Cortical plasticity following intramuscular lidocaine injection

Injeção intramuscular de lidocaína e plasticidade cortical

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ABSTRACT

BACKGROUND AND OBJECTIVES: The manipulation of peripheral neuronal activity can alter the excitability of the primary motor cortex; however, it is not known whether this occurs after intramuscular injections of lidocaine. Therefore, the investigation focused on neurophysiological changes, assessed with transcranial magnetic stimulation, after lidocaine (0.5mL, 2%) injection in the first dorsal interosseous muscle of the dominant hand of healthy individuals.

METHODS: Exploratory, double-blind, parallel laboratory study**.** Twenty-eight healthy subjects (mean age: 29.6 years, 15 women). Measurements with transcranial magnetic stimulation included resting motor threshold, motor evoked potential, intracortical facilitation, and short intracortical inhibition. Lidocaine injection (LID group) was compared to dry needling (DRY group), saline injection (SAL group), and no intervention (CTL group). Participants were randomly placed in each group. Muscle strength and measures of peripheral excitability (rheobase and chronaxie) were also evaluated to detect whether the interventions generated changes in the peripheral neuromuscular excitability. Evaluations were performed over four time points: immediately before and after intervention and 30 and 60 minutes after intervention.

RESULTS: A generalized linear model was used to identify differences between the LID, DRY, and SAL groups and the CTL group. The results showed that motor evoked potentials were modified in the LID group ($p<0.005$).

CONCLUSION: The injection of lidocaine into the first dorsal interosseous muscle in the dominant hand of healthy adults alters motor evoked potentials.

Keywords: Anesthesia, Local anesthesia, Pain, Transcranial magnetic stimulation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A manipulação da atividade neuronal periférica pode alterar a excitabilidade do córtex motor primário; entretanto, não se sabe se esse fenômeno ocorre após a injeção intramuscular de lidocaína. Investigaram-se alterações eletrofisiológicas através de estimulação magnética transcraniana após injeção de lidocaína (0,5mL, 2%) no músculo primeiro interósseo dorsal da mão dominante de indivíduos saudáveis.

MÉTODOS: Estudo paralelo, exploratório, duplo-cego, realizado em laboratório. Vinte e oito voluntários saudáveis (idade média: 29.6 anos, 15 mulheres). Foram avaliados através de estimulação magnética transcraniana no limiar motor de repouso, potencial evocado motor, facilitação intracortical e inibição intracortical. A injeção de lidocaína (grupo LID) foi comparada com agulhamento a seco (grupo DRY), injeção de solução salina (grupo SAL) e nenhuma intervenção (grupo CTL). Os participantes foram distribuídos randomicamente em cada grupo. Força muscular e medidas de excitabilidade periférica (reobase e cronaxia) foram também estudadas. As avaliações ocorreram em quatro momentos: imediatamente antes e após a intervenção e 30 e 60 minutos após a intervenção.

RESULTADOS: Foi utilizado modelo linear generalizado para identificar as diferenças entre os grupos LID, DRY, SAL e CTL. Os resultados mostraram que o potencial evocado motor foi modificado no grupo LID ($p<0,005$).

CONCLUSÃO: Em indivíduos saudáveis, a injeção de lidocaína intramuscular pode alterar o potencial evocado motor.

Descritores: Anestesia, Anestesia local, Dor, Estimulação Magnética Transcraniana.

INTRODUCTION

While consistently demonstrated after neural lesions[1], there is additional evidence that musculoskeletal disorders, especially in the upper limbs, are accompanied by aberrant neurophysiologi-

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cal states within the cerebral cortex[2]. It is unclear whether this altered condition can return to normal in response to interventions that target musculoskeletal pain[3] and decrease abnormal inputs to the central nervous system (CNS). However, these interventions also change inputs to the CNS through the promotion of anesthesia and increased local receptivity to control pain. Invasive therapies such as dry needling and injection of local anesthetics in trigger points and taut bands in muscles of individuals with myofascial pain are widely used[4] for treatment of musculoskeletal and neurological disorders[5]. It is possible that these procedures may act through the reversal or prevention of maladaptive changes in the brain, such as central sensitization[6], although there are few studies on the actual mechanisms of these therapies[7].

Previous studies in healthy humans have used anesthetic nerve blocks[8,9], cutaneous anesthesia[10,11] or ischemic nerve blocks[12,13] of the upper limb to investigate changes in primary motor cortex (M1) excitability. This is of special interest, as M1 excitability changes happen in parallel with the primary somatosensory cortex (S1), which is activated during sensory peripheral manipulations[14]. After the reduction of sensory input to the CNS from a specific region of the body, the adjacent regions whose sensory supply is functioning normally generate evoked responses to a greater extent in the S1. Thus, the corresponding areas of deafferentation appear to be reorganized lead by collateral expansions[15] due to disinhibition or changes in synaptic efficacy of the corticocortical connections. It is proposed that these disinhibitions of previously silent neuronal projections are mediated by GABAergic and dopaminergic pathways[13,14]. Consistently, excitability increases in muscles proximal to the nerve block and decreases in the anesthetized area, suggesting the occurrence of non-peripheral phenomena associated with peripheral interventions[15,16].

Although there is extensive data regarding the central consequences of anesthetic deprivation of sensory inputs to the CNS, the effect of sensory deprivation using local intramuscular anesthetic injection on corticomotor pathways has not yet been described. This intervention is of extensive use for treatment of muscle and myofascial pain; thus, it is important to understand the mechanisms of muscular anesthetic blocks on M1 excitability/plasticity. Therefore, the aim of this preliminary study was to evaluate whether injection of lidocaine in the first dorsal interosseous (FDI) muscle of healthy individuals can affect corticomotor pathway functions assessed by single- and paired-pulse transcranial magnetic stimulation (TMS).

METHODS

Thirty-two healthy volunteers were included in the study and were recruited from the local population. Further inclusion criteria were adults aged between 18 and 60 years, who wished to participate in the study from personal contact and without contraindications for performing TMS (presence of metals in the skull or implanted devices, history of epilepsy, pregnancy) or use of recreational and psychotropic drugs, anticonvulsants, antidepressants or antipsychotics. Participants unable to understand the content of the evaluation tools used, with a history of diseases with possible confounding factors, fibromyalgia and other chronic pain, with a history of allergies or insensitivity to local anesthetics, coagulopathies and use of anticoagulants, or infection at the injection site were excluded from the study. Participants following data collection who had insufficient electrophysiological data for analysis, with loss of more than 25% of the data were excluded.

Experimental procedure

This randomized, parallel, and placebo-controlled study was conducted at the Functional Electrical Stimulation Laboratory at the Federal University of Bahia. Subjects were assessed with TMS at four time points: before treatment (baseline), immediately after treatment, and 30 minutes and 60 minutes after treatment. The treatment assigned to each subject was determined from previous randomization and kept in sealed envelopes. Healthy participants received an injection of lidocaine (0.5mL, 2%) in the FDI of the dominant hand (LID group) to explore changes in corticomotor and corticocortical excitability of this muscle and adjacent muscles. Three other groups of healthy volunteers were also formed: saline injection (0.5mL, 0.9%) (SAL group), dry needling (DRY group), and no intervention (CTL group). Injection procedures were performed by an experienced anesthesiologist using sterile techniques and needle of 29G (12.7mm). The investigators who performed the behavioral tasks and TMS assessment were blinded to the treatment allocation.

Electrophysiological measurements

Excitability of the M1 was evaluated using TMS (BIStim, Magstim, United Kingdom). After cleaning the skin with alcohol and an abrasive solution (NUPREP, Weaver and company, USA), auto-adhesive electromyography (EMG) Ag/AgCl electrodes (Miotec, Brazil) were positioned on the FDI muscle of the dominant hand. Participants were comfortably seated in a chair and kept awake throughout the evaluation protocol. A pre-marked polyester cap with a 1x1cm grid oriented in the cartesian plane was placed on the participant's head and served as reference for TMS. TMS was applied through a figure-of-eight coil (diameter 70mm). Randomized single and paired monophasic pulses were administered every 6 seconds, while EMG activity was amplified and converted to a digital signal (1401 and 1902, CED, United Kingdom United Kingdom) and monitored in real time through Signal software (CED, UK). The hot spot was identified, and the resting motor threshold (RMT) was estimated as the lowest TMS intensity capable of generating a motor evoked potential (MEP) with a peak-to-peak amplitude of 50 μV using the TMS Motor Threshold Assessment Tool (www.clinicalresearcher.org) software. The MEP, short intracortical inhibition (SICI), and intracortical facilitation (ICF) were estimated using single pulses at 120% of the RMT to estimate MEP and paired 80% and 120% pulses of RMT to estimate SICI (2 ms interval) and ICF (15 ms interval). Twenty random pulses were applied for each measurement, resulting in 60 pulses for each assessment time point. As assessments were conducted at baseline, immediately after intervention and 30 and 60 minutes after intervention, each participant received 240 pulses by the end of the experiment. This study was approved

by the ethics committee of the University of Bahia Institute of Health Sciences (CAE 51500615.6.0000.5662) and written Free Informed Consent Term (FICT) was obtained from all subjects.

Statistical analysis

Sample size estimation was performed considering an effect size of 30% for anesthetic block on MEP, alpha value of 5% ($p<0.05$), power of 80%, four groups (LID, SAL, DRY, CTL), four timepoints of assessment, correction between repeated measures of 0.5, and correction for non-sphericity of 1 for repeated measures analysis of variance. Continuous data were presented as means and standard deviation, and categorical data represented by absolute and relative frequencies. Linear mixed models were used to identify differences between the LID, DRY and SAL groups and the CTL group. Differences in means for each outcome at each assessment time point were compared between groups. Baseline values for the outcomes were placed in the model as covariables. When necessary, post-hoc comparisons were performed using the Bonferroni adjustment for multiple comparisons. All data were analyzed using IBM SPSS Software v.20 for Windows. The level of significance was 5% ($p\leq0.05$).

RESULTS

Data from 28 participants, mean age 29.6 years, 15 women, were retained for MEP, SICI, and ICF analysis**.** Data from four participants due to the loss of more than 25% of electrophysiological measures were excluded. The RMT values ranged between 40 and 60 (50 ± 10%) of maximum magnetic stimulator output for the FDI.

The behavior of MEP, SICI, and ICF for the FID was evaluated at the four assessment time points (Figures 1, 2, and 3). Paired *t*-tests confirmed that there were no between-session differences in SICI and ICF analysis for FDI between groups. In the LID group, there was intragroup MEP variation immediately after the injection in relation to that 30 and 60 minutes after. Lidocaine injection was associated with a significant decrease in the MEP value from baseline immediately after the procedure and 30 min after the procedure ($p<0.005$). In the comparison between groups, the LID group and the DRY group were different 30 minutes after each intervention ($p<0.005$). The LID group was also different from the CTL group immediately after the injection and at the end of the 60 minutes from the SAL group ($p<0.05$).

The stimulus–response curves of the LID and DRY groups show a significant decrease in stimulus intensity from baseline to the 30- and 60-min follow-ups ($p<0.05$).

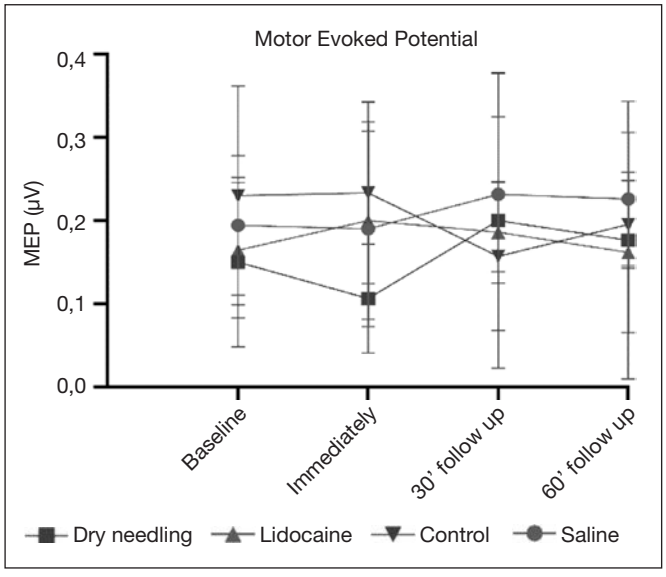

Figure 1. Amplitudes of motor evoked potentials (MEP) in the first dorsal interosseous at baseline; immediately after lidocaine injection, dry needling, saline injection, and no procedure (control group); and 30 min and 60 min after interventions

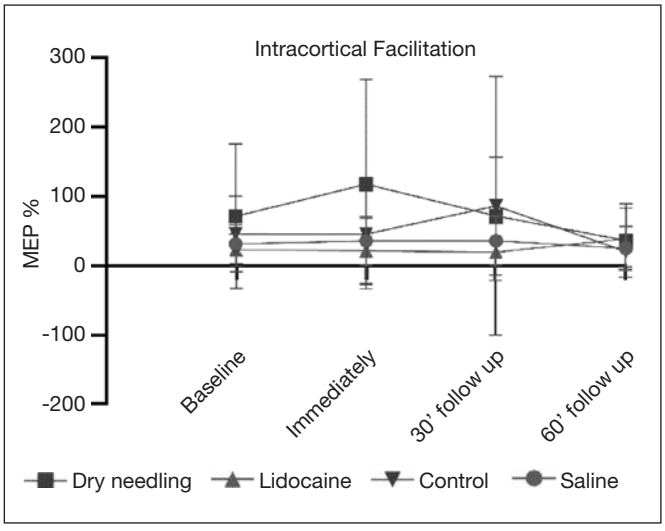

Figure 2. Amplitudes of intracortical facilitation in the first dorsal interosseous at baseline; immediately after lidocaine injection, dry needling, saline injection, and no procedure (control group); and 30 min and 60 min after interventions

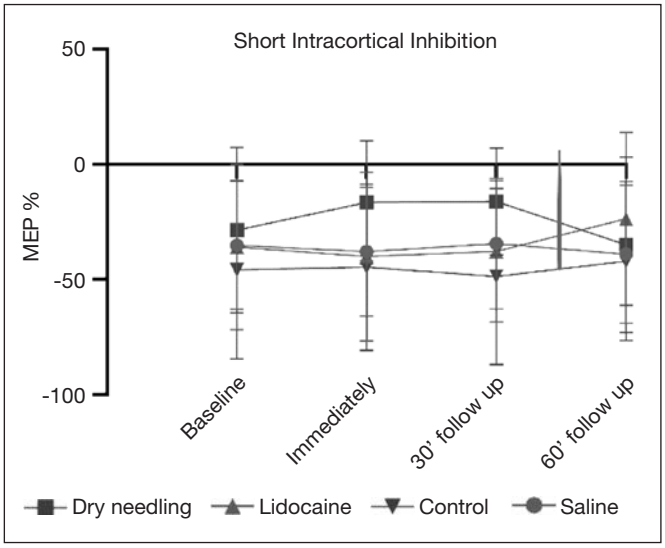

Figure 3. Amplitudes of motor evoked potentials (MEPs) in the SICI at baseline; immediately after lidocaine injection, dry needling, saline injection, and no procedure (control group); and 30 min and 60 min after interventions

The stimulus–response curves of the LID and DRY groups show a significant decrease in stimulus intensity from baseline to the 30- and 60-min follow-up ($p<0.05$).

The LID and DRY groups demonstrated a decrease in MEP value immediately after the intervention (with a greater decrease in the LID group), with an increase in MEP values above the baseline at 30 minutes following intervention, for a later decrease in MEP, returning to values discreetly larger than those at the baseline ($p<0.05$).

DISCUSSION

This study aimed to investigate the effects of lidocaine injection on M1 excitability of healthy participants assessed through TMS. To assure that the possible effects were not due to needle insertion or anesthetic volume, the lidocaine injection was compared to dry needling, saline injection, and no intervention. The results demonstrated that injection of lidocaine on FID and MEP in the contralateral M1 did not alter intracortical inhibition or facilitation in M1. However, it seems that there was a slight influence of the interventions in ICF and SICI, although not statistically significant.

Experimental studies have consistently demonstrated the existence of modifications in cortical excitability after peripheral interventions, with changes observed in the M1 organization of the muscle representations proximal to an anesthetized region in the upper limb[9,11,17-21]. This phenomenon appears to be associated with decreased cortical inhibition and a reactive increase in cortical excitability of the representation of those muscles that did not receive any intervention. It has also been shown that this increase in excitability may be associated with improved function and tactile discrimination of both the region proximal to the anesthetized area and the contralateral region[22]. Some studies suggest that the presence of functionally silent or inhibited sensory pathways, which can be activated during the effective deafferentation period, is a possible mechanism associated to such changes[15,23]. The effect of topical anesthesia, neural blocks, and ischemic upper limb blocks has been the subject of many electrophysiological studies. However, this is the first study to evaluate the effect of intramuscular injection of anesthesia through TMS. The small occurrence of verifiable effects can be attributed to several factors. Firstly, the decrease in sensory impulse is not always capable of causing changes in electrophysiological parameters in healthy individuals[10,16,24]. Many of the previous studies involved patients diagnosed with complex regional pain syndrome or post-stroke status; since these populations present a pathological condition, it is possible that peripheral anesthetic manipulation may exert a different effect than those seen in healthy volunteers[21]. This suggests that individuals with previous motor dysfunction and sensory deficits have a greater potential to respond to this type of intervention.

Previous studies have evaluated interventions that had a complete deafferentation[9,25-27]. It is possible that the magnitude of those interventions was a key factor to cause rapid reorganizational phenomena in latent corticocortical or thalamocortical connections. As the intervention only targeted a small muscle, it is reasonable to accept that it was not enough to induce M1 excitability changes.

This study presents some potential limitations. Interventions targeted to muscles also stimulate cutaneous nerve fibers, which can be considered an important confounding factor. For this reason, some studies have attempted to perform topical anesthesia of the region to minimize skin effects prior to muscle intervention, although the subtraction of the cutaneous stimulus does not always have a different effect on the intervention[24]. The lack of ultrasonography to guide the procedure and ensure correct dispersion of the anesthetic volume in the muscle can also be considered as a limitation[26].

Although there is already a considerable number of published articles exploring the effects of interventions using local anesthetics in cortical excitability, knowledge about this topic is still developing. Most of the current research involves heterogeneous methodologies, which make the results difficult to compare.

CONCLUSION

Lidocaine injection in the FDI alters MEP but does not alter the SICI and ICF of this muscle in an evaluation verified by TMS in healthy individuals.

AUTHORS' CONTRIBUTIONS

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Statistical Analysis, Conceptualization, Project Management, Research, Methodology, Writing - Preparation of the original, Writing – Review and Editing, Visualization

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Fuad Ahmad Hazime
Data Collection, Methodology, Writing - Preparation of the original, Writing - Review & Editing, Software, Validation

Abrahão Fontes Baptista
Statistical Analysis, Data Collection, Conceptualization, Project Management, Methodology, Software, Supervision, Validation, Visualization

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