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DOENÇA FALCIFORME, DOR CRÔNICA E SAÚDE FUNCIONAL: ESTUDO SECCIONAL MULTIDIMENSIONAL E DESENVOLVIMENTO DE PRODUTO TÉCNICO EDUCACIONAL

TESE DE DOUTORADO

Salvador-Bahia

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Tese apresentada ao curso de Pós-graduação em Medicina e Saúde Humana da Escola Bahiana de Medicina e Saúde Pública para obtenção do título de Doutora em Saúde Humana.

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Tese apresentada à Escola Bahiana de Medicina e Saúde Pública, como requisito parcial para a obtenção do Título de Doutora em Medicina e Saúde Humana.

Salvador, 18 de setembro de 2023.

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LISTA DE ABREVIATURAS

DF - Doença Falciforme

DTM - Disfunção Temporomandibular

ETCC - Estimulação Transcraniana com Corrente Contínua

PES - Estimulação Elétrica Periférica

CS - Sensibilização Central

QV - Qualidade de Vida

SCD - Sickle cell disease

TMD - Temporomandibular Disorder

tDCS - Transcranial Direct Current Stimulation

PES - Peripheral Electrical Stimulation

CVOs - Crises Vaso-oclusivas

SUS - Sistema Único de Saúde

DOENÇA FALCIFORME, DOR CRÔNICA E SAÚDE FUNCIONAL: ESTUDO SECCIONAL MULTIDIMENSIONAL E DESENVOLVIMENTO DE PRODUTO TÉCNICO EDUCACIONAL

RESUMO

INTRODUÇÃO: A doença falciforme (DF) é a hemoglobinopatia hereditária mais comum no mundo, com 275.000 recém-nascidos anualmente. A polimerização da hemoglobina leva à rigidez eritrocitária e vaso-oclusão, o que leva à dor e a alterações nos órgãos. Se desenvolve com o tempo como uma síndrome de dor crônica, com disfunções mal adaptativas do sistema nervoso central e periférico, evoluindo para disfunções emocionais, afetando seriamente a qualidade de vida. A disfunção temporomandibular (DTM) é uma síndrome de sensibilização central não explorada nos indivíduos com DF, carecendo ainda mais de proposições de terapias alternativas. A neuromodulação é uma terapia promissora que pode ajudar indivíduos com dor crônica refratária, mas sua viabilidade, plausibilidade e segurança deve ser analisada devido à baixa presença de oxigênio em indivíduos com DF. **OBJETIVOS:** O objetivo primário desta tese foi testar a hipótese de que a dor crônica da articulação temporomandibular (ATM) em pessoas com DF pode ser tratada sem risco com a neuromodulação não invasiva. Os objetivos secundários foram: avaliar a modulação endógena da dor em pessoas com DF e DTM; avaliar o impacto da dor e dos sintomas mentais na qualidade de vida; avaliar a influência dos tipos de religiosidade na dor; desenvolver e validar uma cartilha para pessoas com DF. **MÉTODO:** Cem adultos com DF, entre 18 e 49 anos de idade, residentes no Recôncavo Baiano, aceitaram responder os instrumentos, entre outubro de 2019 e dezembro de 2022. Foram aplicados o Inventário de Sensibilização Central, o Inventário Breve de Dor, o Índice de Religiosidade de Duke, a Escala Hospitalar de Ansiedade/Depressão, a Escala de Catastrofização da Dor, o Questionário de Qualidade de Vida SF-36 e o Índice Anamnésico de Fonseca. As pessoas com DF e DTM participaram do estudo piloto randomizado, cruzado e duplo-cego. Intervenções foram feitas em três grupos: Estimulação Transcraniana com Corrente Contínua (ETCC) + Estimulação Elétrica Periférica (EEP) ativa, ETCC ativa + EEP simulada e ETCC simulada + EEP simulada, com intervalo de uma semana. O tamanho do efeito e o tamanho de amostra foi calculado com o software WinPepi, comparando o resultado após a intervenção de ETCC ativo + EPP sham e ETCC sham + EPP sham. Posteriormente, foi confeccionada uma cartilha para a prevenção de perdas na qualidade de vida das pessoas com DF que foi avaliada por especialistas na área. **RESULTADOS:** Seis artigos científicos compõem a presente tese. Como resultado primário, nenhum efeito negativo importante foi identificado na intervenção com ETCC, com uma tendência à diminuição da dor. Dez mulheres foram identificadas com DTM, idade média de 38,9 ± 6,08 e dor média foi de 6,3 + 1,56 na escala visual analógica. Todas tinham dor crônica generalizada e altos índices de sensibilização central (SC). Os diagnósticos com RDC/DTM Eixo I mostraram que nove apresentavam dor miofascial e artrose articular, oito apresentaram facilitação da dor e cinco delta anormal (inibição da dor). Para os objetivos secundários, 100 indivíduos foram entrevistados, com genótipos HbSS/HbSC. 69% eram mulheres, com idade de 34,14 ± 10,12 anos. A intensidade da dor foi de 4,20 ± 2,67; 71% para os que tinham dor crônica; 60% tinham dor generalizada; 59% tinham SC; 33% tinham ansiedade; e 18% tinham depressão. O menor escore médio de QV foi para o domínio Aspecto Físico (35,55±40,16). Ansiedade, dor média, SC e catastrofização correlacionaram-se com todos os domínios da QV. O resultado do tamanho de efeito foi Cohen´s d = (2.88 - 1.80)/0.91=1.17. Resultando em um tamanho amostral para o Ensaio Clínico Randomizado

(ECR) de 11 indivíduos por braço. **CONCLUSÃO:** A ETCC e EEP são seguras, e podem ser usadas por mulheres com doença falciforme e disfunção temporomandibular, mas um ensaio clínico com um maior tamanho amostral precisa ser realizado. Os achados destacam a necessidade de cuidados em saúde mental em pacientes com doença falciforme devido ao impacto da ansiedade, depressão, catastrofização e sensibilização central na qualidade de vida, com a necessidade de incluir o fator religiosidade/espiritualidade na equação da intervenção da equipe multidisciplinar.

Palavras chaves: Doença Falciforme, Sensibilização Central, Saúde Mental, Qualidade de Vida, Disfunção temporomandibular, Estimulação Transcraniana com Corrente Contínua.

SICKLE CELL DISEASE, CHRONIC PAIN, AND FUNCTIONAL HEALTH: MULTIDIMENSIONAL SECTIONAL STUDY AND DEVELOPMENT OF A TECHNICAL EDUCATIONAL PRODUCT

ABSTRACT

INTRODUCTION: Sickle cell disease (SCD) is the most common hereditary hemoglobinopathy in the world, with 275,000 newborns born annually. Hemoglobin polymerization leads to erythrocyte rigidity and vaso-occlusion, which leads to pain and organ changes. It develops over time as a chronic pain syndrome, with maladaptive dysfunctions of the central and peripheral nervous system, evolving into emotional dysfunctions, seriously affecting quality of life. Temporomandibular dysfunction (TMD) is an unexplored central sensitization syndrome in individuals with SCD, further lacking proposals for alternative therapies. Neuromodulation is a promising therapy that can help individuals with refractory chronic pain, but its feasibility, plausibility and safety must be analyzed due to the low presence of oxygen in individuals with SCD. **OBJECTIVES:** The primary objective of this thesis was to test the hypothesis that chronic temporomandibular joint (TMJ) pain in people with SCD can be treated without risk with non-invasive neuromodulation. The secondary objectives were: to evaluate endogenous pain modulation in people with PD and TMD; assess the impact of pain and mental symptoms on quality of life; evaluate the influence of types of religiosity on pain; develop and validate a booklet for people with SCD. **METHOD:** One hundred adults with SCD, between 18 and 49 years of age, living in Recôncavo Baiano, agreed to answer the instruments, between October 2019 and December 2022. The Central Awareness Inventory, the Brief Pain Inventory, the Religiosity Index were applied. Duke, the Hospital Anxiety/Depression Scale, the Pain Catastrophizing Scale, the SF-36 Quality of Life Questionnaire and the Fonseca Anamnestic Index. People with SCD and TMD participated in the randomized, crossover, double-blind pilot study. Interventions were carried out in three groups: Transcranial Direct Current Stimulation (tDCS) + active Peripheral Electrical Stimulation (EEP), active tDCS + simulated EEP and simulated tDCS + simulated EEP, with an interval of one week. The effect size and sample size were calculated with the WinPepi software, comparing the result after the intervention of active tDCS + sham EPP and sham tDCS + sham EPP. Subsequently, a booklet was created to prevent losses in the quality of life of people with SCD, which was evaluated by experts in the field. **RESULTS:** Six scientific articles make up this thesis. As a primary result, no important negative effects were identified in the tDCS intervention, with a tendency towards decreased pain. Ten women were identified with TMD, mean age was 38.9 ± 6.08 and mean pain was 6.3 + 1.56 on the visual analogue scale. All had widespread chronic pain and high rates of central sensitization (CS). Diagnoses with RDC/TMD Axis I showed that nine had myofascial pain and joint arthrosis, eight had pain facilitation and five had abnormal delta (pain inhibition). For the secondary objectives, 100 individuals were interviewed, with HbSS/HbSC genotypes. 69% were women, aged 34.14 ± 10.12 years. Pain intensity was 4.20 ± 2.67; 71% for those with chronic pain; 60% had generalized pain; 59% had CS; 33% had anxiety; and 18% had depression. The lowest average QoL score was for the Physical Appearance domain (35.55±40.16). Anxiety, average pain, SC and catastrophizing correlated with all QoL domains. The effect size result was Cohen's d = (2.88 -1.80)/0.91=1.17. Resulting in a sample size for the Randomized Clinical Trial (RCT) of 11 individuals per arm. **CONCLUSION:** TDCS and EEP are safe, and can be used by women with sickle cell disease and temporomandibular disorder, but a clinical trial with a larger sample size needs to be carried out. The findings highlight the need for mental health care in patients

with sickle cell disease due to the impact of anxiety, depression, catastrophizing and central sensitization on quality of life, with the need to include the religiosity/spirituality factor in the multidisciplinary team intervention equation.

Keywords: Sickle Cell Disease, Central Sensitization, Mental Health, Quality of Life, Temporomandibular Disorder, Transcranial Direct Current Stimulation.

SUMÁRIO

1. INTRODUÇÃO

A doença falciforme (DF) é uma doença genética autossômica recessiva causada por uma mutação pontual na cadeia β da hemoglobina, que resulta na formação de hemácias em forma de foice e na ocorrência de crises vasculares, dor crônica, incapacidade e baixa qualidade de vida (KATO, 2018). A DF é uma das doenças hereditárias mais comuns no mundo, principalmente no continente africano, onde a prevalência pode chegar a 25% da população em alguns países (AYGUN, 2012). No Brasil, estima-se que cerca de 4% da população tenha o traço falciforme e que entre 60.000 e 100.000 pessoas tenham DF. A Bahia é o estado brasileiro com maior número de nascidos vivos com DF, com um a cada 650 (CANÇADO, 2007). A DF representa um importante problema de saúde pública e um grande ônus econômico para os pacientes e a sociedade (AYGUN, 2012).

As crises vaso-oclusivas (CVOs) são episódios de dor aguda que ocorrem frequentemente em pacientes com DF, devido à obstrução dos pequenos vasos sanguíneos pelas hemácias em forma de foice (KATO, 2018). Essas crises podem levar a hospitalizações, limitações físicas e isquemia nos órgãos e tecidos (DARBARI, 2015). As CVOs podem afetar qualquer parte do corpo, mas são mais comuns no tórax, abdômen e membros (BALLAS, 2015). A dor pode ser excruciante e de início súbito ou gradual (BRANDOW, 2018). As CVOs podem se tornar recorrentes e crônicas, causando danos permanentes nas articulações, ossos e músculos (SIL, 2016). Além disso, as CVOs podem comprometer a qualidade de vida dos pacientes, gerando ansiedade, depressão e isolamento social (PANEPINTO, 2012).

O sistema único de saúde (SUS) disponibiliza as medicações necessárias para minimizar as crises dolorosas das pessoas com DF. Os tratamentos ofertados são comumente medicamentosos: ácido fólico, analgésicos, anti-inflamatórios, antibióticos e hidroxiuréia (PANEPINTO, 2012; BORGES, 2022). O ácido fólico é um suplemento que ajuda na construção das células do sangue e é necessário para a formação de novas células sanguíneas, ou seja, de hemácias. Pessoas com doença falciforme devem fazer a suplementação contínua do ácido fólico. A hidroxiuréia é um medicamento muito preconizado, do qual estudos tem asseverado que impacta na melhora da qualidade de vida dos pacientes, reduzindo o número de crises vaso-oclusivas e, consequentemente, de hospitalizações, de eventos neurológicos agudos e baixando a taxa de mortalidade (YANG, 2022). Contudo, seus efeitos colaterais por

uso contínuo ainda são desconhecidos (PANEPINTO, 2012).

A DF pode causar fadiga crônica devido à capacidade reduzida do transporte de oxigênio do sangue. A anemia, uma condição caracterizada por uma baixa contagem de glóbulos vermelhos, é comum na DF e pode contribuir para sensações de fraqueza, cansaço e diminuição da resistência física (SINGH., 2020). A DF pode levar a danos e disfunção de vários órgãos, incluindo baço, pulmões, rins, fígado e olhos (KAVANAGH, 2022). Podendo resultar em complicações como infecções recorrentes, hipertensão pulmonar, doença renal, acidente vascular cerebral e problemas de visão, impactando ainda mais a qualidade de vida. Lidar com uma doença crônica como a DF pode ter consequências emocionais e psicológicas (REES, 2010). Indivíduos com DF podem apresentar ansiedade, depressão, estresse e dificuldade em lidar com os desafios físicos e emocionais da doença. Também pode afetar as relações sociais e contribuir para uma sensação de isolamento (LEVENSON, 2008; REES, 2010).

A DF também tem um impacto na educação e no emprego, podendo afetar a frequência escolar, o desempenho acadêmico e a capacidade de manter um emprego regular (PIRES, 2022). Visitas hospitalares frequentes, episódios de dor e necessidade de cuidados médicos contínuos podem afetar os objetivos educacionais e profissionais, levando a limitações nas oportunidades de carreira e estabilidade financeira. O manejo da DF geralmente requer consultas médicas regulares, medicamentos, transfusões de sangue e, às vezes, tratamentos mais invasivos, como transplante de medula óssea (DARBARI, 2015; DARBARI, *et al.*, 2020). As complexas necessidades de saúde e os custos financeiros associados à DF podem sobrecarregar os indivíduos e suas famílias (LEE, 2019; PIRES, 2022).

É importante observar que, com os avanços nos cuidados médicos e no suporte, a expectativa de vida das pessoas com DF aumentou. O diagnóstico precoce, cuidados abrangentes, estratégias de controle da dor e medidas preventivas, podem ajudar a mitigar algumas das complicações associadas à DF e melhorar o bem-estar geral (KATO, 2018). No entanto, pesquisas ofertando maior conscientização e indicação de cuidados não medicamentosos continuam sendo fundamentais para os indivíduos que vivem com a doença falciforme.

2. FUNDAMENTAÇÃO TEÓRICA

A DOENÇA FALCIFORME E DOR ARTICULAR CRÔNICA

A dor crônica nas articulações é um sintoma comum experimentado por indivíduos com DF. Diante da dor, o sistema neuromusculoesquelético sofre modificações motoras adaptativas que afetam o controle motor e a mecânica articular, uma proposta teórica refere que em primeiro lugar ocorre uma adaptação do controle motor à dor, que é consequência da redistribuição da atividade dentro e entre os músculos. Em segundo lugar a mudança no comportamento mecânico, que inicialmente tem uma função protetora, mas logo provoca mais dor ou lesão. A longo prazo, envolvem alterações em vários níveis do sistema nervoso, que levam ao aumento da carga articular, diminuição da mobilidade, variabilidade do movimento e fraqueza muscular (HODGES, 2011).

No caso do indivíduo com DF, esta situação pode ser provocada e ampliada pelas crises vaso-oclusivas (BALLAS & DARBARI, 2020). As dores articulares são muitas vezes identificadas como necrose avascular ou osteonecrose, estas ocorrem quando há um suprimento sanguíneo reduzido para as articulações, levando à morte do tecido ósseo. A necrose avascular é uma complicação significativa da DF. Geralmente afeta os quadris (HODGES, 2011), ombros (KENNON, 2016) e joelhos, mas também pode ocorrer em outras articulações. A falta de fluxo sanguíneo adequado para as articulações causa a quebra do tecido ósseo e, eventualmente, leva à dor, amplitude de movimento limitada e pode provocar deformidade articular, hoje descrita como uma doença que acelera o envelhecimento (IDRIS, 2022).

A dor articular crônica pode afetar significativamente a qualidade de vida de indivíduos com DF, e pode limitar as atividades físicas, a mobilidade e a funcionalidade geral. A dor crônica pode levar à diminuição da participação na escola, no trabalho e em atividades sociais, podendo causar sofrimento emocional e redução da sensação de bem-estar. O manejo da dor articular crônica na DF requer uma abordagem multidisciplinar. Essa abordagem baseada em equipe visa o controle da dor, prevenir mais danos nas articulações e otimizar o atendimento geral ao paciente (BRANDOW *et al.*, 2020). Embora não seja possível prevenir totalmente danos nas articulações, certas medidas podem ajudar a reduzir o risco e a gravidade das complicações articulares. Isso inclui manter um bom controle da doença por meio de acompanhamento médico regular, evitar o uso excessivo de corticosteroides, otimizar a

hidratação e minimizar a exposição a outros potenciais fatores de risco (BRANDOW *et al.*, 2020).

A plasticidade maladaptativa refere-se a alterações anormais no sistema nervoso central (SNC) que podem contribuir para o desenvolvimento e manutenção de condições de dor crônica, incluindo dor osteomiarticular (APKARIAN, 2011). A plasticidade maladaptativa pode levar a um fenômeno conhecido como sensibilização central, onde o SNC se torna hipersensível aos sinais de dor. No contexto da dor osteomioarticular, sinais nociceptivos persistentes de ossos ou articulações danificados ou inflamados podem resultar em respostas de dor exageradas. As alterações neuroplásticas abrangem a estrutura e função do SNC, podendo ocorrer no nível da medula espinhal, tronco cerebral e regiões cerebrais superiores, envolvidas no processamento da dor, como o córtex somatossensorial e o sistema límbico (APKARIAN & RECKZIEGEL, 2019). Modificações nas conexões sinápticas, liberação de neurotransmissores e excitabilidade neuronal contribuem para o desenvolvimento de estados de dor crônica (KUNER, R. & KUNER, T., 2021).

Compreender a plasticidade maladaptativa é crucial para a escolha de tratamentos eficazes para estes indivíduos. Abordagens terapêuticas que visam as alterações neuroplásticas subjacentes, como medicamentos que modulam a atividade do neurotransmissor, técnicas de neuroestimulação ou intervenções cognitivo-comportamentais, podem ajudar a modular o processamento da dor e melhorar o controle da dor. Por isso a avaliação clínica da pessoa com Doença Falciforme, desde um ponto de vista de dor crônica com maladaptação do sistema nervoso central, poderá conduzir propostas de tratamentos diferenciados. Ver revisão da literatura no artigo 1: ***Sickle Cell Disease Chronic joint pain: Clinical assessment base on maladaptative central nervous system plasticity***. No final deste capítulo.

Se a dor crônica nas articulações é um sintoma comum experimentado por indivíduos com DF, os estudos podem e devem, incluir a articulação temporomandibular, participante fundamental na alimentação e na comunicação, por tanto a seguir se discute a disfunção temporomandibular, reconhecendo que sua fisiopatologia envolve processos de sensibilização periféricos e centrais (CONCEIÇÃO, 2022).

DISFUNÇÃO TEMPOROMANDIBULAR E DOENÇA FALCIFORME

A DTM é um termo coletivo que abraça um número de problemas clínicos que envolvem os músculos do sistema mastigatório, a ATM e estruturas associadas. Os sinais e sintomas mais comuns são dor, sensibilização na região pré-auricular e/ou nos músculos mastigatórios; a diminuição e/ou a alteração da amplitude de movimento (ADM) sons articulares, tais como cliques e/ou crepitações, durante os movimentos mandibulares (SHARMA *et al.*, 2011).

Trata-se de uma condição prevalente, atingindo aproximadamente de 10-15% da população adulta que refere sinais e sintomas, sendo que entre cinco e sete por cento da população geral precisa de tratamento. A DTM mostra uma distribuição peculiar na população geral, com predominância de mulheres acometidas que torna-se mais forte na idade entre os 20 a 40 anos (LOMAS *et al.*, 2018).

Os mecanismos patológicos subjacentes da DTM são multifatoriais, tais como alterações neuromusculares, posturais, desarmonia côndilar ou discal, parafunções, fatores psicológicos, alterações proprioceptivas e desequilíbrios oclusais. Existem estudos que associam o surgimento dessas disfunções em decorrência de alterações nos mecanismos corticais relacionadas à área motora que controlam o comportamento motor orofacial e o sistema neuromuscular mastigatório (LOMAS *et al.*, 2018; SHIBUKAWA *et al.*, 2007).

A DTM associada à dor afeta significativamente a vida do portador, podendo comprometer especialmente as atividades laborais, escolares, sono, apetite e de alimentação. Esta dor se caracteriza por ser surda, com características neuropáticas e muitas vezes aparece concomitante com cefaleias (CONTRERAS *et al.*, 2018). Estudos têm demonstrado que dores persistentes e recorrentes têm um impacto potencial na vida diária, principalmente nas áreas de desconforto psicológico, disfunção física e limitação funcional, o que acarreta limitação na qualidade de vida (APKARIAN, 2011).

Apesar da dor crônica provocada por DTM severa possuir características altamente limitantes, estressantes e impactantes na diminuição da qualidade de vida das pessoas que convivem com este diagnóstico, até o momento existem mínimas referências na literatura que descrevem pessoas com DF e DTM. Plantin (2021), descreve crise vaso-oclusiva da ATM

chamando de “um achado incomum na doença falciforme”. Será que achados na articulação temporomandibular em pessoas com DF é incomum ou está subdiagnosticado? Estudo realizado em Salvador-BA, pesquisou a saúde bucal de pessoas com doença falciforme (TICIANELI, 2020), dentre as oitenta pessoas com DF entrevistadas 10% foram identificados com DTM severa, segundo o Índice anamnésico de Fonseca. Não identificamos na literatura nenhum estudo de prevalência, nenhuma proposta de protocolo de tratamento não farmacológico para os indivíduos com DF e DTM.

Para o diagnóstico da DTM, o instrumento confiável para pesquisas é o RDC/DTM (*Diagnoses criteria for temporomandibular dysfunction)*. Este instrumento oferece a melhor classificação para DTM. O eixo I inclui itens para a classificação diagnóstica física das DTM, tais como tempo de dor, local da dor, tipo de dor, limitação na abertura bucal e desvios laterais, e comprometimento dos músculos da mastigação. O eixo II contribui com questionamentos sobre a intensidade e o impacto da dor crônica na vida do individuo, identificando repercussões na função e por tanto na qualidade de vida e rastreamento de aspectos depressivos (BARROS, 2009). O RDC/DTM foi atualizado como DC/DTM (SCHIFFMAN & OHRBACH, 2016), mas não foi utilizado para esta pesquisa, por não ter sido validado ao português.

O RDC/DTM caracteriza-se por ter boa confiabilidade Inter e intra examinadores, provendo um critério diagnóstico padronizado, através de algoritmo para a classificação dos eixos I e II. Essa ferramenta permite classificar o indivíduo com DTM em três subgrupos de diagnósticos. O grupo I é assim classificado por desordens musculares; o grupo II por deslocamento do disco articular; e o grupo III por artralgia, artrite ou artrose (MANFREDINI *et al.*, 2010).

Dentre os benefícios deste instrumento é importante ressaltar que não é um sistema hierárquico. Ele tem a capacidade de classificar diagnósticos diferentes para cada ATM tendo como benefício correlacionar a fatores psicológicos durante a avaliação. Utiliza um protocolo de pontuação para classificar a dor crônica, onde: grau 0 – sem dor por DTM nos últimos seis meses; grau I – baixa intensidade; grau II – alta intensidade, estas últimas sendo classificadas como baixa incapacidade e as próximas como alta incapacidade referente ao grau III – limitação moderada, grau IV limitação severa (MANFREDINI *et al.*, 2010). A compreensão da dor

crônica proveniente ou concomitante com a disfunção temporomandibular torna-se importante especialmente para o entendimento do tratamento proposto nesta pesquisa.

A cronificação da dor ocorre por mecanismos de neuroplasticidade. No caso da DTM trata-se de uma adaptação não funcional, reconhecida como plasticidade mal adaptativa do processamento central da dor. A perpetuação da dor desencadeará processos de memorização e modificações nas redes cerebrais, dificultando respostas às modalidades terapêuticas (BRANCO *et al.,* 2008). Portanto trata-se de dor crônica secundária, é a dor em um ou mais regiões anatômicas que persiste ou recorre por mais de 3 meses e está associada a sofrimento emocional significativo ou incapacidade funcional significativa (interferência nas atividades da vida diária e participação em papéis sociais) e que está relacionada a outra condição (TREEDE *et al.,* 2019).

O conhecimento atual estabelece que a dor aguda se caracteriza pela ativação do córtex somatosensitivo, ínsula e córtex angulado; enquanto a dor espontânea e alodínia ativa o córtex pré-frontal e região límbica. A dor crônica é diferente e evoca um padrão de atividade cerebral único para cada doença ou disfunção, o que é chamado de assinatura morfológica cerebral (APKARIAN, V. A. *et al.,* 2011; BALIKI *et al.,* 2011). Os mecanismos neurais, tais como inibição e plasticidade cortical, são fundamentais para a função do cérebro. Os fenômenos de inibição e facilitação intracortical e inibição transcalosa estão alterados em pessoas com dor aguda, e os autores sugerem que esta alteração é o fator desencadeante da má adaptação cortical em casos crônicos (APKARIAN, A. V., 2011).

Dentro do contexto da dor orofacial e da disfunção da ATM, o que se entende hoje como normalidade e anormalidade a nível cerebral? Em primeiro lugar, é necessário definir a atividade cerebral na função normal da ATM. Esta se caracteriza pela ativação do cerebelo, córtex motor, córtex caudado, angulado e tronco cerebral, havendo mudanças de intensidade durante as diferentes etapas da mastigação (QUINTERO *et al.,* 2013; TAMURA *et al.,* 2003). Estudos iniciais têm comprovado comprometimento da substância branca, nervos periféricos (Trigêmeo), corpo caloso na presença de DTM crônica. A pesquisa mais próxima à prática clínica observou a ativação cerebral no apertamento unilateral em pacientes com sinovite temporomandibular e dor ao morder, analisado com ressonância magnética funcional. Este estudo demonstrou que o giro frontal inferior e o giro pré-central cumprem uma função

essencial na tarefa de apertamento. A ativação do córtex cingulado anterior foi associada aos pacientes com sinovite com maiores níveis de stress psicológico (OGURA *et al.*, 2012).

Finalmente, estudos têm analisado o porquê dos pacientes com DTM, desenvolverem escores baixos em testes neurofisiológicos de função cognitiva. A hipótese é que as respostas comportamentais lentas ou dessincronizadas demonstram atividade cerebral anormal devido à dor crônica, não obstante, cabe ressaltar que pesquisas também sugerem que o comprometimento cerebral, especificamente a redução no volume da substância cinzenta, na presença de dor é reversível pela eliminação da dor crônica (OGURA *et al.*, 2012; WEISSMAN-FOGEL *et al.*, 2011; ZHAO *et al.*, 2011). Estes estudos oferecem, portanto, uma fundamentação científica para o raciocínio da utilização de estimulação cortical em presença de dor orofacial especificamente da DTM. A neuromodulação se converte em uma terapia promissora que pode ajudar indivíduos com disfunção tempoormandibular crônica (BABILONI, 2018), mas sua viabilidade, plausibilidade e segurança devem ser analisadas cuidadosamente para pessoas com DF, devido à baixa presença de oxigênio. (SINGH., 2020).

NEUROMODULAÇÃO COM ESTIMULAÇÃO TRANSCRANIANA COM CORRENTE CONTÍNUA

A neuromodulação através de correntes elétricas é uma das formas de se interferir na plasticidade cortical relacionada à dor crônica. Dentre as formas disponíveis para se modular a atividade neuronal com correntes elétricas está a estimulação transcraniana com corrente contínua (ETCC). A ETCC tem se mostrado efetiva, por ser uma corrente monofásica, que induz mudanças na excitabilidade dependente da polaridade, no córtex motor. O ânodo (polo positivo) atrai ânions (íons negativos), provocando aumento da excitabilidade no SNC (20-40%), aumento do Ca2+ intracelular e um efeito de bloqueio do canal de sódio. O cátodo tem efeito oposto ao ânodo e é usado para provocar diminuição da excitabilidade de neurônios corticais (FREGNI *et al.*, 2006), apresentando efeitos fisiológicos inversos ao ânodo.

O mecanismo de ação da ETCC envolve efeitos essencialmente neuromodulatório (durante a aplicação) e neuroplásticas (quando cessada a aplicação). Em um primeiro momento o efeito está relacionado às mudanças que ocorrem no potencial de repouso da membrana neuronal. A estimulação anódica inicia oscilações na membrana celular que apresentam

características de alta frequência e baixa amplitude durante a despolarização. A duração do efeito é dependente da síntese de proteínas, acompanhadas de modificações intracelulares e nos níveis de cálcio (FREGNI *et al.*, 2006; NITSCHE, M. A. *et al.*, 2007). Os efeitos de uma única aplicação de ETCC na excitabilidade corticoespinal depende da intensidade do estímulo e sua duração (NITSCHE & PAULUS, 2000). Um estudo dos mesmos autores demostrou que 13 minutos de estimulação anódica com ETCC sobre M1 provocava excitabilidade corticoespinal até 90 min de duração, após a sessão (NITSCHE & PAULUS, 2001). Portanto, uma sessão de ETCC pode ser útil para gerar dados que podem dar base ao uso mais prolongado desta técnica.

A colocação dos eletrodos segue o sistema 10-20 (eletroencefalograma). Para controle da dor, o ânodo (+) é colocado na região C1 ou C2, que corresponde ao córtex motor primário, enquanto o cátodo (-) é posicionado na região supra orbital contralateral. O ânodo é colocado do lado contralateral a dominância do indivíduo ou ao principal local de sintomas. Os parâmetros de estimulação em geral são: duração entre 5 a 30 minutos, intensidade de 0,5 mA - 2,0 mA, o tamanho dos eletrodos entre 20cm2- 35cm2 (BAPTISTA *et al.*, 2019).

Uma revisão sistemática (BOGGIO *et al.*, 2009) mostrou que o ETCC sozinho possui um efeito pequeno quanto ao controle da dor, por isso novos estudos têm proposto associação de técnicas para aumentar esse efeito. A Estimulação Elétrica Periférica (EEP) associada com ETCC tem se mostrado mais efetiva (HAZIME, *et al.*, 2017; SCHABRUN & CHIPCHASE, 2012). Estas associações terapêuticas assumem que a responsividade cerebral para uma terapia em particular, pode ser facilitada por outra que altera a excitabilidade cortical. A EEP é uma técnica neuromodulatoria que pode produzir mudanças na excitabilidade cortical, dependendo da intensidade da estimulação, frequência e duração (CHIPCHASE, *et al.*, 2011; MCKAY *et al.*, 2002). A EEP com intensidade no limiar sensorial diminui a excitabilidade, enquanto que no limiar motor tem o efeito oposto (CHIPCHASE, *et al*., 2011).

Quando dois estímulos excitatórios são associados, uma resposta nula ocorre, mas a associação entre estímulo inibitório e excitatório resulta em um efeito sinérgico (HAZIME, F. A. *et al.*, 2017; SCHABRUN, *et al.*, 2012; BOGGIO *et al., 2009*). Portanto, a EEP em um limiar sensorial associado a ETCC anódico produz um efeito analgésico somatório. Um exemplo disto foi o resultado de Boggio, que obteve uma redução da intensidade da dor de

36,5% na união das duas técnicas, quando o ETCC sozinho teve como resultado a diminuição da dor de 15% (BOGGIO *et al.*, 2009).

Dentro de nosso conhecimento não tem sido realizado nenhum ensaio clínico para DTM em sujeitos com DF. Portanto, nossa proposta é identificar pessoas com DF e DTM que aceitem participar do protocolo que poderá contribuir para ajudar a aliviar os sintomas dolorosos intensos que ocorrem na DTM e na DF de forma duradoura e com menor chance de efeitos adversos e colaterais.

A saúde mental é um aspecto crucial a ser considerado em indivíduos com DF, a natureza crônica da doença, a dor associada e o impacto na vida diária podem ter efeitos psicológicos e emocionais significativos, por este motivo, associamos nesta pesquisa a necessidade de se conhecer o estado emocional dos participantes.

SAÚDE MENTAL EM INDIVÍDUOS COM DOENÇA FALCIFORME

Indivíduos com DF podem sentir ansiedade e depressão devido aos desafios e incertezas associados à sua condição (HARRIS, 2023). Lidar com a dor, visitas frequentes ao hospital, limitações nas atividades físicas e o potencial para complicações com risco de vida podem contribuir para sentimentos de angústia e tristeza (JONASSAINT, 2016).

Viver com DF pode resultar em estresse crônico, pois os indivíduos geralmente precisam controlar a dor, as consultas de saúde e o impacto da doença em suas vidas diárias. O estresse associado à DF pode levar à fadiga, dificuldades de concentração, distúrbios do sono e redução geral da qualidade de vida (JOHNSTON, 2022; HARRIS, 2023). Como resultado, a DF pode afetar as relações sociais e o bem-estar emocional. Indivíduos com DF podem enfrentar estigmatização, falta de compreensão dos outros e sentimentos de isolamento. As limitações impostas pela doença, como faltas à escola ou ao trabalho, também podem impactar nas interações sociais e na autoestima (JOHNSTON, 2022).

Há também as hospitalizações frequentes, os episódios dolorosos e as intervenções médicas que podem resultar em sintomas de estresse pós-traumático em indivíduos com DF, desde a infância. Experiências traumáticas associadas à DF podem desencadear ansiedade, flashbacks e sofrimento emocional (MOODY, 2022). Felizmente os indivíduos com DF podem

desenvolver várias estratégias de enfrentamento para lidar com os desafios físicos e emocionais de sua condição. Essas estratégias podem variar de buscar apoio social, envolver-se em atividades que proporcionem alívio emocional, praticar técnicas de relaxamento ou buscar apoio profissional de saúde mental (TOUMI, 2018). Assim, o acesso a profissionais de saúde mental que entendam os desafios únicos da DF é importante. Psicólogos, psiquiatras e conselheiros podem ajudar os indivíduos a desenvolver estratégias de enfrentamento, fornecer suporte para o bem-estar emocional e abordar suas preocupações psicológicas (ROBBINS, 2020).

A religiosidade, ou o nível de crença e prática religiosa, pode desempenhar um papel significativo na vida dos indivíduos com DF. Para muitos indivíduos com DF, a religiosidade e a espiritualidade servem como importantes mecanismos de enfrentamento (CLAYTON-JONES, 2016). A religião pode proporcionar uma sensação de conforto, esperança e significado diante dos desafios físicos e emocionais associados à doença. Acreditar em um poder superior, orar, rezar e implementar práticas religiosas podem oferecer consolo e apoio em tempos difíceis. Reuniões religiosas, como serviços religiosos ou grupos de oração, podem servir como locais onde as pessoas com DF podem encontrar compreensão, empatia e encorajamento. O sentimento de pertencimento e o apoio de outros crentes podem impactar positivamente o seu bem-estar geral (GOMES, 2019).

A religiosidade pode ter efeitos positivos no bem-estar psicológico, como maior resiliência, melhores habilidades de enfrentamento e um senso de propósito e esperança. Pode contribuir para reduzir o estresse, a ansiedade e a depressão em indivíduos com DF. É importante notar que a religiosidade e seu impacto em indivíduos com DF podem variar muito dependendo de crenças pessoais, fatores culturais e da comunidade religiosa específica em questão (WEBER, 2014). Os profissionais de saúde devem ser sensíveis às necessidades religiosas e espirituais dos pacientes e respeitar suas crenças, integrando-as em seus cuidados gerais sempre que apropriado (GOMES, 2019).

É essencial que os profissionais de saúde considerem as necessidades de saúde mental dos indivíduos com DF como parte integrante de seus cuidados gerais. Uma abordagem multidisciplinar que combine tratamento médico com suporte de saúde mental pode melhorar significativamente a qualidade de vida dos indivíduos que vivem com DF, pode também

aumentar a conscientização, reduzir o estigma e fornecer educação sobre como a saúde mental pode contribuir para um ambiente mais favorável para pessoas com DF. Por isto, a educação de práticas promotoras de saúde são fundamentais para estas pessoas.

PRÁTICAS PROMOTORAS DE SAÚDE PARA PESSOAS COM DOENÇA FALCIFORME

A prevenção desempenha um papel crucial na manutenção e melhoria da qualidade de vida dos indivíduos. Ao tomar medidas proativas para prevenir hábitos nocivos, lesões e outras condições adversas de saúde, os indivíduos podem reduzir o impacto em seu bem-estar físico, mental e emocional. A prevenção se concentra na promoção da saúde e bem-estar geral, adotando comportamentos saudáveis e escolhas de estilo de vida. Isso inclui manter uma dieta equilibrada, praticar atividade física regular, evitar o consumo de tabaco e álcool e controlar o estresse. Ao praticar medidas preventivas, os indivíduos podem reduzir o risco de desenvolver doenças crônicas, melhorar seu sistema imunológico e aumentar sua vitalidade geral, estas premissas estão indicadas no manual de educação em saúde, para o autocuidado do indivíduo com DF, desenvolvido pelo governo com acesso on-line (BRASIL. MINISTÉRIO DA SAÚDE, 2008 https://bvsms.saude.gov.br/bvs/publicacoes/manual_ educacao_saude_volume 1. Pdf). Mas em nossas entrevistas, ficou evidenciado que nada disto é ensinado para as pessoas com DF do recôncavo baiano.

A prevenção está intimamente ligada ao aumento da longevidade e ao envelhecimento saudável. Ao priorizar medidas preventivas ao longo da vida, os indivíduos podem potencialmente estender sua vida útil e melhorar sua saúde geral. Ações preventivas, como exames regulares de saúde, exames para doenças comuns e manutenção de um estilo de vida saudável, contribuem para melhores resultados de saúde, maior independência e maior qualidade de vida nos anos posteriores. A prevenção não é benéfica apenas para os indivíduos, mas também para a sociedade como um todo. Ao prevenir doenças e condições, a carga sobre os sistemas de saúde e os custos associados podem ser significativamente reduzidos. As medidas preventivas concentram-se na intervenção precoce, o que pode ajudar a evitar hospitalizações e tratamentos de longo prazo dispendiosos (HULIHAN et al. 2017).

A prevenção capacita os indivíduos assumirem o controle de sua saúde e a tomar decisões informadas. Ao fornecer educação, recursos e apoio para medidas preventivas, os indivíduos podem se envolver ativamente no gerenciamento de sua própria saúde. Essa sensação de empoderamento e autoeficácia contribui para uma maior sensação de bem-estar, confiança e melhoria da qualidade de vida. É importante observar que a prevenção é um esforço para toda a vida e requer compromisso e esforço contínuos, por isso podemos incluir todo o grupo familiar como participantes para assegurar o sucesso. Os materiais educativos podem ser, vídeos, artigos e panfletos, dentre outros, tendo amplo suporte para a qualidade de sua produção (MOREIRA et al. 2003).

Adotando hábitos saudáveis, buscando cuidados preventivos regulares e fazendo escolhas informadas, as pessoas podem melhorar significativamente sua qualidade de vida e promover bem-estar a longo prazo, este foi o objetivo do panfleto desenvolvido pelo grupo de pesquisa tendo como base conceitos de saúde preventiva (ABDALA *et al.,* 2018).

2.1. ARTIGO 1: SICKLE CELL DISEASE CHRONIC JOINT PAIN: CLINICAL ASSESSMENT BASE ON MALADAPTATIVE CENTRAL NERVOUS SYSTEM PLASTICITY.

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Sickle cell disease chronic joint pain: Clinical assessment based on maladaptive central nervous system plasticity

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Chronic joint pain (CJP) is among the significant musculoskeletal comorbidities in sickle cell disease (SCD) individuals. However, many healthcare professionals have difficulties in understanding and evaluating it. In addition, most musculoskeletal evaluation procedures do not consider central nervous system (CNS) plasticity associated with CJP, which is frequently maladaptive. This review study highlights the potential mechanisms of CNS maladaptive plasticity related to CJP in SCD and proposes reliable instruments and methods for musculoskeletal assessment adapted to those patients. A review was carried out in the PubMed and SciELO databases, searching for information that could help in the understanding of the mechanisms of CNS maladaptive plasticity related to pain in SCD and that presented assessment instruments/methods that could be used in the clinical setting by healthcare professionals who manage chronic pain in SCD individuals. Some maladaptive CNS plasticity mechanisms seem important in CJP, including the impairment of pain endogenous control systems, central sensitization, motor cortex reorganization, motor control modification, and arthrogenic muscle inhibition. Understanding the link between maladaptive CNS plasticity and CJP mechanisms and its assessment through accurate instruments and methods may help healthcare professionals to increase the quality of treatment offered to SCD patients.

KEYWORDS

musculoskeletal pain, symptoms assessment, red cell disorders, practical reasoning, evidence-based medicine

Introduction

Sickle cell disease (SCD) is a set of hereditary diseases caused by substituting glutamine acid for valine at the sixth position of the hemoglobin β chains, which leads to the presence of hemoglobin S (HbS). Conditions such as low oxygen concentration, hypovolemia, and others can precipitate the structure twisting of HbS molecules fibers forming the sickle-shaped red blood cell membrane causing vaso-occlusive crises, which are the main reason for pain complaints in this population throughout life (1). The pain in SCD individuals can be acute or chronic and can emerge from nociceptive, inflammatory, and neuropathic mechanisms (2). SCD pain syndromes are classified as intermittent, persistent pain between vaso-occlusive crises and chronic pain complications (3).

Among the chronic pain complications, chronic joint pain (CJP) is a common condition in SCD that may also be associated with several musculoskeletal problems such as osteomyelitis, dactylitis, arthritis, and osteonecrosis both in adult and pediatric individuals (4–6). These chronic pain complications have a higher incidence in SCD and play an additional role in chronic pain generation (4, 5). The CJP may be focal when involving a single joint or multifocal when involving more than one joint (7). However, to date, few studies demonstrate the influence of maladaptive plasticity in the central nervous system (CNS) in the maintenance of CJP in SCD individuals, although these individuals have chronic pain with nociceptive, neuropathic, and possible nociplastic pain characteristics (8, 9). The presence of central sensitization, for example, is related to more episodes of pain crisis and frequent hospitalizations (10). Of utmost importance, few studies were developed explicitly for CJP in SCD.

The poor correlation between structural lesions, the intensity of self-reported pain (11), and the diffuse nature of the symptoms make CJP assessment a challenge for clinicians and healthcare professionals. In general, healthcare professionals have poor knowledge about pain neuroscience mechanisms (12) and reliable ways of assessing it (13, 14). This poor knowledge goes against the International Association Study of Pain (IASP) recommendation in the declaration of the Montreal meeting, which highlights that all people with pain have the right to have access to appropriate assessment and treatment of the pain by adequately trained healthcare professionals (15). Thus, considering the potential relation between CJP and central maladaptive plasticity in SCD individuals and the deficit in healthcare professionals' knowledge about pain neuroscience mechanisms and pain assessment, this review aims to highlight the mechanisms of CNS maladaptive plasticity that might be related to CJP in SCD and propose a battery for reliable musculoskeletal assessment adapted to those patients.

Method

This review was carried out in the PubMed and SciELO databases, searching for information that could help in the understanding of the mechanisms of CNS maladaptive plasticity related to pain in SCD and that presented assessment instruments/methods that could be used in the clinical setting by healthcare professionals who manage chronic pain in SCD individuals. There was no limit placed on the publication year, and the searching was carried out through a combination of keywords such as Sickle Cell Disease and Joint Pain or Chronic Pain or Pain Assessment or Central Sensitization Evaluation or Painful Movement Assessment, Chronic Joint Pain and Cortical Reorganization or Arthrogenic Muscle Inhibition or Chronic Inventory Central Sensitization or Quantitative Sensory Test or Clinical Evaluation. In addition, the reference list of papers also was searched.

Chronic joint pain in SCD: An overview of the problem

International Association Study of Pain defines pain as "An unpleasant sensory and emotional experience, associated with, or resembling that associated with, actual or tissue damage" (16). Pain plays a vital role in the organism's defense reaction to a hostile environment, and evidence of this is that in individuals with pain insensitivity, injuries are not perceived as such, decreasing life expectancy (17). On the other hand, chronic pain is persistent beyond 3–6 months, has no functional role, and is responsible for rendering dysfunctional several biological systems (18). In SCD, the constant joint tissue injuries secondary to the vaso-occlusive crisis are critical in developing chronic joint pain.

Primary afferent nociceptors richly innervate the joint in their capsule and synovium (19). These fibers are mostly from types Aδ and C and can be classified into two types: (a) True nociceptors; (b) Silent nociceptors. True nociceptors respond to mechanical nociceptive stimuli even in non-pathological conditions. As for the silent nociceptors, to respond to this type of stimuli, they must be primarily sensitized by inflammation-inducing aggressors (19, 20). The primary afferent nociceptors have on their membranes a wide variety of transient receptor potential ion channels that are responsible for the transduction of a wide variety of noxious stimuli arising from high magnitude mechanical, thermic, or chemical origins (21, 22). The nervous system sensitization occurs basically by neurogenic inflammation, mast cell activation, N-methyl-D-aspartate (NMDA) receptors activation, and glial activation (1, 2), which play an important role in the maintenance and subsequent pain chronicity in SCD individuals.

After joint tissue injury, the pro-inflammatory mediators such as bradykinins and prostaglandins interact with receptors or transient receptor potential vanilloid type 1 (TRPV1) of nociceptive fibers and sensibilize them to augment their response to a noxious stimulus (2, 22). Once activated, the nociceptors release peptides and neurotransmitters such as calcitonin gene-related peptide and substance P, which further contribute to the inflammatory response, causing vasodilation, swelling, and mast cell activation. Mast cells act by degranulation of histamine, which further sensibilize nociceptors (23). Interestingly, serum levels of substance P are increased in SCD individuals during the vaso-occlusive crisis and baseline state (24) and have been associated with to use of hydroxyurea (25). This cascade of biochemical events lowers the activation threshold of true nociceptors and recruits previously unresponsive silent nociceptors, which induce hyperalgesia and allodynia in joint pathologies in SCD individuals (26).

N-methyl-D-aspartate receptors are involved in the long-term potentiation process and are a crucial player in the chronicity of pain (27). At the spinal cord level, the constant nociceptive information arrives in the dorsal horn and provoke the release of glutamate neurotransmitter in presynaptic terminals that interacts with NMDA receptors post-synaptic (3). When NMDA receptors are activated, the nitric oxide is synthesized in the presynaptic terminals, increasing the expression of voltage-gated Ca2+ channels mainly responsive to P substance and glutamate (3). Concurrently, glial activation releases pro-inflammatory cytokines and more glutamate in this synaptic environment (1, 3). Thus, these series of intracellular signaling cascades augment and facilitate the transmission of nociceptive information.

These nociceptive information reaches higher encephalic areas, such as Rostral Ventromedial Medulla (RVM), Periaqueductal Gray Matter (PAG), thalamus, amygdala, anterior cingulate cortex, somatosensory, prefrontal, and motor cortices (28, 29) that process and modulates the nociceptive information. However, nociceptive modulation can occur before reaching the thalamus and other brain structures (30). Once that nociceptive information reaches the thalamus, it processes it and redirects it to cortical areas of the primary and secondary somatosensory cortex through thalamocortical and thalamus-amygdala connections (29). The PAG, in turn, receives inputs from these superior centers and sends them to the RVM medulla, which through axonal fibers of "on" and "off" cells, modulate neuronal activity, facilitating or inhibiting the transit of nociceptive information in the dorsal horn of the spinal cord both presynaptic and post-synaptic (30, 31). This complex endogenous mechanism forms a pain processing and control system, often presenting a maladaptive function in chronic joint pain (Figure 1).

Maladaptive CNS plasticity mechanisms and ways to evaluate it

Dysfunction of descending inhibitory control in CJP

Central nervous system has various ways of inhibiting the input of pain information to higher processing centers. Descending inhibitory control is a mechanism of diffuse pain inhibition. Studies with conditions of CJP similar to SCD, such as hip and knee osteoarthritis, showed that the descending inhibitory control dysfunction might be an important triggering factor for central sensitization and chronic pain (32). Although some studies have found no consistent results about dysfunctions of descending inhibitory control in adult SCD individuals (10, 33), neuroimage data from another study with adult SCD individuals showed that there is an increased resting-state functional connectivity between the PAG and cerebellum in SCD individuals (34) which can affect RVM's "on" and "off" cells activity. In pediatric SCD individuals, the dysfunctions of the descending inhibitory control are few explored, but data from non-SCD individuals has shown that deficient endogenous pain inhibition can stem from painful experiences during infancy (35, 36). Therefore, these data make us think that the function of the descending inhibitory control system in SCD still needs to be better understood and evaluated in the clinical context.

One of the traditional ways of assessing descending pain inhibitory system is through the paradigm of Conditioned Pain Modulation (CPM), previously known as "counter-irritation," "pain inhibits pain," and "heterotopic noxious conditioning modulation," and "diffuse noxious inhibitory control"(37). This phenomenon is activated after a set of intense and/or noxious stimuli, making it a protective endogenous response to aggression. The evaluation of descending inhibitory control by the CPM method should be recommended for SCD individuals due to the malfunctioning of this mechanism is closely related to the persistence of joint pain in musculoskeletal conditions such as osteoarthritis and temporomandibular dysfunction (32, 38, 39) (Figure 2). However, clinicians should be aware that the long-term pain, and the use of opioid agents can result in a reduced response of CPM scores (40).

In CPM assessment, a pressure threshold meter for applying painful mechanical stimulus in the thenar region of the non-dominant hand has a good coefficient of intra-session reliability (ICC >0.75). It seems to be a reliable method for performing a Painful Stimulus Test (PST). The pain caused by the mechanical stimulus must be of moderate intensity (41, 42). In turn, the Painful Conditioning Stimulus Test (PCST) can be done with cold or hot water. However, the immersion of the dominant hand in a water vessel with a temperature of 46.5°C has a good Intraclass Correlation Coefficient (ICC = 0.79) (42) and

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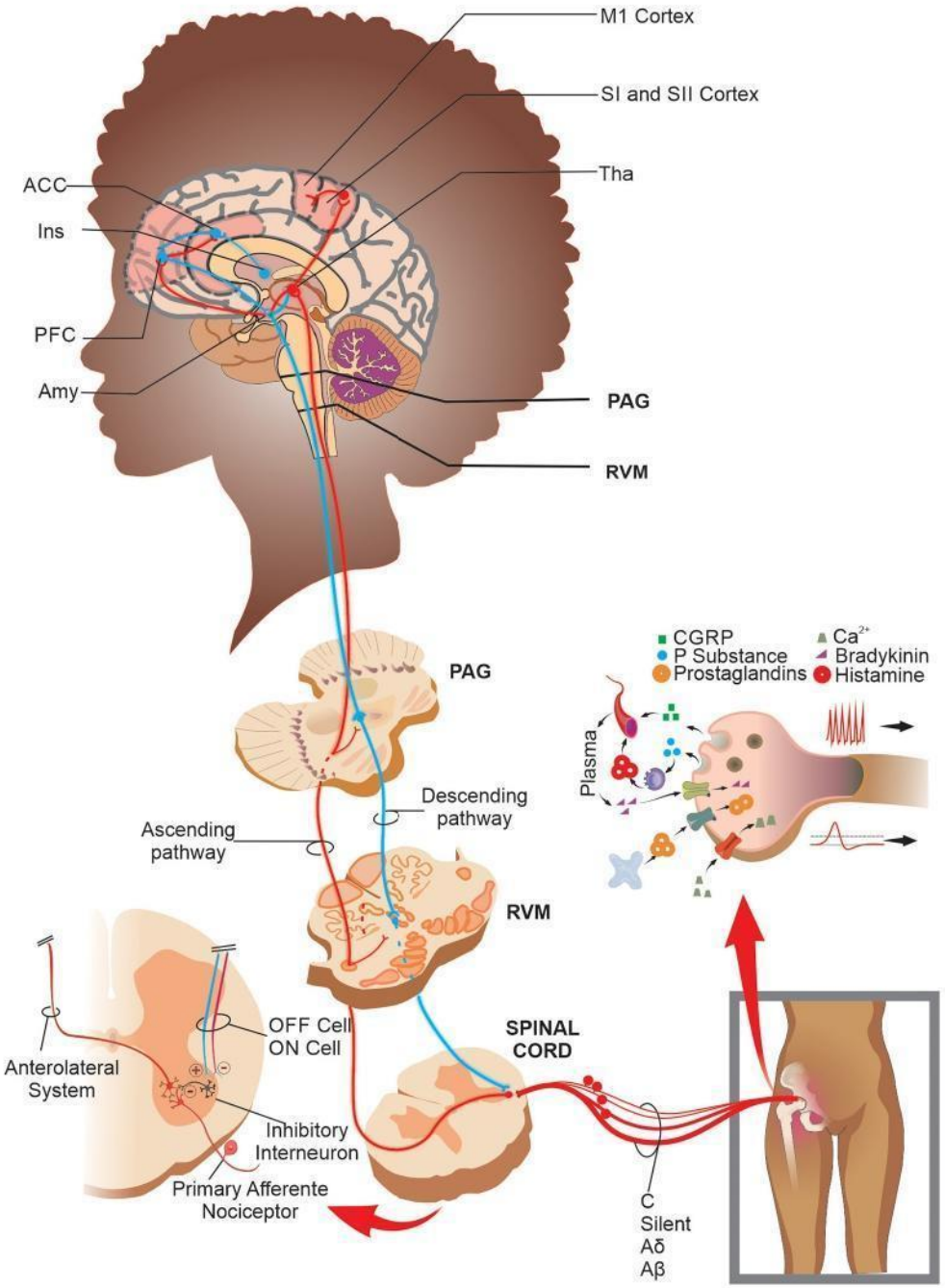

FIGURE 1
Schematic drawing of the peripheral sensitization, processing, and nociceptive modulation in joint pain: After a noxious stimulus in the joint, the TRP channels in true nociceptors transduce the nociceptive information and lead it to second-order neurons in the spinal cord. In addition, when there is a joint injury, a massive release of the pronociceptive chemical substances in/by free nerve endings promotes a depolarization threshold decrease and an increase in firing frequency rate in both true and silent nociceptors and mechanical receptors. The nociceptive information reaches the CNS, which processes and modulates it through brain networks and the PAG-RVM system. Specifically, in SCD patients, there is increased functional connectivity in areas such as PFC, ACC, M1, SI, and SII cortices. Abbreviations: ACC, anterior cingulate cortex; Amy, amygdala; CGRP, calcitonin gene-related peptide; Ins, insula; M1, primary motor cortex; PAG, periaqueductal gray matter; PFC, prefrontal cortex; RVM, rostral ventromedial medulla; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; Tha, thalamus; TRP, transient receptor potential.

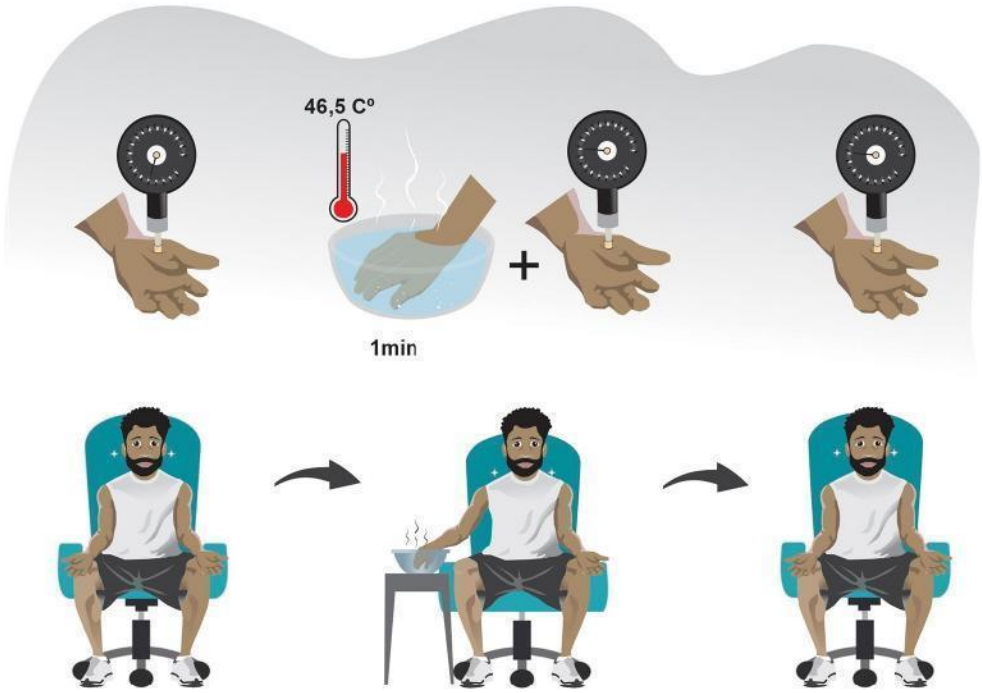

FIGURE 2
Schematic drawing of the conditioned pain modulation assessment: CPM can be assessed in three steps in the clinical setting. (1) A PST is made in the non-dominant side of the body (usually the thenar eminence). (2) After a sufficient period so that the pain caused by the PST has ceased, a PCST is made in a heterotopic region distant from the initially stimulated region and preferably on the contralateral side of the body, lasting 1 minute. (3) The PST is again applied immediately after or concomitantly to a PCST. Abbreviations: CPM, conditioned pain modulation; PST, painful stimulus test; PCST, painful conditioning stimulus test.

is more recommended in the SCD context because it can avoid a vaso-occlusive crisis during the evaluation. Using a thermometer to verify the heat dissipation and ensure the ideal temperature during immersion and using the same kilograms-force generated by the pressure threshold meter during the PST before and after the PCST may decrease potential measurement biases (41, 42).

The quantification of the CPM can be made according to the following equation:

$$CPM = piPST1 - piPST2$$

Where piPST1 corresponds to the pain intensity caused by the first painful stimulus test and piPST2 pain intensity caused by a second painful stimulus test. A positive result indicates the presence of a preserved descending inhibitory control, while a negative result indicates the opposite (42).

Central sensitization in CJP

Previously, the term "centralized pain" was often used to classify the pain experienced by patients with central sensitization. However, this term was not part of recognized by the IASP. Following the proposition of a research group (43), an IASP force task recently added a new pain term called "nociplastic pain" into the list of taxonomic definitions for pain (44), even though it caused a comprehensive discussion related to its real need and the best way for it to be defined (45–47). This new term proposes to differentiate the "pain that arises from altered nociception, despite there is no clear evidence of actual or threatened tissue damage that causes peripheral nociceptor activation or evidence of disease or injury to the somatosensory system that causes pain" from those kinds of pains typically classified only as nociceptive or neuropathic.

The central sensitization mechanisms involve the perpetuation of joint pain that can be favored by poor descending inhibitory control, which over time causes phenotypic alteration of Aβ fibers specialized in conducting non-painful stimuli (30). In addition, nociceptive information is not properly inhibited in the dorsal horn of the spinal cord and advances freely until it reaches higher areas of the nervous system, causing a central sensitization of multiple structures (48). Central sensitization of multiple structures involves a maladaptive change of important anatomic/functional networks that process information in all pain dimensions, i.e., sensory,

emotional, and cognitive (49). Due to the important role in pain processing, these anatomic/functional networks are called the pain connectome (49).

In conditions of chronic non-SCD pain, the default mode network (DMN), the salience network (SLN), the sensorimotor network (SMN), and the antinociceptive system are connectome strongly affected by central sensitization (49, 50). The DMN includes the medial prefrontal cortex, posterior cingulate cortex, precuneus, and lateral parietal cortices and is activated in a resting state of the mind when the individual is instructed not to think about anything specific (49). Next, SLN comprises the bilateral insula cortices, anterior cingulate cortex, and middle cingulate cortex and is activated by salient stimuli that stand out from the environment (e.g., nociceptive stimulation caused by the movement of an inflamed joint) (51). The SMN includes bilateral primary and secondary somatosensory cortices, primary motor (M1) cortex, and the supplementary motor area (SMA) and is involved in the descriptive sensory processing of pain (51). Finally, the antinociceptive system comprises the PAG and RVM, which, as previously discussed, are core structures involved in pain modulation (49). This pain connectome is dynamic due to the capacity to generate connections within and between themselves (49).

In SCD individuals with chronic pain, some studies using functional Magnetic Resonance Image (fMRI) alone or coupled with Electroencephalography (EEG) have found a maladaptive change in the pain connectome (34, 51–53). Their results showed that SCD individuals with high levels of pain and hospitalizations had an increased resting-state functional connectivity between SLN, DMN, and SMN structures (e.g., dorsal anterior cingulate cortex and the right precuneus, secondary somatosensory cortex, and the left precuneus, inferior parietal lobule and the middle cingulate cortex, right posterior cingulate cortex and the right primary somatosensory cortex) when compared with individuals with low levels of pain and hospitalizations (52). SCD individuals also presented hypoconnectivity of SMN structures (i.e., motor cortex) compared to healthy controls and between other regions outside of the SMN, such as the dorsolateral prefrontal and parietal cortices (51). In addition, this same study found that SCD increased functional connectivity between DMN and SLN structures (e.g., precuneus/ posterior cingulate cortex and temporal regions) (51). Finally, studies comparing SCD individuals and healthy controls found changes in functional connectivity of the PAG (a core structure of the antinociceptive system) (34, 53). Functional connectivity between the PAG and the anterior cingulate cortex (a structured core of SLN) is decreased in SCD patients when compared to healthy individuals but increased between the PAG and several cortical regions that play functions of sensory processing, motor processing/executive function, emotion and memory/learning when SCD patients were compared with those without pain (53).

The sensitization of the pain connectome may be associated with multiple musculoskeletal and non-musculoskeletal symptoms found in individuals with severe chronic pain. These include decreased pain threshold, expansion of pain receptive field to further regions unrelated to pain, interpretation of non-painful stimuli as painful, photophobia, bowel diseases, and sleep, attention, and mood-altering (54, 55). The emergence of these phenomena may trigger the change of the clinical status from a musculoskeletal disease to a multi-systems disease. Typically, those symptoms are under-evaluated by clinicians and are not related to the presence of persistent pain. However, these aspects are essential as they help in decision-making and prediction of patient outcomes, as evidenced by a study that showed that individuals with central sensitization due to chronic pain secondary to osteoarthritis of the knee are five times more likely to have pain refractory to surgical treatment of total knee arthroplasty (56). In SCD individuals, central sensitization has been associated with increased vaso-occlusive crises, poor sleep quality, and psychosocial disorders (10). For this reason, this should be considered during the evaluation since this is probably one of the main causes of refractory joint pain (57).

Sensitivity hyperphenomena, such as allodynia or hyperalgesia to thermic and vibratory stimuli, and mechanical and thermal temporal summation, have been associated with central sensitization in non-SCD individuals with chronic pain (57). These sensitivity deficits are also found in pediatric SCD individuals, among lower mechanic pain, cold pain, heat pain, thermal detection thresholds, and heat pain tolerance (58). In addition, studies with adult SCD individuals showed that they also present sensory alterations expressed by a higher intensity of cold pain, heat pain, thermal temporal summation, and mechanic pain is found in compared with healthy controls (33, 59).

Some methods are essential in evaluating central sensitization/nociplastic pain characteristics in clinical and research settings because they can help evaluate whether CJP in SCD is influenced and/or supported by central sensitization. The central sensitization inventory (CSI) is an evaluation instrument that, although non-specific to SCD, is highly recommended to be used in clinical practice in the SCD context (54). The CSI is divided into two parts, A and B. In part A, 25 descriptive alternatives of multidimensional symptoms are associated with central sensitization. Each alternative has a score varying from zero (never) to four (always), with a maximum total score of 100 points. In part B, 10 alternative clinical conditions are recognized as central sensitivity syndromes (CSS) (60). The cut-off at 40 points has excellent levels of sensitivity (81%), specificity (75%), positive predictive (2.93), and negative predictive value (0.52) to recognize central sensitization (60). However, despite these good diagnostic accuracy values, the CSI still needs to be validated in SCD individuals, and its results should be interpreted with caution. Due to the need for severity ratings of central sensitization, a 10-point classification

with severity intervals was created, consisting of the following categories: subclinical (≤29), mild (30–39), moderate (40–49), severe (50–59) and extreme (≥60) (61). This severity rating allows better utilization of CSI in clinical practice and may help as a parameter of the therapeutic response. This instrument has been culturally translated and validated in several languages (62, 63).

Quantitative sensory tests (QST) are another way to assess central sensitization (10, 57, 64). All systematic sensory evaluations that allow quantified responses can be viewed as a QST. However, a set of QST (mechanical, thermal, and vibratory) was standardized to evaluate the integrity of the somatosensory system and to guarantee the accuracy and reproducibility of the findings (65). QST protocols consider several sensory parameters, as well as biological aspects ranging from body temperature to trophic changes in the musculature (64, 65). However, although QST protocols can be performed in both bedridden and non-bedridden individuals, their complete execution is time-consuming and can be impracticable in some clinical contexts. In this context, there are some attempts to validate a bedside QST as a low-cost and time-efficient alternative (66, 67).

The bedside QST can be easily applied in clinical routine, and its execution does not require a large training time. Studies showed that bedside QST protocol using low-cost equipment could be used in each step of the sensory assessment procedure, such as (a) 3 cm^2 metal coin/piece with 22°C or 37°C (cold/warm detection thresholds); (b) cotton wool/Q-tip (mechanical detection threshold); (c) tuning fork (vibration detection threshold); (d) 10-ml syringe sealed or toothpick (mechanical and pressure pain threshold); (e) glass vial filled with hot water 40°C or metal pieces with 45°C (heat pain threshold); (f) ice cubes in a plastic bag or metal piece with 8°C (cold pain threshold); (g) toothpick (temporal summation) (66, 67). However, the correlation between bedside QST and standard QST protocol is variable and impacted by the expertise of a healthcare professional.

A study proposed three steps of a decision tree that helps clinicians to interpret the findings of QST evaluation of mechanical detection threshold (Aβ fibers), cold pain (Aδ fibers), and heat pain (C fibers), specifically in SCD individuals (8). In the clinical setting, QST stimuli should be evaluated in both painful and non-painful sites. In the first step, if all QST findings are negative, the clinical interpretation must be that there is no central or peripheral sensitization. In the second step, if mechanical stimuli findings in the non-painful site are positive, then the clinical interpretation must be that there is central sensitization. In the third step, if cold or heat pain is present in the painful site and these same painful stimuli result negative in the non-painful site, then the clinical interpretation must be that there is peripheral sensitization. Finally, the decision tree proposes that if all three steps result in negative findings, then the interpretation must be that there is mixed pain (8).

The safety of the QST protocol in the clinical setting has been previously tested in subjects with SCD, and there was no perpetuation or worsening of pain after its application (8). However, attention is necessary because data show that after QST testing in SCD patients, there are changes in pro-inflammatory biomarkers such as increased levels of Interleukin 6 (IL-6), substance P, and tumor necrosis Factor-alpha (TNFα) (33). In SCD, the thermal pain threshold (TPT) to cold <17.01°C and heat <43.91°C are indicative of impaired nerve sensitivity, and pressure pain threshold (PPT) <4.42 g is indicative of the existence of altered sensory function (68). Thermal pain threshold (TPT) assessment with temperature in 32°C baselines and an increasing/decreasing temperature at a rate of 1.5°C/s is used in clinical settings (ICC >0.55) (69). In cases of non-SCD pain, specifically osteoarthritis of the knee, the PPT increasing pressure at a rate of 0.5 kgf/s has a good diagnostic reliability value varying according to the evaluated joint site (ICC: 0.64–0.73) (70).

Finally, another way of assessing central sensitization in individuals with SCD uses its typical clinical criteria checklist (71) developed by a consensus of experts. Although this checklist is non-specific to SCD individuals, it is also useful for clinicians and healthcare professionals because it helps identify signs and symptoms characteristic of central sensitization, such as pain disproportionate to injury, disproportionate aggravating/easing factors, and psychosocial symptoms, and diffuse palpation. These discriminative items indicate the presence of central pain sensitization with excellent accuracy values (sensitivity 91.8%, specificity 97.7%, positive predictive value 91.8, and negative predictive value 97.7) (72). Thus, using these instruments during the evaluation of SCD individuals with CJP may help in the more precise knowledge of the mechanism underlying the patient's pain. This clinical criteria checklist provides a basis for better clinical decision-making and possibly less chance of non-adherence to the proposed treatment.

Motor control modifications and cortical reorganization in CJP

In the face of pain, the neuromusculoskeletal system undergoes adaptive motor modifications that affect motor control and joint mechanics. These modifications have been studied over time due to the importance of their understanding for both clinicians and researchers. Therefore, one theoretical model (73) was established to clarify the interaction between pain and motor control changes making the following propositions: Firstly, the adaptation of the motor control to pain is a consequence of the redistribution of the activity within and between muscles. Secondly, the change in mechanical behavior

initially has a protective function of preventing further pain or injury. However, in the long term, it involves changes in various levels of the nervous system, which lead to increased joint load, decreased mobility, and variability of movement and muscle weakness (73).

In the presence of CJP, motor and sensory primary cortical reorganization are associated with motor control impairment. This cortical reorganization has been demonstrated in non-SCD adult individuals with low back pain (74, 75), chronic lateral epicondylalgia (76), osteoarthritis of the knee (77), and chronic patellofemoral pain (78), but there is no study with pediatric individuals. This cortical reorganization is expressed through the overlap (i.e., blurring) or retraction in the areas of somatotopic representation of the motor homunculus. The greater the cortical reorganization, the greater the perpetuation of the pain (77).

The intracortical inhibitory system, modulated by tonic GABAergic activity, plays an important role in the development of cortical somatotopic representations. This specific function is due to mechanisms that differentiate cortical efferent motor actions, either by facilitating muscle activation during a motor task or by inhibiting undesirable muscular activations (79). Although changes in intracortical inhibition are not a consensus (80), intracortical inhibitory dysfunction mediated by GABAergic connections has been demonstrated in individuals with chronic pain (81) through Transcranial Magnetic Stimulation (TMS), a technique that has been often used to assess cortical connectivity.

Transcranial magnetic stimulation also allows the evaluation of muscles' cortical representations through cortical mapping. Briefly, cortical mapping through TMS is made using a set of pulses with intensity fixed in accord with a percentage of the maximal stimulator output (82). This set of pulses

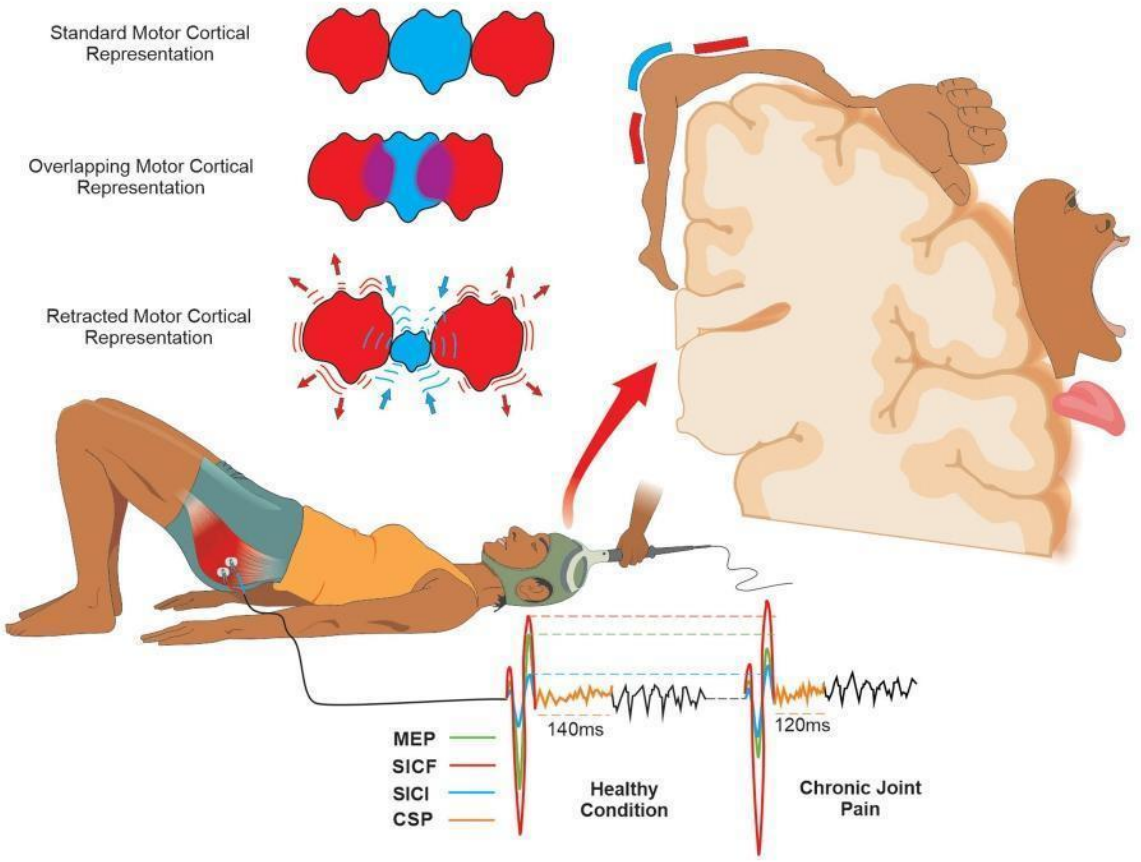

FIGURE 3
Schematic drawing of the measures of motor cortical excitability with tms and mapping of motor cortical representation in joint pain condition: Using TMS, Motor Cortical Excitability can be expressed by corticospinal (MEP) and intracortical measures (ICF, IIC, and ǂCSP). In the CJP, the CSP, SICI, and MEP are decreased, and the SICF is increased compared to the healthy condition. The Standard Motor Cortical Representation in the presence of pain can classically be changed into two possible basic forms. (1) An Overlapping of the Motor Cortical Representation adjacent to that affected by pain; (2) A Retraction of the Motor Cortical Representation affected by pain and an increase in the adjacent representation. ǂCSP is obtained only when the assessment is made during a muscle contraction. Abbreviations: CSP, cortical silent period; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; MEP, motor evoked potential; TMS, transcranial magnetic stimulation.

should be applied at various scalp sites using a figure-of-eight coil and a spatial coordinate system referenced to the vertex (83), and the amplitude of MEPs evoked in contralateral muscles is measured (82). However, although the assessment of cortical mapping through TMS can be useful in clinical settings, there are no studies evaluating its diagnostic reliability (Figure 3).

In SCD individuals, CJP is possibly associated with maladaptive motor behavior and cortical representation changes due to their chronic and disabling pain (7). The changes in functional connectivity of the structures are involved in the descending inhibitory control of nociceptive information in individuals with SCD (34) and can be associated with intracortical inhibition (84). Thus, although TMS evaluation is not specific to SCD individuals, clinicians and healthcare professionals should be used to investigate these possible cortical alterations both in adult and pediatric SCD individuals with CJP.

Arthrogenic muscle inhibition and CJP

It is common that after joint injuries, there is the presence of weakness in the adjacent involved musculature. The possible cause for this muscle weakness is the presence of a central reflex inhibition that can provoke a failure to fully recruit the motor units and/or a suboptimal firing of the motor units that are recruited (85), preventing the complete activation of the surrounding musculature to the injured joint during a maximal voluntary muscular contraction. This phenomenon has been called Arthrogenic Muscle Inhibition (AMI) (86).

Arthrogenic muscle inhibition can be interpreted as a mechanism of physiological protection to prevent new lesions and potentiation of tissue repair (87). However, AMI may persist for several months or even years after injury (88). This persistence may compromise the rehabilitation process by negatively impacting strengthening protocols, thus, contributing to injury progression and

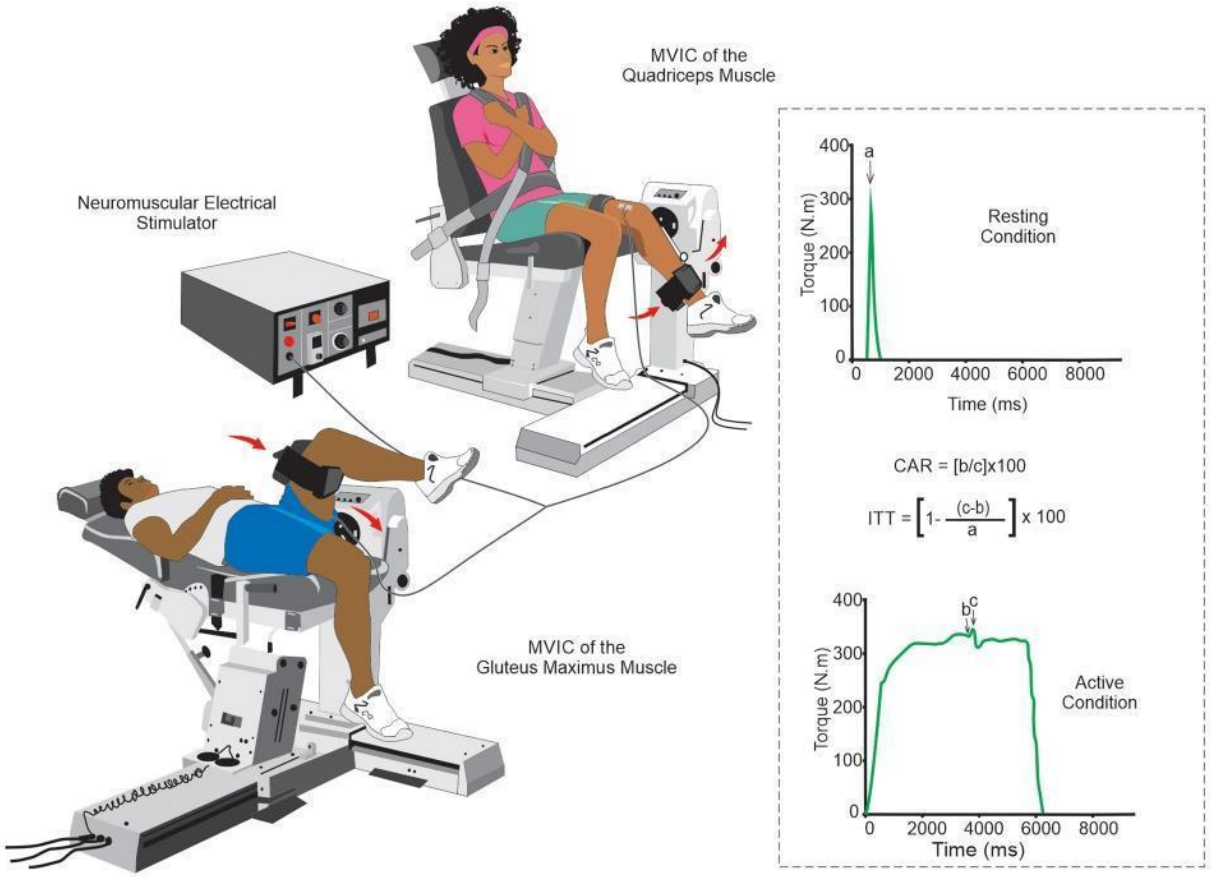

FIGURE 4
Schematic drawing of the arthrogenic muscle inhibition evaluation by central activation rate and interpolated twitch technique: Although the knee joint is the most evaluated with the CAR and the ITT methods, their methodological simplicity allows the assessment of AMI to be also used in other joints (e.g., the hip joint in the figure above). The quantification of the evaluation can be done using specific mathematical formulas for each method. a. stimulus-evoked torque at rest; b. voluntary torque at the time of stimulus delivery; c, peak torque evoked due to the electrical pulse. Abbreviations: AMI, arthrogenic muscle inhibition; CAR, central activation rate; ITT, interpolated twitch technique.

TABLE 1 Summary of the main central nervous system maladaptive changes, assessment methods, clinical interpretation, and diagnostic reliability that can be used in CJP related to sickle cell disease.

CNS maladaptive changes in chronic joint pain	Assessment methods or instruments	Clinical interpretation	Diagnostic reliability
Insufficiency of descending inhibitory control	• Conditioned pain modulation (42)	• piPST1 > piPST2 = Descending inhibitory control is functioning • piPST1 < piPST2 = Descending inhibitory control system is faulty	• PST: Pressure threshold meter (ICC >0.75) • PCST: Hot water in 46.5°C (ICC = 0.79)
Central sensitization	• Central sensitization inventory (60,61)	• Severity ratings: Subclinical (≤29) Mild (30-39) Moderate (40-49) Severe (50-59) Extreme (≥60)	• Cut-off at 40 points: Sensitivity (81%) Specificity (75%) Positive predictive value (2.93) Negative predictive value (0.52)
	• Quantitative sensory test (68-70)	• TPT to cold <17.01°C and heat <43.91°C are indicative of impaired nerve sensitivity • PPT <4.42 g is indicative of the existence of an altered sensory function	• TPT: 32°C baselines with decreased/increased temperature at a rate of 1.5°C/s (ICC >0.55) • PPT: Increasing pressure at a rate of 0.5 kgf/s (ICC: 0.64–0.73)
	• Clinical criteria checklist (71,72)	• Pain disproportionate to injury disproportionate aggravating/easing factors; psychosocial symptoms; diffuse palpation	Sensitivity (91.8%) Specificity (97.7%) Positive predictive value (91.9) Negative predictive value (97.7)
Modifications of motor control and cortical reorganization	• Cortical mapping by transcranial magnetic stimulation (77)	• There is an overlap (blurring) or retraction in the areas of somatotopic representation of the motor cortex	
Arthrogenic muscle inhibition	• Central activation rate (91,96)	• When the central activation rate is below 95%, it is an indication that there are muscle fibers that are not being activated by central neural pathways	• CAR: Within- measurement (ICC = 0.94) Between-measurement (ICC = 0.86)
	• Interpolated Twitch Technique (85,87)	• The higher the proportion, the greater the number of muscle fibers that are not centrally activated	• ITT: Within measurement (ICC = 0.89)

Abbreviations: CAR, Central Activation Rate; ITT, Interpolated Twitch Technique; ICC, Intraclass Correlation Coefficient; PCST, Painful Conditioning Stimulus Test; piPST1, pain intensity of first Painful Stimulus Test; piPST2, pain intensity of second Painful Stimulus Test; PST, Painful Stimulus Test; TPT, Thermal Pain Threshold; PPT, Pressure Pain Threshold.

associated dysfunction (87). Common conditions such as joint pain, ligamentous laxity, and joint effusion are potential factors that facilitate the establishment of AMI (86).

In the AMI, there is an alteration of the firing of the joint receptors that send signals for the medullary inhibitory interneurons, causing inhibition of the activity of the alpha motoneurons and, consequently, the musculature involved in the affected joint (87). Joint pain may contribute to the AMI due to the alteration of the excitability of the flexor reflex pathway (86), which has the characteristic of facilitating the flexor and inhibiting the extensor muscles in the region surrounding the painful joint (89). In addition, joint pain in the knee has been associated with decreased muscle activation of the quadriceps (90, 91).

Although a systematic review has shown that the mechanisms of AMI are mostly studied in knee joint injuries (91), it may also be observed in individuals with pathologies in the hip. In this condition, AMI may be represented by a decrease in Gluteus maximus activation during extension activity in pronation (92). In this sense, as the most affected joint in SCD is the hip due to avascular osteonecrosis (7), the healthcare professional must be aware of the possibility of AMI playing an important role in this condition. However, many SCD individuals are likely quite physically deconditioned due to limited physical activity because of fatigue (93) or concerns about triggering vaso-occlusive crises after physical activity (94). This clinical characteristic in SCD individuals can make AMI assessment challenging because of the potential confounding biases related to physical deconditioning or

structural musculoskeletal alterations, especially in bilateral affections. On the other hand, in unilateral affections, these confounding biases can be minimized by comparison with the unaffected side. To date, no studies have evaluated AMI mechanisms in both adults and pediatric SCD individuals, and in future studies, the impact of physical deconditioning on AMI assessment should be better clarified.

In the clinical setting, AMI can be assessed using two quantitative methods: the Central Activation Rate (CAR) and the Interpolated Twitch Technique (ITT) (85, 91, 95). In both methods, the individual is asked to make a maximal voluntary isometric contraction (MVIC), and the force/torque generated by the muscle is registered. Then, when the force/torque plateau is reached, a maximal or supramaximal electrical stimulus is introduced. However, in the ITT method, this electrical stimulus can also be made initially with the muscle at rest (85, 91, 95). For electrical stimulus, 10 pulses, 100 Hz,200 μs pulse duration, and 400 V appear to be a reliable stimulation parameters for muscle contraction (85). Individuals with CAR >95% have a muscle fully activated by voluntary central stimulation, and those with less than that have some central muscle inactivation (91). In the ITT method, the higher the index score, the greater the number of fibers that are not centrally activated (85). Both methods seem simple, easily performed, and therefore feasible in clinical practice and research (Figure 4).

When comparing CAR and ITT in the capacity to estimate the quadriceps muscle activation, there was a significant variation between methods, with an estimated difference of up to 5.5% (85). In addition, it is suggested that ITT is a more accurate measure since the CAR might overestimate voluntary muscle activation (85). Some articles have assessed and reported good reliability of these methods in knee joints (96, 97), and the CAR method was found reliable within- (ICC = 0.94) and between-measurement sessions (ICC = 0.86) (96) while in the ITT method the reliability within measures was (ICC = 0.89) (97). Unfortunately, no studies evaluated the diagnostic value of these methods in joints frequently affected by SCD individuals, such as the hip, shoulder, and elbow. Although both CAR and ITT are not specific to SCD individuals, these methods should be used in clinical practice to evaluate CJP in SCD individuals.

Final remarks and conclusion

Chronic joint pain in patients with SCD might be related to maladaptive plasticity in the CNS, as it shares mechanisms with many known joint pathologies. Some of these maladaptive changes in the CNS are already known and include mainly poor descending inhibitory control, central sensitization, motor control impairments, reorganization of the motor cortex motor, and inhibition of induced maximal voluntary contraction. These changes may be assessed by a set of tests and/or questionnaires that are already available and could be useful in the clinical assessment and research in SCD. In the clinical setting, every healthcare professional can measure these maladaptive changes through instruments and methods with good diagnostic reliability (Table 1). These maladaptive plasticity changes may contribute to persistent pain in SCD, but there is a substantial lack of evidence regarding this aspect. However, future studies should be performed to elucidate and confirm these possible maladaptive changes in the nervous system in SCD individuals related to CJP to understand and treat the pain in those patients with better results.

Author contributions

All authors contributed to the development of the article in specific activities, such as planning, designing, and drafting/revising the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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3. OBJETIVOS

3.1. OBJETIVO PRINCIPAL

Testar a hipótese de que a dor crônica da articulação temporomandibular (ATM) em pessoas com doença falciforme pode ser tratada sem risco com neuromodulação não invasiva.

3.2. OBJETIVOS SECUNDÁRIOS

- Avaliar a modulação endógena da dor na DF;
- Avaliar o impacto da dor e dos sintomas mentais na qualidade de vida;
- Avaliar a influência dos tipos de religiosidade na dor;
- Desenvolver e validar uma cartilha para pessoas com DF.

4. MÉTODO

O estudo primário trata-se de um ensaio clínico randomizado, crossover, controlado duplo cego, realizado nas cidades do recôncavo baiano. Também apresentamos resultados transversais, decorrentes das entrevistas iniciais com todas as pessoas com DF que participaram da triagem para DTM. Visitas foram realizadas aos secretários de saúde de cada município, para pedir autorização de entrevistar adultos com DF. Ao receber a autorização de forma escrita e oficial, também recebemos a lista de cada UBS com o contato da enfermeira responsável e os nomes das pessoas com DF.

As enfermeiras de cada UBS, convidaram as pessoas com DF, através dos agentes comunitários, para ir até a UBS ao encontro dos pesquisadores. As entrevistas foram realizadas em espaço privado dentro da UBS. Para todas as pessoas foi explicado o objetivo da pesquisa e convidados a assinarem o TCLE (TCLE 1). O tempo médio para responder os questionários foi de 35 minutos. Após a triagem, os indivíduos com DF e DTM foram convidados a ler o segundo TCLE (TCLE 2) para aceitar ou não participar da pesquisa foco. Transporte foi ofertado para a Clínica Adventista da Bahia – FADBA, Cachoeira – BA., para realizar o protocolo de intervenção. Para triar a DTM foi utilizado primeiramente o Índice anamnésico de Fonseca, muito utilizado para este fim (CHAVES, 2007). Quando o índice anamnésico indicou DTM, foi aplicado o questionário RDC/DTM (CAMPOS, 2007), esse instrumento possibilitou classificar as pessoas como possuindo DTM de origem miofascial e/ou articular.

4.1. CRITÉRIOS DE INCLUSÃO PARA ENTREVISTA INICIAL

a) Pessoa adulta com diagnóstico de DF genótipo HbSS e HbSC, confirmado por eletroforese; b) ter entre 18 – 49 anos; c) Concordar em participar da entrevista por meio da assinatura voluntaria do termo de consentimento livre e esclarecido.

4.2. CRITÉRIOS DE NÃO INCLUSÃO

a) Estar em crises ou ter tido crise vaso oclusiva nos últimos 15 dias.

4.3. MÉTODOS DE AVALIAÇÃO

Este estudo foi desenvolvido em quatro etapas (ou encontros), no dia 1, foram feitos os procedimentos de triagem e caracterização da amostra. No dia 2, participaram apenas as pessoas

identificadas com DTM pelo Índice anamnésico de Fonseca, precisando ser confirmado pelo RDC/DTM. Aqueles que não tiveram o diagnóstico confirmado pelo RDC/DTM foram convidados a cancelar a sua participação. Aqueles que tiveram o diagnóstico de DTM confirmado foram atendidos na clínica-escola, em três oportunidades, com um intervalo de sete dias cada.

Dia 1

A) Triagem: foi realizada pelo pesquisador principal. Após os participantes assinarem o termo de consentimento livre e esclarecido número 1 (TCLE1) (ANEXO 1) foram submetidos aos critérios de elegibilidade, após isso todos responderam questionário sociodemográfico contendo como variáveis, idade, nível escolar, profissão, estado marital e raça. Também responderam questionários de dor e de saúde mental. O Índice anamnésico de Fonseca foi o principal instrumento de avaliação para convidar para o dia 2. No caso da pessoa ter DF e DTM, foi convidada a ler o TCLE 2 (ANEXO 2) para autorização ou não da participação no protocolo de intervenção.

B) Avaliação através de questionários. Aplicação dos questionários pelo pesquisador principal no dia 1:

- Escala Hospitalar de Ansiedade e Depressão (HAD) composto de duas subescalas de 7 itens cada uma, que devem ser respondidas com números ordinais de zero (sem sintomas) até três (3, sintomas muito severos) o resultado apresenta a tendência a ter ansiedade e/ou depressão (PAIS-RIBEIRO, 2007).
- Inventário de Sensibilização Central é subdividido em duas partes, A e B, na qual a A contém 25 perguntas relacionadas a sintomas de sensibilização central, com respostas categorizadas em nunca, raramente, às vezes, frequentemente e sempre. A parte B é composta por uma lista de condições clínicas dolorosas já reconhecidas como síndromes de sensibilização central, o participante registra se possui alguma das síndromes enumeradas e em qual ano foi diagnosticado (CAUMO, 2017).
- Escala de pensamentos catastróficos sobre a Dor (B-PCS) composto por 13 afirmações que podem ser respondidas de mínimo igual a zero, tendo a opção de leve, moderado, intenso e muito intenso com valor máximo de quatro (SEHN, 2012).
- Inventário breve da dor, possui nove perguntas sobre a percepção de dor, além de oferecer um mapa da dor para serem marcados os locais onde se sente dor. Muito

apropriado para o entendimento da dor osteomioarticular generalizada do indivíduo com DF (FERREIRA, 2011).

- Questionário de Qualidade de vida SF – 36 são perguntas sobre a percepção da saúde em geral e como ela é capaz de realizar suas atividades da vida diária. Divididos em domínios: capacidade funcional, aspectos físicos, aspectos emocionais, dor, estado geral de saúde, vitalidade, aspectos sociais e saúde mental (CICONELLI, 1999).
- Questionário de religiosidade de Duke pergunta à frequência de visita a templo ou local religioso, tempo individual de atividades religiosas, presença do espírito santo e se as crenças religiosas estão dentro do modo de viver (TAUNAY, 2012).

Os objetivos destes questionários foram avaliar em primeiro lugar a possibilidade de sensibilização central foco desta pesquisa, tendência ao catastrofismo fato que interfere nos resultados de estudos de dor crônica e a percepção da dor, como ela afeta a vida diária, e finalmente a saúde mental. Todos os detalhes do protocolo de intervenção iniciando desde o segundo ao quarto dia, estão descritos no artigo 2 já publicado por nome: ***The immediate effect Transcranial Direct Current Stimulation combined with Peripheral Electric Stimulation in the control of Temporomandibular pain in subjects with Sickle Cell Disease: a protocol for one session, randomized, crossover, double- blind clinical trial.*** (OLIVEIRA, 2021). Apresentado no final deste capítulo.

4.4 ASPECTOS ÉTICOS

Esta pesquisa foi submetida ao Comitê de Ética em Pesquisa da Faculdade Adventista da Bahia (CAAE n. 94835218.8.0000.0042) (ANEXO 3). Durante todo o estudo foram observadas as diretrizes sobre a pesquisa com seres humanos da Resolução 466/2012 do Conselho Nacional de Saúde. Todos os voluntários receberam explicações quanto a liberdade de sua participação e de interromper a participação em qualquer momento. Este estudo foi cadastrado no sistema brasileiro de registro de ensaios clínicos, REBEC, com o número UTN: U1111-1243-3020. Nenhum dos pesquisadores participantes deste estudo, declararam qualquer conflito de interesses.

4.5 ARTIGO 2: THE IMMEDIATE EFFECT TRANSCRANIAL DIRECT CURRENT STIMULATION COMBINED WITH PERIPHERAL ELECTRIC STIMULATION IN THE

CONTROL OF TEMPOROMANDIBULAR PAIN IN SUBJECTS WITH SICKLE CELL DISEASE: A PROTOCOL FOR ONE SESSION, RANDOMIZED, CROSSOVER, DOUBLE- BLIND CLINICAL TRIAL.

Registered Report

The immediate effect of transcranial direct current stimulation combined with peripheral electrical stimulation in the control of temporomandibular pain in subjects with sickle cell disease: A protocol for one session randomized, crossover, double-blind clinical trial

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ABSTRACT | INTRODUCTION: Temporomandibular disorder (TMD) is currently considered a central sensitization syndrome that belongs to the orofacial nociplastic pain group and offers great clinical practice challenges. It can also be identified in individuals with sickle cell disease. Neuromodulation is a promising therapy that can help individuals with chronic refractory pain. To our knowledge, there is no treatment proposal for these individuals with chronic orofacial pain resulting from sickle cell disease. **OBJECTIVE:** This is a protocol of a randomized, double-blind, cross-over clinical trial. The purpose of this protocol is to investigate whether the immediate effect of transcranial direct current stimulation can be increased by adding the effect of peripheral sensory electrical stimulation. **METHODS:** Twenty women between 18 and 49 years of age will be screened to participate in this cross-over study, where they will all receive the three types of a protocol with a one-week washout. Active transcranial Direct Current Stimulation (tDCS) + active Peripheral Electrical Stimulation (PES); Active tDCS + PES sham and tDCS sham + PES sham. Stimulation with tDCS will be at 2 mA anodic over the motor cortex for 20 minutes ipsilateral to the most painful temporomandibular joint (TMJ). Peripheral electrical stimulation will be at 100 Hz over the most painful TMJ masseter muscle for 30 min. **OUTCOME:** The main outcome will be pain intensity assessed by a VAS scale and a pressure algometer in grams. Endogenous pain modulation will be analyzed through the temporal summation of pain with Aesthesio precision tactile sensory filaments and conditioned pain modulation (CPM) evaluated by an algometer and thermal conditioned stimulus as secondary outcomes. Data will be analyzed using ANOVA of repeated measures, controlling for confounding variables.

KEYWORDS: Neuromodulation. Endogenous pain modulation. Sickle cell disease. Temporomandibular dysfunction.

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Introduction: Background and rationales

Due to several events of vaso-occlusive crisis, individuals with Sickle Cell Disease (SDC) are more likely to develop musculoskeletal pain; thus, approximately 30% of adults suffer chronic pain[1]. Besides, studies have shown that chronic pain has a potential impact on daily life. Psychological discomfort, physical dysfunction, and functional limitation may further limit individuals' quality of life with SCD. Therefore, there is an increasing awareness that chronic pain is part of the experience of individuals with SCD[2].

Among the painful musculoskeletal manifestations in individuals with SCD, Temporomandibular Disorder (TMD) is classified as Central Sensitivity Syndrome (CSS) and therefore is incredibly challenging. The CSS is a category of interrelated disorders with Central Sensitization (CS) as a common etiology[3]. CS is a physiological phenomenon involved in the nociceptive process[4]. However, this phenomenon's persistence has been associated with maladaptive plasticity in the central nervous system, which can include dysfunction in modulatory control of pain in descending and/or ascending pathways[5]. In addition, a study showed that there is an association between dysfunction in modulatory control of pain in descending and intracortical inhibition[6].

Maladaptive plasticity resulting from central sensitization has been identified in SCD and seems to play an essential role in maintaining and chronicity in this population[7]. A recent study showed that high central sensitization had been associated with pain and clinical measures, such as more insufficient sleep, higher situational catastrophizing, higher frequency of vaso-occlusive crisis, and pressure pain threshold in SCD individuals[8]. In addition, SCD individuals with chronic pain compared to those without chronic pain showed significant differences in functional connectivity between the periaqueductal gray (PAG) and in pronociceptive brain regions[7,9].

Neuromodulation through electric currents is one way to interfere with cortical plasticity related to chronic pain. Among the available interventions to modulate neuronal activity with electric currents is Transcranial Direct Current Stimulation (tDCS). The tDCS is effective as a single-phase current that induces changes in polarity-dependent excitability in the motor cortex, plasticity induction, functional modulation within the primary motor cortex M1[10,11].

The mechanism of action of tDCS includes neuromodulatory (during application) and neuroplastic (after application) effects. At first, the effect is related to changes that occur in the neuronal membrane's resting potential. Anodic stimulation initiates cell membrane oscillations that exhibit high frequency and low amplitude characteristics during depolarization. The effect's duration depends on protein synthesis, accompanied by intracellular changes and calcium levels[12]. The effects of a single application of tDCS on corticospinal excitability depend on the intensity of the stimulus and its duration. A study by Nietsche MA, Paulus W, the same authors showed that 13 minutes of anodic stimulation with tDCS on M1 caused corticospinal excitability up to 90 min after the session[13]. Therefore, a tDCS session may be useful for generating data that may suggest more prolonged use of this technique.

Studies show that tDCS alone has a moderate (20-40%) effect on pain control[14]; however, it has been proposed as an association of techniques to increase this effect[15]. These therapeutic associations assume that brain responsiveness to a particular therapy can be facilitated by another that alters cortical excitability. Peripheral Electrical Stimulation (PES) is a neuromodulatory technique that can produce cortical excitability changes, depending on stimulation intensity, frequency, and duration. Inversely the PES sensory threshold decreases excitability, whereas the motor threshold has the opposite effect[16].

When two excitatory stimuli are associated, a null response can occur due to meta-plasticity. However, the association between inhibitory and excitatory stimuli can also result in a synergistic effect[17]. Therefore, PES at a sensory threshold associated with anodic tDCS produces a summing analgesic effect. For example, Boggio[15] experienced a decrease in pain intensity by 36.5% with the two techniques' union, when tDCS alone resulted in only a 15% decrease in pain.

Finally, maladaptive brain plasticity may suggest chronic pain and explain why some individuals with SCD display refractory pain and are not responsive to pharmacological and non-pharmacological analgesic treatment[18]. It is why new treatments are necessary. There are already new proposals for using neuromodulation for chronic pain of SCD patients, but results have not been published[19] and are not focused on TMD. Therefore, these studies provide a scientific basis for the reasoning behind cortical stimulation in the presence of orofacial pain in patients with SCD.

Objectives

Primary Objective

1. To determine the immediate effect of anodic tDCS and sensory PES on chronic myofascial and atherogenic TMD pain intensity in sickle cell disease individuals.

Secondary Objective

1. To determine the neuromodulatory effect of anodic tDCS and PES stimulation on endogenous pain modulation in individuals with chronic myofascial and atherogenic TMD.

Materials and methods

Methods: Study design, participants, interventions, and outcomes

It is a clinical, crossover, controlled, block-randomized, double-blind trial. To determine the immediate effect of anodic tDCS on M1 and sensory PES on myofascial and atherogenic TMD pain intensity in individuals with sickle cell disease with different combinations and determine the neuromodulatory effect of anodic tDCS and PES stimulation on endogenous pain modulation.

The participants of this study will be recruited among patients with SCD registered in the Basic Unit of Health of their neighborhood of the 31 st Regional Health Directorate (DIRS–BA). They will be evaluated for TMD and be interviewed on their willingness to participate in the study. Next, three encounters will be scheduled in the Bahia Adventist College's Academic Clinic in Cachoeira – Bahia, Brazil.

Inclusion criteria

A. Women between 18-49 years old with SCD diagnosis and TMD with 3 months or more of myofascial pain over the temporomandibular joint.

B. Pain intensity above 3 to 10 points of visual analogic scale (VAS).

C. Women with SCD of genotype HbSS or HbSC only.

Exclusion criteria

A. Any contraindication to using tDCS or PES such as cochlear implants, cardiac pacemaker or metal implants in the skull/brain, pharmaceuticals that modify the threshold of neuronal activation (i.e., antidepressant, anticonvulsant, and antipsychotic); the history of seizure or epilepsy; and pregnancy.

B. Metal implants in the PES site.

C. Occurrence of infectious disease in the week before inclusion in the study.

Criteria for discontinuity

A. A moderate adverse effect, uncomfortable enough to interfere with the patient's usual activities.

The potential adverse effects described by the literature are Itching, tingling, skin redness, somnolence, concentration issues, headache, fatigue, lightheadedness, and skin burning under the electrode (rare). The intensity of any of these adverse effects depends on the subject's sensitivity, defining the decision to continue or not in the study[14].

B. Participant withdraws consent at any stage of the study.

Individuals who will perform interventions

Researcher 1: will do the screening and enrollment, will apply the sociodemographic and specific questionnaires.

- Catastrophic thoughts about pain (BP–PCS)
- Brazilian Portuguese Central Sensitization Inventory (BP–CSI)
- Hospital Anxiety and Depression Scale (HADS)
- Brief Pain Inventory (BPI) to Brazilian patients
- Short Form Health Survey 36 (SF-36)
- Duke's religiosity index

This researcher will give the questionnaires to the participants in a silent room of the Basic Unit of Health of their neighborhood. 45 minutes will be allotted for this questionnaire. Then will schedule the next session in the clinical setting.

This researcher will have the function of evaluating before and after the intervention, ignoring what protocol the patient underwent. This function will include applying the Research Diagnostic Criteria for the Temporomandibular Disorders RDC/TMD, the evaluation of Temporal Summation of Pain (TSP), and Conditioned Pain Modulation (CPM). This process will have 30 minutes lasting and reviewed in one room of the Academic Clinic.

Assistant Researcher 1: On day two, this researcher will have the duty to receive all participants at the Academic Clinic's front desk and will lead them to the room of researcher 1 for pre-evaluations. Then will guide the participants to assistant researcher 2 for randomization and intervention. Finally, it will guide the participants back to researcher 1 for the post-tests. Assistant researcher 1 will not have access to the database or randomization until the end of the research.

Assistant Researcher 2: This researcher will have the function of conduct computational randomization and will apply intervention as randomization indicates. Active tDCS + active PES or active tDCS + sham PES or sham tDCS + sham PES. After completing the treatment, a questionnaire on safety will evaluate the immediate adverse effects. The second and third day of treatment was scheduled by Assistant Researcher 2 in advance by telephone, and they asked if there was a moderate adverse effect that affected the individual's daily activities. If positive, the treatment will be discontinued. Any other mail effect will be registered. Only assistant researcher 2 is to know the treatment offered to the participant in the crossover process. This process will be completed in the Academic Clinic and will take about 40 minutes.

Researcher 2: This researcher will have the function to process the data in spreadsheet excel and do inferential analysis in SPSS

Intervention

This study will be developed in four steps (Figure 1), divided into four days with a one-week washout. On the first day, the screening procedures and sample characterization will be performed. In the next three days, randomization and intervention protocol will be performed, having before and after three evaluations (RDC/TMD, TSP, and CPM), obeying randomization allocation. (Figure 2).

Figure 1. Randomization and allocation

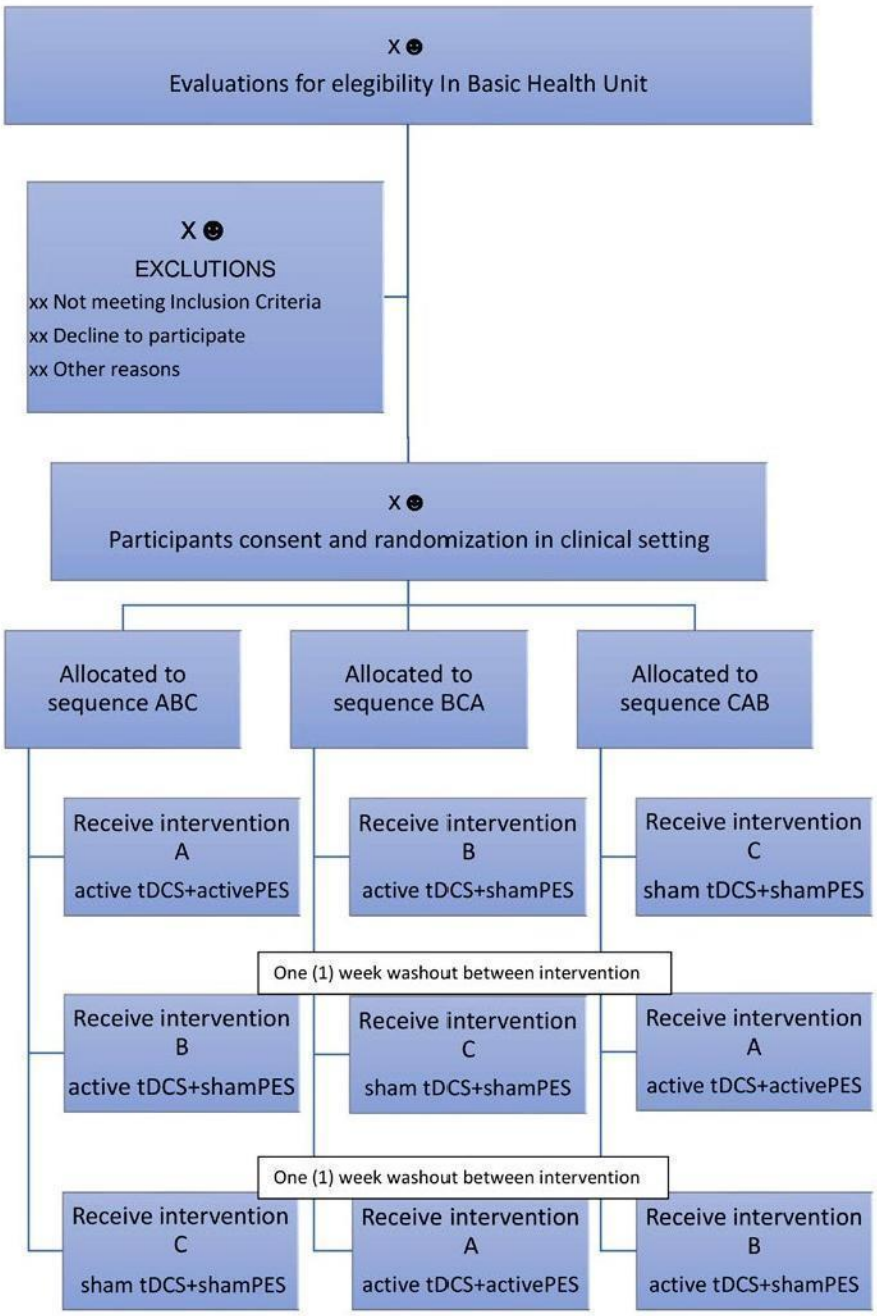
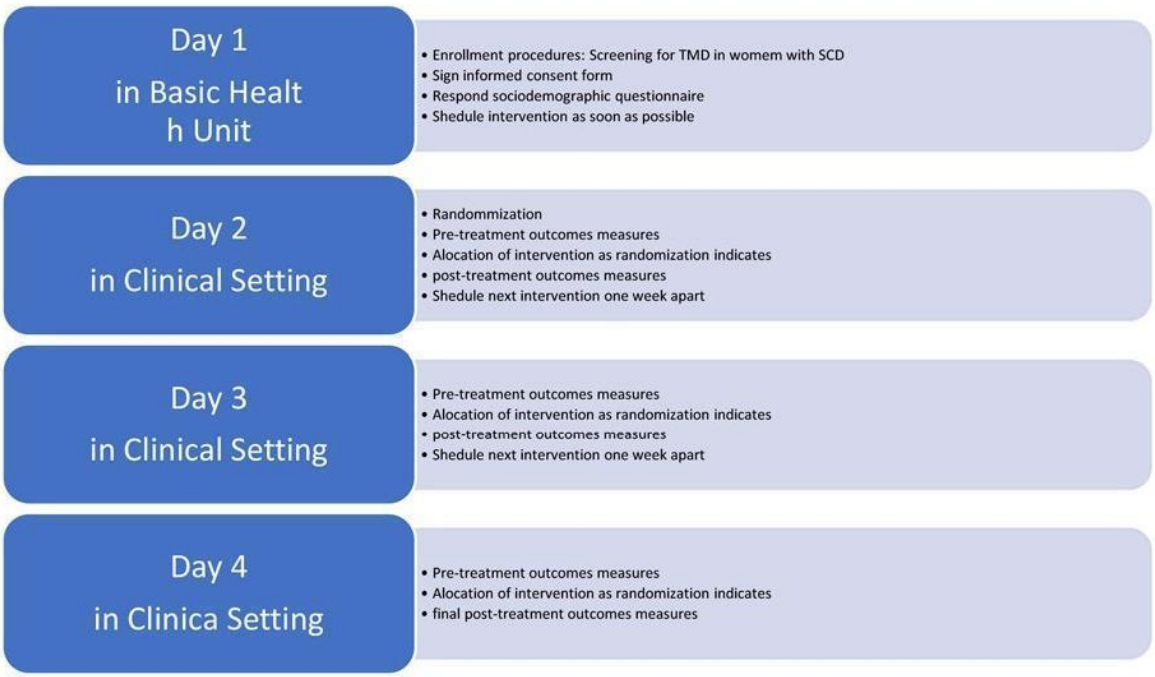


Figure 2. Timeline of study procedures



Day 1

The participant with SCD diagnosis will be invited to undergo screening at their local Basic Health Unit. Researcher 1 will guide the participant in a quiet room to explain the goals of the research. In the first step, we will identify women with SCD who also have pain secondary to temporomandibular dysfunction. An informed consent form will then be read and signed. Next, an evaluation will be conducted, and the questionnaires answered. Common psychological pathologies may interact with complications associated with SCD; this is why it has been recommended to screen these comorbidities using standardized screening tools[20,21].

A. The sociodemographic questionnaire gathers information on age, education level, profession, marital status, race, religion, and pain levels in the temporomandibular joint. The type of sickle cell disease is also recorded; information is taken from a medical statement (printed or written manually) that the subject presents for this first interview. Inclusion and exclusion criteria are assessed at the beginning of the interview.

B. Brazilian Portuguese Pain Catastrophizing Scale (BP-PCS) - This questionnaire consists of 13 items evaluating self-reported catastrophizing thoughts, feelings, and behaviors when one is in pain[22].

C. Brazilian Portuguese Central Sensitization Inventory (BP–CSI). Is a self-report questionnaire of health symptoms. It is designed as an easy-to-administer screen for patients at high risk of having central sensitization and helps classify chronic pain patients. It consists of 25 questions with five possible answers from never to always. It is an ordinal scale, and each response has one value from zero to four[23].

D. Hospital Anxiety and Depression Scale (HADS) comprises 14 self-reported questions that are divided into two subscales. The subject will rate each item using an ordinal scale varying from zero (non-existent symptom) to three (very severe symptom)[24].

E. Brief Pain Inventory to Brazilian patients (BPI) consists of nine items that are arranged in two dimensions: the intensity of pain and the impact of pain in the patient's life. The BPI asks patients to rate their pain intensity and the pain interference with general activities, mood, walking ability, regular work, relationships with others, sleep and enjoyment of life in an 11-point scale ranging from zero (no pain) to ten (as bad as it can be). It includes a corporal diagram to assess pain location, measures the percentage of pain relief, and asks patients to describe which treatments are being used to control pain. A high score represents a high pain intensity or pain interference[25].

F. Short Form Health Survey 36 (SF-36) comprises 36 multidimensional questions that will give a raw scale of eight different concepts as functional capacity, physical aspects, pain, general health, vitality, social aspects, emotional aspects, and mental health. It has a final score from zero to 100, where zero corresponds to the worst general health and 100 the best general health[26].

G. Duke's religiosity index is a five-item scale measuring three dimensions of religious involvement related to health outcomes. Organizational religiosity, non-organizational religiosity, and intrinsic religiosity. It is recommended that the values are not summed but analyzed separately[27].

Day 2 First moment

The participant will check-in at the Academic Clinic front desk and receive the assistant researcher 1. Assistant researcher 1 will document the following: caffeine intake, medications taken in the last 24 hours, menstrual state, and hour of the day. Caffeine intake will be classified into three categories: low (<100 mg/day), moderate (101-200 mg/day), or high (>201 mg/day). The menstrual state will be divided into: menstrual, follicular, periovulatory, luteal, and premenstrual. Next, the patient will be guided to researcher 1, an experienced physical therapist, to review three evaluations.

A. Research Diagnostic Criteria for Temporomandibular Dysfunction (RDC/TMD). This instrument consists of a detailed evaluation of the stomatognathic system involved in the conditions of temporomandibular disorder. It consists of two axes. Axis I evaluate the clinical aspects with ten questions. Axis II psychosocial aspects, with 31 questions. In this diagnostic regimen, the patient is framed in 3 groups: Group I - Muscular Disorders; Group II - Disk Displacement; Group III - Other Joint Conditions[28,29]. Currently, this instrument has a new version called Diagnostic Criteria for Temporomandibular Dysfunction (DC/TMD)[30]. However, it has not been validated for the Portuguese Brazilian population.

B. Endogenous Pain Modulation Testing. Patients will be seated in a comfortable armchair in a quiet room with an ambient temperature of 23°C.

a. To evaluate pain facilitation, the Temporal Summation of Pain (TSP) will be tested with Aesthesio precision tactile sensory evaluator filaments.

i. Evaluation of the mechanical detection threshold of each individual. A pinprick instrument was chosen from a custom-made weighted set of 20 calibrated instruments (Aesthesio, USA, DanMIc global, LLC, revised May 2017, 0.2 mm diameter flat contact surface, target force from 0,008g to 300g). The selected instrument will be held in a vertical position perpendicular to the skin surface to apply three stimuli, over the skin of the thenar region of the dominant hand and the masseter region of the most painful side. Participants will be instructed to verbalize when they feel the stimulus. The stimulus will end once the filament bends-approximately two seconds. It will be considered a mechanical detection threshold that is perceived at least two out of three times. Each patient will be asked to keep their eyes closed.

ii. Evaluation of pain detection. The test uses over four levels of the pinprick instrument registered as a mechanical detection threshold. Each patient will be asked to declare a sensation of pain, one to ten, on the Visual Analogic Scale (VAS). Zero, being no pain, and ten, the most insupportable pain felt. After identifying and registering this threshold, testing will continue to detect pain type three of VAS.

iii. Temporal Summation. TSP will be performed according to a standardized protocol[31] using pinprick stimuli that provoke pain level three on the VAS scale over the skin of the thenar eminence of the dominant hand and the facial skin overlying the middle of the masseter muscles, on the painful side (TMJ). Following a ten-second interval, a series of ten pinprick stimuli will be delivered over a 1-2 cm area near the single stimulus site at 1 Hz frequency determined using a metronome, and the perceived pain elicited by 10-stimuli series will be rated by the participant and registered by the researcher.

b. Pain inhibition will be assessed by the conditioned pain modulation (CPM) paradigm[32]. First, a test stimulus by an algometer will induce pain of intensity 3 on the VAS (Dukan CTS Gauge, George Medial Hood River, OR. Pat. N° 5301683, USA) over the region of the long extensor carpialis muscle, next to the lateral epicondyle of the dominant side. Then the participant will be asked to place their non-dominant hand in a stainless-steel container with 1 Lt. of hot water at 46°C for one minute; this will be the conditioned stimulus. In order to follow the curve of the inhibition mechanism, the test stimulus is reevaluated immediately after the conditioned stimulus and at 30, 60, and 90 seconds.

Day 2 Second moment

Assistant Researcher 1 will guide the participant to Assistant Researcher 2, who will then conduct computational randomization for all sessions. The intervention will be held as randomization indicated. Active tDCS + active PES or active tDCS + sham PES or sham tDCS + sham PES. The room will be at 23°C, and the patient will have a comfortable chair with arms to sit on.

A. tDCS: will be applied with a constant current stimulator (Microestim Genius transcranial stimulation device – NKL electronic products, Brazil), connected to two 5 x 7 (35 cm²) silicone sponges. Saline-moistened electrodes (0.9%) will be positioned on the scalp according to the 10-20 electroencephalography system[30], with the anode in the individual's primary painful C3 or C4 motor area and the cathode in the supra region. supraorbital contralateral orbital. The 2mA stimulation will last for 20 min with the rise and fall of the 30s. The researcher will ask if there is any bothersome sensation during the trial and will wet the silicone sponges every 5 minutes.

B. PES: A pulsed generator (Neurodyn II, Ibramed, Sao Paulo, Brazil) will be used to administer the PES. Will be used 2.0 cm² disposable electrodes located in the TMJ region and masseter muscle. Stimulus intensity will be maintained at a sensory threshold of 100Hz and a pulse duration of 200µ, with a total duration of 30 minutes.

C. The safety questionnaire will be administered by Assistant Researcher 2.

After finishing this process, Assistant Researcher 1 will guide the patient to Researcher 1 to repeat the evaluation process explained in Day 2 first moment, finishing Day 2.

Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence

To improve adherence to the protocol, at first contact and during all the processes, all participants will receive a card (brochure) to register the intensity of pain and acute pain in the morning and evening. This brochure will have our contact number in case they wish to ask any questions. All participants will receive financial aid for round trip transportation, as well as a meal voucher. They will also receive SCD care recommendations and genetic counseling. In the end, all participants will be offered 5 sessions of the most effective intervention for their pain.

Relevant concomitant care and interventions that are permitted or prohibited during the trial

Individuals who participate in the trial need to have had 15 days without acute pain that resulted in a hospital visit. In addition, they need to be without pain medication for at least 24 hours. All other medications used will be registered.

Potential for adverse effects and damage

tDCS can generate relatively subtle, self-limiting, and short-term adverse effects that include a mild tingling sensation, itching, burning, mild pain under the electrodes' surface, fatigue, and sleepiness. All of these potential adverse effects can be avoided through appropriate training in the management of the technique. Besides, these adverse effects will be monitored with a specific questionnaire.

Every participant will be adequately informed about these risks when recruitment and declaration of free and informed consent. The academic clinic comprises physiotherapists and physicians, and they all will be accessible to assist in case of any risk of harm to the participant in this study.

Outcomes

Primary Outcome Measure

Pain intensity will be measured at the temporomandibular joint by algometer in kilograms and by the VAS being zero no pain and 10 the most pain imaginable, before and after each treatment.

Secondary Outcomes Measures

Endogenous pain modulation measured with Temporal Summation of Pain and Conditioned Pain Modulation. Identified with Aesthesia precision tactile sensory evaluator in grams for TSP and registered in grams with algometer for CPM. The amplitude of mouth opening at the pain limit and maximum mouth opening. The number of tender points on the body, the intensity of pain in muscles of mastication.

Participant timeline

Enrollment of participants will take place between October 2019 and July 2020. All participants will be identified at the Basic Health Unit of cities of the Bahian Recôncavo. It is the geographical region located around Todos-os-Santos Bay, covering the coast and the entire inland region surrounding the Bay. It has been identified as the region with a higher population of SCD individuals in Brazil[33]. (Figure 1)

Sample size

The sample size was calculated using the G-Power software version 3.1.9.2. The study's primary objective is to test the hypothesis that the therapeutic combination of anodic tDCS in the primary motor cortex and peripheral electrical stimulation at the sensory level promotes a more significant analgesic effect on pain intensity in individuals with DF and TMD after a single session. The sample estimate was based on a randomized sample equally in three crossover groups, two measures (pre- and post-intervention), 80% power, 5% alpha, and 0.35 effect size on the primary pain intensity outcome. Using these parameters, the sample was estimated at 20 individuals.

Assignment of interventions and blinding

Twenty women will participate in this trial. Since this is a randomized crossover trial, the women will receive the three possible treatments to compare results between them. The order of the allocation will be randomized with a computer program, results of the randomization results will be registered and put in a sealed envelope by assistant researcher 1, who will take care of the information and conduct the treatment protocol.

The sham protocol of the tDCS has been specially programmed for this research by the company (NKL electronic products, Brazil). It has been programmed with 30sec of the rising ramp, 30sec of stimulus, 30sec descent ramp. 20 minutes of sham stimulation, and again, a 30sec of the rising ramp, 30sec of stimulus, 30sec descent ramp.

All participants are blinded for the type of treatment that they will undergo. Researcher 1 and assistant researcher 2 will be blinded as well until the end of the study. Only assistant researcher 1 that will conduct treatment will know each participant's order of allocation and will conduct blind evaluations after each treatment. This evaluation consults adverse effects and asks if the device was turned off or not, and the degree of certainty.

Methods: Data collection, management, and analysis

Each researcher will do one or more research, but two researchers will not do the same data collection to avoid differences in the collection, as aforementioned.

Researcher 2 will be the only participant of team research that will transcribe all data from the questionnaires on an excel spreadsheet and analyze it with the SPSS program. All questionnaires will be kept safe for ten years.

The Kolmogorov-Smirnov test will be applied to the continuous variables for analysis of normality. Continuous variables: TMJ pain intensity, age, amount of body tender points, amount of painful masticatory muscles, mechanical detection threshold and pain threshold, temporal pain summation, CPM, mouth opening in millimeter. They will be presented with measures of central tendency and dispersion.

Categorical variables: education, type of sickle cell disease, use of medicines, religion, professional activity, the tendency to depression and anxiety, quality of life, degree of catastrophism, and degree of central awareness. Will be presented in relative and absolute frequencies. The quantitative data used during the sample characterization will be analyzed through one-way ANOVA if the variances are homogeneous. Otherwise, the Kruskal-Wallis test will be used.

To test the neuromodulatory effect of the different therapeutic combinations of anodic tDCS and sensory PES on pain intensity outcomes and endogenous pain modulation, ANOVA repeated measures would be used for each outcome separately if there is normal distribution using the TIME factor. If there is no normal distribution, the Freedman test will be used. All analyses will be performed using the Statistical Package for Social Sciences (SPSS) version 22.0, with a significance level of 5%.

Ethics aspects

Volunteers will receive an explanation regarding their participation and the freedom to remove consent at any time during the study. They will read and receive answers to any questions before signing an informed consent form (ICF), prepared according to Resolution 466/2012 of the Brazilian National Council of Health. This study has been approved by the Ethics and Research Committee (ERC) of the Faculdade Adventista da Bahia (CAAE No. 94835218.8.0000.0042). The study is registered at REBEC, the Brazilian registration for clinical trial number UTN: U1111-1243-3020. Any changes in the study protocol will be informed to both the ERC and the REBEC. None of the authors acknowledge any potential sources of conflict of interest.

Disclosure

These trials' results will be shared with the Recôncavo Bahiano local city Basic Health Unit healthcare professionals. The participants are from cities in Recôncavo Bahiano. In addition, each participant will have the opportunity to receive five sessions of the treatment combination that is most effective for their cases. We will also make the results public in an open-access review.

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Author contributions

Oliveira LAB wrote the manuscript. Lopes TS, Baptista AF and Sá KN contributed with critical intellectual content.

Competing interests

No financial, legal, or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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5. MANUSCRITOS E PUBLICAÇÕES

5.1. ARTIGO 3: TRANSCRANIAL DIRECT CURRENT STIMULATION AND PERIPHERAL ELECTRICAL STIMULATION IN INDIVIDUALS WITH SICKLE CELL DISEASE AND TEMPOROMANDIBULAR DYSFUNCTION: RANDOMIZED, CROSSOVER, DOUBLE-BLIND - PILOT STUDY.

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ABSTRACT

INTRODUCTION: Temporomandibular dysfunction (TMD) is a frequent central sensitization syndrome that offers clinical challenges. Also, TMD treatments have not been explored in individuals with Sickle cell Disease (SCD). Neuromodulation is a promising therapy that can help individuals with chronic refractory pain. Still, a pilot study is needed to indicate the treatment's feasibility, plausibility, sample calculation, and safety because of the low oxygen presence in SCD individuals. **METHOD:** This is a randomized, crossover, double-

blinded-pilot study. Three groups' interventions: Active transcranial Direct Current Stimulation (tDCS)+active Peripheral Electrical Stimulation (PES), active tDCS+sham PES, and sham tDCS+sham PES, with a one-week washout. Stimulation with tDCS was at 2mA anodic over the motor cortex for 20 minutes ipsilateral to the most painful temporomandibular joint (TMJ). Peripheral electrical stimulation was at 100hz over the most painful TMJ masseter muscle for 30 min. The effect size and the sample size were calculated with the WinPepi software, comparing the result after the intervention of active tDCS + simulated EPP and simulated tDCS + simulated EPP. **RESULTS:** Ten women were identified as having Temporomandibular Dysfunction (TMD) during the evaluation of a hundred adults with SCD. Seven had SCD genotype HbSS, and three had HbSC. An average age of 38.9±6.08. The pain was 6.3±1.56 on the visual analog scale (VAS). Of them, all had chronic, widespread pain and central sensitization (64.62±13.92), three had depression, and eight had anxiety. The diagnoses with RDC/TMD Axis I showed that nine individuals had myofascial pain and joint arthrosis, eight had pain facilitation, and five had abnormal pain inhibition curves. Without intending to test the hypothesis, repeated measures ANOVA with a Greenhouse-Geisser correction didn't show differences in pain over the TMJ for time and group (F[2.000, 25.000] =0.304, p=.740). A post hoc pairwise comparison using the Bonferroni correction showed differences in all three groups. Similar results for evaluating pain over the left TMJ region for time (F [2.000, 25.000] = 1.26, p = .301). ANOVA with a Greenhouse-Geisser correction showed that CPM scores differed significantly in the measured time (F[5.544, 69.304] =2.725, p=.022). A post hoc pairwise comparison using the Bonferroni correction did not show group differences. Finally, ANOVA with a Greenhouse-Geisser correction showed that Quantitative sensory testing (QST) of moderate pain over the TMJ differed significantly in the measures of time (F[1.000, 25.000] =4.489, p=.044). A post hoc pairwise comparison using the Bonferroni correction showed group differences for active tDCS and PES p=0.032. Adverse reactions declared after active tDCS were tingling (five), drowsiness (three), and itching (two). Tingling and drowsiness were also declared in the sham tDCS allocation. No major adverse effect was observed in any session. The effect size result was Cohen´s d = (2.88 -1.80)/0.91=1.17. Resulting in a sample size for the Randomized Clinical Trial (RCT) of 11 subjects per group. **Conclusion:** tDCS is a secure technic that may be applied in individuals with SCD and TMD. No adverse effects were registered, including pain crises. tDCS may be effective for women with SCD and TMD, but the RCT needs to be performed.

Keywords: sickle cell disease, temporomandibular dysfunction, transcranial direct current stimulation, central sensitization.

INTRODUCTION

Chronic pain is a common and debilitating symptom of sickle cell disease (SCD), a genetic condition, with vaso-occlusive crisis being the leading cause. This painful episode occurs when blood vessels block, causing reduced oxygen supply to tissues and organs (Kato et al., 2018). Chronic joint pain is a common consequence of musculoskeletal injury in SCD individuals due to damage caused by recurrent vaso-occlusive crises (Brandow & DeBaun, 2018). Chronic joint pain can significantly impact an individual's quality of life, limiting their ability to perform daily activities and affecting their emotional well-being. It can lead to social

isolation, depression, anxiety, sleep disturbance, and decreased productivity at work, home, or school (Karafin et al., 2019; Osunkwo et al., 2021; Panepinto & Bonner, 2012; Sil et al., 2016).

Temporomandibular Disorders (TMD) is a source of chronic joint pain that can be present in individuals with sickle cell disease, associated with temporomandibular joint dysfunction and muscle involvement with the masticatory system, but has been rarely published (Plantin et al., 2021; Caracas et al., 2013; el-Sabbagh & Kamel, 1989). Temporomandibular Disorders (TMD) are a frequent musculoskeletal manifestation of central sensitivity syndrome (Kindler et al., 2011). This chronic complicated condition involves alterations in the central nervous system's processing of sensory information, leading to amplified pain perception and widespread hypersensitivity (Kindler et al., 2011; Millan, 2002). The complex interplay between biological, psychological, and social factors contributes to the development and perpetuation of this condition (Schaible et al., 2009).

Recent studies have shown that maladaptive plasticity resulting from central sensitization can be identified in SCD individuals (Karafin et al., 2019). Central sensitization refers to the process by which the nervous system becomes hyper-responsive to stimuli, causing an increased sensitivity to pain and other sensations (Campbell et al., 2016). Maladaptive plasticity, on the other hand, refers to changes in neural circuitry that result from chronic pain or injury, leading to aberrant sensory processing and further exacerbation of symptoms (Uhelski & Simone, 2019). In SCD individuals, maladaptive plasticity can lead to persistent pain and decreased quality of life (Osunkwo et al., 2021). Furthermore, research has demonstrated that targeting these maladaptive processes through targeted therapies may relieve those suffering from SCD-related complications. Understanding the complexities of maladaptive plasticity resulting from central sensitization in SCD is crucial for developing effective treatments and improving outcomes for individuals with this debilitating condition (Lopes et al., 2022).

In this context, transcranial direct current stimulation (tDCS) has emerged as a promising non-invasive technique for managing chronic pain in patients with maladaptive plasticity (O'Connell et al., 2014). tDCS is able to stimulate specific brain areas, modulating neural activity and altering cortical excitability to promote long-term relief from chronic pain

conditions such as low back pain, neuropathic pain (Bonifácio de Assis et al., 2022), migraine headaches (Hong et al., 2022) and TMD (Herrero Babiloni et al., 2018; Oliveira et al., 2015).

Questions arise about safety in this group of people. The study by Zheng (Zheng et al., 2011) provides valuable information regarding blood flow. In his study, he observed that anodal stimulation caused a 17% increase in blood flow, with a return to normality when the current was turned off. He also observed a correlation between the strength of the current and an increase in blood flow. Today the amount of tDCS interventions have been widely publicized, allowing protocols that respect safety, ethical, legal regulatory, and application guidelines (Antal et al., 2011). However, to date, there are no studies using neuromodulation techniques in SCD individuals with chronic pain and TMD. Thus, TMD treatments have yet to be explored in individuals with SCD, understanding that both diagnoses are related to central sensitization. Neuromodulation is a therapy that can help individuals with chronic refractory pain. A pilot study was proposed before the full clinical trial to ensure the treatment's feasibility, plausibility, and safety.

MATERIALS AND METHODS

Trial design and eligibility

This is a pilot study of a clinical, randomized, crossover, double-blind, registered in REBEC n. TN: U1111-1243-3020, with women diagnosed with Sickle Cell Disease and temporomandibular dysfunction. Inclusion criteria were having a diagnosis of sickle cell disease and, after evaluation, having a second diagnosis of temporomandibular dysfunction, having between 18 and 49 years old, and not having had any acute crises in the last fifteen days. The exclusion criteria were contraindications of tDCS or PES, such as epilepsy, pregnancy, cochlear implants, cardiac pacemakers, or metal implants in the skull/brain. Also, exclusion criteria included Pharmaceuticals that modify the threshold of neuronal activation (I.e., antidepressants, anticonvulsants, and antipsychotics) (O'Connell et al., 2018).

The participants of this study were recruited between October 2019 and December 2022 from the Primary Health Centers in the cities of Recôncavo Baiano and recruited from the association of sickle cell disease in the town of Feira de Santana-BA. All adults with SCD were interviewed using clinical and sociodemographic questionnaires. After the specific

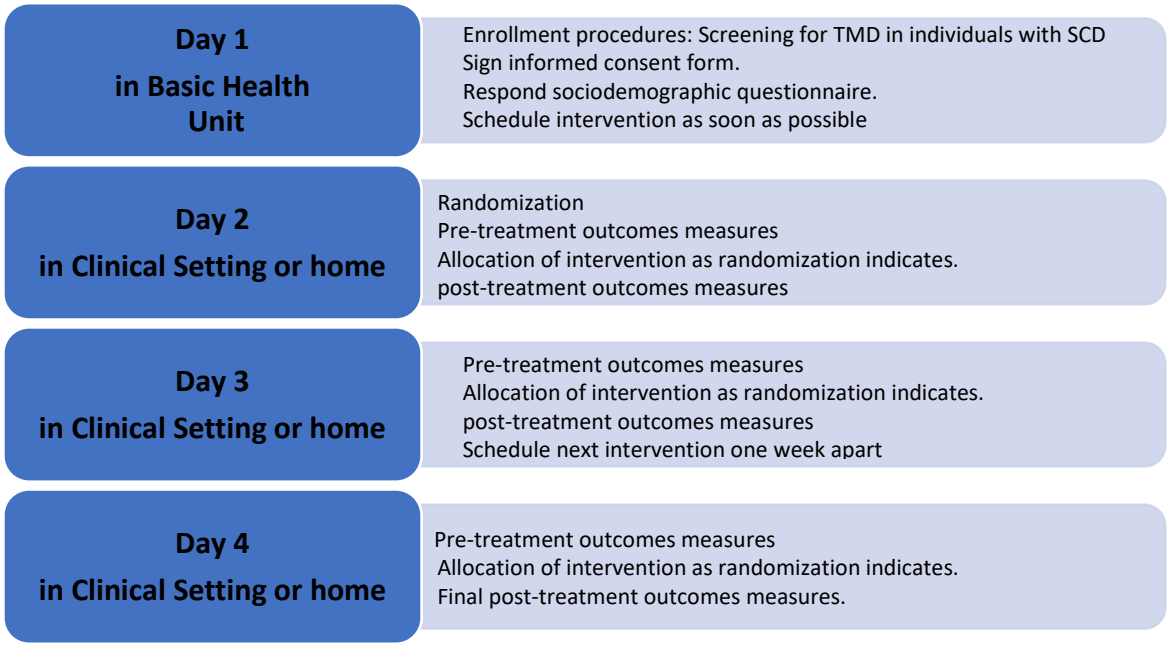
participants for this study were identified, a more extensive temporomandibular evaluation was done. The sample was for convenience. Two properly trained researchers applied all screening questionnaires.

The Informed Consent Forms were available to all participants under the 466/2012 Resolution of the National Health Council of Brazil. This study was approved by the Ethics and Research Committee of Faculdade Adventista da Bahia (CAAE No. 94835218.8.00000.0042). It was clarified for everyone that they were free to deny participation or leave the interview at any time. After reading, they signed the acceptance document.

Study protocol

The study had four steps (Figure 1) developed over four days with a one-week washout. The screening procedures and sample characterization were performed on the first day after signing the Informed Consent Form, which was read for each participant. All the individuals that met the inclusion criteria were invited to participate in the intervention sessions, signing the second Consent Form.

Figure 1: Timeline of study procedures



The individuals with SCD underwent screening at their local Primary Health Center or home. After the informed consent form was read, explained, and signed, next, questionnaires were responded to. In this study, the researchers read each question for everyone. The sociodemographic questionnaire gathers information on age, gender, education level, marital status, race, religion, and pain levels.

Screening instruments. It was applied to participants: the BP-CSI, the BPI, the BP-PCS, the HADS, and the SF-36 instruments, The Fonseca Anamnestic Index described below.

Brazilian Portuguese Central Sensitization Inventory (BP–CSI). Designed as an easy-to-administer screen for individuals at high risk of central sensitization and helps to classify chronic pain. It comprises twenty-five questions with five possible answers from never to always. It is an ordinal scale; each response has one value from zero to four (Caumo et al., 2017).

Brief Pain Inventory to Brazilian Patients (BPI). It consists of nine items arranged in two dimensions: the intensity of pain and its impact on the patient's life. The BPI asks to rate their pain intensity and the pain interference with general activities, mood, walking ability, everyday work, relationships with others, sleep, and enjoyment of life on an 11-point scale ranging from zero (no pain) to ten (as bad as it can be). It includes a corporal diagram to assess pain location, measures the percentage of pain relief, and asks to describe which treatments are being used to control pain. A high score represents a high pain intensity or interference (Ferreira et al., 2011).

Brazilian Portuguese Pain Catastrophizing Scale (BP-PCS). The BP-PCS questionnaire consists of thirteen items evaluating self-reported catastrophizing thoughts, feelings, and behaviors when in pain. It is divided into three domains: helplessness, magnification, and rumination. Items are rated on a 5-point Likert-type scale in which both intensity and frequency information are represented, with the following five levels of response for each item: (0) not at all, (1) to a slight degree, (3) to a moderate degree, (4) to a great degree, (5) and all the time. The PCS total score ranges from 0 to 52 points (Sehn et al., 2012).

Hospital Anxiety and Depression Scale (HADS). It comprises 14 self-reported questions divided into two subscales: one for anxiety and the other for depression. The subject will rate

each item using an ordinal scale varying from zero (non-existent symptom) to three (very severe symptom) (Pais-Ribeiro et al., 2007).

The Fonseca Anamnestic Index was used to screen for TMJ pain on the first day, and The Research Diagnostic Criteria for Temporomandibular Dysfunction (RDC/TMD) was for diagnostic purposes.

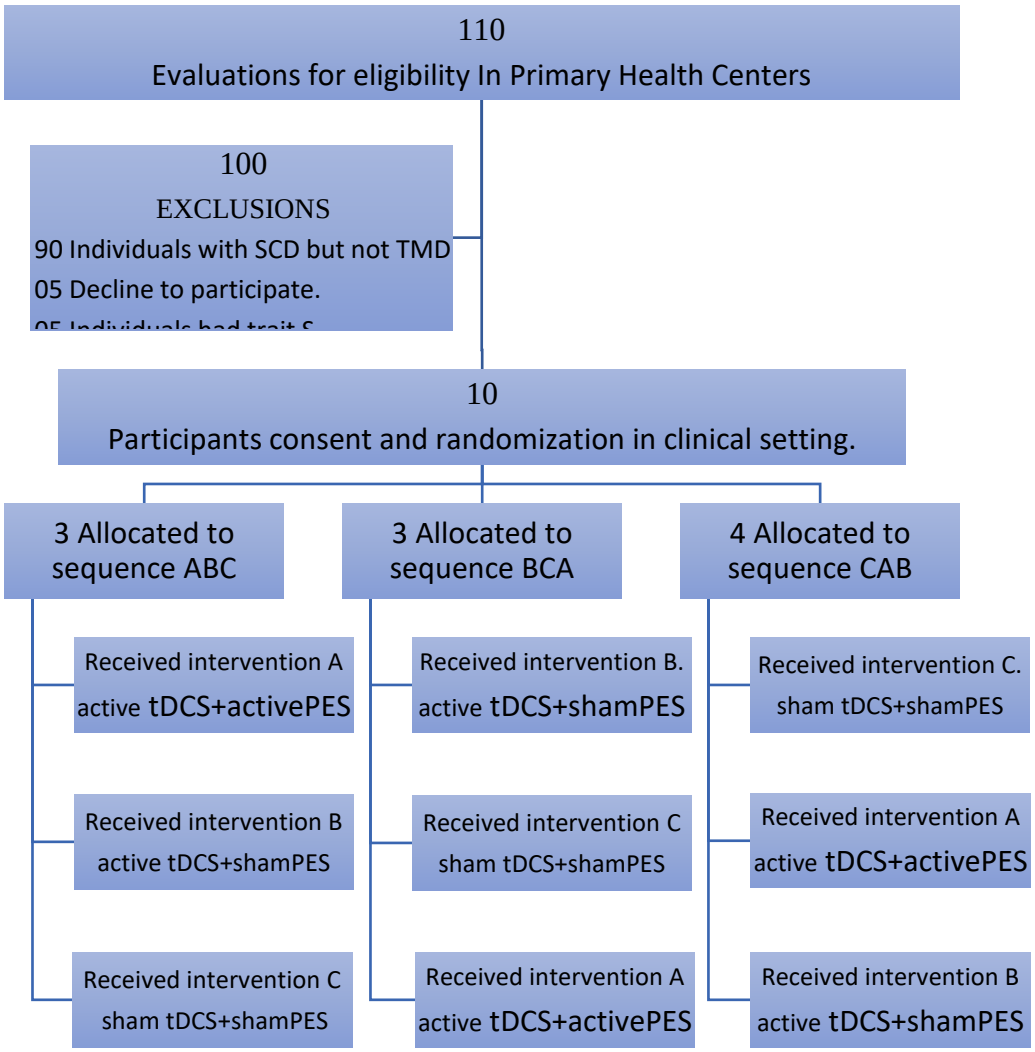
RDC/TMD is a complex instrument to evaluate the stomatognathic system involved in the conditions of temporomandibular disorder. It consists of two axes. Axis, I evaluate the clinical aspects with ten questions. Axis II analyzes psychosocial aspects with 31 questions. In this diagnostic regimen, the patient is framed into three groups. Group I - Muscular Disorders; Group II - Disk Displacement; Group III - other joint conditions. This instrument has a new version called Diagnostic Criteria for temporomandibular dysfunction (DC/TMD). However, it had yet to be validated for the Portuguese Brazilian population when this study began (Campos et al., 2007).

Intervention Days:

Evaluations

Randomization and allocation are described in Figure 2. The intervention protocol was preceded and followed by the evaluation protocol, composed of three evaluations: the physical exam of RDC/TMS, Temporal Summation of Pain (TSP), and Conditioned Pain Modulation (CPM).

Figure 2: Eligibility and Randomization



To evaluate Endogenous Pain Modulation Testing, women were seated in a comfortable armchair in a quiet room with an ambient temperature of 23°C.

1. Pain facilitation was evaluated with the Temporal Summation of Pain (TSP) and was tested with Aesthesio precision tactile sensory evaluation filaments.
    a. The mechanical detection threshold of everyone was evaluated through a pinprick instrument chosen from a custom-made weighted set of 20 calibrated instruments (Aesthesio, USA, DanMic global, LLC, revised May 2017, 0.2mm diameter flat contact surface, target force from 0.008g to 300g). The selected instrument was held vertically perpendicular to the skin surface to apply three stimuli over the skin of the thenar region of the dominant hand and the

temporomandibular region of the most painful side. Participants were instructed to verbalize when they felt the stimulus. The stimulus ended when the filament bent approximately after two seconds. The mechanical detection threshold was considered after the participant declared two out of three detections. Everyone was asked to keep their eyes closed during the process.

b. Evaluation of pain detection. The test used four levels up of the pinprick instrument registered as a mechanical detection threshold. Each women was asked to declare the first pain sensation, one of ten, on the Visual Analogic Scale (VAS). Zero, no pain, and ten, the most insupportable pain felt. After identifying and registering this threshold, testing would continue to detect pain type three of VAS. Abnormal pain was defined if a subject reported pain below 10g filaments, and tolerance pain below 26g. (Ezenwa et al., 2016).

c. Temporal Summation (TSP). TSP was performed according to the standardized protocol (Rolke et al., 2006), using pinprick stimuli that provoke pain level three on the VAS scale over the skin of the thenar eminence of the dominant hand and the facial skin overlying the middle of the masseter muscle, on the painful side (TMD). Following a ten-second interval, ten pinprick stimuli were delivered over a 1-2 cm area near the single stimulus site at 1 Hz frequency (determined using a metronome). The perceived pain elicited by the 10-stimuli series was rated by the participant and registered by the researcher.

2. Pain inhibition was assessed by the conditioned pain modulation (CPM) paradigm (Kennedy et al., 2016)**.** First, a test stimulus by an algometer induced pain of intensity three on the VAS over the region of the insertion of the muscle Extensor carpi radialis longus; next to the lateral epicondyle of the dominant side (Dukan CTS Gauge, George Medial Hood River, OR. Pat No 5301683, USA). Then the participant was asked to place their non-dominant hand in a stainless-steel container with 1lt of water at 46oC, the conditioned stimulus, for one minute. To follow the curve of the inhibition mechanism, the test stimulus was reevaluated immediately after the conditioned stimulus and at 30, 60, and 90 seconds.

Interventions

Depending on previously defined allocation, the intervention was de crossover randomized treatment with tDCS and FES.

a. The tDCS was applied with a constant current simulator connected to two 5x7 (35cm2) silicone sponges. (Microestim Genius transcranial stimulation device - NKL electronic products, Brazil). Saline-moistened electrodes (0.9%) were positioned on the scalp according to the 10-20 electroencephalography system (Schiffman et al., 2014), with the anode in the individual´s primary painful C3 or C4 motor area and cathode in the supra region. Supraorbital contralateral orbital. The 2mA stimulation lasted for 20 min. It was asked if there was any bothersome sensation during the trial, and the silicone sponges were wet every 5 minutes. Microestim Genius transcranial stimulation device was specially programmed for this research by the company NKL. It was programmed with 30sec of the rising ramp, 30sec of stimulus, and 30sec the descent ramp. 20 minutes of sham stimulation, and again, a 30sec of the rising ramp, 30sec of stimulus, 30sec descent ramp.

b. The PES pulsed generator (Neurodyn II, Ibramed, São Paulo, Brazil) was used to administer the peripherical stimulation. Disposable electrodes 2.0cm2, located in the TMJ region and the masseter muscle. Stimulus intensity was maintained at a sensory threshold of 100Hz and a pulse duration of 200μ, with a total duration of 30 minutes. The electrodes were put in the location for sham PES, and the device was turned on, but the stimulation was not.

All participants were blinded by the type of treatment that they underwent. Research 1 and assistant researcher three were also blinded until the end of the study. Only assistant researcher 2, who conducted the treatment, knew each participant's allocation order.

Randomization

The allocation order was determined by researcher 2, who conducted randomization with a computer program. Results were registered and deposited in a sealed envelope by researcher 2, responsible for the information and conducting the treatment protocol**.**

Implementation: Researchers' participation in the study Screening moment protocol: (first day)

Researcher 1 coordinated the screening and enrollment, applying the sociodemographic questionnaire and the Fonseca Index. Researchers 2 and 3 applied the questionnaires and scheduled the next session in the clinical setting if the individual had the inclusion criteria.

On intervention day (second to fourth day)

Assistant Researcher 3 received the participants in the clinical setting, taking them to room 1, where evaluations were performed by Researcher 1. Assistant Researcher 3, after initial evaluation, conducted the participants to Researcher 2, who realized randomization, conducted the intervention, and applied the side effects questionnaire. Finally, Assistant Researcher 3 conducted the participants to Researcher 1 for re-evaluation and defined the next day of the intervention. Researcher 4 conducted the statistical analysis of the major study and analyzed some conclusions for this pilot study.

Statistical analyses

Data were organized in spreadsheets and analyzed using Statistical Package for the Social Sciences (SPSS) v20.0, and the normality distribution was assessed by the Shapiro-Wilk test. The sample characterization of the demographic and clinical variables and the adverse effect of interventions were described using the main and standard deviation or median and interquartile interval according to normality distribution. The effect of the intervention on the CPM curve was analyzed by two-way ANOVA with a factor group (i.e., active tDCS + active PES, active tDCS + sham PES, Sham tDCS + Sham PES), and a factor of time (i.e., 0s, 30s, 60s, and 90s after conditioned stimulated stimulus). The Bonferroni Post-hoc test and the partial eta-squared (η^2) effect sizes were calculated for ANOVA analyses. In all statistical tests, the significance level alpha was 5%, and the Beta of 80%.

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of all individuals are presented in Table 1. Ten women were identified as having TMD during the screening evaluation of a hundred adults diagnosed with SCD. They were identified in primary health centers in six cities in the Bahian

Recôncavo. Seven women had SCD genotype HbSS, and three had HbSC, with an average age of 38.9 ± 6.08 years old. All clinical and sociodemographic characteristics are listed for the reader's knowledge (supplementary material).

The pain (mean pain of the last 3 months) of the ten women participating in the study was 6.3 ± 1.56. All of them had chronic pain, established as having daily pain in the same region at least in the last three months, and all had central sensitization 64.62 ± 13.92. Distribution of pain: 100% had widespread pain, 30% had probable depression, and 80% had probable anxiety. Concerning the pain symptoms, 80% of individuals described pain in the head and neck, 90% in upper limbs, and 100% in lower limbs.

In the first interview, the individuals were asked which drugs they ingested daily: 100% used Folic acid, 20% used Hydroxyurea, 50% used Dipyrone, 20% used tramadol, and 30% paracetamol. All participants in this study were asked to avoid taking pain medication 24 hours before applying neuromodulation (Table 1 and supplementary material).

Table 1. Demographic and clinical characteristics of SCD participants with TMD

	SCD participants
Age, mean (SD)	38.9 (6.08)
Sex, n (%)	
Female	10 (100%)
Pain intensity last 3 months	6.3 (1.56)
Widespread pain, n (%)	10 (100%)
Central Sensitization, n (%)	10 (100%)
Catastrophism n. (%)	8 (80%)

SD = standard deviation

After palpation, the pain over the right and left side of the temporomandibular region and the weight needed to elucidate pain over the masseter muscle were evaluated with an algometer (kg). These were done before any intervention. Right TMJ pain was 4.46 ± 2.00, and left TMJ pain was 4.71 ± 2.30. Right masseter 1.5 ± 32 and left masseter 1.55 ± 0.35. Pain in the right masseter was 3.56 times more than in the right temporal muscle. Pain in the left masseter was 2.69 times more than in the left temporal muscle (data from RDC/TMD).

The diagnoses of TMD with RDC/TMD Axis I showed 90% of the individuals with myofascial pain and 10% with myofascial pain with open limitations. The second diagnosis more frequent was 90% with joint arthrosis (RDC/DTM diagnosis in supplementary material). The results obtained by Axis II were an average value of 2,6 degrees for chronic pain, (which means pain characteristics over 50/100 and less than three points of incapacity, being 3 points of incapacity the maximum). 2,43 degrees of depression, 2,3 degrees of physical symptoms with pain, and 2,49 degrees of physical symptoms without pain were all classified as severe (Piccin et al., 2016; Ezenwa et al., 2016).

Endogenous Pain Modulation Testing: Pain Facilitation

To evaluate pain facilitation, the average of three assessments before any intervention was calculated using pinprick stimuli over the thenar and the TMJ region, (1) mechanical threshold, (2) Pain mechanical threshold, (3) Pain 3/10, nine of the ten women did all the sessions, and the results are the average of the three sessions, of thenar region and temporomandibular region (Table 3). The mean and standard deviation (SD) was established. We observed that pain facilitation was present in eight of the ten women (Ezenwa et al., 2016). The pain over the thenar region of the right hand was 4.39 $\pm$ 0.73 after TS, and the pain over the TMJ region of the most painful side was 5.26 $\pm$0.71 after TS (Table 3).

Table 3: Mean and standard deviation for mechanical threshold, pain threshold, pain, and Temporal Summation.

	THENAR REGION				TEMPOROMANDIBULAR REGION			
Subjects	**Mechanical Threshold (g)**	**Pain mechanical Threshold (g)**	**Tolerance Pain (g)**	**TS (EVA)**	**Mechanical Threshold (g)**	**Pain Threshold (g)**	**Pain (g)**	**TS (EVA)**
1	0.04(0.00)	2.33(2.30)	3.33(2.30)	3.33(0.57)	0.02(0.00)	0.85(0.63)	1.66(1.22)	5.33(0.57)
2	0.4(0.00)	3.33(1.15)	6.66(1.15)	5.0(2.0)	0.27(0.37)	1.20(0.72)	3.80(2.30)	6.33(1.15)
3	0.03(0.01)	3.13(1.50)	5.33(1.15)	5.33(0.57)	0.02(0.00)	0.66(0.30)	1.80(0.34)	6.0(1.0)
4	0.22(0.32)	3.66(2.51)	6.00(0.00)	5.33(0.57)	0.05(0.01)	2.1(1,60)	5.13(3.38)	5.66(1.52)
5	0.07(0.00)	3.13(2.50)	8.00(0.00)	3.33(0.57)	0.032(0.03)	1.26(0.80)	4.00(2)	4.33(1.52
***6**	0.04	1.40	6.00	4.00	0.008	0.16	4.00	5.00
7	0.03(0.01)	3.06(4.27)	5.33(4.16)	4.66(1.52)	0.02(0.01)	0.88(1.00)	4.00(3.46)	5.33(0.57)

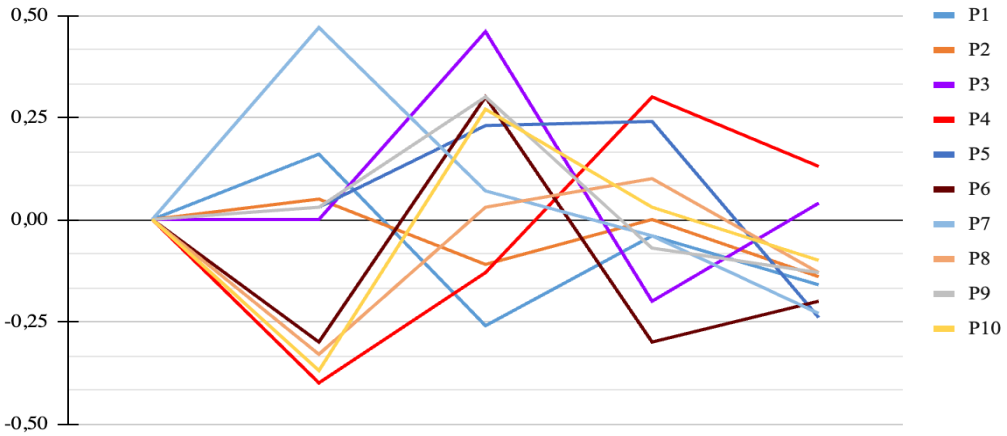
8	0.03(0.01)	2.46(1.36)	5.33(2.3)	4.33(1.15)	0.01(0.006)	0.72(0.48)	2.20(1.70)	5.00(0.00)
9	0.02(0.00)	14.66.0(9.86)	33.6(23.45)	4.00(1.0)	0.01(0.006)	10.46(7.85)	48.6(19.62)	4.00(1.00)
10	0.026(0.01)	13.33(2.88)	100(0.00)	4.66(0.57)	0.008(0.00)	25.66(30.43)	75.3(42.72)	5.66(1.52)

***This woman participated in only one intervention**
TS = Temporal Summation.

Endogenous Pain Modulation Testing: Pain inhibition

Pain inhibition was induced by immersion of the right hand in hot water. The pain felt just before immersion, right after, 30, 60, and 90 seconds after, was registered. The average of three assessments before any intervention was computed, providing the curves presented in Figure 3. The results show five apparent normal curves of endogenous pain modulation of patients P4, P6, P7, P9, and P10.

Figure 3: Conditioned Pain Modulation (CPM) in women (P) with SCD and TMD



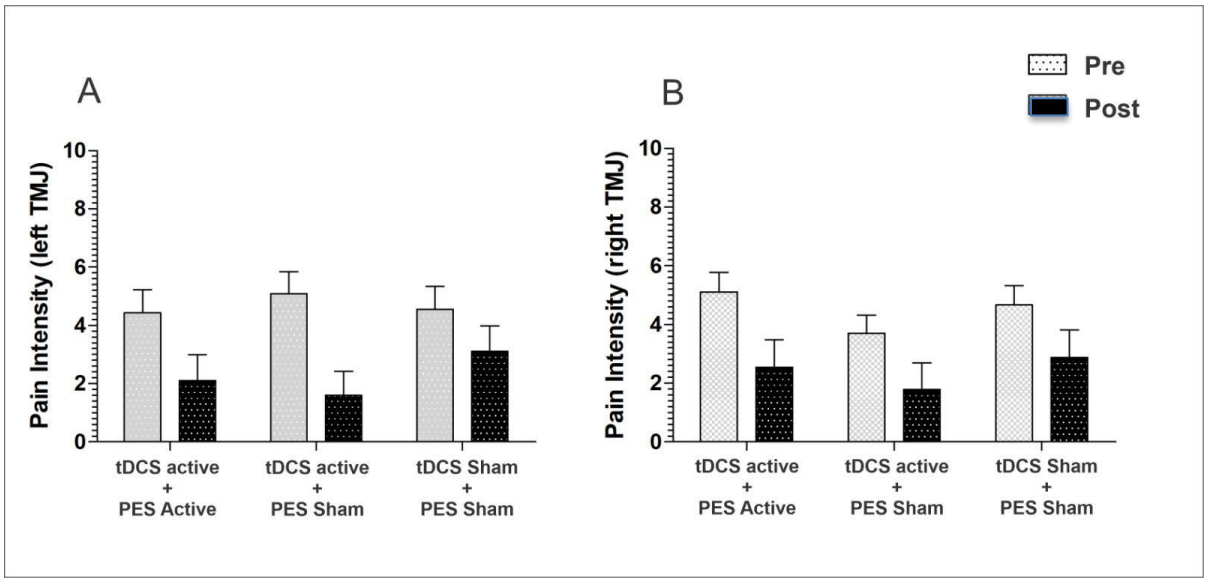
P = Patients

Intervention results

Without intending to draw conclusions in this pilot study, we analyzed pain over the right and left temporomandibular joint, according to VAS before and after the group's intervention. A repeated measures ANOVA with a Greenhouse-Geisser correction showed that the evaluation of pain over the right TMJ region didn't differ significantly in the measures of time and group (F [2.000, 25.000] =.304, p =.740). The post hoc pairwise comparison using the Bonferroni correction showed differences in all three groups. For active tDCS and active

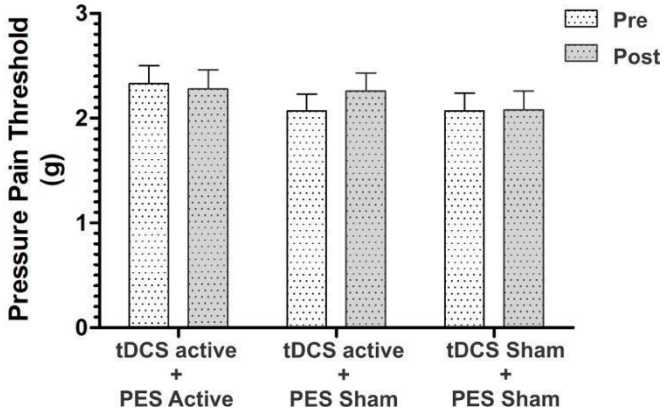
PES p = .003; for active tDCS and sham PES p = .014; and sham tDCS and sham PES p = .028. Similar results for evaluating pain over the left TMJ region for time (F [2.000, 25.000] = 1.26, p = .301). A post hoc pairwise comparison using the Bonferroni correction showed differences. For active tDCS and PES p = .021 and for active tDCS and sham PES p = .001, and no changes for sham tDCS and sham PES p = .139. Figure 4.

Figure 4: Comparison between groups before and after intervention for VAS of pain over Left (A) and Right (B) TMJ.



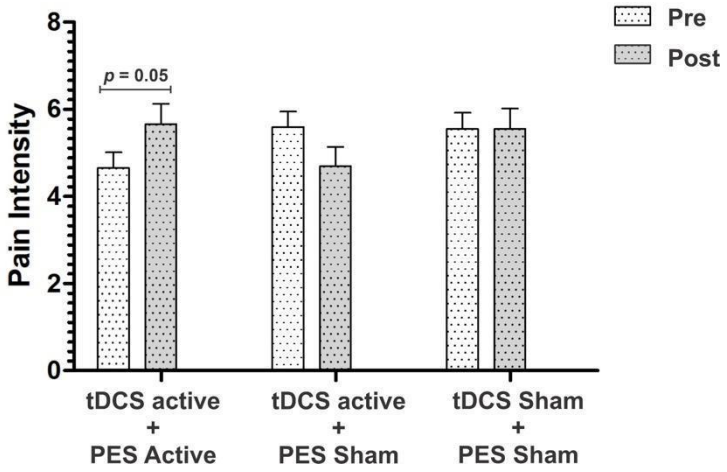
Some differences were observed when analyzing the behavior of endogenous pain modulation before and after interventions. A repeated measures ANOVA with a Greenhouse-Geisser correction showed that CPM scores differed significantly in the measures time (before and after intervention) (F (5.544, 69.304) = 2.725, p =.022). A post hoc pairwise comparison using the Bonferroni correction did not show group differences. For active tDCS and PES, Pre (2.33±0.17[SE]) vs. Post (2.29±0.18[SE]) P = 0.666; for active tDCS and sham PES, Pre (2.07±0.16[SE]) vs. Post (2.26±0.17[SE]) P = 0.073; and sham tDCS and PES, Pre (2.07±0.17[SE]) vs. Post (2.08±0.18[SE]) P = .951 (Figure 5)

Figure 5: Comparison between groups before and after intervention for CPM



A repeated measures ANOVA with a Greenhouse-Geisser correction showed that QST of temporal summation over the TMJ region differed significantly in the measures of time (before and after intervention) (F (2.000, 25.000) = 3.843, p = .034). A post hoc pairwise comparison using the Bonferroni correction showed group differences. For active tDCS and PES, Pre (4.66±0.37[SE]) vs. Post (5.66±0.47[SE]) P = .05; for active tDCS and sham PES, Pre (5.60±0.35[SE]) vs. Post (4.70±0.45[SE]) P = 0.06; and for sham tDCS and PES, Pre (5.55±0.37[SE]) vs. Post (5.55±0.47[SE]) P = 1.00 (Figure 6).

Figure 6: Comparison between groups before and after intervention for QST



Adverse reactions and blinding

After each session, adverse reactions and blinding were registered. After the application of active tDCS, the adverse reactions declared were tingling (50%); drowsiness (30%); itching (20%), and mood swings (10%). Tingling and drowsiness were also declared in the sham tDCS allocation. Only one adverse reaction was declared for PES, tingling under the electrode. No major adverse effect was observed in any session.

The conditioned pain modulation paradigm was conducted using a room at 23ºC. It was requested to put the non-dominant hand first in a stainless-steel container with water at 23ºC and, after one minute, put the same hand in a similar container with hot water at 46ºC. There was no adverse reaction to the hot water, but most did not like it at 23ºC, declaring it cold, and complained about the air conditioning. We maintained the protocol.

Only one participant defined correct allocation for the three sessions; 60% declared being always in an active tDCS allocation group.

Adherence to participating in the screening and intervention protocol

The participants of the major study were recruited from the Primary Health Centers of nine of the twenty-two cities of Recôncavo Baiano; first, the municipal health coordinator was visited by the researchers, asking for endorsement to conduct the study; after the consent, the chief nurse of each Primary Health Center was informed about this authorization so they would allow a visit to inform about the study and protocol. This was the primary factor, getting acquainted with the nurses who, in turn, put us in contact with the community health agents who invited individuals with SCD. This was allowed easily in six cities, and we can affirm that all adults with SCD were interviewed. However, in two cities, we had important limitations in getting in touch with the subjects, and a lack of cooperation from the nurses was evident. In the largest city, the interviews were only possible thanks to the collaboration of the SCD carriers' association. In this last case, we focused on women between 30 and 49 years old.

Feasibility of the study and sample size

The study with a larger number of participants can be carried out and is recommended for its contribution, but we propose that the five sessions of tDCS described in the literature be carried out in the primary health care centers near the home at an established time of the day when it is quiet and peaceful. Transport to the clinic is difficult due to the distance and absence of direct public transport. However, it is worth emphasizing the willingness of individuals to collaborate in favor of SCD research.

Based on the pilot study, the effect size was calculated using the WinPepi software calculator, inserting the mean pain of TMJ, and the standard deviation after the intervention of tDCS active + EPP sham and tDCS sham + EPP sham. The result obtained was Cohen´s d = (2.88 -1.80)/0.915341 = 1.179888. With these data and with the same software, we calculated the appropriate sample size for the Randomized Clinical Trial (RCT). The calculator result was a need for 11 individuals per group. However, to meet international RCT guidelines, we propose that the trial has 25 individuals per group.

DISCUSSION

This study provides evidence that transcranial direct current stimulation can be safely used by women with SCD and TMD. The analysis through ANOVA, identified trends to differences before and after the intervention session for pain over TMJ, and endogenous modulation. There was decreased temporomandibular pain with the tDCS and active PES protocol and the active tDCS protocol with sham PES. There were also differences in the evaluation of endogenous pain modulation for facilitation, in this case by mechanical stimulation on the temporomandibular joint, showing differences between the tDCS and active PES group. ANOVA also showed differences in time with the inhibition stimulus, but no differences were found between groups. These results are encouraging, considering the sample size.

Adverse reactions with tingling, drowsiness, and itching were reported in both the active and sham sessions. We registered the frequent complaints of the participants regarding the temperature of 23 degrees Celsius in the air-conditioned room and the complaint of putting the hand first in cold water at the same temperature to initiate endogenous pain modulation.

This confirms data from the literature that people with sickle cell disease prefer heat to cold. (Brandow & Panepinto, 2016). Blinding was efficient, demonstrating that the equipment was adequate, compared to a previous study by this same group of researchers where the participants identified the location with the same intensity of tDCS. Differences in knowledge were significant, the actual study was done with the general population with secondary education, and the previous study was done with physical therapy students (Oliveira, 2015).

This study helps to understand the depth and breadth of chronic pain of women with SCD and TMD, not described in the literature, within our knowledge. The pain of the last three months was high, and all women declared chronic and generalized pain. All women reported pain in the lower limbs, nine in the upper limbs, and eight in the neck and head. The central sensitization questionnaire classified all with high rates, but the endogenous pain modulation tests offered more details. Impairment of pain facilitation was present in most of the women with TMD and SCD, and impartment of pain inhibition was less compromised, as described by Ezenwa (2016) for SDC patients and also by Moana-Filho for TMD patients (Moana-Filho & Babiloni, 2019) (Darbari & Brandow, 2017). These results do not cancel the possibility of peripheral sensitization. Inflammatory components such as synovitis can interfere with pain in patients with TMD but are only confirmed by laboratory and radiological tests, where a definitive differentiation is made between the presence or absence of inflammatory degenerative changes (Kothari et al., 2016; Pihut et al., 2018). Eight women had catastrophic thoughts, which can also interfere with pain responses and sensitization mechanisms, a frequent fact in people with TMD and people with sickle cell disease (Mathur et al., 2016). This is a broad discussion because catastrophism has been associated with depression and quality of life but less with pain. (Bakshi et al., 2018).

The degrees of depression are those already described for the population with sickle cell disease, but eighty percent were classified as possible carriers of anxiety, a value much higher than that stated in the literature. Greater pain sensitivity and psychological distress (Bair et al., 2016). We can affirm that these women had more body pain in all extremities, with a complicating factor, TMD, diagnosed in the vast majority by myofascial pain and joint arthrosis, which may interfere with speech and ingestion.

As for medications, all use folic acid, only two use hydroxyurea, and nine out of ten reported daily use of pain medication. The most frequent is dipyrone, which they abstained from on the days of the interventions. Hydroxyurea has been presented as the mainstay for disease-modifying therapy (Brandow & Liem, 2022; Yang et al., 2022), but there is still no evidence of long-term benefits, especially in the case of the prevention of chronic complications, nor is there any evidence about the effect of its prolonged use (Nevitt et al., 2017).

Limitations

The limitations of this pilot study are the number of people who participated, limiting the possible conclusions. We recognize that the population with SCD and TMD is not simple to identify, but it exists and needs to be recognized and treated.

CONCLUSION

This study provides evidence that women with SCD and TMD can safely use transcranial direct current stimulation. Our results suggest the potential of using tDCS+PES for these individuals with SCD and TMD, which may promote using an easy-to-apply technique as part of multidisciplinary treatment. tDCS may be effective for women with SCD and TMD, but a larger study needs to be done. No adverse effects were registered, implicating pain crises.

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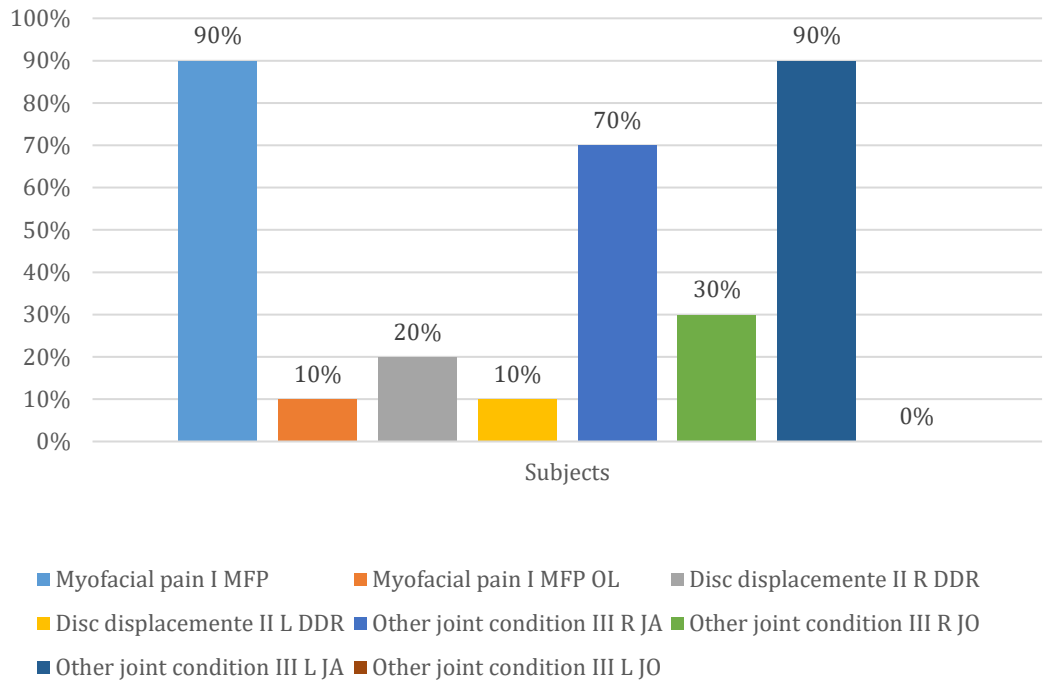
SUPLEMENTARY MATERIAL

Supplementary material 1: Diagnosis of RDC/TMD Axis I.



Supplementary material 2: Complete Demographic characteristics

	10 SCD with TMD	
	Mean (SD)	**Number (%)**
Sex		
Male		0 (0%)

Female		10 (100%)
Age, in Years	38.9 (6.08)	
18 - 29		0 (0%)
30 - 39		7 (70%)
40 - 50		3 (30%)
Education Level		
Incomplete and Complete Elementary School		6 (60%)
Incomplete and Complete High School		3 (30%)
Incomplete and Complete Higher Education		1 (10%)
Marital Status		
With a partner		6 (60%)
No partner		4 (40%0
Self-declaration of race		
Black		9 (90%)
Brown		1 (10%)
White		0 (0%)
SCD Genotype		
HbSS		7 (70%)
HbSC		3 (30%)
Government Benefit		
With Benefit		6 (60%)
Without Benefit		4 (40%)
Work with a formal contract		0 (0%)

Sample size – 10 with Temporomandibular dysfunction

Supplementary material 3: Complete Clinical Characteristics

	10 SCD with TMD	
	Mean (SD)	**Number (%)**

Pain		
Average pain of the last 3 months	6.3 (1,56)	
Pain at the moment of the interview	3.6 (2.6)	
With chronic pain		10 (100%)
Distribution of pain		
Localized pain		0 (0%)
Regional pain		0 (0%)
Widespread pain		10 (100%)
Average Number of painful points	21.2 (12.0)	
Pain in lower limbs		100%
Pain in upper limbs		90%
Pain in dorsum lumbar region		80%
Pain in head and neck		80%
Pain in thorax region		40%
Pain in abdomen and perineum		40%
Medication use		
Daily quantity of medications use	3.00 (2.00)	
Polypharmacy (use of at least 4 medications)		60 (60%)
Level of improvement after using pain medication (%)	48.00 (0.29)	
Central Sensitization		
Average	64.62 (13.92)	
With Central Sensitization		10 (100%)
Catastrophism		
Over 40 points		8 (80%)
Average	42.7 (5.6)	

Sample size – 10 with Temporomandibular dysfunction

5.2 ARTIGO 4: IMPACT OF AVERAGE PAIN, ANXIETY, CATASTROPHIZING, CENTRAL SENSITIZATION, DEPRESSION, AND TRIGGER POINTS ON QUALITY OF LIFE IN INDIVIDUALS WITH SICKLE CELL DISEASE.

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ABSTRACT

Introduction: Sickle cell disease (SCD) is the most common hemoglobinopathy in the world, with 275,000 newborns annually. Hemoglobin polymerization leads to erythrocyte rigidity and Vaso-occlusion, which leads to pain and other changes in the body, seriously affecting the quality of life (QoL) of carriers. **Objective:** to analyze the impact of trigger points in the body, average pain, Catastrophizing, Central Sensitization (CS), anxiety, and depression on the QoL of adults with SCD. **Method:** This is a descriptive cross-sectional study. It collected sociodemographic data and applied the Brazilian-Portuguese Central Sensitization Inventory, the Brief Pain Inventory, the Hospital Anxiety/depression Scale, the Brazilian-Portuguese Pain Catastrophizing Scale, and the Short Form Health Survey 36. Statistical analysis was done to define associations (Chi-square or Fisher's Exact) and correlation (Pearson correlation test). The alpha level was 5%, and the Beta of 80%. **Results:** 100 individuals participate, with genotypes HbSS/HbSC. 69% were women, age 34.14+10.12 years. Pain intensity was 4.20+2.67; 71% had chronic pain; 60% had widespread pain; 59% had CS; 33% had anxiety; and 18% had depression. The lowest mean score for QoL was for the Physical Aspect domain (35.55+40.16). Anxiety, average pain, CS, and catastrophizing correlated with all the domains of QoL. Anxiety and CS showed a significant negative influence over the Mental Health domain ($F(2.95)=43.014$ $p< .001$; adjusted $R2=.464$), explaining 46.6% of the outcome. Catastrophizing and CS had a significant negative influence on the General Health Status ($F(2.95)=21.592$ $p<.001$; adjusted $R2=.298$), explaining 29.8% of the outcome; and anxiety, pain in lower limbs, and depression had a significant negative influence on Pain domain ($F(2.95)=15.207$ $p<.001$; adjusted $R2=.270$), explaining 27% of the outcome. **Conclusion:** Anxiety, depression, catastrophizing, and CS are significant factors that impact QoL. In a population of SCD individuals, the primary objective is to control pain, which leads to chronic pain directly affecting these predictors and, inevitably, QoL.

Keywords: Sickle Cell Disease, Quality of life, Central sensitization, Catastrophizing, Depression, Anxiety.

INTRODUCTION

Sickle cell disease (SCD) is the most common hemoglobinopathy in the world, with 275,000 newborns annually with this disease (Aygun & Odame, 2012). Haemoglobin polymerization leads to erythrocyte rigidity and vaso-occlusion, which leads to pain and other changes in virtually every organ in the body (Darbari, Sheehan, and Ballas, 2020). Therefore, the most frequent symptoms in individuals with SCD are acute joint pain, intense fatigue, delayed growth, leg ulcers, pallor, and jaundice, with comorbidities, such as infections, heart disease, kidney failure, stroke, and proliferative retinopathy (Rees, Williams, and Gladwin 2010). This disease is characterized by its prevalence in underdeveloped countries, reaching the low-income population (Aygun & Odame, 2012). For example, Brazil has high rates, with

higher prevalence in the state of Bahia (Cançado & Jesus, 2007); (W. Silva et al., 2016); (Kato et al., 2018).

SCD has been extensively studied, focusing on the pathophysiology and treatments that lessen acute attacks leading to hospitalization (Ballas, 2015). Medical treatments have increased life expectancy, allowing individuals to be exposed for a longer time to the comorbidities of the disease. (Brandow & DeBaun, 2018). In this context, chronic pain syndrome has developed in 30-40% of adults with SCD (Brandow et al., 2017), significantly impacting the functionality of individuals with SCD (Sil et al., 2016). The participation of central sensitization (CS) in the perpetuation and increase of pain in individuals with SCD has been studied in several research centers providing sufficient evidence of its contribution to the chronicity of pain (Woolf & Salter, 2000; Darbari et al., 2017; Uhelski & Simone, 2019; Karafin et al., 2019). The assessment of central CS in SCD individuals in clinical settings context has been recommended (Lopes et al., 2022). Using reliable methods such as Quantitative Sensory Testing (QST), Conditioned pain modulation (CPM), and the Central Sensitization Inventory can help clinical professionals better understand the changes that chronic pain brings to these individuals and how much it can impact their QoL (Woolf & Salter, 2000; Darbari et al., 2017; Uhelski & Simone, 2019).

Quality of life is conceptualized as an individual's "appraisal of how his/her well-being and level of functioning, compared to the perceived ideal, are affected by individual health" (Panepinto & Bonner, 2012). The SF-36 is a valid and reliable instrument designed to scrutinize health status for clinical practice and research, health policy studies, and general population investigations. QoL has eight domains that can be divided into physical components, the first four (functional capacity, physical aspects, pain, and general health status); and emotional aspects (vitality, social aspects, emotional aspects, and mental health) that assist in its approach for the definition of treatments of individuals with diminished QoL (Ware & Sherbourne, 1992; Rodrigues et al., 2021).

In the last decade, studies on the impact of pain on QoL have increased due to the development of chronic pain. Studies have analyzed financial burden (Lee et al., 2020; Amaeshi et al., 2022), education, work, and disease management (Osunkwo et al., 2021; Keenan et al., 2021), with the publication of recommendations (Brandow et al., 2020). Some

studies have associated the high and low QoL in sickle cell individuals with several daily life issues, such as Prejudice (Rodrigues et al., 2021). Emotional dysfunctions such as depression, in the first place, then anxiety and Catastrophizing have been identified as participants in the clinical picture of patients with SCD, interfering with the pain profile (Levenson, McClish, Dahman, Bovbjerg, de A Citero, et al. 2008; Edwards et al., 2009; Mathur et al., 2016). These studies have shown that the QoL in sickle cell disease can be impacted by complex factors that clinicians and researchers should understand better.

This study analyzed the impact of trigger points, average pain, catastrophizing, central sensitization, depression, and anxiety on the QoL in individuals with Sickle Cell Disease. We hypothesized that these individual characteristics have a meaningful impact on the eight domains of QoL.

MATERIALS AND METHODS

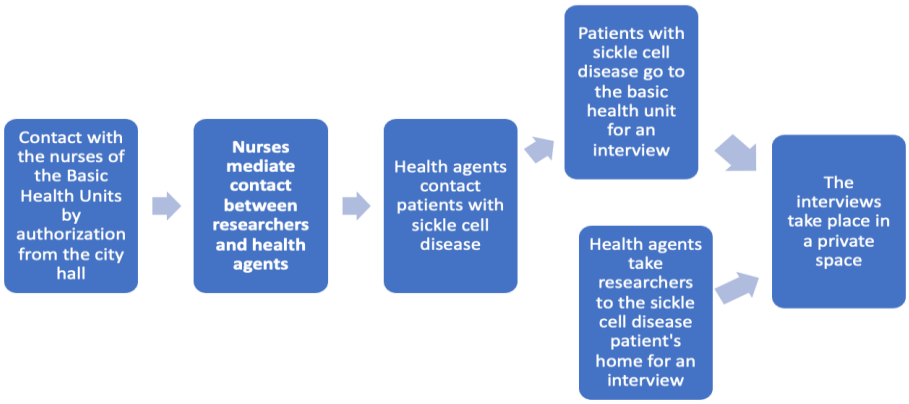
This descriptive cross-sectional study is part of a crossover randomized clinical trial registered in REBEC n. TN: U1111-1243-3020, already published (Oliveira et al., 2021), with adults diagnosed with SCD. Inclusion criteria were being diagnosed with SCD, being of legal age, and not having had acute crises in the last ten days.

The Primary Health Center invited one hundred and ten individuals. After acquiring information about the study, five individuals declined to participate, declaring a lack of time or interest. Five other individuals were discharged after being identified as having S traits and not SCD. One hundred individuals completed all the questionnaires. The study participants were recruited between October 2019 and October 2022, registered in the Primary Health Centers from Recôncavo Baiano, and members of the association of sickle cell disease of the city of Feira de Santana-BA.

The Informed Consent Form was read to all participants under the 466/2012 Resolution of the National Health Council of Brazil. This study was approved by the Ethics and Research Committee of Faculdade Adventista da Bahia (CAAE No. 94835218.8.00000.0042). It was clarified for everyone that they were free to deny participation or leave the interview at any time. After reading, they signed the acceptance document.

The process of contact with SCD carriers occurred in two ways (Figure 1). The sample was for convenience. Two properly trained researchers applied the questionnaires to all participants.

Figure 1: Bearer access process



Procedures. The individuals with SCD underwent screening at their local Primary Health Center or home. After the informed consent form was read, explained, and signed, questionnaires were responded to by the participants to the researchers. In this study, the researchers read each question to everyone. The sociodemographic questionnaire gathers information on age, gender, education level, marital status, race, religion, and pain levels. Several collect instruments were applied, as described below.

Brazilian Portuguese Central Sensitization Inventory (BP–CSI). Designed as an easy-to-administer screen for individuals at high risk of central sensitization and helps to classify chronic pain. It comprises twenty-five questions with five possible answers from never to always. It is an ordinal scale; each response has one value from zero to four (Caumo et al., 2017).

Brief Pain Inventory to Brazilian Patients (BPI). It consists of nine items arranged in two dimensions: the intensity of pain and its impact on the patient's life. The BPI asks to rate their pain intensity and the pain interference with general activities, mood, walking ability, everyday work, relationships with others, sleep, and enjoyment of life on an 11-point scale ranging from

zero (no pain) to ten (as bad as it can be). It includes a corporal diagram to assess pain location, measures the percentage of pain relief, and asks to describe which treatments are being used to control pain. A high score represents a high pain intensity or interference (Ferreira et al., 2011).

Brazilian Portuguese Pain Catastrophizing Scale (BP-PCS). The BP-PCS questionnaire consists of thirteen items evaluating self-reported catastrophizing thoughts, feelings, and behaviors when in pain (Oliveira et al., 2021; Sehn et al., 2012). It is divided into three domains: helplessness, magnification, and rumination. Items are rated on a 5-point Likert-type scale in which both intensity and frequency information are represented, with the following five levels of response for each item: (0) not at all, (1) to a slight degree, (3) to a moderate degree, (4) to a great degree, (5) and all the time. The PCS total score ranges from 0 to 52 points.

Hospital Anxiety and Depression Scale (HADS). It comprises fourteen self-reported questions divided into two subscales: one for anxiety and the other for depression. The subject will rate each item using an ordinal scale varying from zero (non-existent symptom) to three (very severe symptom) (Pais-Ribeiro et al., 2007)).

Short Form Health Survey 36 (SF-36). It comprises thirty-six multidimensional questions that will give a raw scale of eight concepts: functional capacity, physical aspects, pain, general health status, vitality, social aspects, emotional aspects, and mental health. It has a final score from zero to 100, where zero corresponds to the worst general health and 100 to the best general health. (Campolina et al., 2011).

Statistical analyses

Data were organized in spreadsheets and analyzed using Statistical Package for the Social Sciences (SPSS) v20.0, and the normality distribution was assessed by the Shapiro-Wilk test. The sample characterization of the demographic and clinical variables was described using the main and standard deviation or median and interquartile interval according to normality distribution. The association between the presence of chronic pain (i.e., yes, or no) and the distribution of pain (i.e., localized, regional, and widespread) were analyzed by Chi-square or Fisher's Exact tests when comparing the frequency distributions. The clinical factors related to pain, such as Anxiety, Average pain, Catastrophizing, Central sensitization, number of medications used, Depression, and body distribution of trigger points (i.e., lower limbs, trunk,

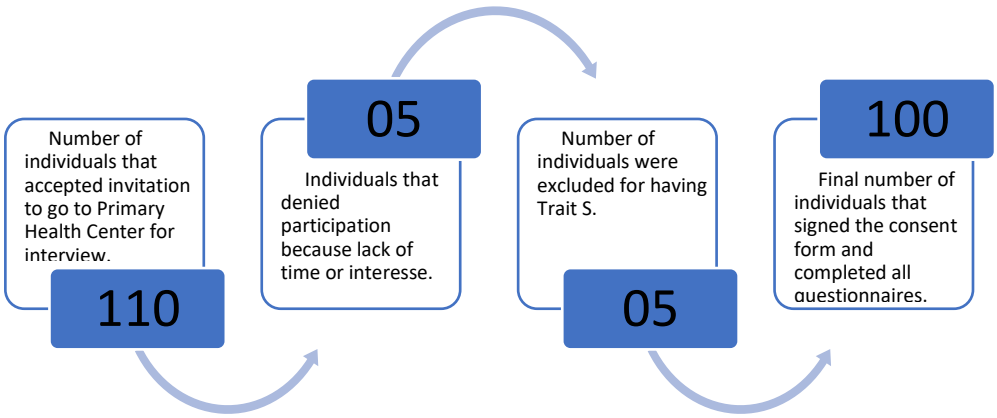
abdominal region, upper limbs, head and neck, shoulders and dorsum, lumbosacral region), were analyzed using the Pearson correlation test with the domains of QoL by SF-36 (i.e., functional capacity, physical aspects, pain, general health status, vitality, social aspects, emotional aspects, and mental health). All significant correlations were included in multiple linear regression analysis models, using the forward method to analyze the impact of overall QoL domains by SF-36. In all statistical tests, the significance level alpha was 5%, and the Beta of 80%.

RESULTS

Demographic characteristics

A hundred adults diagnosed with SCD, identified in primary health centers in six cities in the Bahian Recôncavo, 65 individuals of this study had genotype HbSS and 35 had genotype HbSC. Sixty-nine were women and thirty-one were men, with an average age of 34.14 (SD ±10.12), were included (Figure 2).

Figure 2. Number of participants



Fifty-eight individuals had some type of government financial aid. The average subject's financial income was less than the country's minimum wage, established at US$ 242.40. The more frequent educational level was Incomplete and Complete High School. 61 participants were single. See supplementary material (1) for complete demographic characteristics.

Clinical characteristics

The average pain of the 100 individuals who participated in the study was 4.20+2.67 (SD) on the visual analog scale (VAS); 71% of them had chronic pain, established as having daily pain in the same region at least in the last three months, and 59% had central sensitization. Distribution of pain: 22% had localized, 18% had regional, and 60% had widespread pain. Of the sample, 18% had probable depression, 33% had probable anxiety, and 10% had probable depression and anxiety. See clinical information in Table 1.

Table 1. Pain characteristics of participants

	Participants with SCD
Average pain (last three months), mean (SD)	4.20 (2.67)
Pain at the moment of the interview, mean (SD)	2.31 (2.80)
With chronic pain, n. %	71 (71%)
Distribution of pain	
Localized pain, n. %	22 (22%)
Regional pain, n. %	18 (18%)
Widespread pain, n. %	60 (60%)
Number of painful points	14.06 (10.12)
Pain in lower limbs, n. %	90 (90%)
Pain in upper limbs, n. %	80 (80%)
Pain in dorsum lumbosacral region, n. %	73 (73%)
Pain in thorax region, n. %	31 (31%)
Pain in abdomen and perineum, n. %	25 (25%)
Medication use	
Daily quantity of medications used, mean (SD)	2.82 (1.45)
Polypharmacy (use of at least 4 medications), n. %	34 (34%)
Level of improvement after using pain medication, n. %	60.50 (32.60)
Central Sensitization	
Mean, (SD)	46.17 (18.48)
With Central Sensitization, n. %	59 (59%)

Catastrophizing	
Over 40 points, n. %	41 (41%)
Mean, (SD)	34.78 (12.17)

Sample size – 100. SD = standard deviation

In the interview, the patients were asked which drugs they ingested daily. 89% used Folic acid, 27% used hydroxyurea, and 61% used Dipyrone. Only three (3%) used medication for Depression and one (1%) for Anxiety. See supplementary material (1).

Quality of life results (SF-36)

The lowest mean scores for QoL were for the Physical Aspect domain (35.55 + 40.16) and General Health Status domain (38,31 + 23.51). See quality life results in Table 2.

Table 2. Quality of life SF-36

Domain	Mean	SD
Functional Capacity	45.79	26.30
Physical Aspect	35.55	40.16
General Health Status	38.31	23.54
Pain	44.67	24.31
Vitality	45.50	21.13
Social Aspect	56.05	30.89
Emotional Aspect	40.11	39.61
Mental Health	53.62	26.11

Mean and standard deviation (SD)

Associations of Pain Descriptors, chronic pain, and pain distribution

Associations were found between chronic pain with anxiety (X^2= 25.32 p=.000) and depression (X^2= 12.71 p=.002). The association was found between pain distribution with anxiety (X^2=13.35, p =.010).

Correlations between the clinical factors related to pain and the eight domains of Quality of Life (QL)

Anxiety, average pain, CS, and catastrophizing were significantly correlated with all eight domains of QoL. Of these results, it is possible to highlight that anxiety presented a negative moderated correlation with the Mental Health domain (r = -.670; p =.000). CS presented a negative moderated correlation with the Mental Health domain (r =-.584 p =.000). CS also presented a negative moderated correlation with the Vitality domain (r = -.530 p = .000). Catastrophizing presented a negative moderated correlation with General Health Status domain (r = -.525 p = .000) (Table 3).

Table 3. Correlation Quality of life Domains (SF-36)

	Quality of life Domains							
Variables	**FC**	**PA**	**Pain**	**GHS**	**V**	**SA**	**EA**	**MH**
Central Sensitization	-.406**	-.301*	-.407**	-.438**	-.530**	-.453**	-.330**	-.584**
Anxiety	-.244*	-.277*	-.404**	-.366**	-.415**	-.453**	-.286**	-.670**
Pain	-.193	-.348**	-.378**	-.386**	-.402**	-.415**	-.401**	-.446**
Catastrophism	-.217*	-.332**	-.332**	-.525**	-.296**	-.384**	-.302**	-.418**
Depression	-.261**	-.137	-.381**	-.342**	-.437**	-.470**	-.313**	-.464**
Amount of trigger points	-.298*	-.263*	-.389**	-.230*	-.175	-.074	-.166	-.249

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Impact of clinical factors related to pain over Quality of Life

The model of multiple linear regression analysis using the forward method showed that CS and depression impact four domains of QoL. Pain impacts three of the eight domains. Catastrophizing and the number of trigger points of the lower limbs impact two domains each.

The results showed a significant (negative) influence of catastrophizing and CS on the General Health Status (physical component) (F (2.95) = 21.592 p<.001; adjusted R2 =.298),

explaining 29.8% of the outcome. Anxiety, amount of trigger points in lower members, and depression had a significant (negative) influence on the Pain Domain (physical component) (F(2.95) = 15.207 p<.001; adjusted R2 =.270), explaining 27% of the outcome. The other covariables of the physical components impacted less than 20%.

As for the mental elements, the results showed a significant (negative) influence of anxiety and CS over the Mental Health domain (F (2.95) = 43.014 p< .001; adjusted R2 =.464), explaining 46.6% of the outcome. CS and depression had a significant (negative) influence over the Vitality domain (F (2.95) = 23.826 p< .001; adjusted R2 =.320), explaining 32% of the outcome. The domain of social aspects was impacted by depression and pain (F2.95) = 19.941 p<.001; adjusted R2 =.28), explaining 28% of the outcome. The other covariables of the mental components impacted less than 20%. Table 4 presents the QoL predictors.

Table 4. Quality of Life predictor variables

	Standardized Coefficients	**95% Confidence Interval**		***t***	**Sig.**	***R^2***	***DR^2***
PREDICTORS	***Beta***	**Lower Bound**	**Upper Bound**				
FUNCTIONAL CAPACITY							
Constant	-	60.953	86.623	11.413	.000	-	-
Central Sensibilization	-.326	-.737	-.180	-3.271	.001	.153	-
Trigger points in lower members	-.195	-2.45	-.003	-1.990	.049	.179	.034
PHYSICAL ASPECTS							
Constant	-	53.983	99.475	6.697	.000	-	-
Average Pain	-.262	-6.994	-.849	-2.534	.013	.114	-
Catastrophizing	-.211	-1.363	-.018	-2.037	.044	.142	.037
PAIN							
Constant	-	62.781	82.575	14.580	.000	-	-
Anxiety	-.430	-1.962	.218	-1.588	.116	.177	-
Trigger points in lower members	-.266	-2.585	-.385	-2.681	.009	.227	.057

Depression	-.266	-2.886	-.373	-2.575	.012	.270	.050
GENERAL HEALTH STATUS							
Constant	-	65.764	91.091	12.295	.000	-	-
Catastrophizing	-.398	-1.151	-.374	–3.897	.000	.269	-
Central Sensibilization	-.229	-.544	-.033	-2.242	.027	.298	.036
VITALITY							
Constant	-	67.125	86.352	15.847	.000	-	-
Central Sensibilization	-.404	-.679	-.237	-4.115	.000	.280	-
Depression	-.252	-2.422	-.310	-2.568	.012	.320	.046
SOCIAL ASPECTS							
Constant	-	78.904	103.375	14.787	.000	-	-
Depression	-.379	-4.468	-1.567	-4.130	.000	.219	-
Average Pain	-.279	-5.328	-1.116	-3.037	.003	.281	.068
EMOTIONAL ASPECTS							
Constant	-	57.826	90.987	8.909	.000	-	-
Average Pain	-.324	-7.589	-1.882	-3.294	.001	.147	-
Depression	-.203	-4.012	-.081	-2.067	.041	.175	.036
MENTAL HEALTH							
Constant	-	82.649	103.112	18.021	.000	-	-
Anxiety	-.501	-3.912	-1.495	-4.432	.000	.447	-
Central Sensibilization	-.228	-.631	-.005	-2.020	.046	.464	.023

DISCUSSION

This study aimed to analyze the impact factor of the amount of trigger points, average pain, catastrophizing, CS, depression, and anxiety over the domains of QoL. In a population with over seventy percent chronic pain, there was no principal, unique, or even most prevalent impact factor over all eight domains of QoL. Anxiety, depression, catastrophism, CS, and amount of trigger points in lower limbs had an important impact on at least one domain as predictors of QoL. So, it is essential to emphasize the need for their evaluation in clinical

practice. The treatment of these individuals should consider this information for assessment and management (Lopes et al., 2022).

The Central Sensitization evaluation with the BP–CSI stands up because 59% of our individuals were diagnosed with it. It is worth mentioning that the second part of this questionnaire had no positive response; this can be defined as underdiagnosis or lack of care, characteristic of this disease in these individuals, a problem of prejudice, and structural racism (Rodrigues et al., 2021). Sixty percent of the sample declared widespread pain, an important characteristic of CS (Arendt-Nielsen et al. 2018).

Average pain was an essential impactor in the QoL domains, the greater the pain, the lower the domain score, specifically over Physical Aspects, Social Aspects, and Emotional Aspects. If pain is undertreated, chronic pain will install and potentiate other contributors as described in this study (Woolf and Salter 2000; Darbari et al. 2017; Uhelski and Simone 2019). The most compromised domains of QoL were physical aspects and general health status, similar to the survey results in north Brazil, related to the perception of stigmatization and prejudice of individuals diagnosed with SCD (Rodrigues et al., 2021).

The individuals in our study had higher anxiety levels than depression in opposition to several studies (Levenson, McClish, Dahman, Bovbjerg, de A. Citero et al., 2008; Wallen et al., 2014). An explanation may be that the adults who participated in this study live in small towns without easy access to the state's capital, where specialized care is provided, such as hospitalization and blood transfusions. The limitations with access may contribute to the higher anxiety levels because of the concern with medical assistance for the subsequent crises; the literature has associated anxiety with the fear that the condition could shorten life expectancy (Toumi, Merzoug, and Boulassel 2018).

Only twenty-seven of the participants in this study used hydroxyurea daily, which remains the mainstay for disease-modifying therapy (A. M. Brandow and Liem 2022) and also elevates QoL (Yang, Elmuti, and Badawy 2022). The cost is eleven times more expensive than folic acid, the primary medication used for SCD, in Brazil, where government health care is responsible for providing these drugs. Dipyrone is mainly used for pain; more than 60% of the subjects use it daily, confirming the high incidence of pain (Amanda M. Brandow et al., 2020). See Supplementary material (2) for complete list of medications used.

Only six individuals in the study work as employees. Generally, individuals with SCD have fewer work opportunities, perhaps due to the fear of frequent absences from their possible employers; it has been registered unfavorable attitudes toward individuals with SCD (Swanson, Grosse, and Kulkarni 2011). SCD has an essential impact on work activities (Pires et al., 2022). Work is essential for livelihood and maintaining mental well-being, gives meaning to life, and drives human growth (H. D. Silva et al. 2013). Individuals with SCD seek government aid because of their lack of autarchy; in this case, almost sixty percent have some benefit. The government benefit is low; more is needed to cover personal expenses, so many depend on their relatives, regardless of age. Therefore, the financial burden that SCD causes in this population may be similar to other populations in underdeveloped countries (Kato et al., 2018), affecting their quality of life.

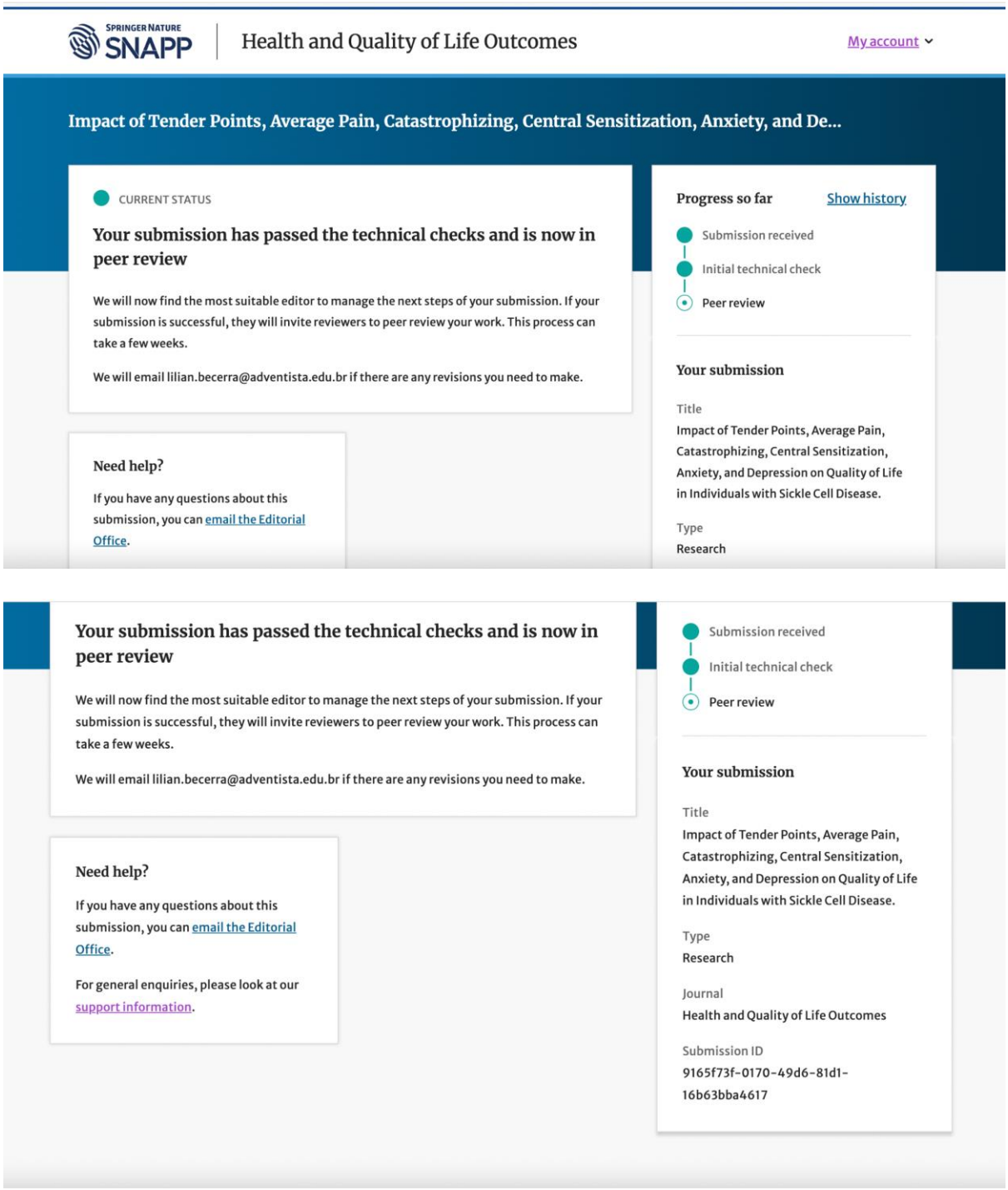
An association between the amount of trigger points in lower limbs and anxiety was identified. The most frequent clinical causes of pain in the lower limbs are avascular necrosis in the hip, chronic infarction in the lower limbs (Ejindu et al., 2007), and vaso-occlusive pain (Kato et al., 2018). The extremities are fundamental for the functionality and independence of the individual. The loss of autonomy may explain the association between anxiety and the amount of trigger points in the lower limbs. These individuals could benefit from light physical exercises recommended by the literature. However, they have yet to have this opportunity in some way due to a lack of knowledge. (Martin et al., 2018).

Our study had limitations on subjects who participated for convenience; also, we decided to publish this predictory study with cross-sectional data because we believe that the results are relevant to be shared; a longitudinal study is necessary to confirm the findings.

CONCLUSION

Anxiety, Depression, Catastrophizing, and Central Sensitization significantly impact the quality of life. In a population of SCD individuals, the primary objective is to control pain, leading to chronic pain directly affecting these predictors and, inevitably, quality of life; This is the responsibility of a multi-professional team and the capability of government initiative.

SUBMISSION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SUPLEMENTARY MATERIAL

Supplementary material 1. Demographic characteristics of participants

	Mean (SD)	Number (%)
Sex		
Male		31 (31%)
Female		69 (69%)
Age, in years	34.14 (10.12)	
18 - 29		35 (35%)
30 - 39		34 (34%)
40 - 50		26 (26%)
Education Level		
Incomplete and Complete Elementary School		33 (33%)
Incomplete and Complete High School		52 (52%)
Incomplete and Complete Higher Education		15 (15%)
Marital Status		
With a partner		39 (39%)
No partner		61 (61%)
Self-declaration of race		
Black		85 (85%)
Brown		14 (14%)
White		1 (1%)
Religion		
Catholic		48 (48%)
Evangelical		35 (35%)
Without religion		15 (15%)
Other		2 (2%)
SCD Genotype		
HbSS		65 (65%)
HbSC		35 (35%)

Government Benefit	
With Benefit	58 (58%)
Without Benefit	42 (42%)
Work with a formal contract	6 (6%)

Sample size – 100. SD = standard deviation

Supplementary material 2: Medication in daily use

Medications	Frequency
Folic acid	89
Dipyrone	61
Hydroxyurea	27
Ibuprofen	18
Tylex	16
Tramadol	12
Paracetamol	8
Losartan	8
Dorflex	6
Diclofenac Sodium	5
Propranolol	5
Nimesulide	4
Torsilax	3
Hydrochlorothiazide	2
Pregabalin	2
Pantoprazole	2
Deferasirox	2
Moratus (Amitriptyline)	2
Profenid	1
Amlodipine Besylate	2
Diazepam	1
Buscopan	1

5.3 ARTIGO 5: RELIGIOSITY, ANXIETY, DEPRESSION AND SUICIDAL IDEATION IN PATIENTS WITH SICKLE CELL DISEASE.

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ABSTRACT

Introduction: Sickle cell disease (SCD) is an inherited hemoglobinopathy that can evolve with time, in some individuals, as a debilitating chronic pain syndrome with emotional dysfunctions. **Objective:** To evaluate different types of religiosities: organizational (ORA), non-organizational (NORA), and intrinsic religiosity (IR), and their correlation with mental health in individuals with SCD. The variables analyzed were depression, anxiety, and catastrophic and suicidal thoughts. **Method:** This is a descriptive cross-sectional study, which is part of a

crossover randomized clinical trial. We recruited adults among individuals with SCD from Bahia-Brazil. We used: Duke's religiosity index, Hospital Anxiety and Depression Scale (HADS), and Brazilian Portuguese Pain Catastrophizing Scale (BP-PCS) data. The Spearman correlation and Fisher exact test were used for statistics considering alpha 95%. **Results:** Of the 131 individuals approached for participation, 75 completed all questionnaires with genotype HbSS and HbSC. Of them, 49 (65,3%) were women, with an average age of 34.13 $\pm$10.02, 66 (88.0%) self-declared black, 63 (84.0%) declared to belong to a religious group, 67 (89.3%) with a high form of religious involvement. The mean of intense pain was 3.86 $\pm$ 2.74; 40 (53.33%) had anxiety, 25 (33.33%) had depression, and 15 (20.0%) declared having suicidal thoughts. There was a negative correlation between depression and IR ($r = -0.240$, $p = 0.038$) and a correlation between average pain and NORA ($r = 0.301$, $p = 0.009$). An association between NORA and chronic pain was verified ($p = 0.023$), OR ($p < 0.001$), NORA ($p = 0.042$), and IR ($p = 0.004$) with evangelical SCD subjects. **Conclusion:** This study highlights the need for mental health care in patients with SCD due to the high rates of anxiety and depression, with the need to include religiosity since it is a frequent and important element in the lives of people with SCD.

Keywords: Sickle Cell Disease, religiosity, depression, anxiety, mental health.

INTRODUCTION

Sickle cell disease (SCD) is an inherited hemoglobinopathy, were some individuals can evolve with time into a debilitating chronic pain syndrome (Brandow & DeBaun, 2018) 30-40% of adult patients (Jonassaint et al., 2016). SCD has characteristics that differentiate other chronic pain conditions, such as onset in early childhood, genetic disease, lifelong duration, and life-threatening (Citero et al., 2007). SCD is Brazil's most common hereditary monogenic disease, occurring predominantly among Afro descendants (Cançado & Jesus, 2007).

Among the emotional dysfunctions (Edwards et al., 2009; Levenson et al., 2008), depression more often than anxiety can be developed in individuals with sickle cell disease. Depression can be accompanied by suicidal thoughts or ideation (Edwards et al., 2009), which can be identified since adolescence (Bhatt-Poulose et al., 2016) because, in addition to the pain, social factors such as body image and mood swings are expected at this stage.

Spirituality/religiosity has been identified as a way of coping with chronic pain diseases (Büssing et al., 2010) and also for SCD (Clayton-Jones & Haglund, 2016). Spirituality can improve quality of life (Adegbola, 2011); is associated with fewer hospitalizations (Bediako et al., 2011); and a significant reduction in pain intensity (Harrison et al., 2005). Religion is

configured as the search for spirituality through some religious institution. Since spirituality does not necessarily need a religion, it is a process where the importance of life is recognized as oriented to something intangible that is beyond or more prominent than themselves (Gomes et al., 2019; Quasie-Woode et al., 2020).

The Duke University Religion Index (DUREL) has been used since 1995, assessing three religious dimensions relevant to the religious involvement in the life of a person, defined at a consensus meeting of the National Institute on Aging and the Fetzer Institute conference. As organizational religious activity (ORA), non-organizational religious activity (NORA), and intrinsic or subjective religiosity (IR). The first, ORA, are public religious activities such as attending religious services or other group-related activities. The second dimension of NORA consists of religious activities performed in private, such as Scripture study, prayer, listening to the radio, or watching religious TV. The last OR assesses the degree of personal religious commitment or motivation that involves pursuing religion as an ultimate end (Koenig & Büssing, 2010).

Therefore, this study aimed to investigate the associations and correlations of different types of religiosities (organizational, non-organizational, and intrinsic) in individuals with SCD with mental health variables such as depression, anxiety, and catastrophic and suicidal thoughts.

MATERIALS AND METHODS

Study design, setting, and participant's description.

This descriptive cross-sectional study is part of a crossover randomized clinical trial registered in REBEC n. TN: U1111-1243-3020, already published (L. A. B. de Oliveira et al., 2021), with adult individuals diagnosed with Sickle Cell Disease. All SCD individuals were recruited between October 2019 and May 2022 in the Basic Health Center (BHC), from cities in the Recôncavo Baiano, in the 31st health region of Bahia (DIRES-BA), and the association of sickle cell disease of the city of Feira de Santana-BA. All SCD individuals received an explanation about the collection data procedures, signed the informed consent form, and voluntarily agreed to participate in this study following Resolution 466/2012 of the National

Health Council of Brazil. This study was approved by the Ethics and Research Committee of Faculdade Adventista da Bahia (CAAE No. 94835218.8.00000.0042).

The Inclusion criteria were having a sickle cell disease diagnosis and being over 18. The Exclusion criteria were the history of hospitalizations for painful crises in the last 15 days and being more than 50 years old (because of the primary crossover study exclusion criteria). The process of contact with sickle cell disease carriers occurred in two ways (figure 1). The sample was for convenience. All adults who attended the interview site or who visited and agreed to participate were included in this research. One adequately trained researcher applied the questionnaires.

Procedures

The SCD participants were invited to undergo screening at their local Basic Health Center or their homes. The sociodemographic questionnaire gathers information on age, gender, education level, marital status, race, religion, and pain levels.

Outcomes and assessment procedures

The predictor, Level of Religiosity:

Duke's religiosity index is a five-item scale measuring three dimensions of religious involvement related to health outcomes: Organizational religiosity (ORA) (i.e., frequency of church attendance); non-organizational religiosity (NORA) (i.e., utilization of private religiosity as prayer or Bible study); and intrinsic religiosity (IR) (i.e., experiencing the presence of the divine, allowing religious beliefs to guide an approach to life, and transporting religion into other areas of life). It is recommended that the values are not summed but analyzed separately (Taunay et al., 2012).

Pain Intensity: measures were assessed by the Visual Analog Scale (VAS), which ranges from zero to 10, where zero represents no pain and 10 is the worst imaginable pain. A high score represents a high pain intensity or pain interference.

Symptoms of anxiety and depression: Assessed with the Hospital Anxiety and Depression Scale (HADS), which comprises 14 self-reported questions divided into two subscales: one

for anxiety and the other for depression. The subject will rate each item using an ordinal scale varying from zero (non-existent symptom) to three (very severe symptom) (Pais-Ribeiro et al., 2007).

Brazilian Portuguese Pain Catastrophizing Scale (BP-PCS): The BP-PCS questionnaire consists of 13 items evaluating self-reported catastrophizing thoughts, feelings, and behaviors when in pain. It is divided into three domains: helplessness, magnification, and rumination. Items are rated on a 5-point Likert-type scale in which both intensity and frequency information are represented, with the following five levels of response for each item: (0) not at all, (1) to a slight degree, (3) to a moderate degree, (4) to a great degree, (5) and all the time. The PCS total score ranges from 0 to 52 points (Sehn et al., 2012).

Avoid record bias: To avoid interviewer bias, only one researcher applied all the questionnaires. All questions were read to avoid comprehension difficulties. There was no contact between the participants. Before applying the questionnaires, everyone was asked if he felt able to answer several questions for 30 to 40 minutes, questions that even covered his emotional state. To control pain measurement bias, medication use was recorded.

Statistical analyses

Data were organized in spreadsheets and analyzed using Statistical Package for the Social Sciences (SPSS) v20.0, and the normality distribution was assessed by the Shapiro-Wilk test. The sample characterization of the demographic and clinical variables was analyzed by Chi-square or Fisher's Exact tests when comparing the frequency distributions and Mann-Whitney or independent Student-t tests when comparing the averages or median. The independent variables, such as ORA, NORA, and IR, were associated and correlated with the dependent variables, such as sociodemographic characteristics (age, sex, civil status, educational level, and financial government aid) and clinical characteristics (pain intensity, depression, anxiety, catastrophic and suicidal thoughts) using Chi-square or Fisher's Exact, and Spearman tests according to respective statistics assumptions. The effects of religious types on pain and clinical outcomes in individuals with SCD were tested with an. In all statistical tests, the significance level alpha was 5%, and the Beta of 80%.

RESULTS

Sociodemographic and illness-related characteristics:

Of the 131 individuals approached for participation in this study, 80 consented to participate, five were ruled out for having traits, and 75 completed all questionnaires. Those who refused to participate indicated a lack of time or interest in participating in a survey.

Seventy-five adults diagnosed with SCD, identified in primary health centers in six cities in the Bahian Recôncavo, participated in this study. The participants had HbSS and HbSC genotypes, 49 women and 26 men. The average age was 34.13 ± 10.02. With average pain 3.86 ± 2.74(SD) on the visual analog scale (VAS). Of these, 66 (88.0%) declared themselves as black, eight (10.7%) declared themselves as brown, and one (1.3%) declared themselves as white. The average subject's financial income was less than the country's minimum wage, established at US$ 242.40 (Table 1).

Table 1. Demographic and clinical characteristics in SCD individuals.

	Average	Number (%)
Sex		
Female		49 (65.3%)
Male		26 (34.7%)
Age, Mean (SD)	34.13 (10.02)	
Education Level		
Illiterate		02 (02.7%)
Elementary School*		25 (33.3%)
High School*		37 (49.3%)
Higher Education*		11 (14.7%)
Marital Status		
Single		45 (60.0%)
Married/Living with a partner		27 (36.0%)
Divorced/Widowed		03 (04.0%)
Religion		

	Catholic	36 (48.0%)
	Evangelical (protestant-neo-Pentecostal)	27 (36.0%)
	Without religion	12 (16.0%)
SCD Genotype		
	HbSS	49 (65.3%)
	HbSC	26 (34.6%)
Average Pain Intensity Median (SD)	3.86 ± 2.74	

SD = standard deviation.

A total of 40 (53.33%) individuals had anxiety, and 25 (33.33%) had depression. Twenty-three (30.66%) of the subjects tended to have anxiety and depression associated. Only two subjects (2.6%) declared a suicide attempt, and 20% declared having or having had suicidal thoughts; however, there was no association or correlation between belonging to a religious organization or any type of religiosity with ideation or attempt to commit suicide.

Correlations between types of religiosities (organizational, non-organizational, and intrinsic) and the illness-related variables and other study measures:

This study showed a high percentage of individuals who declared that they belonged to a religious group (84.0%), with intrinsic religiosity being the most frequent form of religious involvement (89.3%), with no significant differences between the sexes. The correlation between religious types and catastrophism, HADS anxiety, HADS depression, and average pain was analyzed by Spearman's test (Table 2). This group of adults with SCD showed a weak negative correlation between depression and intrinsic religiosity (r = -0.240, p = 0.038). A correlation between average pain and non-organizational religion was also identified (r = 0.301, p = 0.009).

Table 2. Religion types and Catastrophism, Anxiety, Depression and Pain Variables

	Duke Religion Index		
Variables	**Organizational Religion**	**Non-Org Religion**	**Intrinsic Religion**

Catastrophism	r = 0.133 (p = 0.256)	r = 0.112 (p= 0.339)	r = 0.141 (p = 0.228)
HADS Anxiety	r = 0.003 (p = 0.982)	r = 0.056 (p = 0.633)	r = -0.023 (p = 0.845)
HADS Depression	r = 0.031 (p = 0.795)	r = 0.001 (p = 0.990)	r = -0.240 (p = 0.038) *
Pain	r = 0.199 (p = 0.088)	r = 0.301 (p = 0.009) *	r = 0.080 (p = 0.498)

*Correlation is significant at the 0.05 level (2-tailed).

Fisher's exact test was used to assess the association between types of religiosities and the presence or absence of chronic pain. We found a significant association between NORA and chronic pain (p = 0.023). The association between the type of religion and adults self-called: Catholic, Evangelical, and non-religious was analyzed using Fisher's exact test. There was a significant association between self-declared Evangelical (protestant and neo-Pentecostal) adults and ORA (p < 0.001 - two-tailed p-value); NORA (p = 0.042 - two-tailed p-value); and IR (p = 0.004 - two-tailed p-value).

Fisher's exact test was used to determine whether there was any association between the level of education and religiosity. There was a significant association between studying in high school (or have stopped at this level) with IR (p = 0.032 - two-tailed p-value) and NORA (p = 0.012 - two-tailed p-value). The mean age of these individuals was 32.75 years old (9.76 SD).

Fisher's exact test was used to determine whether there was a significant association between type of religiosity and marital status. There was a statistically significant association between IR and married subjects (p = 0.014 - two-tailed p-value). There was also an association between ORA and married marital status (p = 0.006 - two-tailed p-value).

It was analyzed if there was an association between type of religion and adults with SCD who received or did not receive a government financial benefit related to their disease. There was a significant association between adults with SCD who did not receive government benefits with NORA (p = 0.016 - two-tailed p-value); and a significant association of these same subjects with IR (p = 0.043 - two-tailed p-value).

DISCUSSION

Our population showed high levels of religiosity compared to previous studies (Harrison et al., 2005; Sehn et al., 2012) (Cooper-Effa et al., 2001) and higher levels of IR. Intrinsic religiosity refers to feeling the presence of the Holy, that religious belief is behind the way of life, and finally, that there is an effort by the individual to live their religious beliefs in all aspects of life.

It is questionable the fact that none of the interviewees declared a religion with African roots, since Umbanda is the most practiced African religion in Bahia, we believe that this can be explained by the African American syncretism between religious practices with African roots and Catholicism. Therefore, we do not rule out that people who declare themselves Catholic can practice an African-based religion (Romão et al., 2018). Religiosity in individuals with chronic pain and sickle cell disease proved to be a protective factor, but not in our study (Santos et al., 2020).

There was a correlation between Pain and NORA. The greater the pain, the greater the NORA, and an association between the presence of chronic pain and again NORA, defined as individual religious activities such as prayers, meditations, and reading the Bible or other biblical texts in their domicile. These individuals with a religious background may tend to religious practice, looking for relief from their pain and comfort, as described as a coping strategy (Cooper-Effa et al., 2001; Gomes et al., 2019).

The subjects of this study showed levels of depression, as the literature demonstrates for individuals with SCD (Edwards et al., 2009), three times higher than the frequency of depression among the northeastern Brazilian population, where the study was carried out (Lopes et al., 2022). However, anxiety levels are much higher (53.33% in our sample) than in the literature. In pain in Sickle Cell Epidemiology Study (PiSCES Project), anxiety was 6.5%. This same study showed that anxiety and depression predict more significant daily pain and poor physical and mental quality of life (Levenson et al., 2008). However, the study carried out with individuals with SCD, in the state of Bahia-Brazil, the percentages of depression and anxiety were even higher (Santos et al., 2021), because they specifically looked for people with pain of neuropathic origin.

For suicidal thoughts, our study showed 20% of participants were affected, which was between the average already exposed in the literature, with 10% identified in 2014 (Wallen et al., 2014) and 29% identified in 2009 (Edwards et al., 2009) and only 2,6% declared suicide attempt. Maybe this percentage relates to the high level of religiosity since some study correlates religion as a protective factor for suicidal thoughts (Oliveira et al., 2021). SCD in Bahia-Brazil, where this research was carried out, is a public health problem (Cançado & Jesus, 2007). However, there is no program aimed at this population for its monitoring and prevention of mental health.

Our study observed a negative correlation between Intrinsic Religiosity and depression. The greater the tendency to depression, the less the feeling of the presence of God or the Holy Spirit, the less the truth that religious beliefs are behind the whole way of living, and the less the effort to live religion in all aspects of life. The apparent symptoms of depression, such as apathy, guilt, general discontent, hopelessness, mood swings, and loss of interest, can explain this. The literature states a positive relationship between mental health and religiosity (Braam & Koenig, 2019; Murakami & Campos, 2012). The frequent seclusion of individuals with depression may explain decreased social activities, less attendance at church, and fewer religious practices (Braam & Koenig, 2019; Murakami & Campos, 2012).

There was a significant correlation between Protestants (and neo-evangelicals) compared to Catholics and individuals who did not declare religion, with all types of religiosities (NORA, IR, and ORA). The literature recognizes that protestant and neo-evangelical adults practice their religion more than catholics, who call themselves non-practicing catholics (Almeida & Monteiro, 2001). ORA and IR showed a correlation with married individuals; as pointed out by other studies, married individuals place religiosity at the center of their lives, compared to singles; married couples with and without children have more frequency to church than singles (Denton & Uecker, 2018)(Czyżowska et al., 2020).

Our study showed a correlation between intrinsic and non-organizational religiosity among individuals who stopped their studies in high school. The average age of these individuals proved to be outside the study age, so it can be concluded that most of these individuals dropped out of high school or did not continue their studies; most of the subjects were in their late twenties and early thirties. The average monthly income of the research

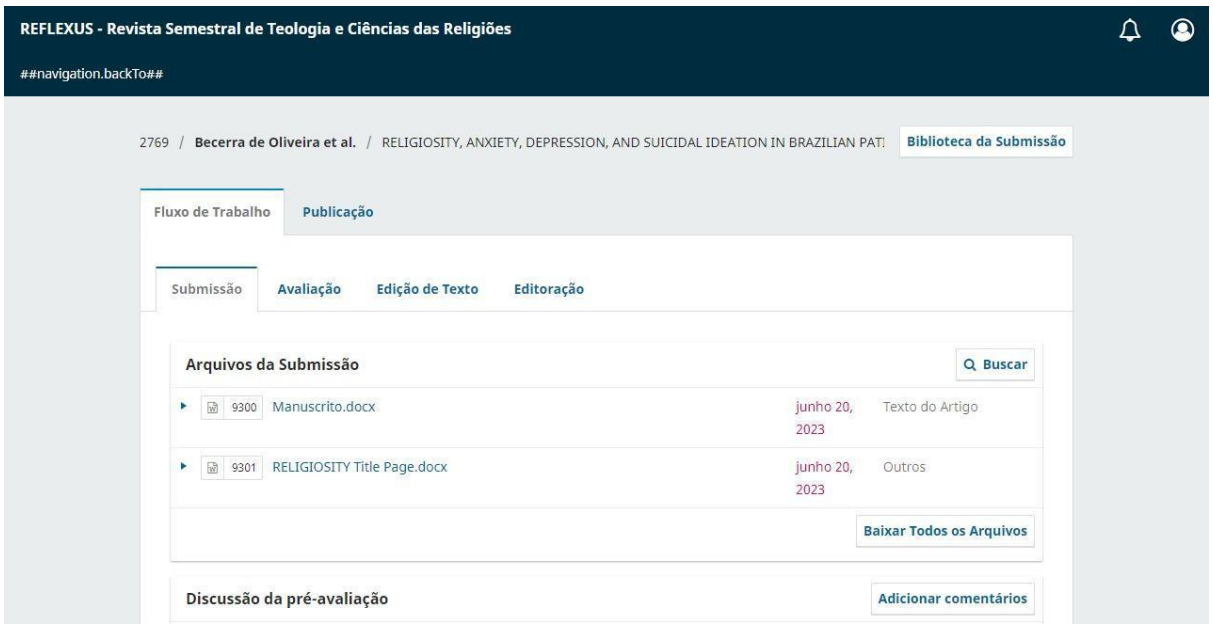
participants was mostly the Brazilian minimum wage. Low income in the population with SCD, may motivate the spiritual search. (Da Silva Souza Rodrigues et al., 2018; Felix et al., 2010).

Our study has some limitations. First, the sample size calculation was not performed because it is an exploratory study carried out with a convenience sample. The sample size may have needed to be increased to show the differences not observed between the groups. Furthermore, as this is a sample from a rural region, the data obtained cannot be extrapolated to other samples of people with sickle cell disease living in large metropolises. Nor can they be extrapolated to other populations, requiring the development of new studies testing our hypotheses in other populations and samples.

CONCLUSION

This study highlights the need for mental health care in patients with SCD due to the high rates of anxiety and depression. Religiosity is a frequent and important element in the lives of people with SCD, as shown by our population's high levels of organizational religiosity and intrinsic religiosity. Health professionals are invited to understand the specific types of religion and their participation in the lives of SCD patients to define a treatment with a holistic multifactorial view. The Bahia state needs a program for monitoring and preventing mental health for these individuals.

SUBMISSION



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5.4 ARTIGO 6: HEALTH PROMOTING PRACTICES FOR INDIVIDUALS WITH SICKLE CELL DISEASE: DEVELOPMENT OF A TECHNICAL EDUCATIONAL PRODUCT.

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ABSTRACT

Introduction: Due to the advances in the management of acute crises of sickle cell disease (SCD), the life expectancy has increased. However, the comorbidities related to the chronicity of SCD have made the use of different therapeutic strategies has become increasingly important nowadays. **Objective:** This study proposes the creation of an educational playful booklet, with the aim of promoting health-promoting practices able to improve the quality of life in SCD individuals. **Method:** The playful booklet creation was made with the following steps: A) A literature review about good health practices involving healthy eating, hydration, sunlight, fresh air, exercise, balance, rest, and spirituality; B) The script was created, and then the drawings were developed; C) The playful booklet was submitting to critical evaluation of 24 expert judges in the area. Content validation was established from Content Validity Index (CVI) greater than 80%. The binomial test was performed to compare whether the proportion

of judges who agreed with the validity of the booklet was statistically equal to or greater than 0.70, with significance $p \leq 0.05$. **Results:** All expert judges agreed that the booklet addresses habits that can benefit SCD individuals. All the corrections related to simplifying vocabulary, changing the font type, and expanding the art of red blood cells were accepted. In addition, all items were assessed as relevant, and the Content Validity Index averaged 0.96. The expert judges approved the booklet. **Conclusion:** The playful booklet was considered valid due to the reliability recognized by professionals specialized in SCD and quality of life, regarding its content, including the language adopted, the topics addressed, and the illustrations. Healthcare providers and community agents should consider using this play booklet on social networks and clinical contexts.

Keywords: Sickle cell disease, health education, health promotion.

INTRODUCTION

In Brazil, sickle cell anemia is the most common single-gene hereditary disease, occurring more frequently among people of African descent. The distribution of the S gene in Brazil is quite heterogeneous, depending on the composition of the population; the prevalence of heterozygotes for Hb S is higher in the north and northeast regions (6% to 10%), while in the south and southeast areas the prevalence is lower (2% to 3%) (1). The comorbidities of sickle cell disease are vast, such as frequency and intensity of pain, use of emergency and hospital care, depression, anxiety, and sleep disorders (2) to the direct detriment of the quality of life.

The factors that most impact the quality of life of people with SCD have been identified as more severe types of SCD, age, sex (3, 4), and low-income population (5). Specific research and training programs have formed a cadre of experienced health professionals working in this field, better patient management, crisis prevention, and increased life expectancy (6). However, there are still challenges to be met to improve the quality of care. In the guidelines established by the Brazilian government for people with sickle cell disease (7), the importance of self-care is determined, defined as self-care, seeking what the needs of the body and mind are, improving the lifestyle, avoiding harmful habits, developing a healthy diet, know and control the risk factors that lead to diseases, adopt disease prevention measures.

Within the prevention measures, the importance of a balanced diet is emphasized (8) from a qualitative and quantitative point of view, as regularity of meals, frequent oral hydration,

avoiding inactivity (9), practicing physical exercises, favoring stretching and flexibility, respecting personal limitations (10, 11), promote sleep and rest (8, 12), clean air (13, 14) for the correct acquisition of oxygen, sunlight for the production of vitamin D (13), develop spirituality/religion (15), to have a better quality of life. The lack of quality-of-life results in loss of social coexistence, decrease or cessation of sexual activity, loss of self-esteem, and lack of life projections for the future, among others (5).

Increased knowledge and experience in engaging occupations facilitate the acquisition of new health habits (17). When acquiring a positive practice concerning his illness, the individual leaves the status of misinformation and dependence on his desire to change, enabling the transformation process. Educational productions stand out, such as booklets, which can contribute positively to making people with sickle cell disease aware of the importance of health-promoting practices and can be used as support material for the visits of health professionals focused on increasing the quality of life of this population (18). The dissemination of correct and accessible information is important so that people can understand that there are preventive measures. Health promotion through health education strategies has been reported as valid in several themes and different publics (19, 20).

Among the ways of scientific communication, comics stand out, as they are considered excellent pedagogical and informative tools reaching a wider audience and are recommended for the dissemination of knowledge in the acquisition of health-promoting habits and the change of harmful habits, aiming at a better quality of life (21). The proposal for a booklet with practices that promote health for people with Sickle Cell Disease emerged as a result of interviews with more than one hundred adult individuals, carriers of Sickle Cell Disease in broader research, one of the objectives being to evaluate the factors that affect the quality of life. During the interviews, the lack of education as a preventive action in health was highlighted, which is why this technical educational product was created.

METHOD

This is methodological research oriented to developing and validating educational, technical production on health-promoting practices recommended for people with sickle cell disease. The production of this educational product was thought of as feedback on doctoral research in human medicine. Therefore, the present research is part of a larger project entitled

"Sickle cell disease, chronic pain, and functional health: multidimensional cross-sectional Study and Development of a technical educational product. Under Resolution 466/12 of the National Health Council, this research is part of the aforementioned project, was submitted to Plataforma Brazil and directed to the Research Ethics Committee of Faculdade Adventista da Bahia, for ethical appreciation, with an opinion of approval, under CAAE 94835218.8.0000.0042.

A narrative review of the literature and consultation with specialists were carried out to structure the content. For the development and operationalization of the textual genre, a playful and attractive way was considered when choosing the format of the educational product. Thus, selecting the booklet format as a comic book. In this sense, guidelines from the literature were considered for this type of educational proposal applied to the health area (22, 23)

For the layout of the booklet and textual structure, recommendations regarding the writing and text formatting of educational technologies were considered (24). Content validation of the support manual was conducted similarly to other productions of educational instruments (25, 26). The operationalization and the validation process were mediated by the evaluation of professionals with expertise in the thematic area of the support manual, acting as judges, who were asked to answer a matrix of closed questions and a space for suggestions on the educational material produced, evaluated with the help of google forms.

Calculation of the sample of evaluators

To define the number of specialists participating in the research, the sample calculation obtained through the formula n=Za2.P(1-P)/e2 was considered, as indicated by (27). The stipulated values were "Za" (level of confidence), "P" (proportion of agreement of the judges), and "e" (accepted difference from what is expected). Therefore, according to the standard normal distribution, the Za coefficient would assume the tabulated value of 1.96, with 85% as the expected proportion of specialists with a difference (error) of 15%. In other words, a 95% confidence interval will be established with values between 70% and 100%. The calculation would be n = 1.962 * 0.85 * 0.15 / 0.152. This resulted in a minimum of 22 experts.

Profile of the evaluators

For the election of those invited to participate as judges (experts), professionals from

different areas with practical experience and minimum postgraduate training in health, communication, or education were considered. The invitations were intentionally made to professionals recognized for their expertise in the subject of interest, taking as evidence their academic or technical production in the health area, particularly related to Sickle Cell Disease. We emphasize that all communication with guests invited to act as judges was done non-face-to-face via WhatsApp. Thus, an invitation to participate in the research was sent via Google Forms, containing the Informed Consent Form, the material for evaluating the technical product, and the technical product (booklet in HQ format). The model of the consent form signed by the judges and questions for evaluating the teaching material were derived and adapted from other works (20), which seemed compatible and relevant for use in the theme of the present research.

RESULTS

Twenty-four specialist judges participated, twelve women and twelve men, having graduated and having at least specialization. See Table 1 for the sociodemographic characterization of the judges. The group was mostly represented by doctors (70.8%), with a variety of ages and training.

Table 1 – Sociodemographic Characterization of expert judges

Variables (N=24)	n (%)
Age group	
until 40 years old	08 (33,3)
from 41 to 59 years old	12 (50,0)
60 or more years old	04 (16,6)
Academic education	
Doctorate	17 (70,8)
Masters degree	04 (16,6)
Specialization	03 (12,5)
Graduation degree	
Nursing	07 (29,1)
Education	04 (16,6)
Portuguese / Social	03 (12,5)

Communication	
Social worker	02 (08,3)
Physical therapist	02 (08,3)
Theology	02 (08,3)
Biology	01 (04,1)
Physical education	01 (04,1)
Psychology	01 (04,1)
Social Science	01 (04,1)
Occupation area	
University Teacher	17 (70,8)
Nurse	01 (04,1)
Physical therapist	01 (04,1)
Social worker	02 (08,3)
Health employee of the government	01 (04,1)
Journalist	01 (04,1)
Pastor	01 (04,1)
Experience Time (years)	
Until 10 years	05 (20,8)
from 11 to 20 years	10 (41,6)
21 to 30 years	06 (25,0)
31 years and more	05 (20,8)

Below we present Table 2 with the judges' agreement regarding the items in the booklet. Of the 21 elements evaluated, 19 had the expected approval, and three were below expectations. Of the three items below 0.8, two were in the Layout assessment, referring to font and visual composition. The third was related to whether the content answers questions, clarifies, and educates the layperson on the subject.

Table 2 - Agreement of professionals regarding the items in the booklet

Quiz	n (%)	IVC – Adequate
1. Content		
1.1 Content is appropriate for the target audience	22 (91,6)	0,91
1.2 The division of titles and subtitles of the material are pertinent	23 (95,8)	0,95
1.3 The key excerpts (highlighted excerpts) are important points and deserve to be highlighted	24 (100)	1
1.4 The content is sufficient to meet the needs of the target audience	20 (83,3)	0,83
2. Language		
2.1 The writing style is compatible with the target audience	20 (83,3)	0,83
2.2 The writing used is attractive	20 (83,3)	0,83
2.3 The language is clear and objective	20 (83,3)	0,83
3. Illustrations		
3.1 The illustrations used are relevant to the content of the material and elucidate the content	22 (91,6)	0,91
3.2 The illustrations are clear and convey ease of understanding	23 (95,8)	0,95
3.3 Image captions are adequate and help the reader to understand the image	22 (91,6)	0,91
3.4 The number of illustrations is adequate for the content of the educational material	21 (87,5)	0,87
4. Layout		
4.1 The font used makes it easy to read.	18 (75,0)	0,75
4.2 The colors applied to the text are relevant and easy to read.	20 (83,3)	0,83
4.3 The visual composition is attractive and well-organized	17 (70,8)	0,70
4.4 The format (size) of the educational material and the number of pages are adequate	24 (100)	1
4.5 The layout of the text is adequate	23 (95,8)	0,95
4.6 The font size of titles, subtitles and texts are adequate	20 (83,3)	0,83
5. Motivation		
5.1 The content is motivating and encourages you to continue	21 (87,5)	0,87

reading		
5.2 The content aroused interest in the reader	21 (87,5)	0,87
5.3 The content responds to doubts, clarifies and educates the layperson on the subject	18 (75,0)	0,75
6. Culture		
6.1 The text is compatible with the target audience, catering to different knowledge profiles	21 (87,5)	0,87
IVC Global from 21 items / mean of IVC of items: 18,24		0,86

Modifications made as proposed by evaluators

The items that were evaluated below 0.8 were all met and there were modifications to the text and writing to make it more understandable.

DISCUSSION

This Study sought to validate educational material, in booklet format, which aims to motivate individuals with SCD to practice healthy habits, support material for lectures and home visits, evaluated by professionals specialized in SCD and quality of life. Several factors have been identified as predictors of low quality of life in individuals with SCD, including age, being female, having a low level of education (low income), and having a more severe type of SCD (HbSS and HbSß)(4). However, the most significant impact factors are pain and depression (29).

Health-promoting practices prevent or reduce these factors that have the most significant impact on pain and depression. Simple walking, stretching, and flexibility exercises can be practiced in parks or external areas, which encourages fresh air, the positive influence of the sun, and the need for water intake, promoting good rest (9-12).

The final evaluation scores reached levels of agreement among the judges. They indicated that the booklet on health-promoting practices for people with SCD is valid and can be used as an educational resource. The professionals interviewed attributed scientific accuracy to the evaluated material. This result motivates professionals' adoption of the material in quality-of-life education activities. Careful practitioners must be more certain about reinforcing erroneous beliefs commonly found on websites and instructional materials not based on

science. With a scientific basis, the material developed appears as a supporting strategy to motivate the lifestyle of people with SCD.

The best-evaluated items with 100% agreement by the judges were: “The key excerpts are important points and deserve to be highlighted” and “The format (size) of the educational material and the number of pages are adequate.” Socio-educational programs influence improving pain and movement, promoting decreased disabilities and the use of health services. The booklet sought to cover the practices that promote health, which can be performed by all people, in this case and can be experienced by the entire family of the individual with SCD. So far, no educational booklets on health-promoting practices for people with SCD have been found. However, educational materials to explain SCD are available online.

Although it is a very satisfactory level, future editions should consider the possibility of improving the illustrations, as pointed out by a judge regarding the concern with caricaturizing people. Information on a diet directed to SCD individuals can also be added. Our most significant limitation was the lack of evaluation of the material by individuals with SCD for comprehension analysis in simple reading or the need for additional explanations. It is suggested that the booklet on health-promoting practices for people with SCD be validated by people with SCD from all over Brazil.

CONCLUSION

The booklet on health-promoting practices for people with sickle cell disease was considered valid due to the reliability recognized by professionals specialized in SCD and quality of life regarding its content, including the language adopted, the topics addressed, and the illustrations. It can be used on social networks and printed for distribution by health professionals and community agents.

SUBMISSION

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6. DISCUSSÃO

Diversas contribuições podem ser oferecidas com o presente estudo. Para as crescentes pesquisas sobre neuromodulação em uma população com dor crônica é uma contribuição original, tanto pela população estudada como pelo método de intervenção combinando estimulação central e periférica. Para a prática clínica, dentro de nosso conhecimento esta é a primeira pesquisa que analisa mulheres com DF e DTM. Quanto ao objetivo principal, este estudo pode confirmar que existe segurança para a aplicação de neuromodulação em indivíduos com DF e DTM. Existia a dúvida se o tratamento poderia provocar dor na região, por possível isquemia, mas não foi o caso nas 19 aplicações ativas de ETCC. Seguindo o protocolo estabelecido e validado pela equipe de pesquisa, a segurança pode ser confirmada (DE SOUZA, *et al.,* 2021; SÁ, *et al*., 2021; BAPTISTA & SÁ, 2020; BAPTISTA, *et al*, 2019.)

Dentre as dez mulheres que participaram, apenas uma paciente realizou somente uma sessão, devido a uma crise vaso-oclusiva cinco dias após a intervenção. O efeito da ETCC tem duração de horas e, por isso, acreditamos que a única sessão não está relacionada com a crise que sofreu a participante (NITSCHE, 2001). Decidimos descontinuar o tratamento porque modificaria a sequência de uma sessão por semana determinada pelo protocolo do estudo. Reações adversas como formigamento, sonolência e coceira foram relatadas nas sessões ativas bem como nas simuladas.

Podemos afirmar que pessoas com DF e DTM se sentem melhores em ambientes tépidos. Registramos a queixa frequente das participantes quanto à temperatura de 23°C na sala climatizada e a queixa de colocar primeiro a mão em água fria na mesma temperatura para iniciar a modulação condicionada da dor. Utilizamos o protocolo de 46 graus celsius para a CPM, e não tivemos queixa quanto ao calor. Isso confirma os dados da literatura de que as pessoas com DF preferem o calor ao frio (BRANDOW & PANEPINTO, 2016). O cegamento foi eficiente, demonstrando que o equipamento era adequado, comparado a um estudo anterior deste mesmo grupo de pesquisadores onde os participantes identificaram a locação com o mesmo protocolo de ETCC. As disparidades de conhecimento fizeram a diferença, pois o estudo atual foi em sua maioria com donas de casa, enquanto que o anterior foi feito com estudantes de fisioterapia (OLIVEIRA *et al.*, 2015).

Nosso estudo contribui para afirmar que existem pessoas com DTM dentro da população com DF. Estas possuem características semelhantes às descritas pela literatura, sendo mais frequente na população feminina, entre 30-45 anos de idade. O diagnóstico mais prevalente foi dor miofascial com dor articular com comprometimento emocional severo, segundo o RDC/DTM. Ao comparar as características do perfil clínico dessas dez mulheres com DTM, junto às características de todas as pessoas com DF, observamos que todos os índices foram maiores, todas as mulheres possuíam sensibilização central, altos índices de catastrofismo, todas possuíam dor generalizada com média de intensidade acima de 6 na EVA, tendência à ansiedade e à depressão. Os escores da qualidade de vida, em todos os domínios, foram 50% menores que a média das pessoas com DF sem DTM (FRAGOSO, *et al.*, 2010).

A literatura descreve alguns casos clínicos de pessoas com DF e DTM. El-Sabbagh & Kamel (1989), é identificado no Pubmed (*National Library of Medicine* disponível em https://pubmed.ncbi.nlm.nih.gov/) como o primeiro estudo a descrever o caso de uma jovem saudita com necrose avascular da articulação temporomandibular esquerda associada a necrose avascular da cabeça do fêmur esquerdo e alterações precoces de infarto da cabeça umeral do ombro esquerdo. Caso semelhante foi descrito por Baykul (2004), de uma jovem turca de 23 anos, com necrose de côndilo mandibular com limitação da abertura bucal. Caracas (2013) publicou um caso clínico de uma jovem mulher brasileira com artrite da ATM esquerda, alertando médicos hematologistas sobre esta possibilidade, estes casos clínicos foram descritos como raridade.

Dentro do nosso grupo de pesquisa, citamos um estudo doutoral sobre saúde bucal que avaliou 80 indivíduos com DF. Destes, 12,5% foram diagnosticados com DTM severa, resultado próximo ao nosso, que identificou 10% de DTM em cem indivíduos. Este estudo foi o único que identificamos na literatura, que apresentou prevalência de DTM em população com DF. Consideramos apenas o grupo diagnosticado com DTM severa, devido ao uso do Índice Anamnésico de Fonseca para diagnóstico (PIRES, *et al*, 2018). Utilizamos este índice apenas como triagem, em nossa avaliação inicial identificamos 15 mulheres com DTM, mas ao avaliar com RDC/DTM cinco foram descartadas, por não possuírem todas as exigências que o diagnóstico propõe. É possível que estas pacientes evoluam para DTM severa no decorrer do tempo, se não receberem tratamento adequado (TICIANELI, 2020).

Também acreditamos ter oferecido alguns parâmetros sobre modulação endógena da dor, avaliada por facilitação através da Somação Temporal da Dor (QST - *Quantitative Sensorial Testing*) e por inibição através do paradigma da modulação condicionada da dor (CPM - *Conditioned Pain Modulation*). Sobre o QST, observamos facilitação na maior parte do grupo de mulheres. Ao ser avaliada a região tênar e a região da ATM com filamentos de pressão, foi identificado que somente duas mulher dentre as dez, possuíam sensibilidade mecânica normal (acima de 10g) e limiar da tolerância da dor considerada normal (entre 26g e 60g), seguindo o padrão estabelecido por Ezenwa com adultos com DF (EZENWA *et al.*, 2016). Quanto ao CPM, cinco mulheres apresentaram dados normais, apresentando um limiar à dor maior após inibição através de temperatura a 46°C. Nossa contribuição foi ter realizado cinco avaliações (antes CPM, logo após CPM, 30seg. após CPM. 60seg. após CPM e 90seg. após CPM), para visualizar a curva resultante. Dentro do nosso conhecimento, este estudo é o primeiro a fornecer informações sobre a modulação endógena da dor em mulheres com DF e DTM.

As entrevistas das cem pessoas com DF contribuíram para apresentar características da saúde mental de adultos com DF do interior da Bahia e como estes fatores impactam na qualidade de vida. Ansiedade, depressão, catastrofismo, sensibilização central e quantidade de pontos-gatilho em membros inferiores, tiveram impacto em pelo menos um domínio como preditores de QV. A média da dor impactou especialmente os domínios: aspectos físicos, sociais e emocionais. Em nosso estudo, diferente do que encontramos na literatura (LEVENSON *et al,* 2008), mostrou maiores níveis de ansiedade que de depressão, sendo a ansiedade o elemento com maior impacto sobre a saúde mental. Esse achado nos leva a teorizar que talvez as dificuldades financeiras e a distância da capital onde estão os centros de referência para o caso de necessidade de internação e de transfusão, possam colaborar para esta diferença. Também foi evidenciado neste estudo o alto nível de religiosidade/espiritualidade das pessoas com DF do recôncavo baiano, sem diferenças estatisticamente significativas entre grupo com e sem religiosidade/espiritualidade. Mas com uma correlação inversa entre religiosidade não organizacional e depressão, entendido pela reação sintomatológica do afastamento das pessoas, do convívio social, o que parece compreensível que também exista um afastamento espiritual (SLAVICH *et al,* 2019). Identificamos neste grupo uma porcentagem análoga à descrita pela literatura sobre pensamentos suicidas, mas uma baixa porcentagem de tentativas suicidas. Resta

se questionar se a religiosidade/espiritualidade possui uma participação, como fator protetivo em pesquisas futuras específicas para tirar conclusões (BHATT-POULOSE, *et al*, 2016; WALLEN, *et al*, 2014; CHRISTOPHER, *et al*, 2009). A religiosidade/espiritualidade é um elemento importante na vida destas pessoas, mas em nossas entrevistas não houve evidências que este fator é considerado pela equipe multidisciplinar.

A presença da dor crônica foi muito significativa, atingindo mais de 70% do grupo de cem pessoas entrevistadas. Destes, 60% com dor generalizada e 59% com sensibilização central, confirmando dados da literatura de forte relação entre dor crônica e sensibilização central (ARENDT-NIELSEN *et al.*, 2018). Se a dor for subtratada, a dor crônica se instalará e potencializará outros contribuintes de sua perpetuação (DARBARI & BRANDOW, 2017); (UHELSKI; GUPTA; SIMONE, 2017). As práticas de medidas preventivas podem reduzir o risco de desenvolver doenças crônicas, melhorar o sistema imunológico e aumentar a vitalidade geral. Estas premissas estão registradas no manual de educação em saúde para o autocuidado do indivíduo com DF, desenvolvido pelo governo com acesso on-line (BRASIL. MINISTÉRIO DA SAÚDE, https://bvsms.saude.gov.br/bvs/publicacoes/manual_educacao _saude_volume1 .pdf). Mas em nossas entrevistas, ficou evidenciado que nada disto é ensinado para as pessoas com DF do recôncavo baiano, nos levando a perceber a falta de um programa específico de prevenção para a manutenção da qualidade de vida destas pessoas, por equipe multidisciplinar, onde somente foi identificado suporte medicamentoso. Estes fatos nos motivaram a criar uma cartilha educativa. Nosso grupo desenvolveu esta cartilha, como resultado secundário das entrevistas realizadas onde se repetia a asseveração, de terem recebido no passar dos anos pesquisadores, que nunca retornaram com alguma devolutiva nem com algum tipo de benefício. Por isso, esta cartilha será parte do reencontro com estas pessoas, para compartilhar os resultados e fomentar o autocuidado preventivo.

É possível que a falta de prevenção seja fator primordial para a incapacidade para o trabalho, evidenciada também nas entrevistas, somente seis indivíduos (6%) tinham carteira assinada, e 58 (58%) recebiam algum tipo de benefício do governo, que pode ou não estar relacionado com a necessidade de suporte financeiro por falta de entradas resultantes de um trabalho fixo ou autônomo. Estimar essas perdas requer um estudo prospectivo que estava fora do escopo desta pesquisa (LUBECK, et al, 2019).

Limitações

Dentro das limitações deste estudo piloto, identificamos o número reduzido de participantes, embora a população com DF e DTM exista e precisa ser reconhecida e tratada. Quanto à avaliação de alguma interferência no fluxo sanguíneo, nenhum sintoma foi registrado. O principal sintoma seria dor, contudo o ideal seria utilizar um equipamento que pudesse avaliar em tempo real o fluxo sanguíneo. Dentro da pesquisa como um todo, indivíduos que participaram por conveniência se constituem em uma outra limitação. Também, decidimos publicar estudo preditivo com dados transversais porque acreditamos que os resultados são relevantes para serem divulgados, porém um estudo longitudinal é necessário para confirmar os achados. Além disso, por se tratar de uma amostra de região rural, os dados obtidos não podem ser extrapolados para outras populações de pessoas com DF residentes em grandes cidades. Quanto à cartilha, deve ser avaliado por indivíduos com DF para análise de compreensão da leitura. Sugere-se que a cartilha sobre práticas promotoras de saúde para pessoas com DF seja validada por pessoas com DF de todo o Brasil. Apesar das limitações deste estudo, sua maior força é a ênfase em indivíduos com DTM dentro da população com DF.

7. PERSPECTIVAS FUTURAS

Pretendemos, que este estudo seja base para a coleta de dados longitudinais, para o acompanhamento das pessoas com DFF do recôncavo baiano. Como grupo de pesquisa pretendemos continuar identificando pessoas com DTM para realizar a pesquisa proposta. Quanto a cartilha, iremos validar ela junto as pessoas com DF. Está dentro de nossos objetivos conhecer mais profundamente a saúde bucal com a realização de exames radiológicos em todas as mulheres identificadas com DTM, e trabalhar na prevenção específica, com mulheres acima dos 30 anos de idade.

Esta tese motivou a criação do grupo de apoio multidisciplinar para pessoas com DF, suporte que será ofertado na Clínica-escola da FADBA-UNIAENE. Serão ofertados, testes diagnósticos, grupos de apoio psicológicos, suporte espiritual, exercícios em piscina aquecida, e tratamentos de neuromodulação para pessoas com dor crônica, além de forte ênfase em educação permanente para pessoas com DF e seus familiares. Os conteúdos incluem desde conhecimentos dos fatores genéticos, frequência e incidência de episódios álgicos, estilo de vida e tratamentos, por equipe formada de médicos, enfermeiras, fisioterapeutas, nutricionistas, psicólogos e odontólogos.

8. CONCLUSÕES ESPECÍFICAS

- A ETCC e a EEP são seguras e podem ser eficazes para mulheres com DF e DTM.
- Compreender a ligação entre a plasticidade mal adaptativa do SNC e os mecanismos de dor crônica articular e sua avaliação por meio de instrumentos e métodos precisos que podem ajudar os profissionais de saúde a aumentar a qualidade do tratamento oferecido aos pacientes com DF.
- Ansiedade, depressão, catastrofização e sensibilização central são fatores significativos que afetam a qualidade de vida. Em uma população de indivíduos com DF, o objetivo primário é o controle da dor, que pode evoluir para dor crônica e inevitavelmente, reduzindo a qualidade de vida. Isso é responsabilidade de uma equipe multiprofissional e de iniciativa governamental.
- A religiosidade é um elemento frequente e importante na vida das pessoas com DF, evidenciada pelos altos níveis de religiosidade organizacional e intrínseca de nossa população. Os profissionais de saúde são convidados a compreender os tipos específicos de religião e sua participação na vida das pessoas com DF para definir um tratamento com visão multifatorial holística.
- A cartilha de promoção da saúde foi considerada válida pela confiabilidade reconhecida por profissionais especializados em DF e qualidade de vida, incluindo a linguagem adotada, os temas abordados e as ilustrações.

9. CONCLUSÃO GERAL

Um conjunto de produções científicas foram desenvolvidas como resultado de testar a hipótese de que a dor crônica da ATM em pessoas com doença falciforme pode ser tratada sem risco com neuromodulação não invasiva. A estimulação transcraniana com corrente contínua e estimulação periférica são seguras, e podem ser usadas por mulheres com doença falciforme e disfunção temporomandibular, mas um estudo clínico maior precisa ser realizado. Este estudo destaca a presença de dor crônica desta população e a necessidade de cuidados em saúde mental devido ao impacto da ansiedade, depressão, catastrofização e sensibilização central na qualidade de vida. Detectou ainda a necessidade de incluir o fator religiosidade/espiritualidade na equação da intervenção da equipe multidisciplinar.

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ANEXO 1: TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO I

Termo de consentimento livre e esclarecido (TCLE)

Título do Projeto: Avaliação do efeito agudo da Estimulação Transcraniana com Corrente Contínua e Estimulação Periférica para Disfunção Temporomandibular em pacientes com Doença Falciforme: Ensaio Clínico Randomizado Duplo Cego.

Pesquisador Responsável: **Lilian Becerra de Oliveira-Fadba (75) 992486867**

Nome do voluntário:_____

O Sr(a)._____está sendo convidado a participar do projeto de pesquisa que procura conhecer mais sobre os sentimentos e dores de uma pessoa com Doença falciforme (DF).

Justificativa e Objetivo
O presente estudo tem como objetivo principal identificar se as pessoas com DF, podem ser beneficiadas pelo uso de dois aparelhos de fisioterapia para as dores da articulação temporomandibular em uma única sessão. Este trabalho se justifica pelo fato de poder auxiliar a pessoas que tem DF e sofrem destas dores. Poucos estudos existem quanto a tratamentos sem medicamentos para DF, por isso esta pesquisa será útil para pessoas que tem dor crônica e desejam outro tipo de tratamento. Mas também é muito importante conhecer a qualidade de vida, ânimo e dores das pessoas com DF.

Passos do Estudo
Em primeiro lugar se faz necessário dizer que todas as informações pessoais (nome, endereço, telefone e dados pessoais) não serão expostas na pesquisa. **É necessário também dizer que os participantes não terão nenhuma despesa financeira relacionada à pesquisa.**
Em segundo lugar você precisa saber que serão aplicados vários questionários, que serão lidos para você, perguntando sobre seu estado de ânimo, sua qualidade de vida e suas dores. Caso você tenha dor na região na região das bochechas próximo ao ouvido, vc será convidado a participar do segundo projeto que é com utilização de aparelhos.

Qualquer dúvida do voluntário em relação a algum procedimento poderá ser respondida diretamente com o pesquisador responsável.

Fica assegurado o direito do voluntário, a qualquer momento do estudo, desistir de participar da pesquisa.

Eu, _____, Declaro ter sido informado e concordo em participar, como voluntário, do projeto de pesquisa acima descrito.

Cachoeira, _____ de _____ de _____,

_____ _____
Nome e assinatura do voluntário Testemunha

ANEXOS 2: TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO II

Termo de consentimento livre e esclarecido (TCLE)

Título do Projeto: Avaliação do efeito agudo da Estimulação Transcraniana com Corrente Contínua e Estimulação Periférica para Disfunção Temporomandibular em pacientes com Doença Falciforme: Ensaio Clínico Randomizado Duplo Cego.

Pesquisador Responsável: **Lilian Becerra de Oliveira**

Instituição a que pertence o Pesquisador Responsável: **Faculdade Adventista de Fisioterapia.** Telefones para contato: **(75) 34425 8025 (75) 3425 8023 (75) 3425 8121**

Nome do voluntário: _____

Idade: _____ anos R.G. _____

A Sra._____está sendo convidada a participar do projeto de pesquisa "**Avaliação do efeito agudo da Estimulação Transcraniana com Corrente Contínua e Estimulação Periférica para Disfunção Temporomandibular em pacientes com Doença Falciforme: Ensaio Clínico Randomizado Duplo Cego"** de responsabilidade da pesquisadora Lilian Becerra de Oliveira.

Justificativa e Objetivo

O presente estudo tem como objetivo principal avaliar a o efeito de dois aparelhos de fisioterapia para as dores da articulação temporomandibular em uma única sessão. Este trabalho se justifica pelo fato de poder auxiliar a pessoas que tem Anemia Falciforme e sofrem destas dores. Poucos estudos existem quanto a tratamentos sem medicamentos para Anemia Falciforme, por isso esta pesquisa será útil para pessoas que tem dor crônica e desejam outro tipo de tratamento.

Passos do Estudo

Em primeiro lugar se faz necessário dizer que todas as informações pessoais (nome, endereço, telefone e dados pessoais) não serão expostas na pesquisa. **É necessário também dizer que os participantes não terão nenhuma despesa financeira relacionada à pesquisa.**
O primeiro passo de nosso trabalho é coletar os dados clínicos através de um questionário padrão (doenças preexistentes, uso de medicamentos entre outras) e de um exame físico (medidas de abertura da boca, dores na região dos músculos do rosto, barulhinhos da articulação temporomandibular (ATM) que se movimenta quando comemos e falamos, a sentimos um pouco à frente do ouvido, de ambos os lados do rosto).
O segundo passo acontece se você tiver de fato dor na ATM. Será responder um questionário para saber como está seu ânimo, ou desânimo, seu estado de humor mais frequente. Após este questionário iremos marcar outra visita, que não poderá ser quando você estiver por menstruar (dois dias antes) ou nos primeiros dois dias de sua menstruação. Por que na maioria das mulheres, nesse momento se sente mais dor que o normal.
O terceiro passo será vir no dia marcado, onde você passará por duas salas, na primeira vamos avaliar sua dor pressionando levemente sua Articulação do lado do ouvido (de ambos os lados), logo você colocará sua mão em aguar fria a 12º C. por um minuto, e voltaremos a avaliar a dor pressionando no mesmo local, anterior ao ouvido. Depois você irá para uma segunda sala, onde você receberá os choquinhos de dois aparelhos de fisioterapia. Não é doloroso, apenas se sente umas formiguinhas, mas nem todas as pessoas sentem. É possível que você não sinta nada.
O aparelho funcionada da seguinte forma: coloca uma esponja humedecida na cabeça e uma segunda na testa. Isso irá humedecer seu cabelo. Venha com o cabelo sempre seco. Logo o segundo aparelho coloca uma plaquinha em sua bochecha do lado do ouvido. O perigo é sentir ardência na testa, mas é só avisar que imediatamente o aparelho será desligado.

O quarto passo será repetir o teste que provocou pressão na região anterior ao ouvido e que coloca sua mão em agua fria por um minuto.
Esta pesquisa por tanto será receber esses testes e choquinhos apenas em um só dia.
Os resultados dos testes serão armazenados e repassados ao voluntário no final da pesquisa.

Esse estudo apresenta risco de momentaneamente aumentar a dor já existente na ATM, após teste de pressão sobre a região. Também tem o risco de provocar ardência que se não avisado pode queimar o local levemente, mas isto será evitado ao ser aplicado os aparelhos de fisioterapia por fisioterapeuta experiente. Também será evitado por que o profissional estará de seu lado todo o tempo da aplicação perguntando se sente ardência. Se a resposta for positiva, será suspensa a única aplicação. Todo o material utilizado é esterilizado e descartável.

Após os testes todos os participantes poderão fazer o melhor tratamento identificado por esta pesquisa de forma gratuita uma vez por semana por dois meses.

Qualquer dúvida do voluntário em relação a algum procedimento poderá ser sanada diretamente com o pesquisador responsável.

Fica assegurado o direito do voluntário, a qualquer momento do estudo, desistir de participar da pesquisa.

Eu, _____, RG nº _____ declaro ter sido informado e concordo em participar, como voluntário, do projeto de pesquisa acima descrito.

Cachoeira, _____ de _____ de 2019,

_____
Nome e assinatura do voluntário

_____ _____
Testemunha Testemunha

ANEXO 3: PARECER CONSUBSTANCIADO DO CEP - FADBA

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: AVALIAÇÃO DO EFEITO AGUDO DA ESTIMULAÇÃO TRANSCRANIANA COM CORRENTE CONTÍNUA E ESTIMULAÇÃO PERIFÉRICA PARA DISFUNÇÃO TEMPOROMANDIBULAR EM PACIENTES COM DOENÇA FALCIFORME: ENSAIO CLÍNICO RANDOMIZADO, CROSS-OVER, DUPLO CEGO

Pesquisador: Lilian Anabel Becerra de Oliveira

Área Temática:

Versão: 3

CAAE: 94835218.8.0000.0042

Instituição Proponente: FACULDADES ADVENTISTAS DA BAHIA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.036.605

Apresentação do Projeto:

A Doença Falciforme (DF) tem como principal comorbidade a dor crônica provocada por lesões musculoesqueléticas após uma série de eventos vaso-oclusivos. Dentre essas lesões musculoesqueléticas encontradas em indivíduos com DF está presente a Disfunção Temporomandibular (DTM), a qual pode ser classificada como miofascial e/ou articular. Entretanto, até o momento, poucos estudos testaram a eficácia de tratamentos não

farmacológicos para indivíduos com doença falciforme e DTM. Atualmente a DTM tem sido considerada como uma síndrome de sensibilização central e por consequência apresenta comprometimento neurofisiológicos no processamento de estímulos dolorosos, como por exemplo, diminuição no controle inibitório descendente da dor. Porém, não é conhecido na literatura se este comprometimento inibitório descendente da dor varia de acordo com o tipo de DTM, uma vez que dados recentes têm mostrado que este mecanismo é diferente entre condições dolorosas de origem estrutural e não estrutural. A Estimulação Transcraniana com Corrente Contínua (ETCC) adicionado a Estimulação Periférica (EEP) tem mostrado resultados positivos para dores crônicas de origem central, por isso este tratamento foi proposto para a dor crônica da articulação

Temporomandibular (ATM) independente se sua origem é miofascial e/ou articular. Este estudo tem

por objetivo avaliar o resultado agudo de uma única aplicação de ETCC + EEP em sujeitos com DF e DTM, e também determinar se existe diferença de resposta dependendo do diagnóstico do subgrupo miofascial ou articular.

Haverá uso de placebo ou a existência de grupos que não serão submetidos em nenhuma intervenção:

Para avaliar o efeito da Estimulação Transcraniana com corrente contínua (ETCC) + estimulação periférica (EEP) será necessário que um grupo use sham, por isso haverão 3 grupos: (1) ETCC ativo + EEP ativo (2) ETCC ativo + EEP sham (3) ETCC sham + EEP sham.

Serão 20 INDIVÍDUOS que irão receber os 3 protocolos com intervalos de 8 dias cada. Desenho ensaio clínico randomizado, Cross-over duplo cego. O efeito do ETCC é de 24 horas por isso não haverá interferência do tratamento anterior.

Objetivo da Pesquisa:

Objetivo Primário:

Determinar o efeito imediato da ETCC anódico e Estimulação periférica sensorial sobre a intensidade da dor em indivíduos com Doença Falciforme e DTM, comparando as diferentes combinações destas técnicas.

Objetivo Secundário:

- Determinar o efeito neuromodulatório da ETCC anódica e estimulação periférica sensorial sobre a modulação endógena da dor (aspetos inibitórios e facilitatórios) em indivíduos com doença falciforme em comparação a diferentes combinações terapêuticas destas técnicas;
- Identificar se existe variação no controle inibitório descendente da dor entre os diferentes subgrupos de DTM; - Avaliar segurança e eficácia neuromodulatoria das diferentes combinações terapêuticas; - Avaliar a saúde bucal das pessoas com Doença falciforme estudados;- Avaliação da saúde emocional do portador de doença falciforme, tendência a depressão e ansiedade.- Identificar a Prevalência de DTM nos sujeitos avaliados.

Avaliação dos Riscos e Benefícios:

No TCLE estão explicitados os riscos decorrentes da aplicação das técnicas ETCC e EP tais como momentaneamente doer a região da ATM, após teste de pressão sobre a articulação. O uso do ETCC tem o risco de provocar ardência na testa da cabeça que se não avisado pode queimar o local levemente. Isto deve ser evitado ao ficar atento a qualquer início de ardor na região. O Fisioterapeuta experiente irá perguntar cada 3 minutos se está sentindo ardência, no caso de a resposta ser positiva, o aparelho será imediatamente desligado. O risco real é em pessoas que tenham espinhas na testa, se este for seu caso, o teste será deixado para outro dia. O aparelho EP se caracteriza por provocar um leve formigamento no local, o único risco é este formigamento incomodar, se for o caso, será diminuído o estímulo ou desligado. Todo o material utilizado é esterilizado e descartável.

Comentários e Considerações sobre a Pesquisa:

Trata-se de uma pesquisa relevante do ponto de vista científico com a possibilidade de responder questões na área clínica e trazer benefícios que apresentam doenças falciformes com disfunção Temporomandibular. Os documentos que compõem o protocolo de pesquisa foram devidamente assinados e apresentados.

Considerações sobre os Termos de apresentação obrigatória:

A Folha de Rosto foi devidamente preenchida e assinada pela pesquisadora e pela responsável pela instituição proponente. O TCLE contempla os principais itens preconizados pela Resolução 466/2012. Também estão anexados cópia do projeto, questionário para avaliação da presença de depressão HAD e critérios para identificação de desordens temporomandibulares.

Recomendações:

Sem recomendações.

Conclusões ou Pendências e Lista de Inadequações:

O protocolo atende às recomendações da Resolução 466/2012 obedecendo os princípios éticos nela contidos justificando assim a sua execução.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_153704 3_E1.pdf	09/04/2020 20:17:10		Aceito
Projeto Detalhado / Brochura Investigador	Projeto_detalhado_3.pdf	09/04/2020 19:52:31	Lilian Anabel Becerra de Oliveira	Aceito
TCLE / Termos de Assentimento /	TCLE_triagem.pdf	09/04/2020 15:33:53	Lilian Anabel Becerra de Oliveira	Aceito

Continuação do Parecer: 4.036.605

Justificativa de Ausência	TCLE_triagem.pdf	09/04/2020 15:33:53	Lilian Anabel Becerra de Oliveira	Aceito
Folha de Rosto	folhaDeRosto2.pdf	09/04/2020 15:31:11	Lilian Anabel Becerra de Oliveira	Aceito
Brochura Pesquisa	cartaparaavaliador.pdf	22/10/2018 11:01:33	Lilian Anabel Becerra de Oliveira	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	18/10/2018 10:58:01	Lilian Anabel Becerra de Oliveira	Aceito
Outros	had_com_escore.pdf	31/07/2018 17:48:45	Lilian Anabel Becerra de Oliveira	Aceito
Recurso Anexado pelo Pesquisador	RDC_Portuguese_Brazil.pdf	31/07/2018 17:47:24	Lilian Anabel Becerra de Oliveira	Aceito

Situação do Parecer:

Aprovado

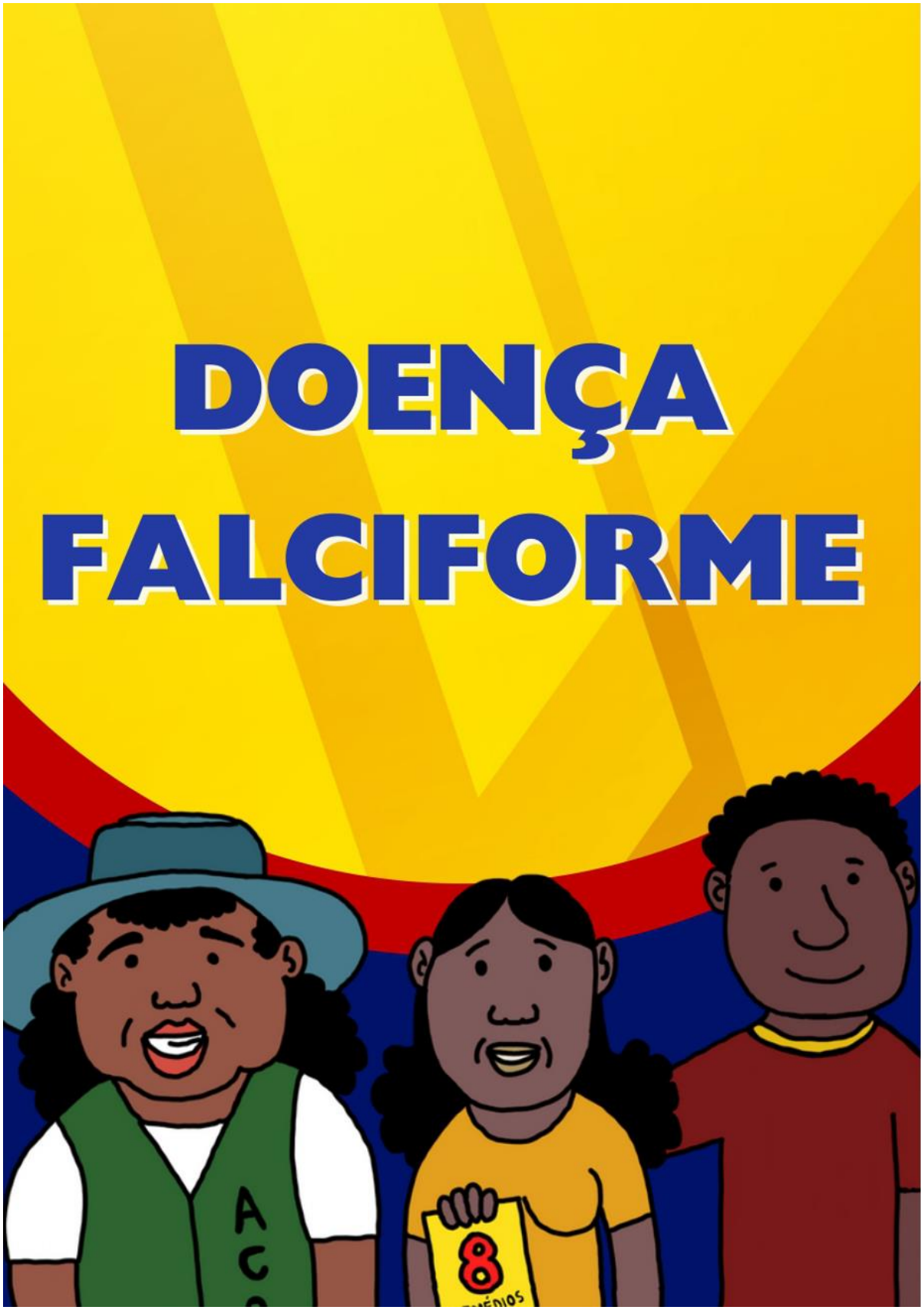
Necessita Apreciação da CONEP:

Não

CACHOEIRA, 19 de Maio de 2020

Assinado por:
Wellington dos Santos Silva

ANEXO 4: PRODUTO EDUCATIVO



AGRADECIMENTOS

A criação deste panfleto foi inspirada pelo desejo de dizer muito obrigado para os homens e mulheres com a Doença Falciforme, do Recôncavo Baiano, que ao longo dos anos tem aceitado compartilhar suas histórias de desafios e vitórias em favor da pesquisa. Sim, para você nosso muito obrigado e nosso desejo de uma melhor qualidade de vida.

FICHA TÉCNICA

CRÉDITOS:
Faculdade Adventista da Bahia
Escola Bahiana de Medicina e Saúde Pública

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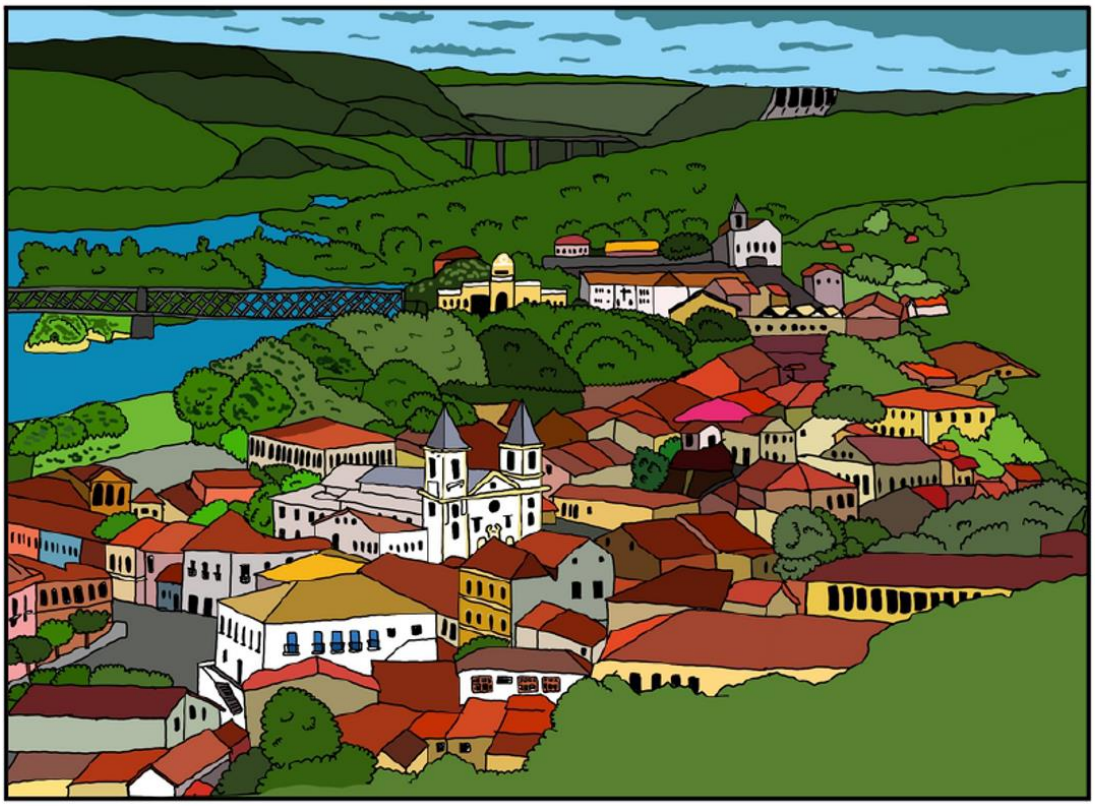
COLABORADORES
Ilustração e diagramação: **Ismaile Barragan**

APOIO:
Associacao Baiana de Pessoas com Doença Falciforme

NUMA CIDADE HISTÓRICA, NO INTERIOR DO RECÔNCAVO BAIANO, DUAS COMADRES CONVERSAM NO QUINTAL DE CASA.



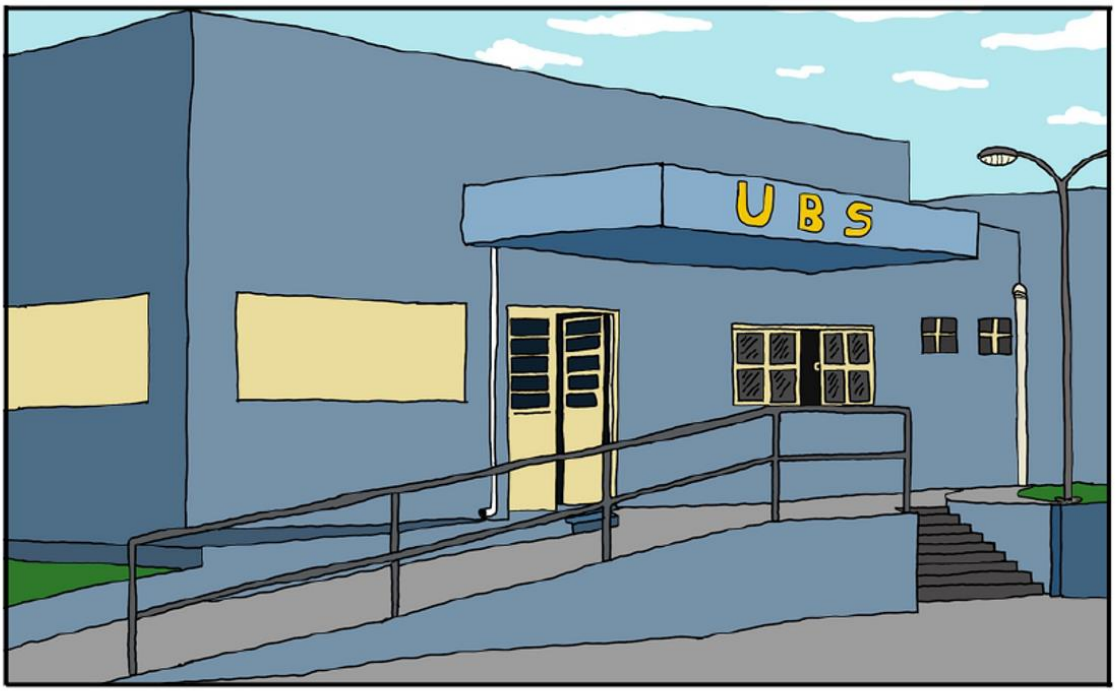
ANGELITA, PERGUNTA A SUA VIZINHA MARIA SE JÁ LEVOU O SEU FILHO RICARDO AO POSTO DE SAÚDE POR CAUSA DA DOENÇA FALCIFORME.

3


EU SEI, ELE TEM RECLAMADO MUITO DE DOR NO CORPO INTEIRO, ALÉM DE ESTAR SE SENTINDO MUITO DEPRIMIDO.
MEU MARIDO ROMÁRIO FOI AO MÉDICO EM SALVADOR E JÁ ESTÁ MELHOR. TEM IDO AO PSICÓLOGO INCLUSIVE.
VÁ AO POSTO E APROVEITA QUE A AGENTE DE SAÚDE VEM AQUI HOJE PARA TIRAR DÚVIDAS!
MULHER, VOU LEVÁ-LO HOJE MESMO! VOU APROVEITAR E CONVERSAR COM A AGENTE DE SAÚDE TAMBÉM!

4

NAQUELE MESMO DIA, MARIA E RICARDO, SEU FILHO, VÃO À CONSULTA COM O MÉDICO NA UBS DO BAIRRO.



S


AS HEMÁCIAS LEVAM OXIGÊNIO POR MEIO DO SANGUE. NA DOENÇA FALCIFORME, AS HEMÁCIAS ADQUIREM FORMATO DE FOICE, PROVOCANDO ENTUPIMENTO DOS VASOS MENORES, O QUE CAUSA DOR.
HEMÁCIA NORMAL
HEMÁCIA FALCIFORME
VASO MENOR ENTUPIDO
NÃO ESQUEÇA DE TOMAR CORRETAMENTE A SUA MEDICAÇÃO E ESTAR COM A SUA VACINAÇÃO ATUALIZADA. LEVE ESSE PANFLETO AQUI, POIS ALÉM DOS REMÉDIOS TRADICIONAIS SÃO NECESSÁRIAS ALGUMAS MUDANÇAS DE HÁBITOS DE VIDA!
8 REMEDIOS NATURAIS


MAS DOUTOR, O QUE TEM NESSE PANFLETO?


DICAS SIMPLES, MAS EFICAZES PARA QUE VOCÊS POSSAM MELHORAR A QUALIDADE DE VIDA!

6

APÓS A IDA À CONSULTA NA UBS, MARIA E SEU FILHO RECEBEM A VISITA DA AGENTE DE SAÚDE.

7


POSSO VER O PANFLETO?
CLARO! OLHE AQUI!


ESTE PANFLETO É SIMPLES, MAS BEM EFICAZ! NUNCA É TARDE PARA COLOCAR EM PRÁTICA!
1 ALIMENTAÇÃO SAUDÁVEL
3 ÁGUA
2 EXERCÍCIO FÍSICO
4 LUZ SOLAR


AGORA, DEIXA EU EXPLICAR POR QUE ESSAS DICAS SÃO BOAS PARA A SAÚDE!
ACS

8


O CONSUMO DE FRUTAS E VERDURAS, AJUDA A MANTER O CORPO MAIS SAUDÁVEL. DIMINUIR O CONSUMO DE REFRIGERANTES, DE BEBIDAS ALCOÓLICAS, DE AÇÚCAR, CONTRIBUI PARA A MELHORA E MANUTENÇÃO DA SAÚDE.
1 ALIMENTAÇÃO SAUDÁVEL


A ATIVIDADE FÍSICA MODERADA É IMPORTANTE, POIS DIMINUI AS DORES, AJUDA A TER MAIS DISPOSIÇÃO E QUALIDADE DE VIDA.
2 EXERCÍCIO FÍSICO

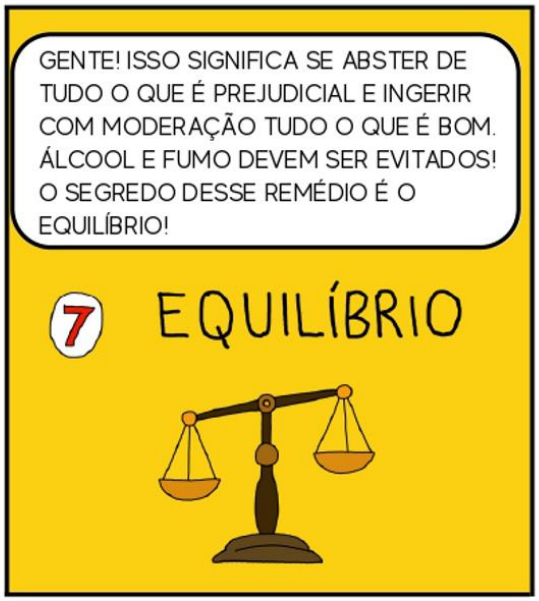

A INGESTÃO DE ÁGUA AJUDA NA DIMINUIÇÃO DO CANSAÇO, DAS DORES DE CABEÇA, ALÉM DE DESINTOXICAR O CORPO!
3 ÁGUA


FICAR DE 10 A 15 MINUTOS POR DIA NO SOL, AJUDA A PRODUZIR A VITAMINA D E CÁLCIO, QUE AJUDA A FORTALECER OS OSSOS. PRODUZ O HORMÔNIO SEROTONINA, QUE PROMOVE A SENSAÇÃO DE BEM-ESTAR.
4 LUZ SOLAR

9


RESPIRAR AR PURO, AJUDA A FORTALECER O SISTEMA IMUNOLÓGICO E O SISTEMA RESPIRATÓRIO.
5 AR PURO


É MUITO IMPORTANTE DORMIR! DORMIR 8 HORAS DIÁRIAS, PROPORCIONA UM MAIOR RENDIMENTO ESCOLAR, NO TRABALHO E NAS DEMAIS ATIVIDADES. O SONO É UM GRANDE RESTAURADOR DO SISTEMA NERVOSO E AJUDA A PREPARAR MELHOR AS FUNÇÕES CORPORAIS DO DIA A DIA.
6 REPOUSO


GENTE! ISSO SIGNIFICA SE ABSTER DE TUDO O QUE É PREJUDICIAL E INGERIR COM MODERAÇÃO TUDO O QUE É BOM. ÁLCOOL E FUMO DEVEM SER EVITADOS! O SEGREDO DESSE REMÉDIO É O EQUILÍBRIO!
7 EQUILÍBRIO


ISSO DIZ RESPEITO A SAÚDE MENTAL. BUSCAR AJUDA PSICOLÓGICA É FUNDAMENTAL. PRINCIPALMENTE QUANDO ESTAMOS COM BAIXA AUTOESTIMA OU ANGUSTIADOS POR CAUSA DOS SINTOMAS DA DOENÇA FALCIFORME. TER FÉ EM DEUS PODE AJUDAR A AUMENTAR O BEM-ESTAR.
8 ESPERANÇA


QUER DIZER QUE SE A GENTE SEGUIR ESSAS ORIENTAÇÕES, RICARDO FICARÁ MELHOR?
NÃO APENAS ELE, TODOS VOCÊS TERÃO MELHOR QUALIDADE DE VIDA! NÃO SIGNIFICA QUE FICARÃO LIVRES DE DOENÇAS, MAS QUE AUMENTARÃO AS DEFESAS NATURAIS DO CORPO!
QUE ÓTIMO! VAMOS TENTAR SEGUIR ESSAS DICAS DE CUIDADO! NÃO É MESMO RICARDO?
VAMOS! E... BOM, EU VOU TENTAR TOMAR MENOS REFRIGERANTE E CUIDAR DE VEZ DA MINHA SAÚDE!
AH! ACABEI DE LEMBRAR QUE A EQUIPE DA NASF ESTÁ PREPARANDO ATIVIDADES DE CUIDADO À PESSOA COM DOENÇA FALCIFORME E VOCÊS PODEM TIRAR OUTRAS DÚVIDAS COM A FISIOTERAPEUTA, NUTRICIONISTA E A PSICÓLOGA!
QUE MARAVILHA! VAMOS SIM! QUERO APRENDER COMO ME CUIDAR E TER MUITO MAIS QUALIDADE DE VIDA, PORQUE A VIDA CONTINUA!
FIM

VOCÊ GOSTARIA DE SE ASSOCIAR AO GRUPO DE APOIO À DOENÇA FALCIFORME DA FADBA?

ENTRE EM CONTATO COM INSTAGRAM DA CLÍNICA-ESCOLA, TELEFONE DA CLÍNICA, E WHATAPP DA CLINICA:

75 9135-3109 WHATSAPP DA CLINICA ESCOLA
75 3425-8025 TELEFONE COMERCIAL CLINICA ESCOLA

VOCÊ GOSTARIA DE SABER COMO ESTÃO SEUS HÁBITOS?

Responda este questionário

Faculdade Adventista
BAHIANA
ABADFAL