SKIN-TO-SKIN CONTACT FOR PAINFUL PROCEDURES IN THE YOUNGEST OF PRETERM INFANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Skin-to-skin contact for pain (SSCP) has been recommended as a pain management strategy broadly for infants but no systematic reviews have focused exclusively on the youngest of preterm infants. Thus, the objective of this study was to conduct a meta-analysis and narrative synthesis to examine the effectiveness of SSCP in these infants. Twenty-three studies were included in our review. In our meta-analyses, SSCP showed mixed evidence of significantly reduced pain-related outcomes, but magnitude of the effects varied significantly according to outcome and time point. Our narrative synthesis results suggest SSCP may not provide better pain management than sweet-tasting solutions. Overall, the certainty of the evidence base, using GRADE criteria, ranged from very low to moderate. These findings call for better quality trials. This vulnerable group deserves special attention as the evidence is unclear about the benefits of SSCP, a critical pain management intervention for infants of a higher gestational age.

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Chapter 1: Introduction to the Study of Skin-to-skin for Pain in Preterm Infants

In Canada, approximately thirty thousand infants are born prematurely (< 37 weeks gestational age [GA]) every year (Statistics Canada, 2023). The accepted age of viability (when a human fetus has a strong probability of survival outside the womb) has become younger as medical advances progress. Currently, viability is commonly accepted to be between 22 and 23 weeks gestational age (World Health Organization, 2012). Hospitalized preterm infants experience an average of 7-17 painful procedures a day (Cruz et al., 2016) and the younger the gestational age at birth, the longer the hospitalization. Preterm hospitalized infants are uniquely challenged by their exposure to constant environmental stressors, as well as their inability to verbally communicate their distress to caregivers (Hashemi et al., 2023). In addition to the immediate stress and pain experienced in the Neonatal Intensive Care Unit (NICU), neonatal pain exposure is linked to long-term adverse effects relating to neurodevelopment (Chau et al., 2019; Duerden et al., 2018), pain reactivity (Taddio et al., 2009), as well as emotional, behavioural, and cognitive outcomes (Schneider et al., 2018; Shiff et al., 2021; Ranger et al., 2015). These outcomes highlight the value of examining pain management in preterm infants since the potential consequences are varied and severe.

In a recent call to action released by the World Health Organization (WHO), experts advocated for a fundamental re-organization of NICU care to accommodate 100% of preterm infants receiving skin-to-skin care (SSC; NICU infant held at least 8 hours of skin-to-skin with parent/day) due to its positive impact on preterm outcomes (Darmstadt et al., 2023). Critically distinct from general skin-to-skin care, is the specific pain management practice of skin-to-skin contact for pain (SSCP). This is where an infant wearing only a diaper is held upright on the

caregiver's bare chest, providing maximal skin-to-skin contact between the baby and parent before, during, and after an acutely painful procedures (e.g., heel lance, venipuncture).

Different from older preterm infants, very and extremely preterm infants (less than 32 weeks gestational age) face more painful procedures over longer duration of hospitalization. These infants are also less physiologically stable, often have more fragile skin integrity, and have a higher demand of infant support devices (e.g., ventilator, feeding tube, intravenous infusion pump) that make SSCP more challenging (Almgren, 2018; Darmstadt et al., 2008; Lee et al., 2012). Thus, the efficacy of SSCP for painful procedures in the youngest of preterm infants must be systematically examined separately than the efficacy of SSCP for older full-term and late preterm infants.

Importance of Preterm Infant Pain Management

The repeated exposure to pain in the NICU has important implications for preterm infants' health and biopsychosocial development beyond hospitalization. Their immature neurobiological systems increase their vulnerability to the detrimental effects of undermanaged pain within the NICU (DiLorenzo et al, 2016; Shiff et al., 2021). Repeated or prolonged pain during such a sensitive period can negatively impact neurodevelopment, possibly resulting in behavioral, emotional, and cognitive challenges later in development (Vinall & Grunau, 2014). There is evidence that pain can contribute to long-term consequences for executive functioning and visual processing (Doesburg et al., 2013). Pain-related stress is also related to structural changes within the brain for preterm infants, resulting in thinner cerebral cortexes, particularly in frontal and parietal lobes compared to term infants (Vinall et al., 2013). Previous research has also found a positive correlation between the number of painful procedures and poorer cognitive and motor outcomes later in development (Cong et al., 2017).

Additionally, preterm infants have heightened pain sensitivity that can persist later in life, potentially influencing lifelong pain perception (Grunau, 2013). Relatedly, preterm infants' ability to discriminate between painful and non-painful stimuli is impaired until reaching 35 weeks gestation (Fabrizi et al., 2011) potentially resulting in non-painful stimulation (such as diaper changes and nurse handling) being perceived as noxious (Grunau, 2002). There are also significant regulatory challenges related to the stress caused by NICU-related pain. Pain experienced in the NICU can impact infant biobehavioural regulation by dysregulating the infant's stress response system resulting in difficulties with feeding, sleeping, irritability and strained parent-infant interactions (Grunau et al., 2007).

The behavioural, cognitive, and structural outcomes related to pain exposure in preterm infants underscore the critical importance of appropriate pain management in the NICU to support short and long-term infant health (Hashemi et al., 2023). This is an especially concerning issue as these repeated acute painful experiences lead to chronically pained infants whose pain resulting from a procedure is exacerbated by the multitude of acute pain procedures previously experienced (DiLorenzo et al, 2016; Pillai Riddell et al., 2009). Mitigating the effects of acute, recurrent, and prolonged pain in the NICU is necessary to improve the developmental trajectories of preterm infants. An important precursor to infant pain management, is accurate assessment.

Measurement and Assessment of Preterm Infant Pain

Accurate pain assessment is a crucial component to adequately managing pain in neonates (Pillai Riddell et al., 2013). Historically, the measurement and assessment of pain in infants has relied on behavioural indicators of pain that serve to communicate infant distress to their caregiver. These observable reactions to pain include changes in facial reactions, crying, general or specific body movements, and sleep/wake states (Holsti et al., 2011). Commonly used

behavioural pain measures include the Neonatal Facial Coding System (NFCS; Grunau & Craig 1987, 1990), the Modified Behavioral Pain Scale (MBPS; Taddio et al. 1995), and Échelle Douleur Inconfort Nouveau-Né (The Neonatal Pain and Discomfort Scale) (EDIN; Debillon et al., 2001). However, related to their ongoing maturation and premature regulatory systems, preterm infants have been found to respond to pain with different behavioural patterns than term infants, often exhibiting a lower magnitude of behaviours (Craig et al., 1993; Johnston & Stevens, 1996). Physiological indicators are also used as readily quantifiable measures of pain (Pillai Riddell et al., 2013). These include heart rate, respiratory rate or pattern, oxygen saturation, blood pressure, and cerebral oxygenation (Holsti et al., 2011).

Multidimensional measures of pain combine both behavioural and physiological pain indicators to examine multiple domains of pain reactivity. Preterm infants often require a wider range of sensitive measures to pick up on their more subtle responses to pain, therefore underscoring the utility of multidimensional measures (Pillai Riddell et al., 2013). Commonly used multidimensional pain assessment tools include the Neonatal Pain, Agitation, and Sedation Scale (N-PASS; Hummel et al. 2008), the Premature Infant Pain Profile (PIPP/PIPP-R; Stevens et al. 1996, 2010), and Neonatal Infant Pain Score (NIPS; Lawrence et al. 1993). The PIPP is one of the most widely used multi-modal pain assessment tools across NICUs globally (Campbell-Yeo et al., 2022). The challenges and differences in preterm infant pain assessment highlight the need to evaluate pain in this population through several measures and domains. Understanding the importance of managing pain and how to assess pain sets an important foundation to exploring optimal ways of managing pain in the NICU, such as the use of non-pharmacological pain management strategies like SSCP.

The Limitations of Evidence Supporting SSCP for Preterm Pain Management

SSC originated in low-and middle-income countries to address a lack of incubators and to reduce nosocomial infections (Conde-Agudelo & Díaz-Rossello, 2016). SSC is recommended by health organizations worldwide (UNICEF UK, 2023; World Health Organization, 2022). Moreover, the WHO recommends an overall care strategy to integrate as much SSC as possible for healthy term and preterm infants. Given the clear evidence of the stress/distress regulatory benefits of SSC broadly, research began exploring SSC before, during, and after painful procedures. As a no-cost, non-pharmacological strategy for managing pain in the NICU that can be implemented by anyone and anywhere with the right preparations, it is a critical intervention to examine in the preterm infant pain context.

In the 2017 Cochrane Review by Johnston et al. assessing 25 randomized controlled trials examining skin-to-skin contact for acutely painful procedures in infants, SSCP was found to be efficacious in reducing pain responding initially and during recovery from painful procedures. However, the review also highlighted important differences across pain outcomes. Notably, behavioural indicators favoured SSCP more strongly and physiological indicators were mixed, with heart rate favouring SSCP but oxygen saturation and heart rate variability showed no difference when compared to a no treatment control. The review noted that purely behavioural indicators tended to favour SSC but with facial actions there is greater possibility of observers not being blinded in the assessment. There was also a high level of heterogeneity in the studies utilizing behavioural or composite outcomes (Johnston et al., 2017). A critical challenge, owing to the vast developmental differences, was that the research at that time could not disaggregate effects for different ages of preterm infants. While additional reviews have concluded that SSCP is a safe and effective pain management intervention in term and preterm infants (Cleveland et

al., 2017; Pados & Hess, 2020) and SSCP has been hypotheisized to be neuroprotective as it reduces the magnitude of pain-related cortical activity in infants (Jones et al., 2021), no work has examined the impact on the youngest of preterm infants. In the comprehensive Cochrane Review, less than a third of all the included studies reported on very and extremely preterm infants and most of those trials did not find SSCP to be effective for reducing pain (Johnston et al., 2017). Thus, there is a compelling need to examine research for SSCP for the youngest of preterm infants separately (Gupta et al., 2021).

The current review sets out to synthesize all existing literature on SSCP in the youngest groups of preterm infants. The systematic examination of the literature using meta-analysis and narrative synthesis will provide clarity on the efficacy and confidence of recommendations supporting SSCP in this population. Superiority of different pain management interventions will be examined as well as any other infant or caregiver factors identified within the research as important for SSCP. The findings of this review will inform both researchers and clinicians by assessing the need for further evidence and for clarifying the established efficacy of this intervention, which, in turn, can provide parents with important knowledge on supporting their preterm infant in the NICU.

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Chapter 2: Systematic Review and Meta-Analysis of Skin-to-skin Interventions[1]

Infant viability, the age in which a human fetus can reasonably live outside the womb, has dropped significantly over the past three decades. Between 22 and 23 weeks gestational age is the current accepted age of viability (World Health Organization, 2012). This medical marvel comes at a great price to the infants who are able to survive as they are subject to extended hospitalizations and on average 6-17 painful procedures a day (Cruz et al., 2016). This repeated neonatal pain exposure has several adverse long-term consequences for neurodevelopment and pain reactivity, as well as emotional, behavioural, and cognitive outcomes (Chau et al., 2019; Duerden et al., 2018; Ranger et al., 2015; Schneider et al., 2018; Shiff et al., 2021; Taddio et al., 2009). These painful procedures also occur in a disparate context from that which would be developmentally optimal – in proximity to a primary caregiver (Bowlby 1969/1982). Research on parental skin-to-skin contact for pain (SCCP; infant wearing only a diaper is held upright on the caregiver's bare chest, providing maximal skin-to-skin contact between the baby and parent during acutely painful procedures, also known as kangaroo care for pain) is critical because of the reality of high pain and the high potential for increasing parental support during neonatal intensive care unit (NICU) hospitalizations.

The 2017 Cochrane review of skin-to-skin contact for procedural pain in neonates summarizes it to be an effective and safe technique, however the evidence was mixed (Johnston et al., 2017). Studies comparing skin-to-skin contact to no treatment showed mixed results for heart rate, with some finding a significant decrease and others showing no change after the procedure. However, skin-to-skin consistently reduced crying after painful procedures. When

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compared to other interventions, skin-to-skin was not more effective than breastfeeding alone on measures of heart rate, oxygen saturation, cry duration or facial reactions, however both interventions were superior to control. Additionally, a combination of skin-to-skin with sucrose and breastfeeding was more effective than skin-to-skin alone. Importantly, the review was not able to separate the data out for very and extremely preterm infants (born at 31 weeks and 6 days or less gestational age).

Very and extremely preterm infants face more painful procedures over longer hospitalizations (Grunau et al., 2006). These infants are also less physiologically stable than older preterm infants thus parents are less able to do general skin-to-skin care in the immediate period following birth due to infant physiological instability, potentially more fragile skin integrity, and there is a higher prevalence of infant support devices (e.g., ventilator and feeding support equipment) that make skin-to-skin contact for acute pain more challenging (Almgren, 2018; Darmstadt et al., 2008; Lee et al., 2012). Thus, the effectiveness of skin-to-skin contact for painful procedures in the youngest of preterm infants must be systematically examined separately than late preterm infants.

Present Study

The purpose of this review is to conduct a meta-analysis and narrative synthesis to examine the efficacy of SSCP in the youngest of preterm infants (See Supplemental Materials-Appendix A PRISMA Checklist). To reduce heterogeneity in synthesized outcomes, the four most commonly used pain-related distress outcomes in this literature will be examined to determine efficacy (Premature Infant Pain Profile, Cry Duration, Heart Rate, and Oxygen Saturation). Furthermore, due to the established difference between an infant's response to painful or distressing stimuli over a pain event (Pillai Riddell et al., 2022; Pillai Riddell et al.,

2023) efficacy will be examined at four time points surrounding an acutely painful procedure (Baseline [pre-procedure], During Painful Procedure, Immediate-after Painful Procedure, Distal-after Painful Procedure).

Methods

Search Strategy

Working with an academic librarian with advanced experience with systematic meta-analysis (EU), a systematic search was iterated using Cochrane Library, Ovid, Embase, CINAHL, and APA PsychInfo in June 2024 for English-language references, and an update was conducted on May 13, 2025. The search was not limited by publication year. Search terms encompassed preterm infant terms (e.g., prematurity, low birthweight infant, infant, newborn, neonate, neonatal, premature), skin-to-skin terms (e.g., kangaroo care, kangaroo mother care, skin-to-skin contact), and pain terms (e.g., procedural pain, acute pain, invasive procedure, heel lance, skin-breaking). See Supplemental Materials - Appendix B for Database Search Strategies. This meta-analysis was registered prior to data extraction on INPLASY (202470099) and is available in full on inplasy.com (https://inplasy.com/inplasy-2024-7-0099/).

Inclusion and Exclusion Criteria and Study Selection

We included interventional, prospective-observational, and retrospective studies on humans who are 32 weeks and 6 days or less gestational age undergoing a painful procedure and using skin-to-skin contact for pain. While very and extremely preterm infants are typically identified as infant < 32 weeks gestational age, we broadened this criterion by a week to provide a more substantive literature base. Studies were excluded if they described nonhuman subjects or did not include a painful procedure (e.g., heel lance, venipuncture, IV insertion), did not have a mean participant age within the expanded very and extremely preterm infant range (32 weeks, 6

days or less), and did not include measures of infant pain. Review papers, book chapters, conference proceedings, case studies, commentaries, and dissertations were also excluded.

Three authors (EC, HH, NG) independently read and reviewed the retrieved abstracts for full-text review in Covidence, a web-based collaboration software that facilitates blinded, independent review of studies (2025). Any disagreements between reviewers were resolved through consensus discussion with senior author (RPR). Full texts of potentially eligible studies were retrieved (see Figure 1) and were reviewed to confirm eligibility for extraction. All articles were again independently reviewed with relevant data extracted.

Data Extraction and Quality Assessment

Study information (e.g., study design, setting, exclusion/inclusion criteria), participant demographics (e.g., sample size, gestational age, postnatal age, sex, birth weight, medical history), procedure information (name of painful event/procedure, duration), intervention information, and results were extracted by reviewers into the Cochrane Review Manager 9.2 (RevMan, 2025).

Risk of bias (ROB) in randomized trials was assessed using a modified Cochrane risk of bias tool (see Supplemental Materials- Appendix C for the modified risk of bias tool). The tool asks reviewers to rate the bias across 6 domains and each domain was assigned a judgement of Low Risk, Some Concerns, or High Risk. The Overall bias score used the same three outcomes based on the domain scores. For observational studies, ROB was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I V2) tool. The tool requires reviewers to rate the bias across 7 domains. Final ROB judgements are labelled as Low Risk, Moderate Risk, Serious Risk, and Critical Risk. All extractions were consensus coded by two of the three primary extractors for quality scores to ensure reliability. Disagreements were minimal and were

resolved through discussion to obtain a final quality decision for each paper (See Supplemental Materials, Appendix C). The level of certainty in the evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. GRADE ratings systematically assess the certainty of evidence based on several study factors, including risk of bias, study design, inconsistency, and publication bias, for a final rating of High, Moderate, Low, or Very Low certainty. Higher certainty indicates higher confidence that the true effect lies close to that of the estimate of the effect.

Analysis Plan and Outcome Measurement

For the meta-analysis of superiority trials comparing SSCP to control and SSCP versus sweet solutions, we analysed the standardised mean difference (SMD) using the generic inverse variance method to determine effect sizes using Cochrane Review Manager 9.2 (RevMan, 2025). Studies that could not be analyzed in the meta-analysis were analyzed using a narrative synthesis. In total, three sets of analyses were conducted: 1. Meta-Analyses for SSCP versus control group, 2. Meta-Analyses for SSCP versus Sweet Solutions, and 3. Narrative Synthesis for articles that could not be integrated into the prior two sets of meta-analyses.

Based on an initial scoping of the articles, four separate pain-related outcomes were selected based on choosing measures that represented key domains of interest in pain measurement and based on what measures were most commonly used in the pain-measurement literature. The first outcome of interest was the Premature Infant Pain Profile (PIPP), a validated multidimensional pain measure specifically designed for preterm infants that encompasses several pain indicators, including GA, heart rate, oxygen saturation, behavioural state, and facial expressions (Stevens et al., 1996). The second outcome selected was the amount of time spent crying or cry duration surrounding the painful procedure. A longer cry duration is indicative of

more distress or pain in infants and was often analyzed separately in the literature. Finally, oxygen saturation (lower reflects higher distress) and heart rate (higher reflects greater distress) were selected to represent physiological outcomes domains due to their common occurrence in the literature.

Results for SSCP versus Standard Care comparisons will be presented first, then SSCP versus Sweet-tasting Solutions comparisons, then the narrative synthesis of different SSCP studies. Within each comparison, results will be organized by outcomes (PIPP, Cry Duration, Oxygen Saturation, Heart Rate) and within each outcome, results will be organized by standardized time points defined by data availability across studies (Baseline [before the painful procedure], During [while the painful procedure is ongoing], Immediate-after [within the first two minutes after the painful procedure has been completed], and Distal-after [longer than two minutes after the painful procedure has been completed]).

Results

Studies Included

The search identified 1932 articles across the 5 electronic databases, and 102 duplicates were removed prior to screening. These articles were then reviewed by title and abstract and were included or excluded based on a priori selection criteria. A total of 49 articles were then reviewed by full-text review, and of these, 23 articles fulfilled the inclusion criteria and thus were included in the final review

Study Characteristics

Table 1 provides an overview of the studies included, including sample size, country of origin, acutely painful procedure, name of intervention, gestational age, postnatal age, and risk of bias result. Studies were from India (n=5), Canada (n=4), United States (n=4), and Brazil (n=3).

Table 1. Study Characteristics

Study	*N*	Country	Gestational age*	Postnatal age**	Acute pain procedure	Name of intervention	Study Design	Risk of Bias
Akcan et al. 2009	25	Turkey	31.3 (1.9)	4.9 days (4.3)	Heel stick	Kangaroo care	Randomized trial	Some risk
Alidadian et al. 2021	60	Iran	32.6 (1.9)	NR	Heel stick	Kangaroo care	Randomized trial	High risk
Campbell-Yeo et al. 2019	81	Canada	32.6 (2.1)	5.6 days (5.1)	Heel stick	Kangaroo care	Randomized trial	Some risk
Castral et al. 2015	42	Brazil	32.5 (1.8)	16.9 days (11.7)	Heel stick	Maternal kangaroo care	Observational	Moderate risk
Castral et al. 2012	42	Brazil	32.5 (1.8)	NR	Heel stick	Maternal kangaroo care	Observational	Moderate risk
Chidambaram et al. 2014	50	India	32.7 (2.1)	6.6 days (4.9)	Heel stick	Kangaroo mother care	Cross-over trial	Some risk
Cong et al. 2012	22	United States	30.4 (2.2)	14.5 days (6.3)	Heel stick	Kangaroo care	Randomized trial	Low risk
Cong et al. 2009	12	United States	30-32	6.0 days (1.0)	Heel stick	Kangaroo care	Randomized trial	Some risk
Cong et al. 2011	28	United States	30-32	5.0 days (1.0)	Heel stick	Kangaroo care	Randomized trial	Some risk
de Sousa Freire et al. 2008	31	Brazil	33.1 (1.6)	4.8 days (3.4)	Heel stick	Kangaroo care	Randomized trial	Some risk
Ferber and Makhoul 2008	30	Israel	28-34	NR	Heel stick	Kangaroo care	Randomized trial	Low risk
Johnston et al. 2012	18	Canada	32.3	NR	Heel stick	Kangaroo care	Randomized trial	Some risk
Johnston et al. 2011	62	Canada	31.6 (2.3)	6.0 days (2.7)	Heel stick	Kangaroo care	Randomized trial	Some risk

Johnston et al. 2008	61	Canada	30.5 (1.0)	220.0 days (6.6)	Heel stick	Kangaroo mother care	Randomized trial	Low risk
Kostandy et al. 2008	10	United States	30-32	6.0 days (2.0)	Heel stick	Kangaroo care	Randomized trial	Low risk
Kristoffersen et al. 2019	35	Norway	28.9^	NR	Retinopathy of prematurity screening	Skin-to-skin contact	Randomized trial	Some risk
Ludington-Hoe et al. 2005	23	El Salvador	31.4 (2.7)	22.0 days (11.4)	Heel stick	Skin-to-skin contact	Randomized trial	Low risk
Murmu et al. 2017	51	India	32.2	NR	Heel stick	Kangaroo care	Cross-over trial	Some risk
Nanavati et al. 2013	25	India	32.7 (2.0)	7.1 days (6.6)	Tape removal	Kangaroo mother care	Randomized trial	Low risk
Olsson et al. 2016	10	Sweden	30.7	6.6 days (4.7)	Venepuncture	Skin-to-skin contact	Cross-over trial	High risk
Padhi et al. 2015	20	India	30.8 (2.3)	NR	Retinopathy of prematurity screening	Reverse kangaroo mother care	Observational	Serious risk
Shukla et al. 2018	50	India	31.7 (2.1)	16.1 days (13.2)	Heel stick	Skin-to-skin care	Randomized trial	Some risk
Wang et al. 2023	36	China	31-33	NR	Heel stick	Kangaroo mother care	Randomized trial	Low risk

Note. NR = not reported.
*Mean GA (standard deviation). Range is reported where mean GA was not reported.
**Mean postnatal age (standard deviation) at time of study.
^Median GA reported instead of mean.

There was one study included from each of the following countries: China, El Salvador, Iran, Israel, Norway, Sweden, and Turkey. The majority of studies were randomized trials and the most common acutely painful procedure that was utilized in the studies was heel stick. Fourteen studies were able to be meta-analyzed and 9 studies were narratively synthesized or summarized.

1 Meta-analysis: SSCP versus Standard Care control

1.1 PIPP score

1.1.1 Baseline. Four studies analysed the effects of SSCP compared to control on baseline PIPP scores (Akcan et al., 2009; Chidambaram et al, 2014; Olsson et al., 2016; Wang et al., 2023). The total number of participants in the analysis was 241 (SSCP = 120, control = 121). There was no difference between SSCP and control on PIPP scores before the procedure with low certainty of evidence (SMD 0.13, 95% confidence interval (CI) -0.12 to 0.38; $I^2 = 0\%$). Using GRADE Criteria, confidence in this effect size estimate was Low. See Figure 2 for forest plot.

1.1.2 During. Two studies analysed the effects of SSCP compared to control on PIPP scores during the painful procedure (Olsson et al., 2016; Wang et al., 2023). The total number of participants in the analysis was 91 (SSCP = 45, control = 46). There was no significant difference between interventions with Very Low certainty of evidence (SMD -1.01, 95% CI -3.33 to 1.31; $I^2 = 94\%$). See Figure 3 for forest plot.

1.1.3 Immediate-after. Four studies analysed the effects of SSCP compared to control on PIPP scores within the first two minutes of the completion of the procedure (Akcan et al., 2009, Cong et al., 2011; Johnston et al., 2008; Wang et al., 2023). The total number of participants in the analysis was 281 (SSCP = 140, control = 141). There was no

significant difference between interventions with Low certainty of evidence (SMD -0.72, 95% CI -1.563 to 0.11; I^2 = 90%). See Figure 4 for forest plot.

1.1.4 Distal-after. Three studies analysed the effects of SSCP compared to control on PIPP scores more than two minutes after the completion of the procedure (Chidambaram et al, 2014; Cong et al., 2011; Johnston et al., 2008). The total number of participants in the analysis was 242 (SSCP = 121, control = 121). Results suggest SSCP may reduce PIPP scores with Moderate certainty of evidence (SMD -0.32, 95% CI -0.52 to -0.12 [small effect size]; I^2 =0%). See Figure 5 for forest plot.

1.1.5 Table 2. Summary of findings 1: PIPP scores for SSCP compared to Standard Care control

(Bolding of Effects indicates significant effect)

Time points	Effects (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)
Baseline (before the procedure)	The SMD of PIPP scores in the SSCP group was 0.13 higher (0.12 lower to 0.38 higher)	241 (4)	⊕⊕⊖⊖ **Low**[a,b]
During	The SMD of PIPP scores in the SSCP group was 1.01 lower (3.33 lower to 1.31 higher)	91 (2)	⊕⊖⊖⊖ **Very Low**[a,c,d]
Immediate-after (0 seconds to 2 minutes post-procedure	The SMD of PIPP scores in the SSCP group was 0.72 lower (1.56 lower to 0.11 higher)	281 (4)	⊕⊕⊖⊖ **Low**[a,e]
Distal-after (longer than 2 minutes post procedure	**The SMD of PIPP scores in the SSCP group was 0.32 lower (0.52 lower to 0.12 lower)**	242 (3)	⊕⊕⊕⊖ **Moderate**[f]

[a]The 95% confidence interval includes 0, suggesting no effect
[b]1/4 studies had high risk of bias, 2/4 studies had some risk of bias
[c]Certainty of evidence was downgraded by one level for inconsistency due to heterogeneity among studies, with an I^2 statistic of 94%
[d]1/2 studies had high risk of bias
[e]Certainty of evidence was downgraded by one level for inconsistency due to heterogeneity among studies, with an I^2 statistic of 90%
[f]2/3 studies have some risk of bias

1.2 Cry duration

1.2.1 Baseline. Two studies analysed the effects of SSCP compared to control on baseline cry duration (Kostandy et al., 2008; Ludington-Hoe et al., 2005). The total number of participants in the analysis was 66 (SSCP = 33, control = 33). These studies found that SSCP was not different from control in baseline cry duration (SMD -0.59, 95% CI -2.50 to 1.32; I^2 = 92%). Using GRADE criteria, confidence in this effect size estimate was Low. See Figure 6 for forest plot.

1.2.2 During. The same two studies analysed the effects of SSCP compared to control on cry duration during the painful procedure (Kostandy et al., 2008; Ludington-Hoe et al., 2005). The total number of participants in the analysis was 66 (SSCP = 33, control = 33). SSCP was not more efficacious than control at reducing crying time during the procedure with Low certainty of evidence (SMD -1.97, 95% CI -5.91 to 1.97; I^2 = 97%). One study did not report exact crying time for each group but reported no significant difference in crying time between SSCP and control (Cong et al., 2012). See Figure 7 for forest plot.

1.2.3 Immediate-after. No studies analysed SSCP compared to control on cry duration within the first two minutes of the end of the painful procedure.

1.2.4 Distal-after. Two studies analysed SSCP compared to control on cry duration longer than two minutes after the procedure (Kostandy et al., 2008; Ludington-Hoe et al., 2005). The total number of participants in the analysis was 66 (SSCP = 33, control = 33). These studies found that SSCP may be more efficacious than control at reducing crying time at the Distal-after time point with Moderate certainty (SMD -0.75, 95% CI -1.25 to -0.25 [moderate effect size]; I^2 =0%). See Figure 8 for forest plot.

1.2.5 Table 3. Summary of findings 2: Cry duration for SSCP compared to Standard Care control
(Bolding of Effects indicates significant effect)

Time points	Effects (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)
Baseline (before the procedure)	The SMD of cry duration in the SSCP group was 0.59 lower (2.50 lower to 1.32 higher)	66 (2)	⊕⊕⊖⊖ **Low**[a,b]
During	The SMD of cry duration in the SSCP group was 1.97 lower (5.91 lower to 1.97 higher)	66 (2)	⊕⊕⊖⊖ **Low**[a,c]
Distal-after (longer than 2 minutes post procedure	**The SMD of cry duration in the SSCP group was 0.75 lower (1.25 lower to 0.25 lower)**	66 (2)	⊕⊕⊕⊖ **Moderate**[d]

[a]The 95% confidence interval includes 0, suggesting no effect
[b]Certainty of evidence was downgraded by one level for inconsistency due to heterogeneity among studies, with an I^2 statistic of 92%
[c]Certainty of evidence was downgraded by one level for inconsistency due to heterogeneity among studies, with an I^2 statistic of 97%
[d]Certainty of evidence was downgraded by one level for biased reporting that did not include insignificant findings for cry duration resulting in small number of studies included in meta-analysis

1.3 Oxygen saturation

1.3.1 Baseline. Three studies analysed SSCP compared to control on baseline oxygen saturation (Chidambaram et al, 2014; Ludington-Hoe et al., 2005; Wang et al., 2023). The total number of participants in the analysis was 219 (SSCP = 109, control = 110). These studies found that SSCP was not different from control in baseline oxygen saturation with Moderate certainty of evidence (SMD 0.81, 95% CI -2.23 to 3.85; I^2 = 93%). See Figure 9 for forest plot.

1.3.2 During. Two studies analysed SSCP compared to control on oxygen saturation during the painful procedure (Ludington-Hoe et al., 2005; Wang et al., 2023). The total number of participants in the analysis was 119 (SSCP = 59, control = 60). SSCP may reduce pain as demonstrated by increased oxygen saturation while the procedure is ongoing based on evidence of Moderate certainty (SMD 1.03, 95% CI 0.65 to 1.42 [large effect size]; I^2 =0%). See Figure 10 for forest plot.

1.3.3 Immediate-after. One study with 73 participants (SSCP = 36, control = 37) analysed SSCP compared to control on oxygen saturation within the first two minutes of the completion of the procedure. The SSCP group had significantly higher oxygen saturation than control indicating reduced pain (Wang et al., 2023).

1.3.4 Distal-after. Two studies analysed SSCP compared to control on oxygen saturation longer than two minutes after the procedure (Chidambaram et al, 2014; Ludington-Hoe et al., 2005). The total number of participants in the analysis was 146 (SSCP = 73, control = 73). These studies found that SSCP was not more efficacious than control (SMD 0.71, 95% CI -6.84 to 8.27; I^2 = 90%), with Very Low certainty of evidence. See Figure 11 for forest plot.

1.3.5 Table 4. Summary of findings 3: Oxygen saturation for SSCP compared to Standard Care control
(Bolding of Effects indicates significant effect)

Time points	Effects (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)
Baseline (before the procedure)	The SMD of oxygen saturation in the SSCP group was 0.81 higher (2.23 lower to 3.85 higher)	219 (3)	⊕⊕⊕⊖ **Moderate**[a,b]
During	**The SMD of oxygen saturation in the SSCP group was 1.03 higher (0.65 higher to 3.85 higher)**	119 (2)	⊕⊕⊕⊖ **Moderate**[c]
Distal-after (longer than 2 minutes post procedure	The SMD of oxygen saturation in the SSCP group was 0.71 higher (6.84 lower to 8.27 higher)	146 (2)	⊕⊖⊖⊖ **Very Low**[a,d,e]

[a]The 95% confidence interval includes 0, suggesting no effect
[b]Certainty of evidence was downgraded by one level for inconsistency due to heterogeneity among studies, with an I^2 statistic of 93%
[c]Certainty of evidence was downgraded by one level for biased reporting that did not include insignificant findings for oxygen saturation resulting in small number of studies included in meta-analysis
[d]Certainty of evidence was downgraded by one level for inconsistency due to heterogeneity among studies, with an I^2 statistic of 90%
[e]1/2 studies had some risk of bias

1.4 Heart rate

1.4.1 Baseline. Five studies analysed SSCP compared to control on baseline heart rate (HR) (Chidambaram et al, 2014; Cong et al., 2009; Cong et al., 2012; Ludington-Hoe et al., 2005; Wang et al., 2023). The total number of participants in the analysis was 287 (SSCP = 144, control = 143). These studies found that SSCP was not different from control in HR before the procedure (SMD 0.16, 95% CI -0.47 to 0.80; I^2 = 64%). Using GRADE Criteria, confidence in this effect size estimate was Low. See Figure 12 for forest plot.

1.4.2 During. Three studies analysed the effects of SSCP compared to control on HR during the painful procedure (Cong et al., 2009; Ludington-Hoe et al., 2005; Wang et al., 2023). The total number of participants in the analysis was 142 (SSCP = 72, control = 70). SSCP was not more efficacious than control at reducing pain during the procedure (SMD -0.38, 95% CI -0.87 to 0.12; I^2 = 49%) and certainty of evidence was Low. Of note, there was an additional study that did not report exact heart rate but noted higher heart rate in the SSCP group compared to control (Ferber and Makhoul, 2008). See Figure 13 for forest plot.

1.4.3 Immediate-after. Two studies analysed SSCP compared to control on HR within the first two minutes of the completion of the procedure (Cong et al., 2012; Wang et al., 2023). The total number of participants in the analysis was 118 (SSCP = 58, control = 60). SSCP may reduce pain as demonstrated by decreased HR immediately after the procedure based on evidence of Moderate certainty (SMD -0.64, 95% CI -1.01 to -0.27 [moderate effect size]; I^2 =0%). Figure 14 for forest plot.

1.4.4 Distal-after. Three studies analyzed SSCP compared to control on HR longer than two minutes after the procedure (Chidambaram et al, 2014; Cong et al., 2009; Ludington-Hoe

et al., 2005). The total number of participants in the analysis was 169 (SSCP = 86, control = 83). SSCP was not more efficacious than control at reducing pain at the distal-after time point based on evidence of Very Low certainty (SMD -0.21, 95% CI -1.61 to 1.20; I^2 =78%). See Figure 15 for forest plot.

1.4.5 Table 5. Summary of findings 4: Heart rate for SSCP compared to Standard Care control

(Bolding of Effects indicates significant effect)

Time points	Effects (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)
Baseline (before the procedure)	The SMD of HR in the SSCP group was 0.16 higher (0.47 lower to 0.80 higher)	287 (5)	⊕⊕⊖⊖ **Low**[a,b]
During	The SMD of HR in the SSCP group was 0.38 lower (0.87 lower to 0.12 higher)	142 (3)	⊕⊕⊖⊖ **Low**[a,c]
Immediate-after (0 seconds to 2 minutes post-procedure	**The SMD of HR in the SSCP group was 0.64 lower (1.01 lower to 0.27 lower)**	118 (2)	⊕⊕⊕⊖ **Moderate**[c]
Distal-after (longer than 2 minutes post procedure	The SMD of HR in the SSCP group was 0.21 lower (1.61 lower to 1.20 higher)	169 (3)	⊕⊕⊖⊖ **Very Low**[a,d,e]

[a]The 95% confidence interval includes 0, suggesting no effect
[b]Certainty of evidence was downgraded by one level for inconsistency due to heterogeneity among studies, with an I^2 statistic of 64%
[c]Certainty of evidence was downgraded by one level for biased reporting that did not include all findings for heart rate
[d]Certainty of evidence was downgraded by one level for inconsistency due to heterogeneity among studies, with an I^2 statistic of 78%
[e]2/3 studies had some risk of bias

1.5 Brief Summary of All SSCP versus no-treatment control (Across Outcomes and Time Points)

Table 6 summarizes the results of the 14 standard mean differences calculated in the meta-analysis of SSCP compared to control with certainty ratings across 4 time points and 4 pain outcomes.

Table 6. Summary of Meta-Analyses Comparing SSCP to Control Group

	Baseline	During	Immediate-after	Distal-after
PIPP	No Difference$_{\textbf{Low}}$	No Difference$_{\textbf{Very Low}}$	No Difference$_{\textbf{Low}}$	**Favours SSCP$_{\textbf{Moderate}}$**
Cry Duration	No Difference$_{\textbf{Low}}$	No Difference$_{\textbf{Low}}$	_____	**Favours SSCP$_{\textbf{Moderate}}$**
Oxygen Saturation	No Difference$_{\textbf{Moderate}}$	**Favours SSCP$_{\textbf{Moderate}}$**	_____	No Difference$_{\textbf{Very Low}}$
Heart Rate	No Difference$_{\textbf{Low}}$	No Difference$_{\textbf{Low}}$	**Favours SSCP$_{\textbf{Moderate}}$**	No Difference$_{\textbf{Very Low}}$

Subscript indicates GRADE certainty. Horizontal line indicates meta-analysis not possible.

2 Meta-analysis: SSCP versus sweet-tasting solutions

Four studies compared SSCP to sweet-tasting solutions (e.g., sucrose, glucose, expressed breast milk [EBM]) on PIPP scores. Three studies were meta-analyzed: two examining SSCP compared to sucrose (Campbell-Yeo et al., 2019; Shukla et al., 2018) and one examining SSCP compared to EBM (Nanavati et al., 2013). The fourth study compared SSCP, glucose, and control, but did not report final PIPP scores (de Sousa Freire et al., 2008).

2.1 PIPP score

There were no studies comparing SSCP to sweet-tasting solutions on pain outcomes at the Baseline or During time points.

2.1.1 Immediate-after. Three studies analyzed SSCP compared to sweet-tasting solutions (sucrose and EBM) (Campbell-Yeo et al., 2019; Nanavati et al., 2013; Shukla et al., 2018). The total number of participants in the analysis was 301 (SSCP = 150, sweet-tasting solution = 151). SSCP was not more effective than sweet-tasting solutions on PIPP at the Immediately-after time point (SMD -0.05, 95% CI -0.37 to 0.27; I^2 =0%) based on evidence of Low certainty. One study comparing SSCP, glucose, and control found a significantly lower PIPP score in the SSCP group compared to the glucose group

at the Immediate-after time point but did not report the final PIPP score so it could not be included in the meta-analysis (de Sousa Freire et al., 2008). This study was assessed as having Some risk of bias. See Figure 16 for forest plot.

2.1.2 Distal-after. Only one study also examined PIPP at the Distal-after time point for SSCP compared to sucrose and found no difference between the groups (p = 0.86) (Campbell-Yeo et al., 2019). The ROB assessment identified Some risk of bias in this study.

2.1.3 Table 7. Summary of findings 5: PIPP for SSCP compared to Sweet-tasting Solutions

(Bolding of Effects indicates significant effect)

Time point	Effects (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)
Immediate-after (0 seconds to 2 minutes post-procedure	The SMD of PIPP in the SSCP group was 0.05 lower (0.37 lower to 0.27 higher)	301 (3)	⨁⨁⨀⨀ **Low**[a,b]

[a]The 95% confidence interval includes 0, suggesting no effect
[b]2/3 studies had some risk of bias

2.2 Summary of SSCP versus sweet-tasting solutions

At the Immediate-after time point, the meta-analysis revealed no difference between SSCP and sweet-tasting solutions on PIPP scores, however one study that could not be meta-analysed qualitatively reported lower PIPP scores in the SSCP group. At the Distal-after time point, one study found no difference between SSCP and sweet-tasting solutions.

3 Narrative Synthesis

Eight studies were not able to be meta-analyzed because they did not have standard care/no-treatment or sweet-tasting solution comparison groups, or because there was insufficient or poor reporting of results. They were narratively synthesized according to similarity of comparison group.

3.1 Alternative caregiver superiority trials

3.1.1 Maternal versus paternal SSCP. A randomized crossover trial with 62 participants compared maternal and paternal SSCP during heel lance. The risk of bias assessment identified some risk in this study. Paternal SSCP resulted in significantly higher PIPP scores than maternal SSCP at the immediate-after time point. However, there was no significant difference in scores at the distal-after time point. Authors concluded that mothers were marginally more effective at decreasing pain response than fathers (Johnston et al., 2011).

3.1.2 Maternal versus alternate female SSCP. A randomized crossover trial with 18 participants compared SSCP delivered by the infant's mother to SSCP delivered by alternative females (e.g., in-laws, nurses, friends). At both immediate-after and distal-after time points, mean differences between groups had small effect sizes indicating slightly lower PIPP scores for maternal SSCP. It is unclear if these results are significant as no confidence intervals were reported for the standard difference and there was no mention of statistical significance. The authors concluded that there is a small difference between mothers and nonrelated females in decreasing pain response (Johnston et al., 2012). This study was assessed as having some risk of bias.

3.1.3 Maternal versus other postpartum mother SSCP versus swaddling. A crossover trial with 51 participants compared maternal SSCP, SSCP with an unrelated postpartum mother, and swaddling. There was some risk of bias identified in this study. At the immediate-after time point, PIPP scores were significantly lower in the maternal SSCP and unrelated mother SSCP groups compared to swaddling with large effect sizes (1.69 and 0.97, respectively). Authors concluded that SSCP with the infant's mother or an

unrelated postpartum mother reduces infant pain more than swaddling (Murmu et al. 2017).

3.2 Other 'one-off' superiority trials

These were 'one-off' studies that compared SSCP to an assumed active intervention.

3.2.1 SSCP versus lullaby. One randomized crossover trial with 30 participants (SSCP = 30, lullaby = 30) compared SSCP to lullaby. In the lullaby group, lullaby music was played for 15 minutes before, during, and 15 minutes after a heel lance. During the procedure, there was a significant difference in oxygen saturation and heart rate favouring SSCP over lullaby. However, at the baseline and distal-after time points, there was no significant difference in oxygen saturation or heart rate (Alidadian et al., 2021). This study had a high risk of bias.

3.2.2 SSCP with sucrose versus parent support with sucrose. One study with 35 participants (SSCP = 16, parent support = 19) compared SSCP in combination with sucrose to parent support in combination with sucrose during screening for retinopathy of prematurity (ROP). In the parent support group, the infants were swaddled tightly in a blanket while parents supported the infants' arms and feet. The risk of bias assessment identified some risk in this study. There was no significant difference in PIPP score during or immediately after ROP screening between the groups (Kristoffersen et al., 2019).

3.3 Observational trials.

Three observational studies examined SSCP in the youngest of preterm infants during painful procedures. These studies did not report on the outcomes and time points of interest, but explored other factors that may impact SSCP.

One comparative prospective study with 42 participants examined infant and mother cortisol in the context of a painful procedure while engaging in SSCP with mothers with post-partum depression and/or anxiety (PPDA) and mothers without PPDA. There was no difference between infants' pre- and 20 minutes post-heel lance salivary cortisol levels, nor was there a difference between infants of mothers with PPDA and those without. Similarly, there was no difference between mothers' pre- and 20 minutes post-heel lance salivary cortisol levels. Infants' post-procedure salivary cortisol levels were positively associated with mother's pre- and post-procedure salivary cortisol levels. The authors concluded that the parallel change in salivary cortisol levels during the heel lance and the lack of change in infant salivary cortisol from before to after the procedure are evidence that SSCP is beneficial for both infants and their mothers (Castral et al., 2015). ROB assessment found Moderate risk of bias in this study.

A descriptive exploratory study with the same 42 participants explored the association between maternal factors (stress, depression and/or anxiety, and behaviour) and infant pain during a heel lance while engaging in SSCP. Maternal salivary cortisol levels were positively associated with infant salivary cortisol levels and Neonatal Facial Coding System (NFCS) score. There was no association between mothers' depression and/or anxiety and infant pain outcomes. Authors concluded that these associations suggest mother-infant co-regulation in the context of neonatal pain during SSCP and that mothers' depression and/or anxiety did not affect the newborns' responses to pain and stress (Castral et al., 2012). ROB assessment found Moderate risk of bias in this study.

Lastly, a prospective single-arm pilot study with 20 participants evaluated reverse-Kangaroo Mother Care (R-KMC) during retinopathy of prematurity (ROP) screening with

respect to infant pain. R-KMC is SSCP where the infant lays supine on the mother's chest which maintains direct contact with the infant's back throughout the procedure. Since infants need to be face up during ROP screening R-KMC provides the opportunity to utilise the reported benefits of SSCP during this stressful and painful procedure. Oxygen saturation, respiratory rate, and heart rate were recorded at baseline and immediately after the procedure. Only the change in respiratory rate was significant. Two infants displayed moderate to severe levels of discomfort displayed through crying, eye squeezing, and brow bulge during the procedure. Authors concluded further research is needed to evaluate this intervention but it may serve as an adaptation to standard SSCP in order to facilitate implementation during ROP screening (Padhi et al., 2015). This study was identified as having a Serious risk of bias.

3.4 Summary of the Narrative Synthesis

Narratively synthesizing results over these individual studies (rated as having Moderate to Serious risk of bias) suggest that maternal SSCP may confer some advantage over other caregiver SSCP. Additionally, the regulatory effect of SSCP may not be impacted if mother struggles with postpartum depression or anxiety. SSCP was not superior to lullaby and parent support with sucrose. Lastly, reverse SSCP (a position necessary for certain medical procedures) may have some benefits for certain babies and has potential to adapt SSCP for a broader range of procedures.

Discussion

This systematic review examined SSCP for the youngest of preterm infants undergoing painful procedures. Three sets of analyses were done: SSCP versus standardized control meta-analyses, SSCP versus Sweet Solutions, and narrative synthesis of studies that could not be included in the earlier meta-analysis sets due to heterogeneity of outcomes or comparisons. For

the first set of meta-analyses over the 14 quantitative Standardized Mean Differences (SMDs) calculated (4 different outcomes X 4 potential time points, with two combinations having no studies) SSCP was shown not to be superior to standard care in 10 analyses and shown to be superior in 4 analyses, with magnitudes varying from small to large. All of the significant SMDs were based on 2-3 studies. However, across the four significant SMDs, there was Moderate certainty in the findings. There was no consistent pattern across outcomes or time points. Of further note, the SMD (based on 3 studies) did not show superiority for SSCP over sweet-tasting solutions, however this could only be analysed for one outcome at a single time point. Finally, the narrative review of individual studies suggested that SSCP was not superior to a number of interventions that are more easily executed such as lullaby and parent support with sucrose. Furthermore, mother SSCP may offer a small efficacy advantage over other caregivers administering SSCP. The following sections discuss these findings in more detail.

Meta-analysis Findings: Effect of SSCP during Painful Procedures on Pain-related Distress Outcomes

Fourteen studies were meta-analyzed to examine SSCP to mitigate pain-related distress outcomes. To understand these findings from a more clinically-relevant perspective, they will be discussed according to the time points of the procedure, as opposed to outcome measure. Following, the discussion of these statistics, these results will be contextualized by the narrative synthesis/summaries.

Pain-Related Distress at Baseline

Baseline is the period when the infant and parent have been left to rest after the transfer from incubator/cot and skin-to-skin contact for a painful procedure is initiated. When measured at baseline, across the four outcome measures (PIPP, cry duration, oxygen saturation, and heart

rate), SSCP did not have a significant effect. Results suggest with generally low confidence in the findings that the youngest preterm infants did not show initial benefit in the period of time lapsing post-transfer to right before the painful procedure, regardless of behavioural or physiological measurement used. This suggests that SSCP is not resulting in a very or extremely preterm child being more regulated than an infant in standard care going into the painful procedure. A recent paper by Jones et al. (2021), suggested that for young preterms the dysregulation of moving a child out of incubator or cot may wash out effects of simply holding the child close by parent. This adds credence to an interpretation that SSCP may be regulating a preterm who was initially dysregulated from transfer pre-procedure, such that there is no difference with a non-dysregulated preterm in cot/incubator during baseline. Work with healthy infants suggests that distress predicts distress, thus the more dysregulated the infant prior to a painful procedure, the higher the potential for pain-related distress post-procedure (Pillai Riddell et al., 2022).

Pain-Related Distress During Procedure

During the painful procedure, infants are experiencing the painful stimulus (e.g., tape removal or heel lance) as it is carried out by the healthcare professional. When pain-related distress is measured during the painful procedure, SSCP resulted in higher oxygen saturation compared to control, indicative of less pain-related stress. However, SSCP did not demonstrate a significant effect for PIPP, heart rate, or cry duration. Interestingly, one study that could not be meta-analysed reported higher heart rate for SSCP preterms compared to control (Ferber and Makhoul, 2008). Results suggest with very low to moderate confidence that there may be some benefit of SSCP for the youngest preterm infants during painful procedures but only on one physiological measure at this one time point.

Pain-Related Distress During 2-minute Period Following Procedure

The first two minutes following a painful procedure encompass initial pain reactivity and then regulatory responses where infants display observable peak pain-related distress responses right after the noxious stimulus/stimuli are applied, then continued markers of distress as they make their initial regulation towards homeostasis. During this initial phase after the procedure was completed, SSCP was not more effective than control on PIPP scores nor did it demonstrate superiority to sweet-tasting solutions. Additionally, SSCP resulted in significantly lower heart rate compared to control. No studies examined cry duration within the 2-minute period following the painful procedure. One narratively summarized study found significantly higher oxygen saturation in the SSCP group compared to control. Results indicate with low to moderate confidence that there may be some benefit of SSCP on physiological outcomes (i.e., heart rate and oxygen saturation) measured within two minutes after the completion of a painful procedure.

Pain-Related Distress Longer than 2 Minutes Following Procedure

Two minutes after the painful procedure has ended, the peak in pain-related reactivity response has passed and the infant is assumed to be in a clear regulatory phase heading towards homeostasis (if not having already achieved it). Interestingly, SSCP did not have a significant effect on physiological outcomes (i.e., heart rate and oxygen saturation) but SSCP did result in reduced crying duration and PIPP score a similar pattern with some of the findings of the 2017 Cochrane Review (Johnston et al.). However, SSCP did not show superiority to sweet-tasting solutions on PIPP scores. Results indicate with very low to moderate certainty that there may be some beneficial effects of SSCP for the youngest preterm infants but only on behavioural and multidimensional outcomes after 2-minutes have elapsed since the procedure.

Narrative Synthesis

Superiority Trials

In addition to the meta-analysis showing non-superiority of sucrose over skin-to-skin contact for pain, the narrative summaries and syntheses followed a similar pattern of mixed results. Looking over the 10 studies, there appeared to be no superiority of SSCP over lullaby or supportive parent hand-hugging. All of these interventions require much less preparation by bedside nurses and parents of the youngest preterm infants to achieve potentially equivalent pain management. SSCP requires co-ordination with a bedside nurse and parent, fear of infant equipment disruption in parents, and significant initial infant dysregulation in being moved from incubator or cot (Alenchery et al., 2018; Maguire et al., 2025; Weber & Harrison, 2019).

Caregiver considerations for SSCP

In studies comparing mothers to alternative caregivers (fathers, unrelated female, other postpartum women) SSCP showed slight advantage when delivered by the infant's mother. These findings suggest a specific benefit associated with this proximal contact with the parent who gave birth to the infant as opposed to any caring adult or other postpartum mother. Additionally, observation studies of SSCP suggested mother infant co-regulation, further contributing to the possible benefits of SSCP between mothers and their preterm infants. These observational studies found that mother depression and/or anxiety does not lower the impact of SSCP on infant pain outcomes.

Limitations and Future Directions

There are some important limitations to the present review. The small number and mixed quality of included studies provide a weak foundation for the certainty of these conclusions. Overall, the certainty of evidence for the recommendations for SSCP in very-extremely preterm infants is very low to moderate. Certainty was downgraded due to small numbers of studies,

sample sizes, poor reporting (e.g., selective reporting of results based on statistical significance), heterogeneity in study methodology, and biased methodologies. Additionally, because the GA inclusion criteria was mean study GA of 32 weeks 6 days or less, studies may have included infants in a wider range of GA. While there were few studies, the ones that supported the efficacy of SSCP did have moderate confidence.

Additional research is needed to determine the efficacy of SSCP in very and extremely preterm infants. Future studies on SSCP for painful procedures in this population should ensure appropriate reporting of both significant and insignificant findings to properly evaluate the efficacy of this intervention on pain outcomes. Finally, several studies did not specify the duration of SSCP, many stated that SSCP lasted for the entire procedure without reporting procedure duration. To understand the true benefit of SSCP and minimum "dosage" required, future research should explore how time spent engaging in SSCP before, during, and after the procedure impacts pain outcomes.

Conclusion

In conclusion, examining statistics across 15 analyses suggests that support for SSCP, in the youngest groups of preterm infants, is mixed at best (4 out of 15 analyses were significant) and not-recommended/not superior at worst (10/14 showed no effect; 1 analysis suggested no superiority to sweet solutions), a worrisome proposition for experts who for important broader reasons recommend broad skin-to-skin care for all preterms. Of note, the 4/15 SMDs that were significant were ground in Moderate confidence based on the quality of the studies. While the 11/15 non-significant/superior SMDs were based on Very Low to Low confidence. It is critical that more research be completed as only 10 studies formed the basis of the 14 SMDs calculated.

Ultimately, there is some evidence indicating SSCP may be an effective intervention for pain management for the youngest of preterm infants but there was little consistency across outcomes and the time points. What is needed are more high-quality trials that more carefully operationalize the skin-to-skin methodology and contextualize skin-to-skin contact for pain in terms of infants' GA at birth, postnatal age at study. Moreover, none of these studies fully operationalized three critical variables - previous SSC experiences between parent and child, parental stress during SSC, and previous pain exposures at time of study. Furthermore, given the acknowledged dyadic co-regulation element of SSCP between mother and child, another major factor to this equation that has been left out of all these studies is maternal stress coming into the procedure (e.g., physical recovery from labour and birth, stressors at home, comfort witnessing skin-breaking and/or blood-involved procedures, their experience with skin-to-skin care and skin-to-skin contact for pain) and maternal-infant experience with skin-to-skin care more broadly. To better inform parents, clinicians, and researchers, if SSCP is truly an effective strategy to manage pain in the youngest preterm infants, it is not just more research that is needed. More nuanced research that better accounts for the developmental and biopsychosocial dimensions of SSCP must be conducted. Given the importance of skin-to-skin care broadly to early infant development in the context of the continuously decreasing age of viability, the question before researchers may actually be what modifications to SSCP do clinicians and parents need to do for this evolutionary strategy to meet its full potential in the youngest of preterm infants.

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Figures

Figure 1. PRISMA Flow Diagram

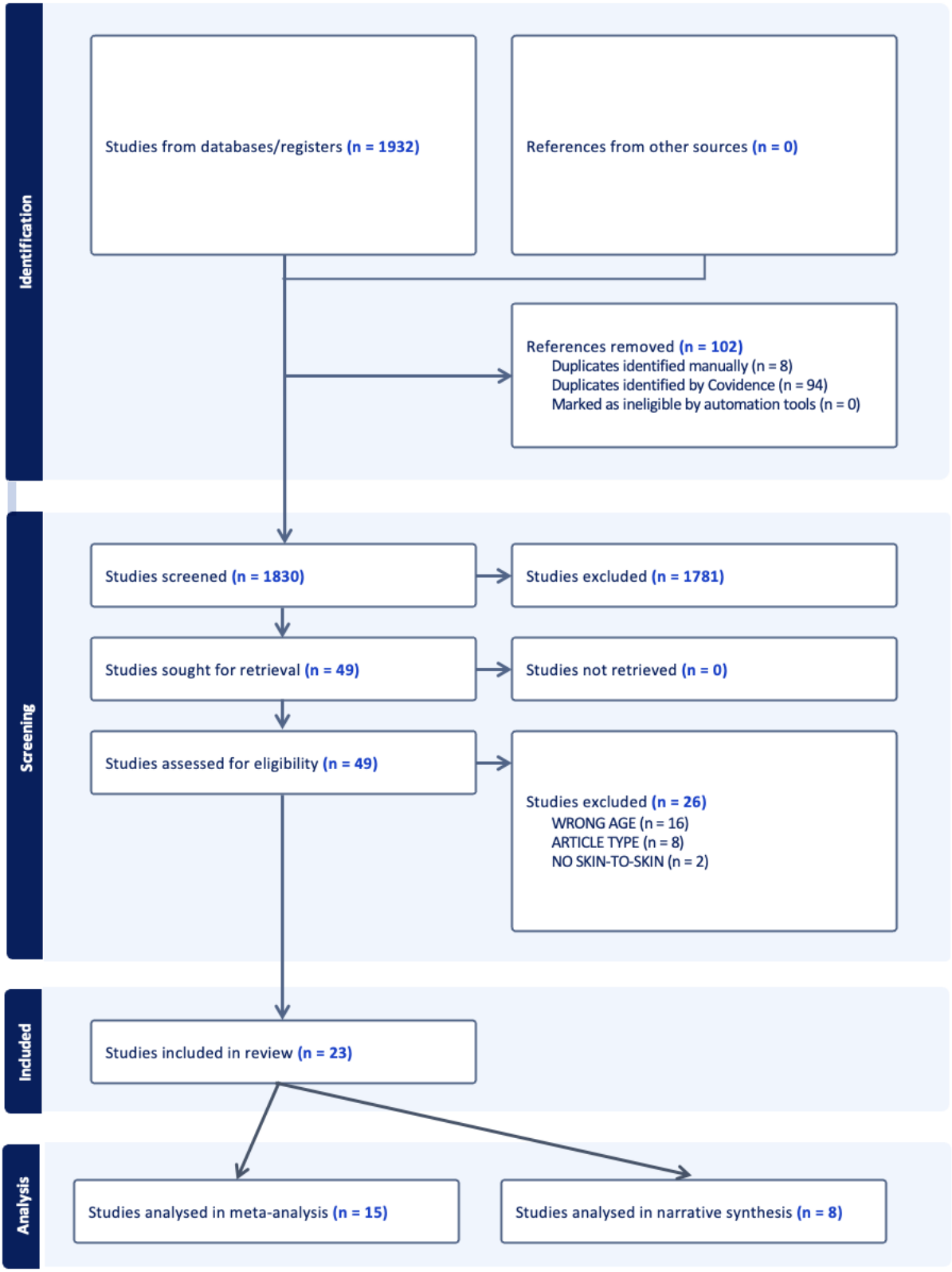
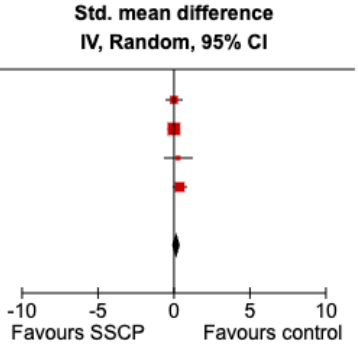


Figure 2. Forest plot SSCP versus no-treatment control: PIPP Baseline

Study or Subgroup	SMD	SE	SSC Total	Control Total	Weight	Std. mean difference IV, Random, 95% CI
Akcan 2009	0	0.282843	25	25	20.9%	0.00 [-0.55 , 0.55]
Chidambaram 2014	-0.003546	0.2	50	50	41.8%	-0.00 [-0.40 , 0.39]
Olsson 2016	0.264767	0.474041	9	9	7.4%	0.26 [-0.66 , 1.19]
Wang 2023	0.371025	0.236223	36	37	29.9%	0.37 [-0.09 , 0.83]
Total (Wald[a])			**120**	**121**	**100.0%**	**0.13 [-0.12 , 0.38]**

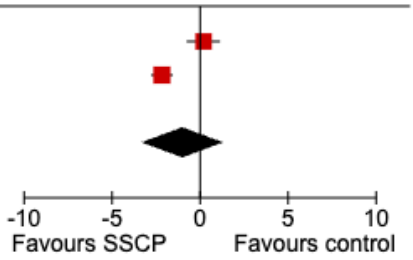


Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 1.78, df = 3 (P = 0.62); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Figure 3. Forest plot SSCP versus no-treatment control: PIPP During

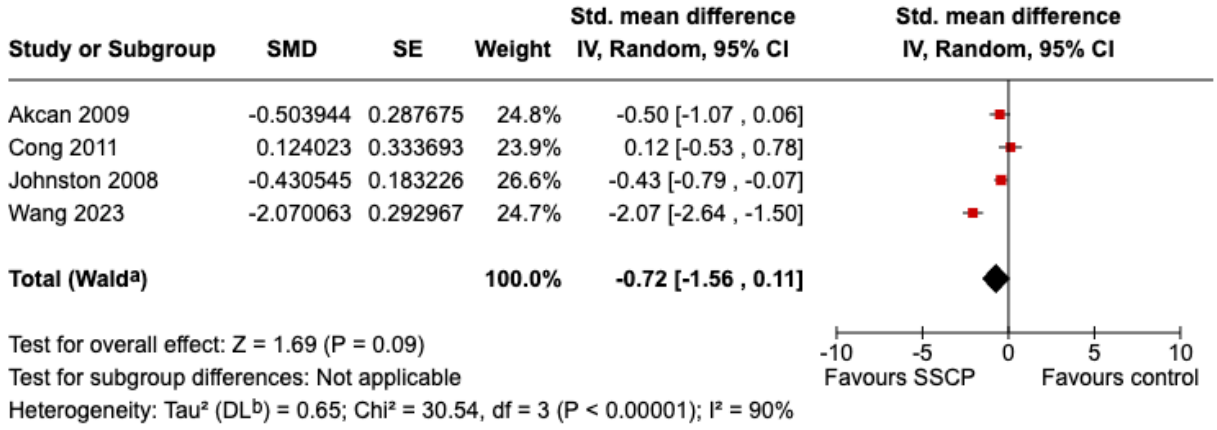
Study or Subgroup	SMD	SE	Weight	Std. mean difference IV, Random, 95% CI
Olsson 2016	0.198806	0.472893	48.8%	0.20 [-0.73 , 1.13]
Wang 2023	-2.16983	0.298148	51.2%	-2.17 [-2.75 , -1.59]
Total (Wald[a])			**100.0%**	**-1.01 [-3.33 , 1.31]**



Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 2.65; Chi² = 17.95, df = 1 (P < 0.0001); I² = 94%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Figure 4. Forest plot SSCP versus no-treatment control: PIPP Immediate-after

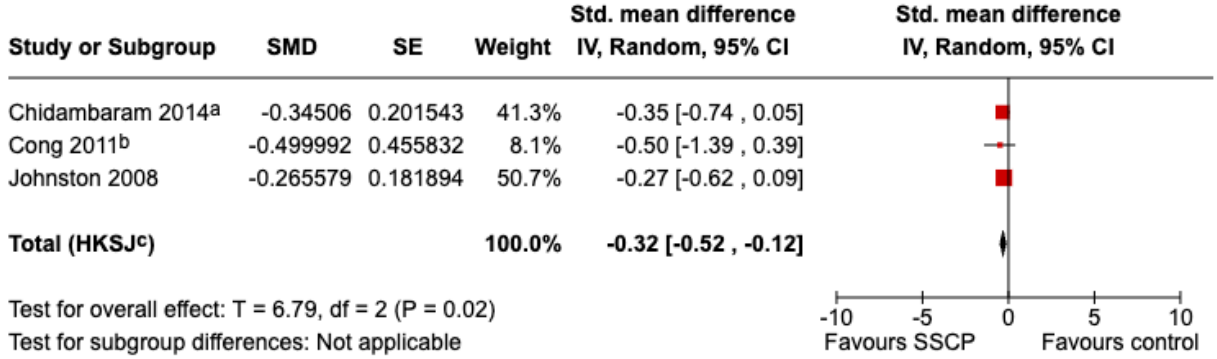


Study or Subgroup	SMD	SE	Weight	Std. mean difference IV, Random, 95% CI
Akcan 2009	-0.503944	0.287675	24.8%	-0.50 [-1.07 , 0.06]
Cong 2011	0.124023	0.333693	23.9%	0.12 [-0.53 , 0.78]
Johnston 2008	-0.430545	0.183226	26.6%	-0.43 [-0.79 , -0.07]
Wang 2023	-2.070063	0.292967	24.7%	-2.07 [-2.64 , -1.50]
Total (Wald[a])			**100.0%**	**-0.72 [-1.56 , 0.11]**

Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.65; Chi² = 30.54, df = 3 (P < 0.00001); I² = 90%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Figure 5. Forest plot SSCP versus no-treatment control: PIPP Distal-after

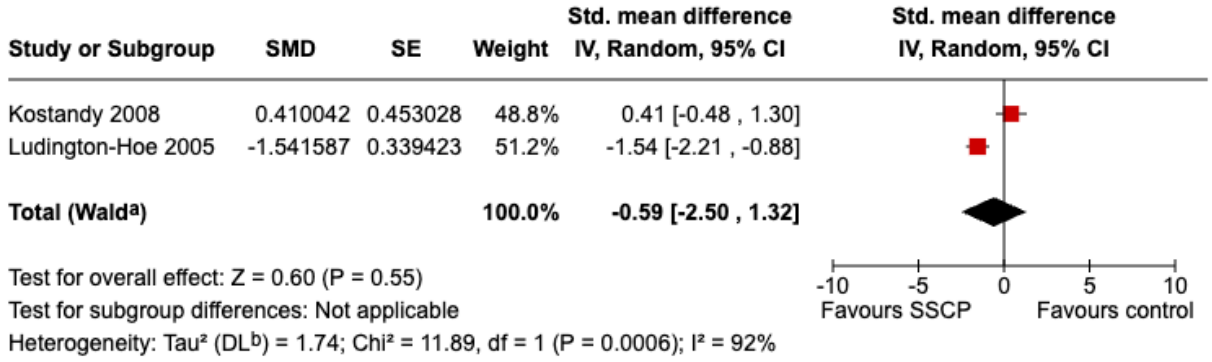


Study or Subgroup	SMD	SE	Weight	Std. mean difference IV, Random, 95% CI
Chidambaram 2014[a]	-0.34506	0.201543	41.3%	-0.35 [-0.74 , 0.05]
Cong 2011[b]	-0.499992	0.455832	8.1%	-0.50 [-1.39 , 0.39]
Johnston 2008	-0.265579	0.181894	50.7%	-0.27 [-0.62 , 0.09]
Total (HKSJ[c])			**100.0%**	**-0.32 [-0.52 , -0.12]**

Test for overall effect: T = 6.79, df = 2 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[d]) = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%

Footnotes
[a]15 mins
[b]4 mins
[c]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[d]Tau² calculated by DerSimonian and Laird method.

Figure 6. Forest plot SSCP versus no-treatment control: Cry duration Baseline

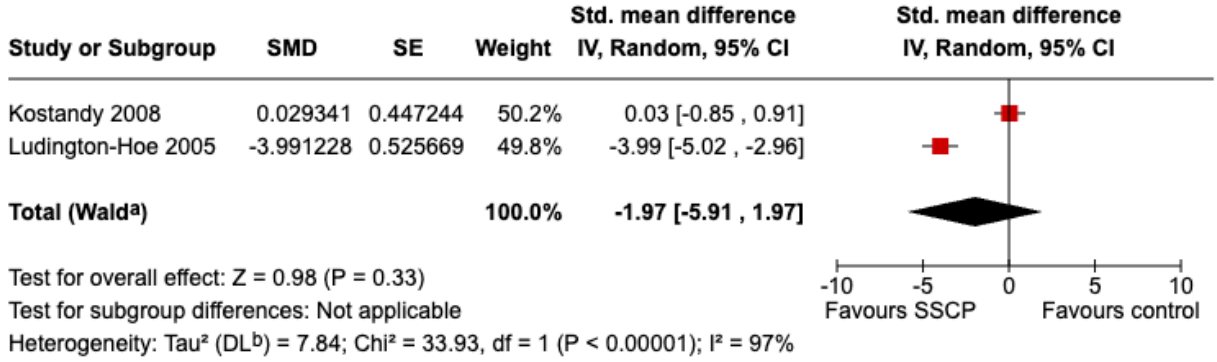


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 7. Forest plot SSCP versus no-treatment control: Cry duration During

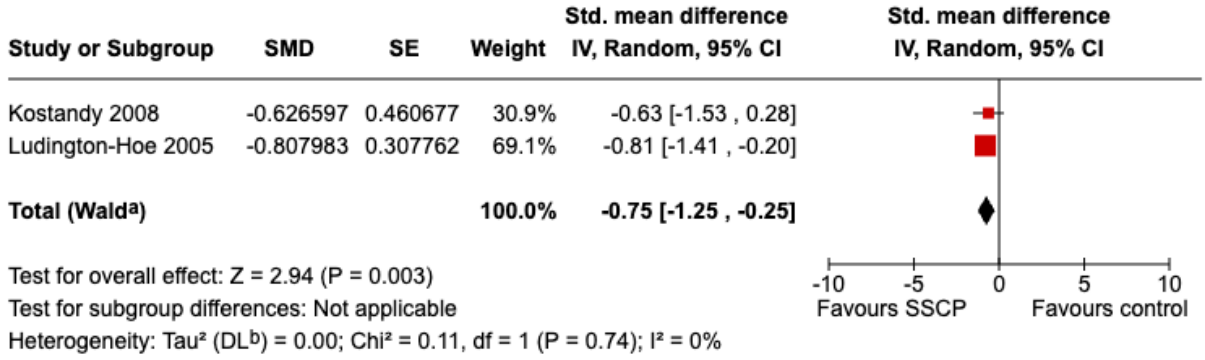


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 8. Forest plot SSCP versus no-treatment control: Cry duration Distal-after

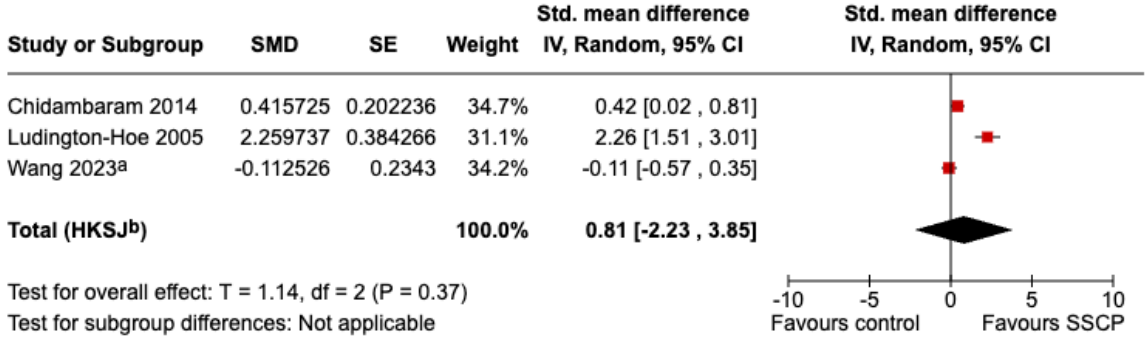


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 9. Forest plot SSCP versus no-treatment control: Oxygen saturation Baseline



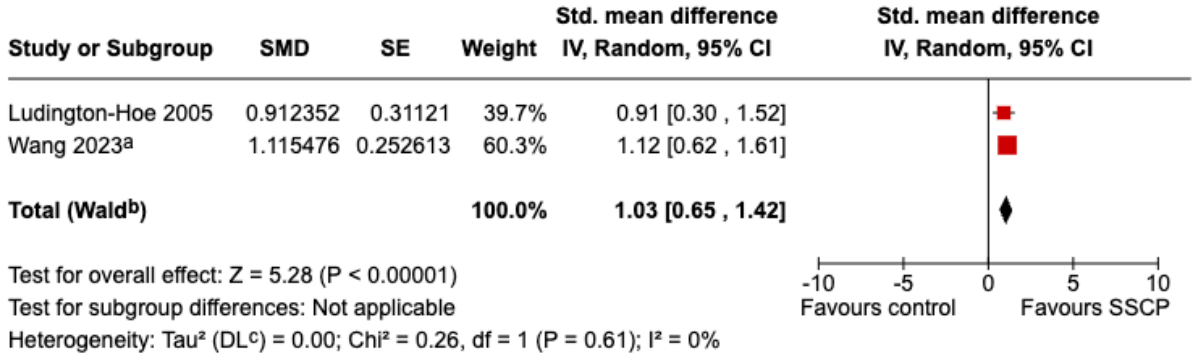
Footnotes

[a]first heel stick only

[b]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[c]Tau² calculated by DerSimonian and Laird method.

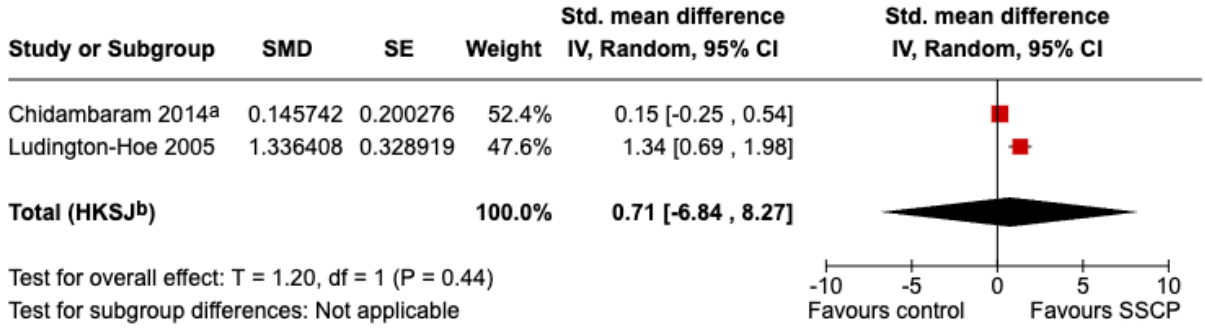
Figure 10. Forest plot SSCP versus no-treatment control: Oxygen saturation During



Test for overall effect: Z = 5.28 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[c]) = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%

Footnotes
[a]first heel stick
[b]CI calculated by Wald-type method.
[c]Tau² calculated by DerSimonian and Laird method.

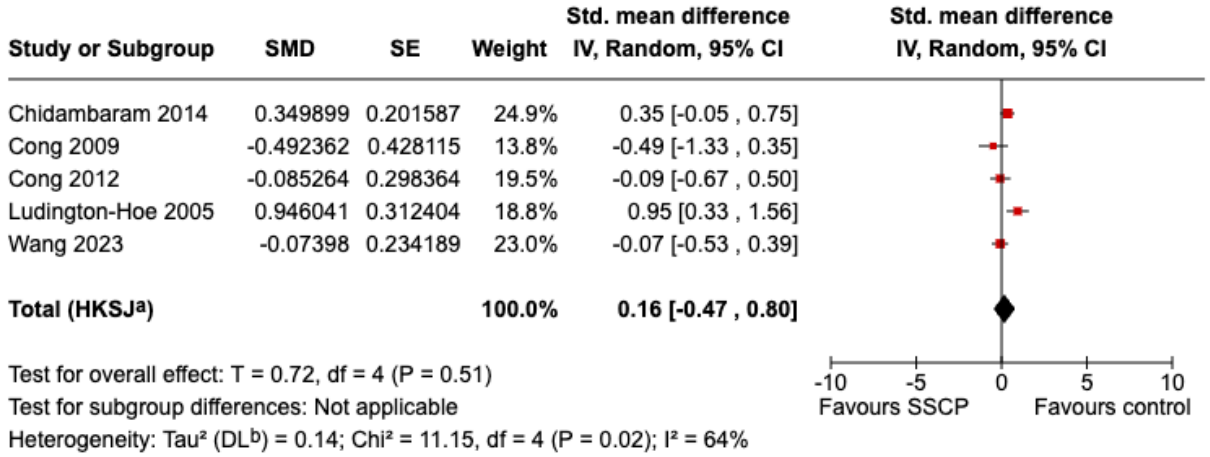
Figure 11. Forest plot SSCP versus no-treatment control: Oxygen saturation Distal-after



Test for overall effect: T = 1.20, df = 1 (P = 0.44)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[c]) = 0.63; Chi² = 9.56, df = 1 (P = 0.002); I² = 90%

Footnotes
[a]15 mins
[b]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[c]Tau² calculated by DerSimonian and Laird method.

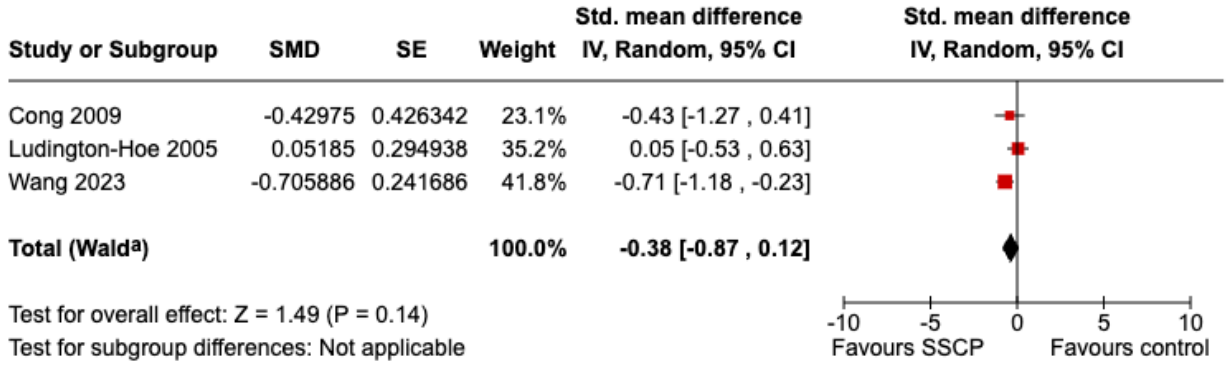
Figure 12. Forest plot SSCP versus no-treatment control: Heart rate Baseline



Test for overall effect: T = 0.72, df = 4 (P = 0.51)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.14; Chi² = 11.15, df = 4 (P = 0.02); I² = 64%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by DerSimonian and Laird method.

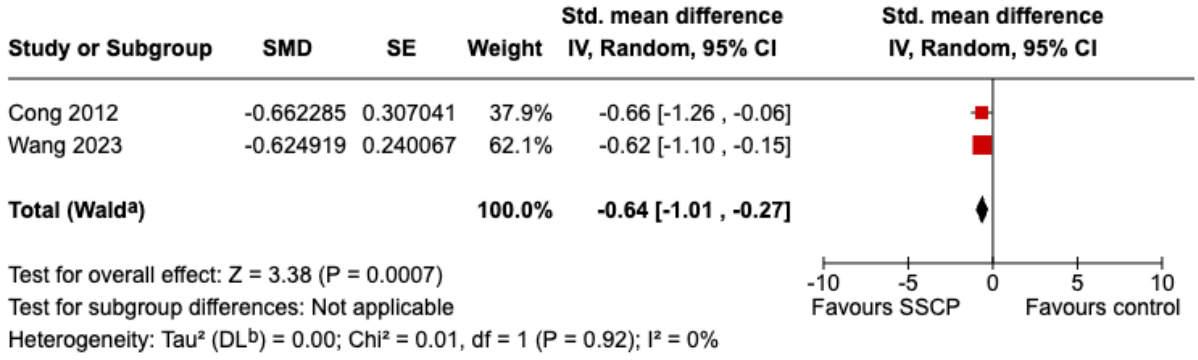
Figure 13. Forest plot SSCP versus no-treatment control: Heart rate During



Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.09; Chi² = 3.95, df = 2 (P = 0.14); I² = 49%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Figure 14. Forest plot SSCP versus no-treatment control: Heart rate Immediate-after

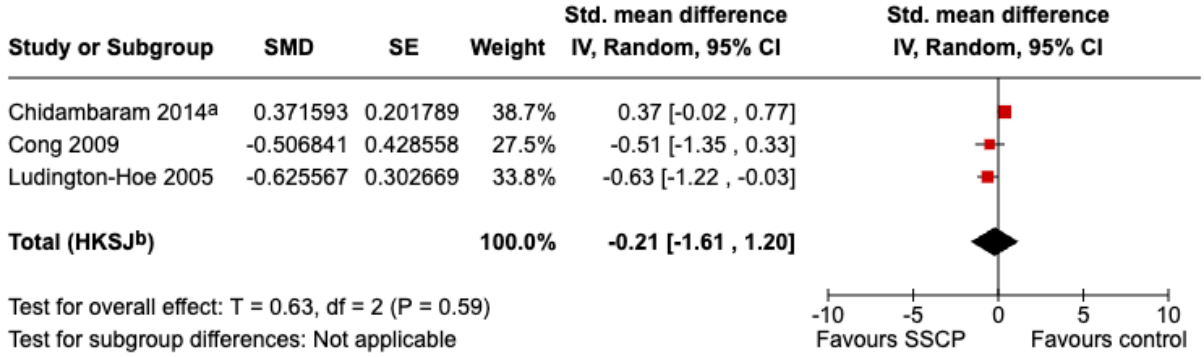


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 15. Forest plot SSCP versus no-treatment control: Heart rate Distal-after



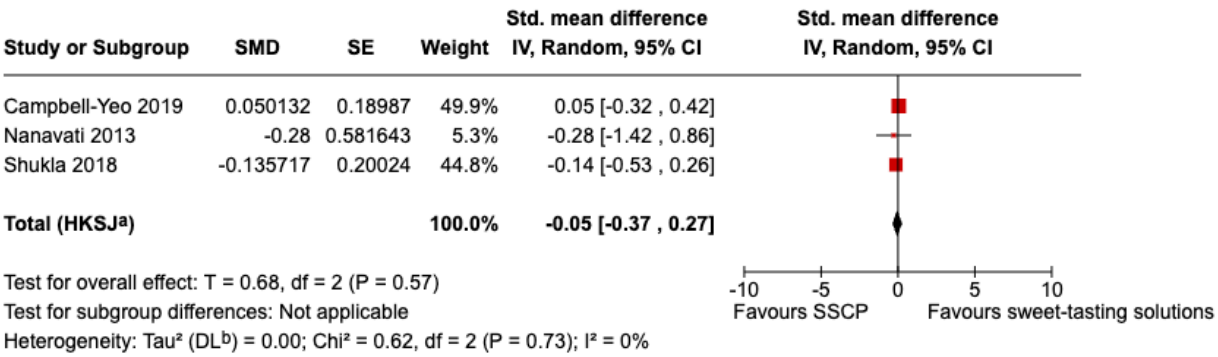
Footnotes

[a]15 mins

[b]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[c]Tau² calculated by DerSimonian and Laird method.

Figure 16. Forest plot SSCP versus sweet-tasting solutions: PIPP Immediate-after



Test for overall effect: T = 0.68, df = 2 (P = 0.57)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%

Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by DerSimonian and Laird method.

Supplemental Materials - Appendix A: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 14
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page ii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 15
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 15
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 16
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 16
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 61
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 16-17
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pages 16-17
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 17-18
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 17
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 17
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 18
Synthesis	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study	Page 18

Section and Topic	Item #	Checklist item	Location where item is reported
methods		intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 18
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 50-57
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 18
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 17
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 18
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 49
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 49
Study characteristics	17	Cite each included study and present its characteristics.	Pages 20-21
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pages 20-21
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 22-30
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 22-32
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 22-30
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pages 22-30
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pages 22-30
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 22-30
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 34-38
	23b	Discuss any limitations of the evidence included in the review.	Page 38
	23c	Discuss any limitations of the review processes used.	Page 38
	23d	Discuss implications of the results for practice, policy, and future research.	Page 40
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 16
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 16
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	In manuscript
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not publicly available

Supplemental Materials - Appendix B: Search Strategies

Cochrane Search Strategy

#1	MeSH descriptor: [Kangaroo-Mother Care Method] this term only
#2	(Kangaroo NEAR/3 Care):ti,ab
#3	(skin NEAR/2 skin NEAR/2 (care or contact)):ti,ab
#4	MeSH descriptor: [Therapeutic Touch] this term only
#5	((Parental or maternal or paternal or therapeutic) NEAR/2 Touch):ti,ab
#6	MeSH descriptor: [Touch] this term only
#7	{or #1-#6}
#8	MeSH descriptor: [Infant, Very Low Birth Weight] explode all trees
#9	MeSH descriptor: [Infant, Premature] explode all trees
#10	(newborn or neuborns or "new-born" or "new-borns" or neonat* or preemie* or prematur* or "pre-mature" or "pre-term" or prematuritas or preterm or "extremely low birth weight" or "very low birth-weight" or ELBW or VLBW or NICU*):ti,ab
#11	MeSH descriptor: [Intensive Care Units, Neonatal] this term only
#12	((neonatal or newborn) NEAR/2 (icu or icus)):ti,ab
#13	((newborn* or neonatal) NEAR/2 intensive NEAR/2 care NEAR/2 unit*):ti,ab
#14	{or #8-#13}
#15	MeSH descriptor: [Pain Measurement] this term only
#16	MeSH descriptor: [Pain Management] this term only
#17	MeSH descriptor: [Pain] this term only
#18	MeSH descriptor: [Acute Pain] this term only
#19	MeSH descriptor: [Pain, Procedural] this term only
#20	MeSH descriptor: [Heel] this term only
#21	(heel NEAR/2 (lance* or lancing* or stick or sticks)):ti,ab
#22	MeSH descriptor: [Punctures] this term only
#23	MeSH descriptor: [Phlebotomy] this term only
#24	MeSH descriptor: [Bloodletting] this term only
#25	MeSH descriptor: [Injections] explode all trees
#26	(phlebotom* or venesection* or venipuncture* or venepuncture* or venisection* or puncture or punctures or bloodletting):ti,ab
#27	(skin-breaking or (skin NEAR/2 breaking)):ti,ab
#28	(injection* or needle* or prick or pricks or poke or pokes or jab or jabs):ti,ab
#29	{or #15-#28}
#30	#7 AND #14 AND #29

MEDLINE (OVID) Search Strategy

1 Kangaroo-Mother Care Method/
2 (Kangaroo adj3 Care).ti,ab,kf.
3 (skin adj2 skin adj2 (care or contact)).ti,ab,kf.
4 Therapeutic Touch/
5 ((Parental or maternal or paternal or therapeutic) adj2 Touch).ti,ab,kf.
6 Touch/
7 or/1-6
8 infant, very low birth weight/ or infant, extremely low birth weight/ or infant, premature/ or infant, extremely premature/
9 (newborn* or "new-born*" or neonat* or preemie* or prematur* or "pre-mature" or "pre-term" or prematuritas or preterm or "extremely low birth weight" or "very low birth-weight" or ELBW or VLBW or NICU*).mp.
10 Intensive Care Units, Neonatal/
11 ((neonatal or newborn) adj2 (icu or icus)).ti,ab,kf.
12 ((newborn* or neonatal) adj2 intensive adj2 care adj2 unit*).ti,ab,kf.
13 or/8-12
14 Pain Measurement/
15 Pain Management/
16 pain/ or acute pain/ or pain, procedural/
17 (pain or pains or painful*).ti,ab,kf.
18 heel/
19 (heel adj2 (lance* or lancing* or stick or sticks)).ti,ab,kf.
20 punctures/ or phlebotomy/ or bloodletting/ or injections/
21 (phlebotom* or venesection* or venipuncture* or venepuncture* or venisection* or puncture or punctures or bloodletting).ti,ab,kf.
22 (skin-breaking or (skin adj2 breaking)).ti,ab,kf.
23 injections/ or injections, intra-arterial/ or injections, intra-articular/ or viscosupplementation/ or injections, intralesional/ or injections, intralymphatic/ or injections, intramuscular/ or injections, intraperitoneal/ or injections, intravenous/ or injections, intraventricular/ or injections, spinal/ or injections, epidural/ or blood patch, epidural/ or injections, subcutaneous/ or injections, intradermal/ or injections, jet/ or biolistics/ or mesotherapy/ or injection, intratympanic/ or microinjections/
24 (injection* or needle* or prick or pricks or poke or pokes or jab or jabs).ti,ab,kf.
25 or/14-24
26 7 and 13 and 25

EMBASE (OVID) Search Strategy

1 kangaroo care/
2 (Kangaroo adj3 Care).ti,ab,kf.
3 (skin adj2 skin adj2 (care or contact)).ti,ab,kf.
4 therapeutic touch/
5 ((Parental or maternal or paternal or therapeutic) adj2 Touch).ti,ab,kf.
6 touch/
7 or/1-6
8 very low birth weight/ or extremely low birth weight/
9 prematurity/ or extremely premature birth/ or very premature birth/
10 (newborn* or "new-born*" or neonat* or preemie* or prematur* or "pre-mature" or "pre-term" or prematuritas or preterm or "extremely low birth weight" or "very low birth-weight" or ELBW or VLBW or NICU*).mp.
11 neonatal intensive care unit/
12 ((neonatal or newborn) adj2 (icu or icus)).ti,ab,kf.
13 ((newborn* or neonatal) adj2 intensive adj2 care adj2 unit*).ti,ab,kf.
14 or/8-13
15 pain measurement/
16 pain assessment/ or grimace scale/ or neonatal infant pain scale/
17 pain/ or procedural pain/
18 (pain or pains or painful*).ti,ab,kf.
19 (heel adj2 lance).ti.
20 heel/
21 (heel adj2 (lance* or lancing* or stick or sticks)).ti,ab,kf.
22 blood sampling/ or phlebotomy/ or puncture/ or micropuncture/ or bloodletting/
23 (phlebotom* or venesection* or venipuncture* or venepuncture* or venisection* or puncture or punctures or bloodletting).ti,ab,kf.
24 (skin-breaking or (skin adj2 breaking)).ti,ab,kf.
25 injection/ or bolus injection/ or injection site/ or jet injection/ or microinjection/ or parenteral drug administration/ or intradermal drug administration/ or intramuscular drug administration/ or subcutaneous drug administration/ or intralesional drug administration/
26 (injection* or needle* or prick or pricks or poke or pokes or jab or jabs).ti,ab,kf.
27 or/15-26
28 7 and 14 and 27
29 7 and 14
30 limit 29 to (epidural or intraarterial or intraarticular or intralesional or intramuscular or intraperitoneal or intraspinal or intrathecal or intravenous or parenteral or subcutaneous or transdermal)
31 28 or 30
32 limit 31 to (conference abstract or conference paper or "conference review")
33 31 not 32

PsycINFO (OVID) Search Strategy

1	*"Kangaroos"/
2	(Kangaroo adj3 Care).ti,ab,id.
3	(skin adj2 skin adj2 (care or contact)).ti,ab,id.
4	physical contact/
5	Tactual Perception/
6	((Parental or maternal or paternal or therapeutic) adj2 Touch).ti,ab,id.
7	or/1-6
8	premature birth/
9	birth weight/
10	(newborn* or "new-born*" or neonat* or preemie* or prematur* or "pre-mature" or "pre-term" or prematuritas or preterm or "extremely low birth weight" or "very low birth-weight" or ELBW or VLBW or NICU*).mp.
11	neonatal intensive care/
12	((neonatal or newborn) adj2 (icu or icus)).ti,ab,id.
13	((newborn* or neonatal) adj2 intensive adj2 care adj2 unit*).ti,ab,id.
14	or/8-13
15	pain measurement/
16	pain/ or acute pain/ or grimaces/
17	(pain or pains or painful*).ti,ab,id.
18	(heel adj2 (lance* or lancing* or stick or sticks)).ti,ab,id.
19	(phlebotom* or venesection* or venipuncture* or venepuncture* or venisection* or puncture or punctures or bloodletting).ti,ab,id.
20	(skin-breaking or (skin adj2 breaking)).ti,ab,id.
21	injections/ or intravenous injections/ or subcutaneous injections/
22	(injection* or needle* or prick or pricks or poke or pokes or jab or jabs).ti,ab,id.
23	or/15-22
24	7 and 14 and 23
25	7 and 14
26	limit 25 to 2500 physiological psychology & neuroscience
27	25 or 26

CINAHL (EBSCO) Search Strategy

S1	(MH "Kangaroo Care") OR (MH "Touch") OR (MH "Therapeutic Touch")
S2	TX (Kangaroo N3 Care)
S3	TX ((skin N2 skin N2 (care OR contact)))
S4	TX (((Parental or maternal or paternal or therapeutic) N2 Touch))
S5	S1 OR S2 OR S3 OR S4
S6	(MH "Infant, Premature") OR (MH "Infant, Very Low Birth Weight")
S7	TX ((newborn* or "new-born*" or neonat* or preemie* or prematur* or "pre-mature" or "pre-term" or prematuritas or preterm or "extremely low birth weight" or "very low birth-weight" or ELBW or VLBW or NICU*))
S8	(MH "Intensive Care Units, Neonatal") OR (MH "Intensive Care, Neonatal")
S9	TX (((neonatal or newborn) N2 (icu or icus)))
S10	TX (((newborn* or neonatal) N2 intensive N2 care N2 unit*))
S11	S6 OR S7 OR S8 OR S9 OR S10
S12	(MH "Pain Measurement") OR (MH "Pain Management")
S13	(MH "Pain") OR (MH "Pain, Procedural")
S14	TX ((pain or pains or painful*))
S15	TX ((heel N2 (lance* or lancing* or stick or sticks)))
S16	(MH "Punctures") OR (MH "Arterial Puncture") OR (MH "Venipuncture") OR (MH "Phlebotomy") OR (MH "Injections") OR (MH "Injection Sites") OR (MH "Injections, Intraarterial") OR (MH "Injections, Intraarticular") OR (MH "Injections, Intradermal") OR (MH "Injections, Intralesional") OR (MH "Injections, Intramuscular") OR (MH "Injections, Intraspinal") OR (MH "Injections, Intravenous") OR (MH "Injections, Intraventricular") OR (MH "Injections, Subcutaneous") OR (MH "Injections, Jet") OR (MH "Z-Track Injection") OR (MH "Blood Patch, Epidural") OR (MH "Injections, Epidural")
S17	TX ((phlebotom* or venesection* or venipuncture* or venepuncture* or venisection* or puncture or punctures or bloodletting))
S18	TX ((skin-breaking or (skin N2 breaking)))
S19	TX ((injection* or needle* or prick or pricks or poke or pokes or jab or jabs))
S20	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
S21	S5 AND S11 AND S20

Supplemental Materials - Appendix C: Risk of Bias Tool

Domain 1: Risk of bias arising from the randomization process

- **Low risk of bias:**
  - Process for allocation sequence was random and concealed until participants were enrolled and assigned to interventions.
  - Baseline differences between intervention groups did not suggest any problems with the randomization process.
- **High risk of bias:**
  - Allocation sequence was not random or not concealed until participants were enrolled and assigned to interventions; there are baseline differences between groups that suggest issues with the randomization process.
- **Some concerns:**
  - Not enough information provided to ascertain whether allocation sequence/randomization process was adequate.

Domain 2: Risk of bias in selection of participants into the study (or into the analysis).
Is there a risk of bias due to poorly defined or poorly applied inclusion and exclusion criteria?

- **Low risk of bias:**
  - Inclusion and/or exclusion criteria were clearly defined by the authors and used to screen participants during recruitment (note: can assume that inclusion/exclusion criteria were applied during recruitment unless evidence suggests otherwise).
- **High risk of bias:**
  - There is evidence that inclusion and/or exclusion criteria were used inconsistently (i.e., different criteria used for different participants) or were used to exclude participants who had already been recruited.
- **Some concerns:**
  - The authors do not provide information on inclusion and/or exclusion criteria **OR** inclusion and/or exclusion criteria had to be inferred.

Note: In addition to confirming that inclusion/exclusion criteria were specified for the study, it is also necessary to confirm that the criteria were applied consistently. Review the "Methods" and "Results" sections to confirm that there is no evidence that some participants' data were excluded after their participation. Information on this can also be gathered by comparing the # of participants recruited and the # for whom data is reported.

Domain 3: Risk of bias arising from measurement of the exposure.
Is there a risk of bias due the exposure (acutely painful procedures) not being clearly defined, valid, reliable, and implemented consistently across all study participants?

- **Low risk of bias:**
  - The procedure is recognized as inducing an acute pain-related response (references provided if applicable)
  - Painful procedure is clearly described in detail (pain onset, pain off-set, duration, stimuli, etc.) in relation to pain measurement
  - Statement was made that the standard operating procedure for the pain procedure and pain measurement was conducted consistently across all participants/groups

    - Statement was made that environmental factors/context (i.e., pain management techniques) were consistent across all participants/groups
    - If certain factors could not be kept consistent across groups, adequate statistical approaches were employed to correct for these effects
- **High risk of bias:**
    - There is evidence that aspects of the exposure delineated above were not kept consistent across all participants/groups and this likely influenced the outcome
- **Some concerns:**
    - Not enough information is provided on the exposure procedure to ascertain whether the exposure was kept consistent across all participants/groups

Domain 4: Risk of bias due to missing data

This item allows us to determine whether missing data biased the results of the study and whether the results of the study are reflective of the population they are intended to reflect. Risks of bias due to missing data can be introduced when some participants are missing data on select measures. This criterion can be verified by comparing the # of participants recruited and the # for whom data is reported.

- **Low risk of bias:**
    - There is a low level of missing data (5% or less)[2] **OR** the authors examined the relationship between missingness and demographic/outcome variables and missingness occurred at random
- **High risk of bias:**
    - There is a high level of missing data (i.e., 20% or more) **AND** either the authors did not examine the relationship between missingness and demographic/outcome variables, or missing data did not occur at random which biased the results
- **Some concerns:**
    - The proportions of outcome missing data were not reported or could not be determined **OR** there is a moderate level of missing data (between 5% and 20%) and authors did not examine relationship between missingness and demographic/outcome variables.

Domain 5: Risk of bias arising from measurement of the outcome

- **Low risk of bias:**
    - Outcomes are clearly named (e.g., physiological (e.g., heart rate), behavioural (e.g., cry duration), multimodal (e.g., PIPP)) and are clearly defined. Measurement or ascertainment of the outcome could not have differed between intervention groups.
- **High risk of bias:**
    - The outcome is not clearly named and/or the authors' have incorrectly defined the outcome (i.e., outcome description does not match the methodology used). Measurement or ascertainment of the outcome could have differed between intervention groups.
- **Some concerns:**

[2] Cochrane risk of bias tool defines low risk of bias as "all or nearly all data points available". We defined this as 95%.

- Outcome is named, but definition is missing some required details that support interpretation of the outcome. Not enough information to determine if measurement or ascertainment of the outcome could have differed between intervention groups.

Domain 6: Risk of bias in selection of the reported results

- **Low risk of bias:**
  - All eligible outcome measurements within the outcome domain are reported. Data reported is consistent with statistics delineated in pre-specified analysis plan.
- **High risk of bias:**
  - There is evidence that selective outcome reporting occurred (without justification), and the fully reported results were likely selected from multiple outcome measurements or analyses of the data on the basis of the results.
- **Some concerns:**
  - Unclear whether selective outcome reporting occurred because there is no statistical analysis plan or not enough detail was given to enable an assessment.

OVERALL ROB (based on decisions across Domains 1-6):

- **Low risk of bias:** The study is judged to be low risk of bias for all domains.
- **High risk of bias:** The study is judged to be at high risk of bias in at least one domain **OR** the study is judged to have some concerns for multiple domains, leading to an additive overall judgement of high risk of bias
- **Some concerns:** The study is judged to have some concerns in at least one domain, but no domains are at high risk of bias.