Non-Pharmacological Management of Burn-related Pain and Distress in Children: A Systematic Review and Meta-Analysis Study

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ABSTRACT

Introduction: Pain and distress during burn-related painful procedures are common. Various non-pharmacological interventions are used to control pain and distress during burn-related painful procedures. Hereby, this study aimed to systematically review the recent literature regarding the efficacy of the non-pharmacological interventions to control pain perception and distress in children undergoing painful burn management procedures.

Methods: the data sources were Cochrane Central Register of Controlled Trials, CINAHL, MEDLINE, and Science Direct databases were searched through 1989-2020. Data extraction was performed by two independent researchers. Selection criteria: Participants included children from birth to nineteen years. Only randomized controlled trials (RCTs) or RCT crossovers that had a no-treatment control comparison were eligible for inclusion in the analyses. Data analysis: The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials. Review Manager 5.4 software was used to calculate standardized mean differences (SMDs) with 95% confidence intervals (CIs). Results: Out of 244 studies found, 15 trials met the inclusion criteria for further review with non-pharmacological interventions that included distraction (n=8), VR (n=5), hypnosis (n=1), and massage therapy (n=1). However, 13 trials out of 15 were included in the meta-analysis with 685 participants. Meta-analysis showed large effects of distraction intervention on self-reported pain (SMD -1.64, 95% CI -3.16, -0.12), observer-reported pain (SMD -3.02, 95% CI -5.85, -0.19), and behavioral distress (SMD -2.82, 95% CI -5.50, -0.14). Besides, distraction intervention showed moderate effects on self-reported distress (SMD -0.33, 95% CI -0.58, -0.08), and no effect on behavioral pain (SMD -1.06, 95% CI -2.44, 0.31). On the other hand, VR reported a large effect on self-reported pain (SMD 1.41, 95% CI 2.52, -0.30), a moderate effect on observer-reported pain (SMD -0.56, 95% CI -0.90, -0.22), and no effect on the behavioral pain (SMD -0.48, 95% CI -1.04, 0.08). Overall, the quality of derived evidence was downgraded due to study limitations, inconsistency, and imprecision.

Conclusion: Distraction and VR are effective non-pharmacological interventions in reducing the pain perception and distress in children during painful burn management procedures.

INTRODUCTION

A burn is a tissue damage injury linked to severe pain and distress (1). Children and adolescents are considered at high risk to be admitted to the hospitals and emergency departments due to burning accidents (2). Pain perception in burns is linked to two sources, the continuous background pain of the injured tissues and the procedural pain experienced during burn management procedures (3). Besides procedural pain, children experience procedural distress as a negative reaction to the medical procedures, this could include anxiety, fear, or stress emotions (4). While background pain is routinely managed with medications, procedural pain is more complicated and requires advanced analgesia for adequate pain control (5, 6). Undertreated or poorly managed pain has adverse effects in the short and long-term, as well as has a negative impact on the healing process, child development and behavior, pain perception, memory, and the emotional status of patients. (5, 7) Besides, it could contribute to diminished social skills, increased fear, and sleep disorders (5, 8).

Non-pharmacological pain relief interventions are used as complementary and alternative interventions to control pain and distress in children and adolescents during medical procedures. Such non-pharmacological interventions include distraction, virtual reality (VR), hypnosis therapy, and massage therapy, which are all considered as noninvasive, easily assessable, with little training needed, suiting most ages. (9, 10) The mechanism of such nonpharmacological intervention in reducing pain is assumed as a result of mindset shifting or modifying the pain-related cognitive and perception pathway.(6)

To the best of our knowledge, there is no recent meta-analysis study that evaluates the potential therapeutic effects of the non-pharmacological interventions on burn-
related pain and distress in children undergoing painful burn management procedures. Hereby, this study aimed to evaluate the effect of non-pharmacological interventions including distraction, VR, hypnosis, and massage therapy on controlling pain and distress outcomes in children aged up to 18 years, and who undergoing or experienced painful procedures during burning management.

METHODS

Search Strategy
The following four electronic databases were searched for relevant trials published between January 1989 and June 2020. A systematic literature review was performed in the Cochrane Central Register of Controlled Trials (88 Studies retrieved), MEDLINE (83 Studies retrieved), Science Direct (40 studies retrieved), and CINAHL(33 Studies retrieved), using the following search terms: (Burn AND wound dressing OR dressing change OR physiotherapy OR hydrotherapy OR painful procedure) AND (cognitive OR behavior OR distract OR hypnosis OR audiovisual OR game OR music OR breathing exercises OR massage OR virtual OR VR) AND (pain OR distress OR discomfort OR fear OR anxiety). Also, a search was conducted through clinical trial registries, conference proceedings, and reference lists of Randomized Controlled Trials (RCTs).

Searches were limited to studies conducted in humans and published in English for which a full text was available. We included RCTs and randomized cross-over trials that were conducted for the non-pharmacological management of procedural burn-related pain and distress in children aged up to 18 years. Studies eligible for inclusion including studies where pediatric patients with burns and undergoing painful burn management procedures. Studies with participants out of the targeted age group, reviewing and meta-analysis studies, studies with abstract only were excluded.

Two authors (SA and MK) extracted the data independently and assessed the quality of trials. To extract the data, a designed standard form was used. Extracted data included (study design, sample size, participants’ characteristics, interventions, comparisons, and outcome measures). For any missing data, the authors of the studies were contacted. Any questions regarding the inclusion of the studies in the meta-analysis were brought for further discussion to both investigators.

Types of participants
Participants included all young children aged day 1 to 18 years old and were undergoing painful burn management procedures either in outpatient or inpatient settings.

Given that research in the area of burn pain management began in the late 1980s, we selected a broad mandate of ‘procedural pain’ rather than any particular type of procedure including dressing changes, hydrotherapy, physiotherapy, positioning, or occupational therapy procedures.

Types of interventions
All included studies examined the effect of at least one non-pharmacological intervention in the intervention group compared with at least one comparator group or control group including (standard care, no treatment control, or another non-pharmacological method). As most non-pharmacological interventions are combined with some doses of pharmacological medications, a decision was made to include studies with combined treatment as long as all the study groups received the same pharmacological intervention.

As that non-pharmacological interventions include a variety of delivering methods, techniques, and devices, the review classified interventions under specific categories based on their mechanism of effect and/or a distinct used strategy. Accordingly, one of the following non-pharmacological categories were included: distraction, VR, hypnosis therapy, and massage therapy.

Types of outcome measures
Pain intensity and distress were selected as primary outcomes. Six pain and distress outcomes including self-reported pain, observer-reported pain, pain behavioral measures, distress self-reported, distress observer-reported, and distress behavioral measures were extracted separately under a condition of the assessed outcomes were measured a validated self-reported measure, observer-reported measures (i.e. caregivers, nurses, researcher), or behavioral measurement scales displayed by children/adolescents. Secondary outcomes include any adverse events as reported and measured by the authors of all included studies.

In terms of the temporal outcome’s assessment, data from the outcomes assessed during the burn painful management procedures were used and included in the meta-analysis. Besides, if outcomes were not assessed during the procedure, the data of the closest point of assessment to the completion of the procedure was used. However, if the outcomes were assessed at both points, during and at the end of the procedure, only data of outcomes assessed during the procedure was included. In addition, in studies that reported outcomes on multiple procedures, only outcomes assessed on the first procedure were included.

Data analysis
Using Review Manager 5.4 (RevMan 5.4), the outcomes from each study were compared using a fixed- or random-effect model according to the heterogeneity of all included studies. (11) If the consistency index [I²] was > 50 (indicating high heterogeneity), the random-effects model was used to interpret the results. Otherwise, the fixed-effects model was used. Significance was set at an alpha of 0.05.

Risk of bias assessment
To assess the risk of bias in individual studies, the ‘Risk of bias’ tool in Review Manager 5.4 (RevMan 5.4) (11) was used. For each study the following types of bias were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), and incomplete outcome data (attrition bias), and selective reporting (reporting bias), and other sources of bias (other bias). Besides, the risk of bias graph and risk of bias summary would be created.

Measures of treatment effects
As the outcome measures represented with continuous data of means and standard deviations, means, and standard deviations were entered in the Cochrane Collaboration freeware RevMan 5.4. As multiple measurement scales were used to assess the same outcome, standardized mean differences (SMDs) with 95% confidence intervals were calculated. SMDs allows for the combination of measures taken using different measurement tools.

The following criteria were used to interpret the effect sizes, SMDs of (0.2) represents a small effect, (0.5)
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represents a medium effect, and (0.8) represents a large effect as recommended by Cohen 1988 (12) Besides, to assess heterogeneity in meta-analysis, I² statistical test was calculated as recommended by Higgins & Thompson. (13) Each category of the non-pharmacological interventions was assessed. Within each category, each outcome of the six primary outcomes was assessed separately. It is important to note that studies of intervention groups that include variations of the same non-pharmacological intervention such as two different types of virtual reality, were combined to create a single pair-wise comparison. Also, in the case of multiple control groups, the condition that most clearly isolates the active effect of the intervention condition was selected.

The quality of evidence was assessed using a customized quality of evidence method based on the grading of recommendation, assessment, development, and evaluation (GRADE) approach. The evidence of the included randomized trials begins as high-quality evidence and could be downgraded to moderate, low, and very low levels based on the following factors: risk of bias, inconsistency, and imprecision. The quality of evidence was downgraded by one level (-1) in the presence of the following: serious limitation to study quality (risk of bias), moderate heterogeneity > 45% (inconsistency), or analysis based on < 400 sample size of group of analysis (imprecision). The quality of evidence was downgraded by two levels (-2) in the presence of the following: considerable heterogeneity > 90% (inconsistency), or analysis based on < 100 sample size of group of analysis (imprecision).

RESULTS

Results of the search.

Utilizing the search criteria, 247 studies were retrieved for review. Out of them, 158 studies were excluded based on the protocol’s inclusion and exclusion criteria. Then, the remained 89 studies went for full-text review. Out of them, 36 studies were removed as they were duplicated articles, and we ended with 53 studies. Then, 38 studies were excluded due to several reasons including not a randomized controlled trial, or reported assignment that was not truly random (n=4, 14-17), participants older than included age range (n= 20,18-37), no painful burn-related procedures (n=3,38-40), the intervention was not primarily non-pharmacological (n=1,41), outcomes not related to pain or distress (n=4, 42-45), participants condition not related to burn painful procedures (n=2,46,47), and missing data necessary for pooling (n=4, 48-51). As a result, we ended with 15 studies (52-66) that were included in the metaanalysis. More details and descriptions of the screening process are presented in the study flow diagram (Figure 1).

Characteristics of included studies

In this review, the 15 studies (52-66) that were included in the meta-analysis had two to four study arms. Thirteen studies (53-64, 66) used RCT design, and 2 studies (52, 65) used a cross-over randomized design. Trials were conducted in a variety of settings, including hospital inpatients and hospital outpatient clinics. Most of the burn-related painful procedures were wound care and during the dressing changes (n=13, 53-59, 61-66). Other painful procedures were during the hydrotherapy sessions (n=2, 52, 60). Eight studies (n=8) included distraction intervention (54, 55, 57-60, 62, 63), five studies included virtual reality interventions (52, 53,

56, 65, 66), one study included hypnosis (61), and one study included massage therapy (64)

Ages of participating ranged from day one to 18 years old. Six studies (n=6, 54, 55, 61, 62, 65, 66) included children ranging from early childhood up to 18 years old. Four studies (n=4, 52, 57, 63, 64) focused exclusively on children in early childhood (i.e. zero to five years old), while another 3 studies (56, 58-60) focused on middle childhood (i.e. 6-12 years old), and one study (63) focused exclusively on adolescents (11 to 17 years old). The characteristics of the included studies are summarized in (Table 1).

Risk of bias assessment

In terms of risk of bias evaluation, there were 6 types of bias have been evaluated: 1) selection bias, 2) performance bias, 3) detection bias, 4) attrition bias, 5) reporting bias, and 6) miscellaneous bias (Figure 2 & Figure 3). In terms of selection bias, the randomization method and allocation concealment procedures were evaluated, where a low risk of selection bias was reported for 13 studies (52-60, 62, 63, 66) that used clear strategies for generating random sequences with enough documentation of evidence used. Only 2 studies (61, 64) were found to have an unclear risk of selection bias as they did not specify the method of randomization. In terms of concealment procedures, 7 studies (52-55, 58, 60, 62) were rated at low risk of bias as they used appropriate allocation concealment methods with enough documentation of the process used. Six studies (56, 57, 59, 61, 63, 66) were rated at unclear risk of bias as they did not provide details about allocation methods. Only two (64, 65) studies did not mention applying allocation concealment and were rated at high risk.

In terms of performance bias, which evaluates the patients and intervention blindness, the nature of the intervention made the blindness of participants and personnel inapplicable in most of the studies, whereby they were rated at high risk of bias. In terms of detection bias that evaluates the blinding of outcomes assessment, 8 studies (54, 56, 58-60, 63, 65, 66) were rated at high risk as they did not use independent assessors, or their assessors were blind to the administered intervention. However, 5 studies (52, 57, 61, 62, 64) were at low risk of bias as the outcome assessors were blinded to the intervention groups, and the remained 2 studies (53, 55) have unclear risk.

In terms of attrition bias, which evaluate the incomplete outcome data, most of the studies (n=11) (52-55, 57-60, 62, 63, 65) were at low risk of attrition bias as they reported sufficiently all outcomes related to the study, did not report any dropouts and reported managing the missing data using “intention-to-treat analysis” method. However, 3 studies (56, 64, 66) had an unclear risk because of an unclear number of analyzed participants, and 1 study (61) was rated at high risk due to unexplained dropouts.

In terms of reporting bias, which evaluates the selective reporting bias, 6 studies (53, 54, 56, 59, 61, 62) were at high risk of selective reporting bias due to their selective outcome measures reporting. However, 5 studies (52, 55, 58, 60, 63) were at low risk of selective reporting bias as they reported clearly all details regarding the primary and secondary outcomes. Whereas the remained 4 studies (57, 64-66) were at unclear risk of selective reporting bias since there was not enough information to judge.

In terms of other miscellaneous bias, 6 studies (52, 53, 57, 59, 60, 66) were clear of other types of bias sources,
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whereas 6 studies (54, 55, 58, 61, 64, 65) reported high risk due to small sample sizes, applying no power analysis, or have concerns regarding measurement tools validity and reliability and questionable differences in pain levels between groups pre-intervention. Besides, 3 studies did not provide enough information to be judged properly (56, 62, 63). Again, the “risk of bias graph and summary” are presented in detail for all included studies in (Figure 2 and Figure 3).

Effects of Non-pharmacological interventions

1) Distraction

Eight studies (54, 55, 57-60, 62, 63) assessed the efficacy of distraction for reducing children’s burn-related procedural pain and distress. Different distraction interventions were used that included video games on computers (n=2, 57, 58), interactive games on computer tablet (n= 1, 60), live music distraction (n= 1, 62), combination or selection of animation, music, and videos on a medical screen (n=1, 63), and interactive stories or games on a handheld electronic device (n=3, 54, 55, 59). Out of these studies assessing distraction, painful procedures included wound care and dressing changes (n=7, 54, 55, 57-59, 62, 63) and hydrotherapy (n= 1, 60).

Across distraction-related studies, distraction efficacy was assessed in children aged from day 1 to 13 years old, in which 6 studies (54, 55, 58-60, 63) included children aged from day 1 to 13 years old, and 2 studies (57, 63) exclusively included children of early childhood (1-6 years old). No adverse events were recorded for distraction intervention.

In terms of pain, 5 studies (54, 55, 58-60) with 245 participants (intervention group = 130) revealed a large effect of distraction on self-reported pain (SMD -.16, 95% CI -0.36 to 0.04, P = 0.12). These studies displayed substantial heterogeneity (I^2 = 96%) (Figure 4). Three studies (54, 55, 60) with 130 participants (intervention group = 75) revealed a large effect of distraction on observer-reported pain (SMD -.30, 95% CI -0.55 to -0.05, Z = 2.09, P = 0.04). These studies displayed high heterogeneity. (I^2 = 97%) (Figure 5). Besides, 4 studies (57, 58, 62, 63) with 307 participants (intervention group = 157) revealed no effect of distraction on behavioral pain measures (SMD 1.06, 95% CI -2.445 to 0.31, Z = 1.51, P = 0.13). These studies also presented high heterogeneity (I^2 = 96%) (Figure 6).

In terms of distress, 3 studies (58, 59, 62) with 250 participants (intervention group = 126) revealed a moderate effect of distraction on self-reported distress (SMD -0.33, 95% CI -0.58 to -0.08, Z = 2.61, P = 0.009). Importantly, these studies displayed zero heterogeneity (I^2: 0%) (Figure 7). Besides, 3 studies (54, 55, 62) with 253 participants (intervention group = 131) revealed a large effect of distraction on behavioral measures of distress (SMD -2.82, 95% CI -0.63 to 0.04, Z = 2.06, P = 0.04). These studies displayed high heterogeneity (I^2: 98%) (Figure 8). The quality of evidence for distraction is very low for all pain outcomes including self-reported pain, observer-reported pain, and behavioral measures of pain. For that, we have very little confidence in the effect estimates. The quality of evidence was low for self-reported distress and very low for behavioral measures of distress. Therefore, further research is likely to have an important impact on the confidence in the estimated effects and could lead to a change in these estimates. Obvious reasons for downgrading the quality of the evidence include serious limitations in the studies (frequent unclear and high risk of bias), high inconsistency represented by considerable heterogeneity, and small numbers of included participants per group in all meta-analyses (imprecision). The details of assessing the quality of evidence are presented in (Table 2).

2) Virtual Reality

Five studies (n=5, (52, 53, 56, 65, 66) assessed the efficacy of virtual reality (VR) for reducing children’s burn-related procedural pain. Different VR devices were used that included VR videogames through a head-mounted display (n=3, 53, 65, 66), augmented hand-held VR system (n=1, 56), and projector-based hybrid VR (n=1, 52). Out of these 5 studies assessing VR, painful procedures included wound care and dressing changes (n=4, 53, 56, 65, 66) and hydrotherapy (n= 1, 52).

Across the five VR-related studies, VR efficacy was assessed in children aged from day 1 to 18 years old, in which 3 studies (56, 65, 66) included children aged from day 1 to 10 years old, single study (52) exclusively included children of early childhood (1-6 years old), and another single study (53) exclusively included adolescents (11-17 years old). No adverse events were recorded for VR intervention.

In terms of pain, 4 studies (53, 56, 65, 66) with 162 participants (intervention group = 80) revealed a large effect of VR on self-reported pain (SMD -1.41, 95% CI -2.52 to -0.30, Z = 2.48, P < 0.00001). Substantial heterogeneity was reported (I^2 = 89%) (Figure 9). Three studies (n=3, 52, 53, 66) with 141 participants (intervention group = 71) revealed a moderate effect of VR on observer-reported pain (SMD -0.56, 95% CI -0.90 to -0.22, Z = 3.24, P = 0.001).

These studies displayed zero heterogeneity (I^2 = 0%) (Figure 10). Three studies (52, 53, 66) with 141 participants (intervention group = 71) revealed no evidence of effect of VR for behavioral pain measures (SMD -0.48, 95% CI 1.04 to 0.08, Z= 1.67, P = 0.09) with substantial heterogeneity reported (I^2 = 62%) (Figure 11). In terms of distress, only a single study (52) assessed the effects of VR in children aged between 6 months and 7 years undergoing a painful hydrotherapy dressing procedure on the observer reported distress. Given only this single study, we cannot run a meta-analysis and no conclusions are available about the efficacy of VR on distress outcomes. No adverse events were recorded. The quality of evidence for VR is low for self-reported pain, and this suggests a little confidence in the effect estimate. Moreover, very low quality of evidence is reported for observer-reported pain and behavioral measures of pain, and further research is expected to have an important impact on the estimate of these effects. Obvious reasons for downgrading the quality of the evidence include serious limitations in the studies (frequent unclear and high risk of bias), high inconsistency represented by considerable heterogeneity, and small numbers of included participants per group in all meta-analyses (imprecision). The details of assessing the quality of evidence are presented in (Table 2).

3) Hypnosis

Only one study (61) assessed the effects of hypnosis in children aged between 3 and 12 years undergoing a dressing change procedure. This study included a behavioral measure of distress and pain measures. Given
Only this single study, we cannot run a meta-analysis and no conclusions are available about the efficacy of this treatment. No adverse events were recorded.

4) Massage Therapy

Only one study (64) assessed the effects of massage therapy in children aged between 1 and 4 years, undergoing a dressing change procedure. This study included outcomes of observer-reported pain and behavioral measures of distress. However, given only this single study, we cannot run a meta-analysis and no conclusions are available about this treatment efficacy. No adverse events were recorded.

DISCUSSION

To the best of our knowledge, this is the first comprehensive review with a meta-analysis result that explored the potential therapeutic effects of the non-pharmacological interventions on pain and distress in children and adolescents undergoing painful burn management procedures.

Summary of main results

The overall findings of this review are summarized succinctly in Table 2 with the explanation of the numbers presented in Table 1. This review represents the results of 15 studies comprising 685 participants of children and adolescents. The results of this review indicate the efficacy of distraction on pain and distress based on a very low to the low quality of evidence and efficacy of virtual reality on pain based on a very low to the low quality of evidence. Regarding other interventions of hypnosis and massage therapy, no conclusions were available. Due to low and very low quality of evidence, a little confidence is applied to these effect estimates, and most likely that future upcoming research could identify different findings.

In terms of distraction, a positive large effect was found on self-reported and observer reported pain, moderate effect on self-distress, and large effect on behavioral measures of distress. However, distraction showed no effect on behavioral measures of pain, and that could be due to the small sample size and a limited number of studies, and most likely that with the presence of additional work in the future these results would change. An important point to mention is that there was a wide range of types of distraction used, therefore it is unclear if the type of distraction could influence the efficacy, and it is unknown if some types of distraction have a superior effect compared to other types.

In terms of virtual reality, a large effect of virtual reality was found on self-reported pain and a moderate effect on observer-reported pain. However, VR showed no effect on behavioral measures of pain. Again, both positive and negative results could tremendously change when more studies with larger sample sizes are available. It should be noted that distress outcome was lacking in studies examined virtual reality. Only one study (52) included distress outcome (observer-reported distress).

In the light of the given results, the evidence is more focused on procedural pain outcome and lesser focus was noticed on procedural distress, however, it is known that procedural distress is positively related to uncooperativeness during treatment procedures and experienced pain.(67) Besides, reducing child distress could make the painful procedure more tolerable and therefore the non-pharmacological interventions may have a more positive effect.(4) Moreover, the assessment of emotional response or experienced discomfort, fear, and stress emotions is a recommended core outcome measure in clinical trials of pediatric acute pain.(68)

As the literature was lacking for studies examining the effect of hypnosis and massage therapy on children and adolescents with burns, we were not able to evaluate their effectiveness, and this highlights the urgent need for future research examining the potential therapeutic effect of hypnosis and massage interventions. The same argument was reported by Provencal et al., 2018, who conducted a systematic review and meta-analysis including six-RCTs and highlighted that studies examining the effects of hypnosis are scarce. (69) Also, no studies were published about massage therapy for burn-related procedural pain in patients with burns since the year of 2001. (64)

Overall completeness and applicability of evidence

The evidence presented by this review is applicable to the efficacy of non-pharmacological interventions for burn-related pain and distress in children and adolescents. Included studies examined different interventions, but more focus was on distraction and virtual reality methods. The trials include both inpatient and outpatient settings, variable children’s ages, and painful burn-related procedures. For that, the applicability of the findings of this review is based on the clinical condition and the studied populations.

The included studies focused more on studying the intervention in the middle childhood age range, while younger children and adolescents were less studied. This could affect the generalizability of the review results and the trustworthiness of the interpretations and effect estimates. For example, the study conducted by Kipping et al.,2012 (53) has examined the effect of a VR intervention and included only adolescents between 11 and 17 years, for that, the results of this study are only applicable to the specific population studied and generalizing its effect to other populations is questionable. Moreover, some painful procedures that come from the rehabilitation treatment sessions (i.e., stretching exercises) were not studied, although these procedures are very painful and stressful. (70) Also, the results indicate an obvious need to include more non-pharmacological interventions such as hypnosis therapy, massage therapy, and breathing exercises in future research, as these interventions were poorly studied in the literature.

Quality of the evidence

Performed meta-analyses showed low to a very low quality of evidence, the low quality was directly linked to multiple reasons, including frequent studies limitation in the methodological quality or bias including selection bias, detecting bias, performance bias, and other bias sources including small sample sizes. Besides, the high heterogeneity in most of the meta-analyses, and imprecision or a low number of participants in almost all meta-analyses. To present more quality evidence in future research, the above-mentioned issues and limitations should be addressed.

Although the highest quality of evidence could not be realistic in the use of non-pharmacological interventions, due to the obvious nature of treatment that is impossible to be blinded in the research, future studies should work on improving the quality through blinded outcome assessments. In addition, ensuring adequate allocation concealment, registering the clinical trials to minimize selective reporting, and the use of larger sample sizes.
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that are based on power calculation are all applicable and feasible procedures that would limit other sources of bias. Finally, when the number of studies increased, the presence of heterogeneity will be limited. Overall agreements and disagreements with other reviews This study would be the first comprehensive meta-analysis that addresses this topic, thereby comparison with other meta-analysis studies would be limited. However, our findings still consistent with the results of previous systematic reviews related to this pediatric burn (71-76). For example, a previous systematic review (71) that examined the potential effect of the psychosocial interventions on burn-related painful management procedures in children reported that distraction interventions had a positive effect on pain, anxiety, and stress symptoms, and they concluded that distraction and virtual reality interventions showed efficacy in controlling patients’ pain and improving short-term stress symptoms. However, the same systematic review did not provide any quantitative synthesis of the results, and the review emphasized the high need for additional work to better support the current evidence and to explore the effects of other non-pharmacological interventions. Another systematic review (72) also reported a positive effect of distraction on reducing children’s pain and distress symptoms during burn dressing changes and needle procedures. Moreover, additional three systematic reviews (73-75) reported a positive effect of non-pharmacological interventions including distraction, VR, and hypnosis on procedural burn-pain relief in adults. Finally, a recent systematic review and meta-analysis of non-pharmacological interventions (76) found evidence supporting the efficacy of distraction and hypnosis for reducing children’s needle-related pain and distress. They also reported a low to a very low quality of overall evidence as a result of methodological and reporting limitations across trials.

Limitations
This study assessed pain and distress outcomes in short terms including the measures of one procedure for each study and did not examine the effect of these interventions on the overall recovery of patients and the improvement of the function. Another important note is that this study combined assessments of reported pain and distress at different points during and after the painful procedure, as some of the included studies conducted outcomes assessments during the procedure and other studies completed assessments after the procedure. This variation in the timing of assessment in the included studies could introduce bias. The used approach of meta-analysis supports the validity of the findings of this study and address the issue of small sample sizes of included studies, however, the results should be interpreted with caution because of the obvious presence of methodological and statistical variability between the studies. The analysis also shows some heterogeneity, and many studies did not report adverse reactions or determine if adverse reactions were seen making it difficult to draw robust clinical conclusions regarding adverse reactions.

CONCLUSION
This review supports the use of distraction to reduce pain and distress and the use of virtual reality to reduce pain during painful burn management procedures. The current evidence is most applicable in the middle-aged children between 4 to 13 years old. These interventions are recommended to be used during clinical practice despite the low quality of the current evidence. Future studies should emphasize targeting the gaps of the existing literature. Interventions that showed efficacy including distraction and virtual reality should be further examined through studies with high quality. While other interventions such as hypnosis and massage therapy are lacking and have the priority to be addressed in future work. Besides, targeting adolescents in future research is recommended. Finally, procedural distress is a core outcome measure that needs to be assessed and reported for children and adolescents in future clinical trials.

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CONFLICT OF INTEREST
The authors have no conflict of interest to report.

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36. Gilboa D, Borenstein A, Seidman DS, Tsur H. Burn patients' use of autohypnosis: making a painful experience bearable. Burns: journal of the


<table>
<thead>
<tr>
<th>Authors (year) (Reference)</th>
<th>Design</th>
<th>Age range (y/o)</th>
<th>Gender (M/F)</th>
<th>Painful procedure</th>
<th>Study groups</th>
<th>Outcome measures</th>
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<tr>
<td>Hua et al. (2015) (66)</td>
<td>RCT 2 arms.</td>
<td>4-16 y/o 31 M.34 F.</td>
<td>Dressing change</td>
<td>Group I (intervention): VR equipment constituted a laptop game, a head-mounted display, and a joystick to play the game. Group II (control): Standard distractions included the use of toys, TV, books, and parental comforting.</td>
<td>Pain measure: Self-reported: FACES scale. Observer-reported: VAS. Behavioral measures: FLACC.</td>
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<td>Kaheni et al. (2016) (57)</td>
<td>RCT 2 arms.</td>
<td>4-6 y/o 45 M.35 F.</td>
<td>Dressing change</td>
<td>Group I (intervention): Distraction using a video computer game on a portable monitor. Group II (control): The procedure was done with no intervention.</td>
<td>Pain measure: Behavioral measures: FLACC.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Children</td>
<td>Intervention Details</td>
<td>Pain Measure</td>
<td></td>
<td></td>
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<tr>
<td>------------------------------</td>
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<td>--------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Khadra et al. (2020) (52)</td>
<td>Cross-over randomised</td>
<td>6 months - 7 y/o 45 M. 35 F. M.</td>
<td>Projector-Based Hybrid VR consisted of a screen with a wide-field view mounted at the end of the hydro-tank with standard pharmacological analgesia.</td>
<td>Observer-reported: NRS-obs.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Hydrotherapy</td>
<td>Condition I (intervention):</td>
<td>Behavioral measures: FLACC.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Group I (intervention): Projector-Based Hybrid VR consisted of a screen with a wide-field view mounted at the end of the hydro-tank with standard pharmacological analgesia.</td>
<td>Distress measure: Behavioral measures: OCCEBECCO scale.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Group II (control): Only standard pharmacological analgesia.</td>
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<tr>
<td>Kipping et al. (2012) (53)</td>
<td>RCT 2 arms.</td>
<td>11 - 17 y/o 28 M.</td>
<td>Off-the-shelf VR system constituted a laptop game, a head-mounted display, and joystick to play the game.</td>
<td>Self-reported: VAS.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>24 F. Dressing change</td>
<td>Group I (intervention):</td>
<td>Observer-reported: VAS.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group II (control): Standard distractions included TV, stories, music, or no distraction based on choice.</td>
<td>Behavioral measures: FLACC.</td>
<td></td>
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<tr>
<td>Miller et al. (2010) (54)</td>
<td>RCT 4 arms.</td>
<td>5 - 10 y/o 47 M.</td>
<td>Interactive distraction stories and games during the procedure.</td>
<td>Self-reported: FACES scale.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 F. Dressing change</td>
<td>Group I (intervention):</td>
<td>Observer-reported: VAS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group II (intervention): PP story pre-procedure and standard distraction during the procedure.</td>
<td>Behavioral measures: FLACC.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Group III: Video game distraction.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Group IV (control): Standard distractions including toys, TV, nursing, and caregiver interaction.</td>
<td></td>
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</tr>
<tr>
<td>Miller et al. (2011) (55)</td>
<td>RCT 2 arms.</td>
<td>3 - 10 y/o 21 M.</td>
<td>PP story pre-procedure and multi-modal distraction during the procedure (either an interactive story or game).</td>
<td>Self-reported: FACES scale.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 F. Dressing change</td>
<td>Group I (intervention):</td>
<td>Observer-reported: VAS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group II (control): Standard distraction pre and during the procedure.</td>
<td>Behavioral measures: FLACC.</td>
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<tr>
<td>Mott et al. (2008) (56)</td>
<td>RCT 2 arms.</td>
<td>3.5 - 14 y/o 30 M.</td>
<td>Augmented VR used the hand-held system both before and during the dressing change.</td>
<td>Self-reported: FPS-R and VAS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 F. Dressing change</td>
<td>Group I (intervention):</td>
<td>Behavioral measures: FLACC.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group II (control): Basic multi-dimensional cognitive techniques including attention-distractive, positive reinforcement, relaxation, and an age-appropriate video program.</td>
<td></td>
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</tr>
<tr>
<td>Nilsson et al. (2013) (58)</td>
<td>RCT 3 arms.</td>
<td>5 - 12 y/o 21 M.</td>
<td>Playing a game with Wii-remote (a remote control) and a laptop.</td>
<td>Self-reported: CAS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 F. Dressing change</td>
<td>Group I (intervention):</td>
<td>Behavioral measures: FLACC Distress measure: Self-reported: FAS.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group II: Lollipops distraction with varied colors.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>66 F. Dressing change</td>
<td>Group I (intervention):</td>
<td>Behavioral measures: COMFORT-B.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group II (control): In standard care, the mother takes the child back to the bed and try to calm the child down.</td>
<td>Distress measure: Self-reported: FACES.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Behavioral measures: DSBD-r.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-Pharmacological Management of Burn-related Pain and Distress in Children: A Systematic Review and Meta-Analysis Study

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Outcomes</th>
<th>No. of studies</th>
<th>Quality Assessment for comparisons</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distraction</td>
<td>Self-reported pain</td>
<td>5</td>
<td>Serious study limitations</td>
<td>Analysis based on &lt; 400 participants per group</td>
</tr>
<tr>
<td>Observer-reported pain</td>
<td>Serious study limitations</td>
<td>3</td>
<td>Considerable heterogeneity ( (I^2) &gt; 90% )</td>
<td>Analysis based on &lt; 100 participants per group</td>
</tr>
<tr>
<td>Behavioral measures of pain</td>
<td>Serious study limitations</td>
<td>4</td>
<td>Considerable heterogeneity ( (I^2) &gt; 90% )</td>
<td>Analysis based on &lt; 400 participants per group</td>
</tr>
<tr>
<td>Self-reported distress</td>
<td>Serious study limitations</td>
<td>3</td>
<td>No heterogeneity</td>
<td>Analysis based on &lt; 400 participants per group</td>
</tr>
<tr>
<td>Behavioral measures of distress</td>
<td>Serious study limitations</td>
<td>3</td>
<td>Considerable heterogeneity ( (I^2) &gt; 90% )</td>
<td>Analysis based on &lt; 400 participants per group</td>
</tr>
<tr>
<td>Virtual Reality Self-reported pain</td>
<td>Serious study limitations</td>
<td>4</td>
<td>Moderate heterogeneity ( (I^2) &gt; 45% )</td>
<td>Analysis based on &lt; 100 participants per group</td>
</tr>
<tr>
<td>Observer-reported pain</td>
<td>Serious study limitations</td>
<td>3</td>
<td>No heterogeneity</td>
<td>Analysis based on &lt; 100 participants per group</td>
</tr>
<tr>
<td>Behavioral measures of pain</td>
<td>Serious study limitations</td>
<td>3</td>
<td>Moderate heterogeneity ( (I^2) &gt; 45% )</td>
<td>Analysis based on &lt; 100 participants per group</td>
</tr>
</tbody>
</table>

Table 2 Quality of evidence assessment table

- **Distraction**: Self-reported pain
- **Observer-reported pain**: Considerable heterogeneity \( (I^2) > 90\% \)
- **Behavioral measures of pain**: Analysis based on < 400 participants per group
- **Self-reported distress**: Analysis based on < 400 participants per group
- **Behavioral measures of distress**: Analysis based on < 400 participants per group
- **Virtual Reality Self-reported pain**: Analysis based on < 100 participants per group
- **Observer-reported pain**: Analysis based on < 100 participants per group
- **Behavioral measures of pain**: Analysis based on < 100 participants per group

\( a = \) Downgraded once for risk of bias; most trials had serious study limitations.  
\( b = \) Downgraded twice for inconsistency: considerable heterogeneity \( (I^2 > 90\% \).  
\( c = \) Downgraded once for imprecision: an analysis based on < 400 participants per group.  
\( d = \) Downgraded twice for imprecision: an analysis based on < 100 participants per group.  
\( e = \) Downgraded once for inconsistency: moderate heterogeneity \( (I^2 > 45\% \).
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Figure captions/legends

Figure 1: Study flow diagram.
Figure 2: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.
Figure 3: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.
Figure 4: Forest plot of comparison: 1 Distraction, Outcome: 1 Self-reported pain.
Figure 5: Forest plot of comparison: 1 Distraction, Outcome: 2 Observer-reported pain.
Figure 6: Forest plot of comparison: 1 Distraction, Outcome: 3 Behavioral measures – Pain.
Figure 7: Forest plot of comparison: 1 Distraction, Outcome: 4 Self-reported distress.
Figure 8: Forest plot of comparison: 1 Distraction, Outcome: 4 Behavioral measures – Distress.
Figure 9: Forest plot of comparison: 2 Virtual Reality, Outcome: 1 Self-reported pain.
Figure 10: Forest plot of comparison: 2 Virtual Reality, Outcome: 2 Observer-reported pain.
Figure 11: Forest plot of comparison: 2 Virtual Reality, Outcome: 3 Behavioral measures – Pain.

Figure 1: Study flow diagram.
Non-Pharmacological Management of Burn-related Pain and Distress in Children: A Systematic Review and Meta-Analysis Study

Figure 2: Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies.

Figure 3: Risk of bias summary: review authors’ judgments about each risk of bias item for each included study.

Figure 4: Forest plot of comparison: 1 Distraction, Outcome: 1 Self-reported pain.

Figure 5: Forest plot of comparison: 1 Distraction, Outcome: 2 Observer-reported pain.
Non-Pharmacological Management of Burn-related Pain and Distress in Children: A Systematic Review and Meta-Analysis Study

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Burns-Nader 2017</td>
<td>2.93</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>Miller 2010</td>
<td>1.75</td>
<td>0.31</td>
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<tr>
<td>Miller 2011</td>
<td>1.98</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>75</td>
<td></td>
<td>55</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 5.99$, $\chi^2 = 81.06$, $df = 2$ ($P < 0.00001$); $I^2 = 97$

Test for overall effect: $Z = 2.09$ ($P = 0.04$)

Figure 6: Forest plot of comparison: 1 Distraction, Outcome: 3 Behavioral measures – Pain.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Nilsson 2013</td>
<td>3.5</td>
<td>2.9</td>
<td>20</td>
</tr>
<tr>
<td>van der Heijden 2018</td>
<td>13.66</td>
<td>4.19</td>
<td>71</td>
</tr>
<tr>
<td>Zhang 2019</td>
<td>8.89</td>
<td>0.31</td>
<td>26</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>157</td>
<td></td>
<td>150</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.88$, $\chi^2 = 80.15$, $df = 3$ ($P < 0.00001$); $I^2 = 96$

Test for overall effect: $Z = 1.51$ ($P = 0.13$)

Figure 7: Forest plot of comparison: 1 Distraction, Outcome: 4 Self-reported distress.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Brown 2014</td>
<td>2.01</td>
<td>2.49</td>
<td>35</td>
</tr>
<tr>
<td>Nilsson 2013</td>
<td>0.535</td>
<td>0.275</td>
<td>20</td>
</tr>
<tr>
<td>van der Heijden 2018</td>
<td>0.31</td>
<td>0.67</td>
<td>71</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>126</td>
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<td>124</td>
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</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 1.96$, $df = 2$ ($P = 0.39$); $I^2 = 0$

Test for overall effect: $Z = 2.61$ ($P = 0.009$)

Figure 8: Forest plot of comparison: 1 Distraction, Outcome: 4 Behavioral measures – Distress.
Non-Pharmacological Management of Burn-related Pain and Distress in Children: A Systematic Review and Meta-Analysis Study

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Miller 2010</td>
<td>1.75</td>
<td>0.31</td>
<td>40</td>
<td>3.8</td>
<td>0.28</td>
<td>20</td>
<td>31.8%</td>
<td>-7.06 [8.47, -5.65]</td>
</tr>
<tr>
<td>Miller 2011</td>
<td>1.9</td>
<td>1.65</td>
<td>20</td>
<td>3.95</td>
<td>1.13</td>
<td>20</td>
<td>33.9%</td>
<td>-1.42 [2.12, -0.72]</td>
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<tr>
<td>van der Heijden 2013</td>
<td>0.31</td>
<td>0.67</td>
<td>71</td>
<td>0.58</td>
<td>1</td>
<td>64</td>
<td>34.5%</td>
<td>-0.30 [-0.63, 0.04]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>131</td>
<td></td>
<td>104</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td>-2.82 [-5.50, -0.14]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 5.38; Chi² = 33.34; df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.06 (P = 0.04)

Figure 9: Forest plot of comparison: 2 Virtual Reality, Outcome: 1 Self-reported pain.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doc 2005</td>
<td>1.3</td>
<td>1.0</td>
<td>7</td>
<td>4.1</td>
<td>2.9</td>
<td>7</td>
<td>22.2%</td>
<td>-1.09 [2.24, 0.06] 2005</td>
</tr>
<tr>
<td>Mott 2008</td>
<td>2.81</td>
<td>0.89</td>
<td>20</td>
<td>5.38</td>
<td>0.58</td>
<td>22</td>
<td>23.6%</td>
<td>-3.39 [-4.36, -2.42] 2008</td>
</tr>
<tr>
<td>Kippin 2012</td>
<td>2.9</td>
<td>2.3</td>
<td>20</td>
<td>4.2</td>
<td>3.2</td>
<td>21</td>
<td>26.7%</td>
<td>-0.46 [-1.08, 0.17] 2012</td>
</tr>
<tr>
<td>Hua 2015</td>
<td>2.42</td>
<td>1.95</td>
<td>33</td>
<td>4.19</td>
<td>2.12</td>
<td>32</td>
<td>27.4%</td>
<td>-0.88 [-1.39, -0.37] 2015</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>80</td>
<td></td>
<td>82</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td>-1.41 [-2.52, -0.30]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.11; Chi² = 26.14; df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.48 (P = 0.01)

Figure 10: Forest plot of comparison: 2 Virtual Reality, Outcome: 2 Observer-reported pain.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hua 2015</td>
<td>4.35</td>
<td>2.64</td>
<td>33</td>
<td>8.25</td>
<td>2.84</td>
<td>32</td>
<td>45.6%</td>
<td>-0.89 [-1.19, -0.59] 2015</td>
</tr>
<tr>
<td>Khadra 2020</td>
<td>1.39</td>
<td>1.9</td>
<td>18</td>
<td>1.71</td>
<td>1.81</td>
<td>17</td>
<td>26.0%</td>
<td>-0.16 [-0.93, 0.50] 2020</td>
</tr>
<tr>
<td>Kippin 2012</td>
<td>2.9</td>
<td>2.4</td>
<td>20</td>
<td>4.7</td>
<td>2.5</td>
<td>21</td>
<td>28.5%</td>
<td>-0.72 [-1.35, -0.09]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
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<td>70</td>
<td>100.0%</td>
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<td></td>
<td></td>
<td>-0.56 [-0.90, -0.22]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.35; df = 2 (P = 0.49); I² = 8%
Test for overall effect: Z = 3.24 (P = 0.001)

Figure 11: Forest plot of comparison: 2 Virtual Reality, Outcome: 3 Behavioral measures – Pain.