

Efficacy of non-pharmacological interventions to reduce pain in children with sickle cell disease: a systematic review

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Abstract

Background: Pain is the clinical hallmark of sickle cell disease (SCD) leading to hospitalization, psychological sequelae and a decreased health-related quality of life. The aim of this systematic literature review is to evaluate the efficacy of non-pharmacological interventions in reducing sickle cell-related pain in children with SCD. **Methods:** A comprehensive literature search up until October 2022 was performed to identify studies that investigated the efficacy of non-pharmacological interventions on (1) pain frequency and/or intensity, and (2) analgesic and health service use in children with SCD. Randomized controlled (RCTs) trials and quasi-experimental designed (QED) studies that investigated non-pharmacological interventions for pediatric patients with SCD until the age of 21 years were considered for inclusion. **Results:** Ten articles (5 RCTs and 5 QED studies) with 422 participants were included. They investigated cognitive behavioral therapy (CBT) (n =5), biofeedback (n=2), massage (n=1), virtual reality (n=1) and yoga (n=1). CBT, biofeedback, massage, virtual reality and yoga significantly reduced frequency and/or intensity of SCD-related pain. Biofeedback also significantly reduced analgesic use. **Conclusion:** Non-pharmacological interventions may be effective in reducing pain in pediatric SCD patients. However, due to the heterogeneity of the included studies a quantitative analysis could not be performed. Awaiting further supporting evidence, healthcare providers should consider implementing these interventions as valuable part of a comprehensive pain management strategy plan to improve the outcome of sickle cell-related pain.

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Abbreviation list

ASH	American Society of Hematology
CBT	Cognitive behavioral therapy
CI	Confidence interval
ED	Emergency department
FU	Follow-up
HA IQR	Hospital admission Interquartile range
LDH	Lactate acid dehydrogenase
LOS	Length of hospital stay
MCV	Mean corpuscular volume
NHLBI	National Heart, Lung and Blood Institute
OPD RCT	Outpatient department Randomized controlled trial
SCD	Sickle cell disease
SD	Standard deviation
USA	United States of America
VOC	Vaso-occlusive crisis
VR	Virtual reality

Abstract

Background: Pain is the clinical hallmark of sickle cell disease (SCD) leading to hospitalization, psychological sequelae and a decreased health-related quality of life. The aim of this systematic literature review is to evaluate the efficacy of non-pharmacological interventions in reducing sickle cell-related pain in children with SCD.

Methods: A comprehensive literature search up until October 2022 was performed to identify studies that investigated the efficacy of non-pharmacological interventions on (1) pain frequency and/or intensity, and (2) analgesic and health service use in children with SCD. Randomized controlled (RCTs) trials and quasi-experimental designed (QED) studies that investigated non-pharmacological interventions for pediatric patients with SCD until the age of 21 years were considered for inclusion.

Results: Ten articles (5 RCTs and 5 QED studies) with 422 participants were included. They investigated cognitive behavioral therapy (CBT) (n =5), biofeedback (n=2), massage (n=1), virtual reality (n=1) and yoga (n=1). CBT, biofeedback, massage, virtual reality and yoga significantly reduced frequency and/or intensity of SCD-related pain. Biofeedback also significantly reduced analgesic use.

Conclusion: Non-pharmacological interventions may be effective in reducing pain in pediatric SCD patients. However, due to the heterogeneity of the included studies a quantitative analysis could not be performed. Awaiting further supporting evidence, healthcare providers should consider implementing these interventions as valuable part of a comprehensive pain management strategy plan to improve the outcome of sickle cell-related pain.

Introduction

Sickle cell disease (SCD) is the most common monogenetic hemoglobinopathy in the world with approximately 300,000 newborns per year.^{1,2} SCD is caused by a gene mutation in the beta-globin chain, resulting in the formation of sickle-shaped red blood cells.^{3,4} These sickled red blood cells cause obstruction within small vessels, leading to chronic hemolytic anemia, acute and chronic pain and irreversible organ damage.⁵

Pain is the clinical hallmark of SCD and has a huge impact on patients' daily life leading to a decreased health-related quality of life.⁶⁻¹⁰ Because of the complexity of pain in SCD patients and the scarce knowledge of its pathophysiology, the management of SCD-related pain is extremely difficult.^{11,12} Acute pain from vaso-occlusive crises (VOCs) can be managed at home using oral or suppository analgesic agents.^{13,14} In case home management fails, hospital admission is required for treatment with intravenous analgesics, anxiolytics and/or sedatives.^{15,16} Pharmacological interventions such as opioid analgesics have been the primary therapy to treat SCD-related pain. However, they can have serious side effects including respiratory depression and constipation on the short term and physical dependence on the long term. Although pharmacological treatment is the backbone of SCD-related pain, non-pharmacological management has proven to be effective in reducing pain in several diseases, including SCD.¹⁷⁻²³ Both the National Heart, Lung and Blood Institute (NHLB) and the American Society of Hematology (ASH) guidelines (2020) indicated non-pharmacological interventions as a valuable addition in the management of SCD-related pain.¹⁴ According to the ASH guidelines non-pharmacological interventions can be classified into: the psychological interventions, physical interventions, and integrative medicine.^{14,17}

Previous reviews have investigated the efficacy of complementary non-pharmacological interventions in reducing pain in patients of all ages seven years ago.^{21,22} In this review we specifically focus on the effect of these interventions on SCD-related pain in children. Children experience pain differently compared to adults, as children have a developing and more adaptable nervous system, a greater developmental potential, and more cognitive and emotional flexibility.²⁴⁻³⁰ This allows greater potential change, behavioral improvement and effectiveness of non-pharmacological interventions.³¹ In addition, frequent pain experiences during childhood can cause negative long-term effects that may last into adulthood including a higher sensitivity to pain and anxiety and depression.³²⁻³⁸ Therefore, the aim of this systematic review is to investigate the effect of non-pharmacological interventions on (1) the frequency and/or intensity of SCD-related pain, and (2) analgesic and health service use in children with SCD.

Methods

Eligibility criteria

Randomized controlled trials (RCTs) and quasi-experimental designed (QED) studies that investigated the efficacy of non-pharmacological interventions for pediatric patients with SCD were considered for inclusion. Non-pharmacological interventions were defined as 'therapies that do not involve taking medicines or any other active substances'.³⁹ QED studies are nonrandomized, pre-post intervention studies or interrupted time-series designs with or without control groups.^{40,41} Systematic reviews, comment articles and case reports were excluded, as well as non-English publications. Furthermore, studies with participants aged above 21 years, were excluded.

Outcome measures

The primary outcomes were pain frequency in a specific period of time and pain intensity of any kind of pain episode. Pain frequency was calculated as the number or percentage of pain days of the total observed days. Secondary outcomes were frequency of hospital admissions for SCD-related pain, emergency department (ED) visits, length of hospital stay (LOS) and analgesic use.

Search strategy and study selection

The complete study protocol was published in the PROSPERO database prior to start (record ID 117416). Relevant articles were identified by the medical information specialist from the electronic databases Medline, PsycINFO and Embase using different terms for ‘sickle cell disease’, ‘pain’ and ‘psychotherapy’, ‘analgesic use’ and ‘health service use’ (**Supplemental Table S1**). Every article published before October 2022 was included for further assessment. Two investigators (SV, JG or CV) independently screened titles and abstracts and identified all studies that met the inclusion criteria using the Rayyan application.⁴² Eligibility was assessed based on the full text article of the remaining studies (SV, CV). Discrepancies were solved by consensus or by the involvement of a third investigator (JG). The reference lists of all included studies and related systematic reviews were checked to ensure no relevant studies were missed. If the full text of an eligible study was not available for full text screening, authors of these studies were approached to provide their data and articles.

Data extraction and analysis

Critical Appraisal

Methodological quality and risk of bias of the selected studies were assessed by two independent investigators (SV, CV) using two modified and extensive versions of the Critical Appraisal Checklist for Randomized Controlled Trial and Quasi-Experimental Studies (Non-Randomized Experimental Studies) by the Joanna Briggs Institute.⁴⁰ Additionally, attrition and selection bias were assessed as well according to criteria of the Handbook of the Cochrane Collaboration for systematic reviews.⁴³

Data extraction

A standardized data extraction form was used to extract data from the included studies for evidence synthesis. Extracted information included: author, publication year, study setting, baseline characteristics of included participants, details of randomization, study methodology and outcomes that were relevant for our review. Data were independently extracted by two reviewers (SV, CV) and any discrepancies were identified and resolved through discussion. If the effect between groups was not stated in the article, we calculated this based on the provided data.

Data analysis

The non-pharmacological interventions were analyzed separately for the inpatient and the outpatient setting and classified in one of the three categories as described in the ASH guidelines:¹⁴

1. Psychological interventions;
2. Physical interventions;
3. Integrative medicine: passive modalities combining different psychological and physical tools and approaches, tailored to individual patient needs. We described data narratively and summarized the main findings in table format including study characteristics, data of previously mentioned outcomes and a calculated quality assessment.

Results

Study selection

A total of 1,048 publications was retrieved and screened by two investigators (SV, JG or CV). Subsequently, 41 studies were assessed for eligibility based on their full text (SV, CV), of which ten studies fulfilled the selection criteria and were included in this review (**Fig. 1**).⁴⁴⁻⁵³ We approached the first author of two studies with unavailable full text articles. However, none of them responded. In total, thirty-one full text articles were excluded. The majority of the excluded studies did not report on our predefined outcomes (n=9).⁵⁴⁻⁶².

Characteristics of included studies

Study characteristics and the risk of bias of the ten included studies are summarized in **Table 1**. The studies included a total of 422 participants aged between 6 and 21 years old. All participants had SCD including the genotypes HbSS, HbSC, HbS β -thalassemia and HbSD. Studies were published between 1987 and 2020. All studies were performed in the USA. The type of intervention studied were psychological interventions (n=7), physical intervention (n=1) and integrative medicine (n=2). In this review, psychological interventions included CBT and biofeedback.^{44,45,47,48,51-53} The physical intervention included the practice of yoga⁵¹, and integrative medicine was provided in the form of massage and virtual reality^{46,50}. In total, five different types of interventions were studied including CBT (n=5),^{44,48,51-53} biofeedback (n=2),^{45,47} yoga (n=1),⁴⁹ massage (n=1)⁵⁰ and virtual reality (n=1).⁴⁶ Eight studies were performed in the outpatient clinic (n=6)^{44,45,47,51-53} or at home (n=2),^{48,50} while two studies were performed during hospital admission.^{46,49}

In the outpatient clinic, children received one single training session in four studies,^{45,46,52,53} in the remaining studies the number of sessions ranged between 2 and 13.^{44,47-51} The duration of the intervention period that included both the training session and the practices ranged from 30 days^{45,50,52} to 4.5 months.⁴⁴ Duration of follow-up after the non-pharmacological invention ranged from 1 to 12 months. Pain-related outcomes were assessed using self-reported daily pain diaries in seven studies,^{45,47,48,50-53} in one of them outcomes were electronically monitored.⁵³ In the other three studies, pain was reported personally to researcher(s) while inpatient or by telephone assessment.

All studies primarily focused on pain. They examined either the frequency of pain (n=2)^{45,48}, the intensity of the reported SCD-related pain on a 5- or 10-point pain scale (n=4),^{44,46,49,50} or both pain outcomes (n=4).^{47,51-53} Four studies clearly defined the type of pain they were targeting, namely acute pain in three studies,^{46,47,49} and chronic pain in one study.⁴⁴ The remaining six studies did not specify the type of SCD-related pain they were targeting.^{45,48,50-53} Therefore, we decided to state this pain as daily pain. In total, eight studies investigated the secondary outcomes that we specified, with seven of them investigating health service use^{44,47-52} and four the use of analgesics.^{47,49,51,52} In total, four of the studies studied both health service and analgesic use.^{47,49,51,52}

Quality assessment of included studies

In this review, five RCTs^{48-51,53} and five QED^{44-47,52} studies were included. The quality of the five RCTs had a mean score of 9.0 out of 13 points. The five included QED studies scored an average of 7.6 out of 10 points. Scores per study are shown in **Table 1**. The detailed scoring is listed in **Supplemental Figure S2**. In RCTs, the lack of follow-up⁴⁸⁻⁵⁰ and selective reporting were the main reasons for a risk of bias.^{50,51,53} Three studies did not report on blinding of outcome and allocation concealment, so risk of bias could not be scored on these items.^{48,50,51} Only one study blinded their outcome assessors for the intervention.⁴⁹ In QED studies, four out of five studies did not include a control group^{45-47,52} and two studies did not have a follow-up causing a risk of bias.^{46,52} In total, five out of the ten studies achieved a follow-up rate of at least 80% of the patients.

Summary of main findings

Effects of interventions

Five studies reported significant reductions in pain-related outcomes after a study period between 1 and 12 months,^{44,46,47,50,52} while one study reported a significant reduction in analgesic use.⁴⁷ None of the included articles reported a significant reduction of health service use. In the following paragraphs the results will be discussed according to setting (in- or outpatient) and type of intervention.

Outpatient setting

Psychological interventions

Among the five studies that investigated CBT,^{44,48,51-53} two showed improvements on pain-related outcomes.^{44,52} First, Dobson et al. showed that after guided imagery, a technique within CBT, the intensity of daily reported pain decreased from 2.4 (SD 1.2) to 0.7 (SD 1.2) on a 5-point scale ($p < 0.01$). In addition, the number of painful episodes per month decreased significantly, from 5.6 (SD 3.3) to 2.5 (SD 4.1; $p = 0.003$). However, no significant changes were reported in the number of ED visits and hospital admissions.⁵² Second, Sil et al. reported reduced chronic SCD pain intensities on a 10-point scale from 5.5 (SD 2.2) to 3.8 (SD 2.8, $p = 0.009$). The other three CBT studies did not show any effects on pain, health service or analgesic use.^{48,51,53} One study used electronic devices to provide CBT electronically (e-CBT) and to record outcomes digitally. In this study, there were large discrepancies between self-reported and device-reported frequencies of skill practice; children reported approximately two to four times more skill practice than what the device recorded.⁵³ The efficacy of biofeedback was examined by two studies, with one showing a significant reduction of the pain-related outcomes.^{45,47} This study by Cozzi et al. studied the effect of biofeedback on acute pain at home.⁴⁷ Pain intensities reduced from 1.9 to 0.5 (SD not reported) on a 5-point scale ($p < 0.001$) and the number of self-treated crises per month decreased from 2.2 to 0.4 ($p < 0.05$). Furthermore, the number of days on which analgesics were taken in a month was reduced from 8.0 to 1.3 ($p < 0.001$), but health service use did not change compared to baseline.

Integrative medicine

Lemanek et al. investigated massage as integrative medicine at the outpatient clinic. They reported a significant decrease of pain-related outcomes after massage ($p = 0.05$), however no specific outcomes or effect sizes were reported.⁴⁹ Therefore, this result was not classified as significant.

Inpatient settings

In the inpatient setting, the effect of yoga and virtual reality were studied for uncomplicated VOCs.^{46,49} Children reported a reduction in acute pain intensity on a 10-point scale after a single VR session from 7.3 (SD 2.7) to 5.8 (SD 3.2, $p < 0.001$). Yoga reduced pain intensity from 5.6 to 5.0 ($p = 0.029$) after an average of 2.5 sessions. No differences were found in LOS and opioid use after yoga.

Discussion

In this systematic review, we investigated the efficacy of non-pharmacological interventions to reduce SCD-related pain in children with SCD. In half of the ten included studies non-pharmacological interventions improved pain-related outcomes. These interventions included CBT and biofeedback in the outpatient setting, and yoga and VR in the inpatient setting. Despite the heterogeneity of the included studies, these findings support that the addition of non-pharmacological interventions to standard medical care seems promising in further reducing SCD-related pain.

The efficacy of non-pharmacological interventions, and in particular psychological interventions, has been well described in various pain conditions.^{21,22,63-65} In this review, seven of the included studies investigated

psychological interventions. Four of the seven psychological interventions were successful in reducing pain. Two of successful psychological interventions included CBT, implying that this intervention could be useful in targeting SCD-related pain in children.^{44,52} One of the CBT studies specifically looked at the effect of guided imagery. Guided imagery is expected to be particularly effective in children, because of their capacity for active and creative imaginations and their high degree of suggestibility.⁶⁶ The other three CBT interventions did not show significant results most likely due to differences in CBT procedures, despite the fact that CBT has the broadest evidence in adults with SCD and in patients with other chronic pain conditions. Schatz. et al focused on electronically delivered CBT. Although authors did not show statistically significant changes on pain-related outcomes, smartphone-assisted skill use was associated with a beneficial effect on next day pain intensity using multilevel modeling.⁵³

In SCD, there are two QED studies examining the effect of biofeedback in children,^{45,47} and only one small observational study in adults.⁶⁷ In adults, biofeedback did not show any significant reduction in pain, health service use nor analgesic use.⁶⁷ In the outpatient setting, massage therapy was also described to result in a significant pain reduction in children with SCD.⁵⁰ Although there are two studies with massage therapy in adults with SCD showing positive results on SCD-related pain^{68,69}, this effect remains unclear in children with SCD as the authors did not report any outcomes⁵⁰.

In the inpatient setting, yoga and the use of VR showed significant positive effects on acute pain in the two included studies.^{46,49} The effect of yoga on pain reduction was previously explored in the outpatient setting and in other pain conditions.^{70,71} Remarkably, a survey among children and adolescents with chronic pain, showed that 32% preferred yoga as first choice of complementary medicine.⁷² According to a systematic review about the effect of yoga, nine out of ten RCTs also reported significant reductions in pain intensity in ambulant adolescents and adults with a variety of pain conditions including lower back pain, osteoarthritis and irritable bowel syndrome.⁷³ The use of VR as a distraction tool may be an effective, and easy-to-use tool in hospitalized children for a VOC. VR is especially appealing for children, as they are often more engaged in magical thinking,⁷⁴ and become more captivated by imaginative play.⁷⁵ Despite the positive results after VR, this study still needs replication in children with SCD, as the study was focused on feasibility rather than efficacy.⁴⁶ Nevertheless, the efficacy of virtual reality in reducing acute pain has previously been well described in children undergoing painful medical procedures and in children hospitalized with burn injuries.⁷⁶⁻⁷⁹

In several studies, painful early life experiences were associated with hypersensitivity to pain and allodynia.^{37,80,81} Pain experienced during early childhood has been suggested to be a significant contributor to the development of chronic pain in children and adults.^{82,83, 84-86} Meanwhile both the prevalence and daily opioid dose in SCD patients increase significantly with age.⁸⁷⁻⁸⁹ Therefore, it is important to reduce opioid use with non-pharmacological interventions to target this issue. We address the effect of these interventions by evaluating analgesic and health service use as outcomes. Only one included study reported reduced analgesic use,⁴⁷ and none of the studies reported a reduced health service use after intervention.^{44,48-52} However, none of the included studies were designed and powered for these outcomes. Also, most studies had a short or even absent period of follow-up to measure these outcomes properly. Furthermore, pain in children in general, is associated with fear of pain, pain anxiety and/ or pain catastrophizing.⁹⁰ These psychological factors could have played a role in the maintained use of analgesics and frequent hospital visits. These psychological effects were not evaluated in the included studies, so these effects on our outcomes could not be ruled out.

There are several limitations of this systematic review that need to be addressed. Due to the heterogeneity of the included studies, firm conclusions about the effect of non-pharmacological interventions cannot be drawn. Within the various interventions, there were great differences with regards to the method or practice. There are no standardized methods for any of the interventions; there is a lack of methodological robustness. In addition, our included studies evaluated the non-pharmacological interventions as add-on intervention. The effect of the intervention alone has not been studied. Variation in managing pain pharmacologically between centers, makes the comparison between our included studies in this systematic review even more difficult. Also, socio-cultural perceptions, socio-economic status and access to care are important factors, that affect patient recruitment and may therefore have biased selection of patients. This may limit the extrapolation

and representativeness of this systematic review.^{91,92} Lastly, the majority of the included studies has small sample sizes ranging from 8 to 101 participants.

Although significant pain reduction was reported in half of the studies after non-pharmacological interventions in children with SCD, specific interventions cannot be strongly recommended yet. We need further studies that address the different subtypes of SCD-related pain (acute, daily, chronic). In addition, to achieve more consistency in future studies, well-designed, adequately-powered studies should incorporate standardized administration and analysis procedures and for each type of non-pharmacological intervention, allowing fair comparison and replication. Lastly, outcome measures such as analgesic use at home and healthcare use should be considered with an adequate duration of follow-up, as these measures accurately reflect the home situation of patients with SCD.

In conclusion, non-pharmacological interventions as a complementary strategy, have the potential to lead to a faster recovery of SCD-related pain with a substantial decrease of side effects and complications; thereby improving quality of life in children with SCD.

Conflict of interest

The authors have no conflicts of interest to declare.

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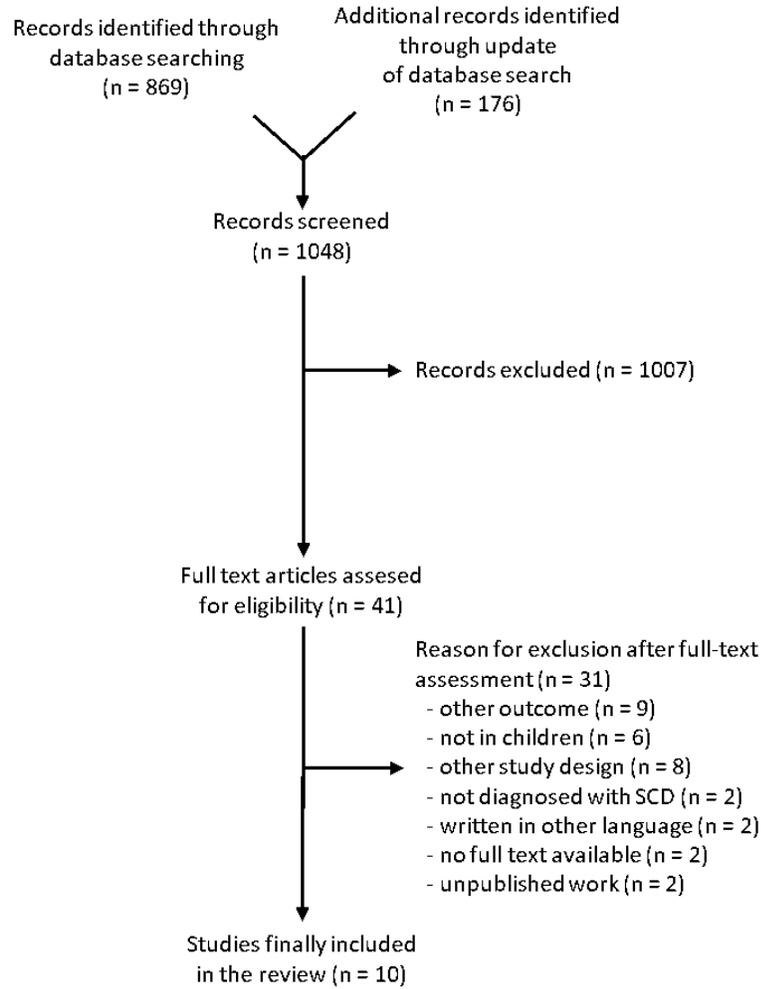
Legends

Figure 1: Flowchart of publications included in this systematic review

Table 1: Summary of findings

Supplemental Table S1: Complete literature search

Supplemental Figure S2: Detailed quality assessment of the included studies (RCTs and QED studies)



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Table 1.docx available at <https://authorea.com/users/572417/articles/617281-efficacy-of-non-pharmacological-interventions-to-reduce-pain-in-children-with-sickle-cell-disease-a-systematic-review>