor area, twice a week for ten sessions. Patients were evaluated previously and immediately after ten treatment sessions by blind examiners. Barthel and Rankin scales were used for functional evaluation and the National Institutes of Health Stroke Scale for neurological rating. Results/Conclusions: Placebo subcutaneous scalp electrical stimulation showed no significant functional and scintilographic quantitative changes in chronic ischemic stroke patients.

ACUPUNTURA NA LITERATURA CIENTÍFICA - DE PLACEBO E RELATOS ANEDÓTICOS A ALTERAÇÕES NO SNC

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Introducao: Acupuntura é uma técnica milenar chinesa de estimulação periférica com objetivos terapêuticos como por exemplo analgesia. As primeiras referências escritas sobre esta modalidade de tratamento referem-se ao livro do Imperador Amarelo, Huang-Ti (2698-2598 a.C). No Ocidente, a acupuntura ficou mais conhecida durante a interação Nixon-Mao, com a visita de Nixon a República Popular da China, quando um homem foi submetido a uma cirurgia cardíaca sob analgesia por agulhas de acupuntura. No Brasil a acupuntura vem sendo oferecida aos pacientes nos Hospitais Universitários desde a década de 80 suscitando curiosidade mas também ceticismo. Provavelmente o ceticismo advém dos resultados empíricos e dos relatos muitas vezes miraculosos de cura, sem um rigor científico adequado, sendo imputados ao poder da sugestão ou até mesmo a um embuste pelos mais céticos. Neste últimos quase 40 anos a ciência vem estudando e desvendando progressivamente os mecanismos de atuação da acupuntura e também do seu possível efeito placebo, principalmente com o desenvolvimento de novos métodos de imagem do funcionamento do sistema nervoso central (SNC). Metodos: Realizar uma revisão do assunto acupuntura na literatura médica indexada avaliando a mudança de comportamento em relação a acupuntura através do PUBMED. Resultados: Utilizando-se o descritor "acupuncture" na base de dados MEDLINE, verificou-se a quantidade de artigos que citam acupuntura nos últimos 40 anos. Posteriormente, avaliamos as publicações iniciais, alguns trabalhos aleatórios no período e os mais recentes estudos em acupuntura com o objetivo de avaliar a mudança de percepção e as recentes descobertas da ciência em relação a essa técnica de tratamento não convencional. Desde que o assunto acupuntura surgiu na literatura médica indexada (Medline), temos um crescente interesse por parte da comunidade científica, por meio do crescimento dos artigos realacionados ao tema nos últimos 40 anos. Em busca realizada no Pubmed com o descritor: acupuntura, vemos que os primeiros relatos são de tratamentos e curas anedóticas como malária, diarréia bacteriana, esquistossomose, mutismo entre outras, publicadas em revistas chinesas e de língua não inglesa. Discussao: No começo da década de 70 com a integração Mao-Nixon há o inicio dos relatos de analgesia com acupuntura em cirurgias realizadas na China .Devido aos relatos muitas vezes milagrosos, a acupuntura suscitou dúvidas e grandes discussões no meio medico, fazendo acreditar que esta modalidade nada mais era do que um meio de auto-sugestão com componente de placebo, hipnose e psicoterapia. Paulatinamente ganhou força e abertura na sociedade médica, mostrando-se eficaz para alguns tipos de doenças e condições: náuseas e vômitos pós operatórios, por exemplo. Dor é uma condição aliviada pela acupuntura mas ainda suscita dúvidas nas metanálises realizadas. As mais recentes descobertas sobre a acupuntura são as no campo da Neuroimagem Funcional: ativação em áreas corticais, límbicas e tronco, responsáveis por componentes sensoriais e afetivos da percepção de dor. Essas áreas que a acupuntura ativa diferem da ativação pelo efeito placebo. As publicações internacionais citando acupuntura vem crescendo nestes últimos 40 anos, deixando os preconceitos iniciais de lado e se tornando uma intrigante ferramenta de tratamento para diversas doenças. O que antes se acreditava que era devido simplesmente ao efeito placebo, a ciencia vem demonstrando diferenças entre os dois processos por meio de neuroimagem funcional. Apesar do grande número de estudos neste período ainda há muito que se estudar para avaliar os reais efeitos e os mecanismos de ação dessa modalidade terapêutica milenar.

ETCC SHAM EM PESQUISAS COM ESTIMULAÇÃO CEREBRAL: UMA ESTRATÉGIA EFICAZ COMO GRUPO CONTROLE

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Nesta revisão são discutidos aspectos relativos ao uso de estimulação transcraniana por corrente contínua sham como grupo controle em investigações sobre o papel da ETCC como ferramenta de neuromodulação. Em estudos com equipamentos, o placebo depende de aparelhos que simulem a terapia investigada – esse tipo de placebo é conhecido como Sham. Sutherland (2007), em busca realizada no ClinicalTrials.gov observa que apenas 0,4% dos estudos cadastrados têm utilizado este método. Apesar do pouco uso de grupo sham, esta abordagem pode auxiliar a reduzir a introdução de variáveis de confusão e viés na análise, traria benefícios em áreas como a atribuição de tratamento, adesão ao tratamento e a avaliação subjetiva dos resultados modificados pelo tratamento. A ETCC é uma técnica de estimulação cerebral não-invasiva, indolor e segura. O equipamento consiste em um estimulador de corrente contínua de baixa intensidade (0 até 2mA), com eletrodos de borracha em esponjas contendo solução salina e um visor que marca a intensidade da corrente. Além disso, o equipamento possui acionador para modo Placebo. Com isso, para a estimulação placebo, o mesmo equipamento é utilizado e todos os procedimentos de montagem dos eletrodos no voluntário de pesquisa são os mesmos. No entanto, na estimulação sham o estimulador é ligado e desligado depois de 20 segundos. Os participantes sentem inicialmente a mesma sensação que os participantes do grupo ativo, mas em seguida não recebem corrente pelo resto do período de estimulação. Além disso, o equipamento utilizado em nosso laboratório mantém o visor indicando que a estimulação está acontecendo. Para testar a qualidade da ETCC sham em estudos como grupo controle, Gandiga, Hummel e Cohen (2006) realizaram levantamento de estudos com essa técnica em um período de 3 anos. Os pesquisadores observaram que os grupos placebo e ativo tiveram sensações de qualidade comparável, como desconforto mínimo por um período curto de tempo, e foram incapazes de distinguir se o tratamento recebido era ativo ou placebo. Além disso, os grupos não apresentaram diferenças na atenção ou motivação. Por outro lado, nos estudos levantados a estimulação ativa resultou em efeitos significativos quando comparado ao placebo nas funções avaliadas e que tinham relação com as estruturas cerebrais estimuladas. Da mesma forma, nosso grupo tem conduzido estudos em neurociência cognitiva na qual um dos principais desafios é controlar variáveis de confusão como atenção e motivação sujeitos aos efeitos da expectativa de estar recebendo algum tipo de estimulação cerebral. Em todos os estudos são comparados os efeitos da ETCC ativa com a placebo, mas também a qualidade da ETCC sham em simular o efeito da ETCC ativa (garantia de que o sujeito esteja cego ao estudo). Até o momento, o uso de ETCC sham vem demonstrando que esta se trata de técnica segura e confiável como ferramenta que garanta a qualidade de um estudo cego e também capaz de fornecer medidas importantes na comparação dos efeitos da ETCC ativa.

ETHICAL CONCERNS ABOUT PATIENTS UNDERSTANDING OF THE INFORMED CONSENT IN CLINICAL TRIALS

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Purpose: To participate in a clinical trial patients have to sign an informed consent(IC), often with misinterpretation words, what concerns researchers and institutions. We thought to realize what do patients understand about the contents of the IC. Methods: Patients(pts) were asked to answer a structured questionnaire with 28 questions. They were divided in two groups according to the use (group I) or not(group II) of placebo pills during the trial. Comparisons between groups were done with X square or Fisher when appropriated and analysis of variance for correlations. 80 pts showed up to answer the questionnaire from 106 who have participated in clinical trials with, during 2002 to 2006. Results: Characteristics in both groups (I, n= 47, II, n= 33), were similar. From all questions, we depicted the following: in both groups 42.5% of pts agreed to participate for the well of science and 66.2% for their own treatment benefit; 50% did not understand the IC and 32.9% did not read it but signed it; 66.7% in group I did not understand the meaning of placebo. Then we correlate the misunderstanding of placebo´s meaning with some variables and found a strong association with no literacy (p=0.022). It was strong the confidence they had in their doctors to accept to participate in a trial. Conclusion: The IC is poorly understood by patients, and the trust in their doctors is crucial for their acceptance to participate in a trial of a drug. Besides, the placebo`s meaning is not so well understood.

AVALIAÇÃO DE COMO OS SUJEITOS DA PESQUISA ENTENDEM A SUA PARTICIPAÇÃO EM ENSAIOS CLÍNICOS NUM HOSPITAL TERCIÁRIO.

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Introdução: Em estudos clínicos, os pacientes (pcs) precisam ler e assinar um termo de consentimento livre e esclarecido (TCLE) que tem várias páginas e palavras que os pacientes podem não entender. Para avaliar o quanto os pacientes entendem o TCLE realizamos esta investigação num hospital público especializado em cardiologia. **Métodos:**Convidamos pcs, participantes de estudos clínicos (hipertensão e doença cornária) de fase II, III ou IV, com fármacos, de jan/2002 a dez/2006, para responder um questionário estruturado (28questões). Dividimo-los em dois grupos, com uso (grupo I) ou não (grupo II) de placebo nos estudos. Para as comparações utilizou-se o X2 ou o teste de Fischer, e a análise de variância para as correlações. Após telefonema, 80 pcs compareceram de 106. Doutros 26 pcs, sete se recusaram , nove não foram localizados, oito foram excluídos e dois faleceram. **Resultados:** As características demográficas dos dois grupos(I,n=47; II, n=33) eram similares. Das respostas, chamaram a atenção: em ambos os grupos: 42,5% participaram dos estudos pelo bem da ciência; 66,2% pelo seu próprio benefício terapêutico; 50% não entenderam o TCLE e 40% sequer o leram, mas o assinaram. No grupo I, 66,7% (n=23) não entenderam o significado da palavra placebo. Fizemos correlações entre não entender o significado do placebo e as variáveis encontrando forte correlação com o analfabetismo funcional (p=0,022). Houve tendência entre ter um companheiro e entender o TCLE (p=0,094), e o nível de escolaridade e conversar com o pesquisador a respeito do TCLE . Com o intuito de complementar as informações obtidas mediante aplicação do questionário, realizou-se também o grupo focal, com sorteio de 12 pcs de cada grupo. Para os pcs o TCLE é considerado difícil e dispensa leitura em virtude do vínculo de confiança estabelecido com a equipe. **Conclusão**: O TCLE é pouco entendido pelos pacientes de um hospital público e a confiança na equipe é crucial para participar de estudos clínicos. Preocupa os TCLE longos e com muitos termos técnicos, e o quanto o profissional pode induzi-los a participar de um estudo clínico.

GABAPENTIN REDUCES ALCOHOL CONSUMPTION AND CRAVING: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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This study examined the efficacy of a 28-day gabapentin treatment in reducing alcohol consumption and craving. A randomized, double-blind, placebo-controlled trial was performed in a Brazilian public outpatient drug treatment center, with 60 male alcohol-dependent subjects with a mean age of 44 years and an average of 27 years of alcohol use, who consumed 17 drinks per day (165 to 170 g/d) over the past 90 days before baseline, and had no other significant medical or psychiatric condition. Following screening, 60 subjects were selected and received diazepam and vitamins as treatment for acute withdrawal for at least 7 days. After the detoxification treatment, 30 subjects were randomly assigned to receive gabapentin (300 mg twice daily) for 4 weeks, and 30 subjects, with similar baseline characteristics, to receive matching placebo tablets for the same period. After 28 days of treatment, the gabapentin group showed a significant reduction in both number of drinks per day and mean percentage of heavy drinking days, and an increase in the percentage of days of abstinence, compared to the placebo group. Also, some improvement in obsessive-compulsive symptoms was noted in both groups after the treatment, but it resulted in a more pronounced decrease in automaticity of drinking and aspects of craving in the gabapentin group than in the placebo group. Gabapentin reduces the alcohol consumption and craving. These results, together with the virtual absence of side effects and a favorable safety profile, support gabapentin as a potential drug for the treatment of alcohol withdrawal and dependence.

PLACEBO EFFECT IN CHILDREN: INSIGHTS FROM ABDOMINAL PAIN STUDIES IN CHILDREN

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Introduction: Placebo is considered an inactive treatment that can induce subjective physical and emotional changes in patients as well as healthy subjects. The placebo-associated improvement does not depend on the actual therapy, but instead can be influenced mainly by the subjects' experience and expectation. It is an interaction among anxiety, hope, and desire. Therefore it is expected to be different in children as compared to adults.Although placebo can occur in several areas of medicine, pain is an interesting model to study placebo effects. We therefore chose to review placebo effect in chronic pain to children. Understanding placebo effect in children is critical as to provide insights for the mechanisms of placebo and also to improve the design of clinical trials in children.We chose to assess functional abdominal pain disorder (FAPD) as this condition is one of the most common complaints in children. Studies reported prevalence rate of 10-20% in this period. We therefore reviewed placebo-controlled studies of FADP in children. **Methods:** We focused this review on the placebo-controlled clinical trials of functional abdominal pain disorders (FAPD) in children such as functional dyspepsia (FD) and functional abdominal pain (FAP). We also preliminarily compared our findings with placebo effects in adults.We performed our search in PubMed with the keywords such as "abdominal pain", "placebo", and "children". We found 126 articles but we chose only two studies because studies were: (i) reviews, (ii) case-reports, (iii) not placebo-controlled and (iv) investigated other conditions.In one of the studies authors investigated the use of femotidine. We therefore, compared to a similar study in adults as to perform a preliminary comparison. We did not find additional studies to perform this comparison.We also calculated the effect size between active drug and placebo for studies on children and adults as to present a preliminary comparison. **Results**: *In study n.1* children treated with Femotidine. They were randomly assigned to Femotidine (F) or Placebo (PL) for a three-week period (treatment 1) and there was a crossover for other three weeks (treatment 2). For both groups the Abdominal Pain Score (APS) did not reach statistical significance (F/P group P=0.10; P/F group P=0.80; overall P=0.16). *In study n. 2* adults treated with Femotidine. Patients were randomized to receive Femotidine or Placebo for 4 weeks and switched to the other treatment for another 4 weeks. Results show a significant improvement in the Gastrointestinal Symptoms Rating Scales score for Abdominal pain (P=0.007), indigestion (P=0.038) and reflux syndrome (P=0.034).*In study n. 3* children treated with Lactobacillus GG (LGG). They were randomly assigned to Lactobacillus GG or placebo, twice daily, orally for 4 weeks. Results show no significant difference compared with placebo for the improvement of symptoms in Funtional Dyspepsia (P=1.00), Functional Abdominal Pain (P=0.39) and overall study population (P=0.76).We calculated the effect sized of placebo effect in the children and adult study and found a larger effect size in the children study (0.61) as compared to the adult study that had a small effect size (0.05). **Conclusion:**This is only an initial preliminary comparison. The next step is to extend this review to other conditions of chronic pain as to increase the number of studies. In addition head to head trials comparing adults and children in the same study would be desirable.

Neural Correlates of Placebo and Chronic Pain

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Introduction: Placebo studies have been conducted since the late eighteenth century. The placebo effect has been observed across different areas of medicine, but one in particular that stands out is chronic pain. Extensive evidence has shown that there is an analgesic effect accompanying its administration. Understanding the mechanisms and neural correlates of placebo and chronic pain might provide insights for the understanding of mechanisms of chronic pain. Reviewing such evidence may allow for further development in targeting a successful therapy using, for instance, brain stimulation for those afflicted with chronic pain. Recent development of neuroimaging tools have facilitated insights on the integral mechanisms involved in human pain processing and placebo effect. Our review is an attempt to shed light on the common network of pain and placebo**. Methods:** We performed a preliminary assessment of neural correlates associated with chronic pain and placebo through a variety of neuroimaging techniques. Using the method of a literature review, we searched for papers investigating chronic pain and the placebo effect using neuroimaging data. Our search through articles in the PubMed website using keywords "chronic pain", "neuroimaging", "placebo", and "healthy subjects" yielded 34 articles that matched our initial inclusion criteria. We narrowed our findings down to the 8 most relevant articles. Using these articles we tried to strengthen knowledge of the similarities of the pain and placebo neural networks. **Results:** The main highlights for these studies are as follows: in *Studies 1 and 2:* In chronic pain patients activation was shown in several areas of the frontal lobe. Decreased cerebral blood flow (CBF) of the medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal PFC, and anterior cingulate gyrus (ACC) was observed. In *Study 3:* In this study with healthy volunteers placebo activation was found in the right ACC, amygdala, and peri-acqueductal grey (PAG). This illustrated the connections between the subcortical learning centers and the ACC. *Study* 4 This PET study has shown increased rCBF in areas of the rACC, MPFC,PFC, and IPL after seven day placebo treatment. In *Studies 5 and 6:* This study was conducted using placebo injection in healthy subjects to study placebo effects on pain. fMRI and PET imaging has shown activation in the DLPFC and ACC. They concluded that these effects are due to cognitive factors such as expectation modulating pain experience. In a similar study they found again that placebo administration was shown to induce hightened activity in the rACC and recruitment of the surrounding areas of the pons, amygdala, and PAG. In *Study 7* Investigators found substantial placebo-induced decreases in reported pain that were both specific to the body part that was treated with a placebo cream and reversed by the opioid antagonist naloxone. In *Study 8* In another placebo study, investigators hypothesized that anticipation of pain represented by PFC inhibits pain experience in the ACC**.** Note: These studies are listed accordingly in the references section. **Discussion:** Our findings suggest that the pain and placebo share a similar neural network. The similar areas are associated mainly with processing of affection and emotions. In fact the placebo effect seems to be largely mediated by psychological factors such as expectation and desire of relief. Its administration produces a global change in pain affect by changing these components. A main finding of the studies is that there is highly significant activation of the anterior cingulate gyrus (ACC) in both groups (placebo and pain). This area has been theorized to be responsible for affect and emotion. The ACC was found to be associated with the placebo analgesic effect. It had increased activity in the placebo controls of all of the studies. This same region was found to have decreased blood flow in the chronic pain patients. This suggests that might be an interesting target for the treatment of chronic pain with, for instance, brain stimulation. Further studies in chronic pain should explore these areas as to develop new therapeutic approaches for the treatment of chronic pain.