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Skin-to-skin care for procedural pain in neonates (Review)

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[Intervention Review]

Skin-to-skin care for procedural pain in neonates

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ABSTRACT

Background

Skin-to-skin care (SSC), otherwise known as Kangaroo Care (KC) due to its similarity with marsupial behaviour of ventral maternal-infant contact, is one non-pharmacological intervention for pain control in infants.

Objectives

The primary objectives were to determine the effect of SSC alone on pain from medical or nursing procedures in neonates undergoing painful procedures compared to no intervention, sucrose or other analgesics, or additions to simple SSC such as rocking; and the effects of the amount of SSC (duration in minutes) and the method of administration (who provided the SSC, positioning of caregiver and neonate pair).

The secondary objectives were to determine the incidence of untoward effects of SSC and to compare the SSC effect in different postmenstrual age subgroups of infants.

Search methods

The standard methods of the Cochrane Neonatal Collaborative Review Group were used. Databases searched in August 2011: Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*); Evidence-Based Medicine Reviews; MEDLINE (1950 onwards); PubMed (1975 onwards); EMBASE (1974 onwards); CINAHL (1982 onwards); Web of Science (1980 onwards); LILACS database (1982 onwards); SCIELO database (1982 onwards); PsycInfo (1980 onwards); AMED (1985 onwards); Dissertation-Abstracts International (1980 onwards). Searches were conducted throughout September 2012.

Selection criteria

Studies with randomisation or quasi-randomisation, double or single-blinded, involving term infants (≥ 37 completed weeks post-menstrual age (PMA)) to a maximum of 44 weeks PMA and preterm infants (< 37 completed weeks PMA) receiving SSC for painful procedures conducted by doctors, nurses, or other healthcare professionals.

Data collection and analysis

The main outcome measures were physiological or behavioural pain indicators and composite pain scores. A weighted mean difference (WMD) with 95% confidence interval (CI) using a fixed-effect model was reported for continuous outcome measures. We included variations on type of tissue-damaging procedure, provider of care, and duration of SSC.

Main results

Nineteen studies (n = 1594 infants) were included. Fifteen studies (n = 744) used heel lance as the painful procedure, one study combined venepuncture and heel stick (n = 50), two used intramuscular injection, and one used 'vaccination' (n = 80). The studies that were included were generally strong and free from bias.

Eleven studies (n = 1363) compared SSC alone to a no-treatment control. Although 11 studies measured heart rate during painful procedures, data from only four studies (n = 121) could be combined to give a mean difference (MD) of 0.35 beats per minute (95% CI -6.01 to 6.71). Three other studies that were not included in meta-analyses also reported no difference in heart rate after the painful procedure. Two studies reported heart rate variability outcomes and found no significant differences. Five studies used the Premature Infant Pain Profile (PIPP) as a primary outcome, which favoured SCC at 30 seconds (n = 268) (MD -3.21, 95% CI -3.94 to -2.48), 60 seconds (n = 164) (MD -1.85, 95% CI -3.03 to -0.68), and 90 seconds (n = 163) (MD -1.34, 95% CI -2.56 to -0.13), but at 120 seconds (n = 157) there was no difference. No studies provided findings on return of heart rate to baseline level, oxygen saturation, cortisol levels, duration of crying, and facial actions that could be combined for analysis.

Eight studies compared SSC to another intervention with or without a no-treatment control. Two cross-over studies (n = 80) compared mother versus other provider on PIPP scores at 30, 60, 90, and 120 seconds with no significant difference. When SSC was compared to other interventions, there were not enough similar studies to pool results in an analysis. One study compared SSC with and without dextrose and found that the combination was most effective and that SSC alone was more effective than dextrose alone. Similarly, in another study SSC was more effective than oral glucose for heart rate but not oxygen saturation. SSC either in combination with breastfeeding or alone was favoured over a no-treatment control, but was not different to breastfeeding. There were not enough participants with similar outcomes and painful procedures to compare age groups or duration of SSC. No adverse events were reported in any of the studies.

Authors' conclusions

SSC appears to be effective, as measured by composite pain indicators and including both physiological and behavioural indicators, and safe for a single painful procedure such as a heel lance. Purely behavioural indicators tended to favour SSC but there remains questionable bias regarding behavioural indicators. Physiological indicators were typically not different between conditions. Only two studies compared mother providers to others, with non-significant results. There was more heterogeneity in the studies with behavioural or composite outcomes. There is a need for replication studies that use similar, clearly defined outcomes. New studies examining optimal duration of SSC, gestational age groups, repeated use, and long-term effects of SSC are needed.

PLAIN LANGUAGE SUMMARY

Skin-to-skin (Kangaroo Care) with newborns cuts down procedural pain

Newborns wearing only a diaper being held next to their mother's bare chest is referred to as skin-to-skin contact and is also sometimes called Kangaroo Care because of its similarity to the way kangaroo mothers care for their young. Newborns, especially those who must spend time in the Neonatal Intensive Care Unit, must have various tests and procedures as part of their care, for example, heel stick, vein puncture, and injections. Giving analgesic drugs for these procedures can often pose problems so that alternatives to drugs must be found. Kangaroo Care appears to reduce the pain response to these frequent procedures, although few studies could be combined to provide strong evidence. As far as it has been reported, Kangaroo Care is safe. Nineteen studies were examined which showed that signs of pain, with a combination of physical and behavioural signs, support the use of Kangaroo Care. Physiological indicators of pain, such as heart rate, did not show a significant difference. Although we believe that Kangaroo Care is effective the size of the benefit may not be large.

BACKGROUND

Description of the condition

The preterm neonate frequently spends the first days or weeks of life in the Neonatal Intensive Care Unit (NICU), where numerous noxious procedures are part of routine care (Johnston 1997; Simons 2003; Stevens 2003; Johnston 2008; Johnston 2011b). There is substantial evidence that long-term blunting of behavioural, autonomic, and hormonal responses to pain is a result of early untreated exposure to pain in preterm neonates (Johnston 1996; Oberlander 2000; Grunau 2007a; Grunau 2007b). The most common painful procedures are heel lance and intravenous line insertions. Topical anaesthetics have not been found to be effective in this population (Larsson 1996; Stevens 1999). Sucrose has been shown to be effective (Stevens 2010a) but frequently repeated doses of sucrose in the very preterm neonate may not be safe (Johnston 2002; Lefrak 2006; Johnston 2007a). Parenteral analgesics either have negative sequelae (Marsh 1997; Anand 2004; Carbajal 2005) or have not been tested for pain in this population (Cuzzolin 2001). Behavioural methods of pain control such as non-nutritive sucking, simulated rocking, facilitated tucking and positioning have been tested, with non-nutritive sucking having a significant effect even in very preterm neonates (Campos 1994; Corff 1995; Stevens 1999a; Akman 2002; Carbajal 2002; Boyle 2004; Cignacco 2007). There is a large volume of literature on pain in neonates, including a review of over 40 measures of pain (Stevens 2007). Several studies have reported important age differences in response, with more preterm neonates having less robust and sustained responses (Craig 1984; Johnston 1993; Stevens 2007; Gibbins 2008).

Description of the intervention

Recently there has been growing interest in how mothers of preterm neonates can contribute to the promotion of growth and comfort in the NICU setting. This has been based on two premises: (1) the loss of comfort-providing roles of parents in critical care settings, and (2) the effect of maternal touch specifically in the skin-to-skin care (SSC) paradigm, or Kangaroo Care (KC), on various parameters of neonatal stability and state regulation. In studies of parents of critically ill children and infants, parents were concerned about pain management and found their child's suffering a primary source of stress (Miles 1992; Youngblut 1992; Moehn 1996; Wereszczak 1997). Even in situations where the staff believed that they were handling the child's pain well and that the parents were not distressed, this was not the case from the parents' perspective (Simons 2001). In a US and UK study of 11 NICUs, with 200 parents, almost all parents reported that their infant had experienced moderate to severe pain that was worse than they had expected (Franck 2001). Concerns about pain predicted the most important variance of parental stress. Another major concern of parents is the loss of their parental role, including to provide comfort (Miles 1989; Shields-Poe 1997; Ko 1998). In the above study of NICU parents (Franck 2002), 87% stated that they would wish to participate in managing their infant's pain. In a study of mothers engaged in KC while their infants underwent routine heel lance in the NICU, 80% of the mothers reported positive feelings and 90% said they would do it again (Campbell-Yeo 2008).

SSC, referred to as KC because of its similarity to marsupial behaviour, was first developed as a method of providing warmth for low birth weight infants in Bogota, Columbia in 1979 (Whitelaw 1985). During SSC, a diaper-clad infant is held upright between the mother's breasts, at an angle of approximately 60 ^{o}, providing maximal skin-to-skin contact between the baby and parent. A survey on the holding policy in 215 NICUs in the US indicated that almost three-quarters of the units allowed parents to hold their extubated infant in SSC (Franck 2002). There is extensive literature on KC in developing countries that is not reviewed here (Charpak 2005).

How the intervention might work

An updated review of clinical trials of SSC on targeted infant outcomes of breastfeeding, behaviour, and physiological adaption in healthy neonates found 30 studies that met the inclusion criteria, four being with late preterm infants (Moore 2007). They reported evidence supporting SSC for success and duration of breastfeeding (Carfoot 2003; Johnson 2006; Moore 2007). Physiological stability and temperature control have been consistently reported as improved during SSC (deLeeuw 1991; Christensson 1992; Bauer 1998; Ludington-Hoe 1999; Gazzolo 2000; Bohnhorst 2001; Chwo 2002; Ibe 2004; Ludington-Hoe 2004; McCain 2005; Hunt 2008). For a newborn, behaviour is primarily based on the sleep and wake state dimension of neurobehavioural organization involving the ability to make smooth transitions between sleep, quiet, and awake phases; and to maintain the most desirable state of quiet sleep (Ludington-Hoe 1996). Several studies have shown that one to three hours spent in SSC resulted in increased frequency of quiet sleep, longer duration of quiet sleep, and decreased crying (deLeeuw 1991; Ludington-Hoe 1992; Michelsson 1996; Feldman 2002; Erlandsson 2007; Kostandy 2008). For example, a randomised controlled trial (RCT) of healthy newborns randomly assigned to receive KC for one hour starting within 15 minutes after birth found that at the four hour observation time KC infants slept longer, were mostly in a quiet sleep state, exhibited more flexor movements and postures, and showed fewer extensor movements (Ferber 2004). Feldman and colleagues have reported sustained neurobehavioural regulation from 30 to 37 weeks gestational age as a result of early KC in the NICU (Feldman 2003). A Cochrane review by Conde-Agudelo reported three studies on mortality and morbidity and did not address pain response (Conde-Agudelo 2003). Given that SSC promotes autonomic sta-

bility and state regulation as well as bonding between the mother and the infant, it is logical that it would be tested as an intervention for pain where the response to noxious stimuli includes autonomic arousal and crying, in addition to giving mothers back their comforting role.

Why it is important to do this review

The American Pediatric Society and Canadian Paediatric Society Committees on Fetus and Newborn incorporated SSC as a recommended intervention. However, no systematic review with the rigour of The Cochrane Collaboration has been conducted. There could, for example, be a publication bias that would favour positive outcomes. There has been a Cochrane review of SSC for mortality and morbidity (Conde-Agudelo 2003), which did favour SSC over usual care controls for infections and weight gain.

OBJECTIVES

Primary objectives

1. To determine the effect of SSC alone on pain from medical or nursing procedures in neonates undergoing painful procedures compared to no intervention, sucrose or other analgesics, or additions to simple SSC such as rocking.
2. To determine the effects of the amount of SSC (duration in minutes), method of administration (who provided the SSC, positioning of caregiver and neonate pair) of SSC in reducing pain from medical or nursing procedures in neonates.

Secondary objectives

1. To determine the safety of SSC care for relieving procedural pain in infants, specifically reports of:
   i) bradycardia (heart rate less than 100 for 15 seconds),
   ii) desaturation (transcutaneous oxygen saturation readings of less than 80% for 15 seconds), or
   iii) apnoea (absence of spontaneous respiration for 20 seconds, or 10 seconds if accompanied by bradycardia or desaturation (Lagercrantz 1992)).
2. To compare the outcomes of neonates receiving SSC in the following postmenstrual age categories: less than 32 weeks, 32 to 36 weeks, full term (37 to 42 weeks).

METHODS

Criteria for considering studies for this review

Types of studies

Studies with randomisation or quasi-randomisation, and blinded (for example, coding video tapes of infant faces only or using physiological data from monitors) or not blinded assessors for pain response were considered for inclusion. This included different designs such as classic randomised controlled trials, randomised cross-over trials, and cluster as well as quasi-experimental designs.

Types of participants

Term infants (≥ 37 completed weeks postmenstrual age (PMA)) and preterm infants (< 37 completed weeks PMA) to a maximum of 44 weeks PMA receiving SSC for painful procedures conducted by doctors, nurses, or other healthcare professionals. The painful procedures that were included are those that are tissue damaging or considered painful, such as endotracheal suctioning (Carbajal 2008).

Types of interventions

The infant, wearing no more than a diaper, in ventral skin contact with another person during a painful procedure. We were interested in any comparisons of dosage (duration of time in SSC), any adjuvant therapies (sucrose or other sweet tastes, pacifier, topical anaesthetics, systemic analgesics), provider of SSC (mother, father, nurse, other), and variations of SSC such as the addition of rocking or music.

Types of outcome measures

Primary outcomes

Pain response to or recovery from an invasive procedure, or both, as measured by at least one of the following.

1. Behavioural indicators (audible cry duration in seconds or milliseconds; proportion of time of total procedure time audible crying; proportion of time of total procedure that had predefined facial actions reflecting grimace e.g., brow bulge, eye squeeze, nasolabial furrow; proportion of time that had predefined body movements e.g., limb thrashing, fisting, finger splaying, limb and torso flexion).
2. Physiological indicator changes from baseline or between groups in heart rate (HR), respiratory rate, oxygen (O_2) saturation/transcutaneous oxygen tension ($tcpO_2$), and near-infrared spectroscopy (NIRS). These measures should be reported before the tissue damaging part of the procedure, during the procedure, and in the time to recovery following the procedure.
3. Hormonal indicators (salivary cortisol, serum beta-endorphins) obtained from body fluids (saliva, serum) with description of analyses e.g., radio-immune assay techniques.
4. Validated composite pain scores (including a combination of behavioural, physiological, and contextual indicators). There

are over 50 measures of pain in neonates in the literature. The ones that we assessed as being valid for neonates undergoing procedural pain include:

i) Premature Infant Pain Profile (PIPP) (Stevens 1996; Stevens 2010b). The PIPP includes gestational age, behavioural state, heart rate, oxygen saturation, and three facial reactions (brow bulge, eye squeeze, and nasolabial furrow). The range is 0 to 21 with a score of 6 indicating pain.

ii) COMFORT scale (van Dijk 2000). This scale measures alertness, calmness, respiratory response or crying, physical movement, muscle tone and facial tension, and separate latent variables for heart rate (HR) baseline and mean arterial blood pressure baseline (MAP).

iii) Behavioral Indicators of Infant Pain (BIIP) (Holsti 2007). The BIIP combines sleep and wake states, five facial actions and two hand actions.

iv) Neonatal Infant Pain Scale (NIPS) (Lawrence 1993). The NIPS includes facial expression, cry, breathing pattern, arms, legs, state of arousal.

v) Neonatal Pain, Agitation, and Sedation Scale (N-PASS) (Hummel 2008; Hummel 2010). N-PASS was originally developed to measure ongoing pain but has recently been validated as a measure of acute pain. It includes crying and irritability, behaviour and state, facial expression, extremities and tone, and vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation). It also has scores that rate sedation as well as pain and agitation.

All of these indicators yield continuous data.

There are repeated measures across time and conditions within participants. For the cross-over design studies, the first condition was analysed.

These indicators were taken immediately prior to, during, and immediately following the painful procedure. The differences between the changes from baseline between groups were used.

Secondary outcomes

Response of SSC provider, including self-report, cortisol, and physiological indicators.

Adverse events including (Lagercrantz 1992):

1. bradycardia (heart rate less than 100 for 15 seconds),
2. desaturation (transcutaneous oxygen saturation levels less than 80 for 15 seconds),
3. apnoea (absence of spontaneous respirations for more than 20 seconds or for 10 seconds if accompanied by bradycardia or desaturation).

These indicators are binary and were categorized as yes or no.

Search methods for identification of studies

Electronic searches

We performed electronic searches using the following sources: Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*; Evidence-Based Medicine Reviews; MEDLINE (1950 to January 2013); PubMed (1975 to January 2013); EMBASE (1974 to January 2013); CINAHL (1982 to January 2013); Web of Science (1980 to January 2013); LILACS database (1982 to January 2013); SCIELO database (1982 to January 2013); PsycInfo (1980 to January 2013); AMED; Dissertation-Abstracts International (1980 to January 2013). The limits were humans, but with no language limits.

The types of articles were: clinical trial, meta-analysis, RCT, review. Duplicates were excluded.

Key words and MeSH terms included: infant/newborn OR premature OR low birth weight AND painful procedure OR invasive procedure OR heel lance OR heel stick OR blood procurement OR venipuncture OR intravenous start OR arterial line insertion OR injection OR immunization AND analgesia OR pain OR comfort AND skin-to-skin OR kangaroo care OR kangaroo mother care AND randomised controlled trial OR controlled clinical trial OR crossover design OR random allocation OR blinding.

Searching other resources

In addition to the electronic searches noted above, we searched the following sources: Canadian Agency for Drugs and Technologies in Health (CADTH), University of British Columbia (UBC) Library, EAGLE, National Technical Information Service (NTIS), PsycEXTRA, Wikipedia, Web of Knowledge. We manually searched bibliographies of the most recent relevant paediatric, neonatal, and pain journals and recent major paediatric pain conference proceedings. We did not include unpublished studies. We listed abstracts under excluded studies. We did not impose language restrictions.

We made efforts to seek unpublished studies using Paediatric Pain and Neonatology Listservs requesting readers to reply.

Data collection and analysis

We developed a data extraction Excel file that allowed decisions to be made about whether or not to include a study for initial selection. We selected studies that addressed the efficacy and safety of SSC compared to another condition for relieving pain in infants. Four review authors (MCY, AF, DI, RZ) independently screened the titles and abstracts of all the references retrieved by the search strategy. At this stage, efforts were made to aim more for sensitivity than specificity, that is, we wished to be more inclusive than exclusive.

We resolved any differences by discussion among the screening review authors as well as a fifth review author (CJ). We used RevMan 5 software to collate the data.

Selection of studies

Using the studies selected from the above steps, we independently assessed the full texts of relevant papers to determine whether or not they met the inclusion criteria. We evaluated studies for methodological quality and appropriateness for inclusion according to the selection criteria. We resolved disagreements by discussion with two review authors (CJ and DS). DS verified the decisions.

We used the electronic form regarding 'Risk of bias' and 'Table 8.5a' from the *Cochrane Handbook for Sysyematic Reviews of Interventions*.

We listed rejected studies in the 'Characteristics of excluded studies' table, and we recorded the reasons for exclusion. Review authors were not blinded to author, institution, journal, or results of a study for its assessment.

All studies meeting the inclusion criteria underwent quality assessment and data extraction.

Data extraction and management

The following data were extracted.

- Study designs: methods of randomisation, intervention, cross-over design, single centre or multi-centric.
- Participants: PMA, sex, postnatal age at time of intervention, setting.
- Interventions: position duration, provider, adjuvant therapies (pharmacologic and non-pharmacologic).
- Outcomes: pain indicator (behavioural, physiological, and composite), recovery times.
- Side effects, provider response, study refusals, withdrawals and dropouts, if reported.

We made attempts to contact the study authors if data were missing or needed to be clarified.

Assessment of risk of bias in included studies

We used the guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Table 8.5a) and the electronic form regarding 'Risk of bias'. We examined:

1. sequence generation;
2. allocation concealment;
3. blinding of participants, personnel, assessors;
4. incomplete outcome data;
5. selective outcome reporting;
6. other possible sources of bias.

There were three possible answers: low risk, high risk, and unclear risk.

Funnel plots were not performed given the small number of papers that could be combined for analysis.

Four review authors (MCY, AF,CJ, RZ) independently scored each study for quality, with verification by a methods expert (DS).

Measures of treatment effect

In studies with continuous data, mean differences (MD) and standard deviations (SD) in each group and effect size (ES) for the total were used.

Unit of analysis issues

The unit of analysis was the neonates receiving SSC. There were instances in which there were repeated measures, for example, scores taken every 30 seconds within a condition (SSC or comparison). There were no cluster randomised trials.

For cross-over trials, the first condition data were used and the study was treated as an RCT (Elbourne 2002).

Dealing with missing data

We contacted all authors of studies for missing data, or if clarification was required. When the contact was not reciprocated, or the author was unable to provide the requested data, the study was excluded from the data synthesis.

Assessment of heterogeneity

The decision to perform a meta-analysis was based on the clinical decision regarding the appropriateness of combining trials and outcomes. Heterogeneity was explored using the I^2 statistic. Given the variability in the type of intervention, outcomes measured, etc., it was safe to assume that we were not estimating a single effect size but rather a distribution of effect sizes. Consequently, we used a fixed-effect model (Erez 1996; Hedges 1998; Overton 1998; Field 2003).

The statistical analysis was performed using RevMan 5.1 software, which is provided by The Cochrane Collaboration. We applied the Chi^2 test (Q test) and the I^2 statistic to assess between-study heterogeneity. With continuous data, we expressed the effect as weighted mean difference (WMD) and 95% confidence interval (CI).

Assessment of reporting biases

We sought protocols in trial registries and compared the reports to the protocols in order to determine if there might be selective reporting. We would have attempted to contact the corresponding authors if there had been discrepancies, but there were none.

In examining the studies for duplication bias, we closely examined articles from repeated authors or sites and compared sample size, characteristic, and details of the studies. When there appeared to be overlap, we attempted to contact the corresponding author, or when everything was similar we assumed it was a duplicate and included only one of the articles.

When we were not successful in contacting authors, the possible sources of reporting bias were included in our conclusions.

We had planned to do an analysis of publication bias to determine if negative results were less likely to be published in peer-reviewed journals. However, we found no examples of significant negative results, other than for one of several outcomes in one study, including in trial registries and in the grey literature. Therefore, this analysis was not conducted.

We examined the range of languages, locations, and citation sources to examine potential bias. Only English language reports were found, although some were from non-anglophone countries.

Data synthesis

For studies using similar outcomes, both in terms of the pain indicator and the time frame examined, data were congregated and analysed together. We computed mean differences and standardized mean differences (log transformations). Data were entered into RevMan via the table of means and standard deviations per group in order to develop a forest plot.

Subgroup analysis and investigation of heterogeneity

We were unable to form group analyses as we had intended for the following categories: gestational age less than 32 weeks, between 32 to 36 weeks, and full term (37 to 42 weeks); or duration or 'dose' of SSC. There were not sufficient studies with similar outcomes to compare the effect of SSC on these factors.

As above, we performed heterogeneity tests using the Chi^2 test and I^2 statistic.

Sensitivity analysis

We were not able to conduct a sensitivity analysis as there were not enough studies examining similar outcomes with similar age groups or procedures.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies below.

Results of the search

A total of 39 studies were identified for possible inclusion in this first review. An additional study (the 38th) was found as an abstract, but had not been published at the time of review preparation. Of the 39 studies, 19 were included. Two reports (Sajedi 2007; Kashaninia 2008) were of the same study, so that only one was included and it counted as one of the 19 unique studies.

Included studies

The 19 included studies reported on a total of 1594 infants. Among the included studies, four were with full term neonates (Gray 2000; Sajedi 2007; Chermont 2009; Saeidi 2011) and the remaining 15 were with preterm neonates (Johnston 2003; Ludington-Hoe 2005; Castral 2008; Freire 2008; Johnston 2008; Kostandy 2008; Akcan 2009; Cong 2009; Johnston 2009; Okan 2010; Cong 2011; Johnston 2011; Cong 2012; Johnston 2012; Nimbalkar 2013). Details of each study are outlined in the tables under Characteristics of included studies.

Most (15) of the included studies examined responses to the painful procedure of heel lance (Gray 2000; Johnston 2003; Ludington-Hoe 2005; Freire 2008; Castral 2008; Johnston 2008; Kostandy 2008; Cong 2009; Johnston 2009; Okan 2010; Cong 2011; Johnston 2011; Cong 2012; Johnston 2012; Nimbalkar 2013) and are shown in Table 1. Three studies (Sajedi 2007; Chermont 2009; Saeidi 2011) examined the response to intramuscular injection (Table 2) and one study (Akcan 2009) included both venipuncture and heel lance (Table 3).

Outcome measures were varied among studies, with many including more than one. Physiological measures included heart rate during the painful procedure (Gray 2000; Johnston 2003; Ludington-Hoe 2005; Sajedi 2007; Castral 2008; Johnston 2008; Freire 2008; Cong 2009; Okan 2010; Cong 2012; Nimbalkar 2013) and after the painful procedure (Gray 2000; Ludington-Hoe 2005; Sajedi 2007; Castral 2008; Johnston 2008; Cong 2009; Cong 2012); heart rate recovery (time to return to baseline levels post-procedure (Johnston 2008; Johnston 2009; Johnston 2011; Johnston 2012)); spectral analysis of electrocardiogram (ECG) signals of low frequency spectrum, high frequency spectrum, and low-to-high frequency ratio (Cong 2009; Cong 2012); transcutaneous oxygen saturation levels (Johnston 2003; Ludington-Hoe 2005; Sajedi 2007; Johnston 2008; Okan 2010; Saeidi 2011); respiratory rate (Ludington-Hoe 2005); and salivary cortisol levels (Cong 2011). Behavioural state was used in two studies (Ludington-Hoe 2005; Cong 2009). Cry duration was an outcome for five studies (Gray 2000; Ludington-Hoe 2005; Kostandy 2008; Okan 2010; Saeidi 2011). Facial grimacing, not according to a validated measure, was used in two studies (Gray 2000; Okan 2010), while in three others the validated Neonatal Facial Coding Scale (NFCS) was used (Castral 2008; Chermont 2009; Okan 2010). Validated composite pain measures that included both physiological and behavioural indicators were used in 13 studies. The Premature Infant Pain Profile (PIPP) was used in 10 studies (Johnston 2003; Freire 2008; Johnston 2008; Akcan 2009; Johnston 2009; Chermont 2009; Cong 2011; Johnston 2011; Johnston 2012; Nimbalkar 2013), and the Neonatal Infant Pain Scale (NIPS) was used in three studies (Sajedi 2007; Chermont 2009; Saeidi 2011).

Excluded studies

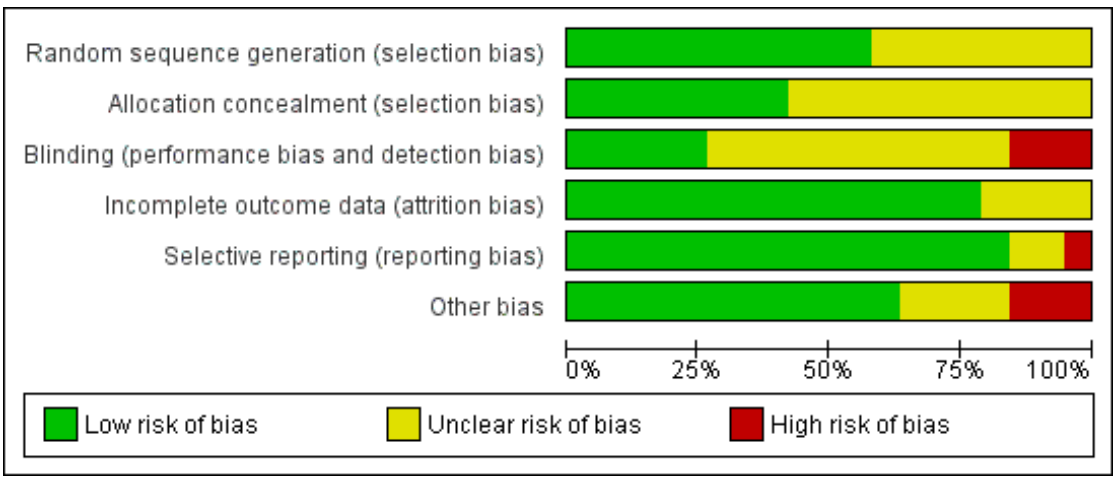
Of the 19 studies that were excluded, two focused on breastfeeding

(Uga 2008; Abdel-Razek 2009), four did not have SSC as defined in this review (Bellieni 2002; Arditi 2006; Bellieni 2007; Vivancos 2010), and three did not have ventral skin contact as a part of their SSC intervention (Reis 2003; Axelin 2009; Campbell-Yeo 2012). Maternal interview was the focus of one study (Silva 2004). One study used maternal voice without actual contact (Johnston 2007b) while another used neurobehavioural scores (NIDCAP) associated with pain, which are not validated as a pain measure (Ferber 2008). One study, Kashaninia 2008, was a duplicate of another (Sajedi 2007). Finally, seven studies reported on SSC alone without implementation of a painful procedure (Mooncey 1997; Gazzolo 2000; Morelius 2005; Miles 2006; Erlandsson 2007; Gabriel 2010; Schlez 2011).

Risk of bias in included studies

The risk of bias for each study may be seen under Characteristics of included studies and as percentages across all included studies in Figure 1.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation, a procedure to avoid selection bias, was adequate in 11 studies. Allocation concealment, another source of selection bias, was deemed adequate for eight studies.

Blinding

Blinding to avoid performance or detection bias was adequate in only five of the studies. Although 13 of the remaining trials did institute measures to overcome detection bias, the outcomes were assessed either by monitoring equipment or by persons naive to the intervention, so some uncertainty remained especially when video observations were made. Only two studies specifically mentioned how they dealt with blinding the observers.

Incomplete outcome data

Incomplete outcome data were rated above low risk in only four studies.

Selective reporting

Reporting was adequate in all but three studies. Two were unclear and one study's parameters as reported in the trial registry were not included in the report.

Other potential sources of bias

There were three individual cases of other bias: there was a combination of two data sets, different times for the painful procedure by group were not included in the regression analysis, and consent was obtained after randomisation. Four other studies had unclear potential bias. In one, there was some potential for inconsistency among sites regarding sucrose use in the usual care group. A power

calculation was not reported in one study, and the washout period was not described in the two others.

Heterogeneity results

There were many outcomes for which heterogeneity could not be measured via the I^2 statistic, that is, where only one study reported an outcome such as change in heart rate or change in oxygen saturation. When the I^2 statistic could be calculated the results showed a wide range, with the physiological outcomes having I^2 values of 0% and some composite measures having values over 50%, for example, PIPP at 30 seconds following heel lance versus control, I^2 = 79%.

Effects of interventions

Inconsistencies in the outcomes prevented all studies from being included in meta-analyses. Each study is thus reported separately and appears in Table 1 and Table 2 below, grouped according to the painful intervention.

1. Effectiveness of skin-to-skin care (SSC) compared to incubator control (Comparison 1)

1.1 Heart rate response

Eleven studies examined heart rate during the heel lance procedure (Gray 2000; Johnston 2003; Ludington-Hoe 2005; Sajedi 2007; Castral 2008; Freire 2008; Johnston 2008; Cong 2009; Okan 2010; Cong 2012; Nimbalkar 2013). Johnston 2008 reported the average heart rate to be significantly lower at 30 ($P < 0.01$), 60 ($P < 0.01$), and 90 ($P < 0.05$) seconds post-heel lance. Only four studies could be combined in an analysis (Castral 2008; Cong 2009; Ludington-Hoe 2005; Cong 2012) since results of the first condition only were not reported in cross-over designs, and not all authors responded to requests for the data for the first condition separately. As well, the duration of time for which the heart rate was collected either varied between studies or was not reported. Finally, when authors did respond, the calculations were conducted differently (that is, maximum, not mean heart rate was acquired). Cong 2012 reported two studies in the same manuscript, one of SSC for 30 minutes and one of SSC for 15 minutes. One other study, Sajedi 2007, examined heart rate during intramuscular injection and reported lower scores, that is, in favour of SSC. Johnston 2003 reported no overall differences, Johnston 2008 provided unpublished data for the first condition on maximum heart rate with significant differences in favour of SSC. Okan 2010 reported the median heart rate for SSC plus breast feeding, SSC alone, and control, and found significantly higher heart rate in the control but similar levels in the two intervention groups. Nimbalkar 2013 reported change in pulse, which significantly favoured SSC, but this was for the total sample and was not for the first condition separately in the cross-over design.

The meta-analysis showed differences between the experimental and control groups ranging from 0.57 to 2.3 beats per minute with a non-significant MD of 0.35 (95% CI -6.01 to 6.71) beats per minute (Analysis 1.1).

1.2 Heart rate recovery

Heart rate following the painful procedure was reported in five studies, but only four could be entered into the analysis (Ludington-Hoe 2005; Castral 2008; Cong 2009; Cong 2012, note the latter report contains two studies). The MD was non-significant at -3.73 (95% CI -8.86 to 1.39) (Analysis 1.2). The remaining studies (Gray 2000; Cong 2009) favoured SSC. Johnston 2008 reported that the time to return to baseline heart rate following the application of the adhesive bandage (signifying the end of blood sampling) was significantly faster at 123 seconds (95% CI 103 to 142) for the KC condition and 193 seconds for the incubator condition (95% CI 158 to 227; $F (61, 1) = 13.6$, $P < 0.0000$).

1.3 Heart rate variability

Two studies reported heart rate variability as an outcome (Cong 2009; Cong 2012). Both studies had a cross-over design and the first condition was separated out for this review. In Cong 2009, the low frequency/high frequency (LF/HF) ratio was lower at heel stick than with SSC, although it was lower in SSC during other phases of the procedure, particularly recovery. Both HF and LF were higher in the SSC condition so that across most phases of the procedure SSC was favoured. In Cong 2012, infants were randomly ordered into 15 minutes of SSC, 30 minutes of SSC, and incubator control. The heart rate variability results were non-significantly different among the conditions.

1.4 Oxygen saturation during painful procedure

Three studies used oxygen saturation as an outcome (Ludington-Hoe 2005; Sajedi 2007; Johnston 2008), however they could not be combined for analysis. Although Ludington-Hoe 2005 and Johnston 2008 examined preterm neonates undergoing heel lance, one reported values averaged over the duration of the procedure while the other reported values averaged over 30 second epochs post-lance for the duration of the procedure. The other study, Sajedi 2007, examined full term neonates receiving intramuscular injection. Ludington-Hoe 2005 did not find significant differences between SSC and incubator care. Johnston 2008 found that the average oxygen saturation levels were significantly higher at 60 ($P < 0.01$) and 90 ($P < 0.05$) seconds post-heel lance compared to incubator controls. Sajedi 2007 reported an almost 4% lower oxygen saturation ($P < 0.001$) in the control group, favouring SSC.

1.5 Oxygen saturation after painful procedure

The same studies as above (Ludington-Hoe 2005; Sajedi 2007) as well as Saeidi 2011 also reported oxygen saturation at the end of the painful procedure. Sajedi 2007 reported a significant 2.8% higher oxygen saturation in the SSC group, but the Ludington-Hoe 2005 study showed wide variance with a similar magnitude of difference which was not significant. Saeidi 2011 reported non-significant differences in oxygen saturation.

1.6 Change in oxygen saturation

Only one study examined change in oxygen saturation (Freire 2008), in which the difference was not significant between SSC and standard care control (Table 1). Nimbalkar 2013's raw data showed a difference in oxygen saturation but following the Bonferroni correction this was not significant.

1.7 Serum cortisol

Only one study (Cong 2011) examined serum cortisol level, comparing 80 minutes and 30 minutes of SSC with a standard care control. The study showed significantly higher serum cortisol levels in the 80 minute SSC group (mean ± SD: 5.73 ± 1.97) than the standard care control group (mean ± SD: 5.32 ± 1.72), P > 0.05. Conversely, serum cortisol levels were lower in the 30 minute SSC group (mean ± SD: 5.63 ± 2.30) than the standard care control group (mean ± SD: 9.15 ± 6.59), P < 0.05 (Table 1).

1.8 Salivary cortisol

Only one study used salivary cortisol levels as an outcome (Cong 2011 (Study 1 and 2)). There were two subsamples in that study, one receiving SSC for 80 minutes and the other for 30 minutes. There were significantly higher salivary cortisol levels in the 80 minute SSC group (mean ± SD: 0.19 ± 0.10) than the standard care control group (mean ± SD: 0.15 ± 0.06), P > 0.05. Conversely, salivary cortisol levels were lower in the 30 minute SSC group (mean ± SD: 0.21 ± 0.12) than the standard care control group (mean ± SD: 0.57 ± 0.61), P < 0.05 (Table 1).

1.*9 Premature Infant Pain Profile (PIPP) at 30 seconds*

Five studies used the PIPP as the outcome for heel lance (Johnston 2003; Freire 2008; Johnston 2008; Akcan 2009; Cong 2011 (Study 1 and 2)). Cong 2011 was analysed for the two amounts of time of SSC so that the first study of 80 minutes SSC was entered first and the second study of SSC for 30 minutes was entered second, although both are listed as Cong 2011. The PIPP was reported in 30 second blocks from the time of the heel lance. At 30 seconds, based on analyses of four of the studies (Johnston 2003; Freire 2008; Johnston 2008; Cong 2011), there was a significant effect in favour of SSC (MD -3.21, 95% CI -3.94 to -2.48), although Cong 2011 (study 1) and Johnston 2008 did not find a significant difference (Analysis 1.9).

1.10 PIPP scores at 60 seconds

Three studies used the PIPP as an outcome for heel lance (Johnston 2003; Johnston 2008; Cong 2011 (Study 1 and 2)) and one used it as an outcome for heel lance or venipuncture (Akcan 2009). There was a significant difference in favour of SSC in the analysis of heel lance (MD -1.85, 95% CI -3.03 to -0.68), and again Johnston 2008 and Cong 2011 (Study 1) did not find a significant difference (Analysis 1.10).

1.11 PIPP at 90 seconds

There was a significant difference in favour of SSC with three studies (Johnston 2003; Johnston 2008; Cong 2011 (Study 2)) for the PIPP score at 90 seconds (MD -1.34, 95% CI -2.56 to -0.13) (Analysis 1.11).

1.12 PIPP at 120 seconds

Three studies used the PIPP at 120 seconds as an outcome for heel lance (Johnston 2003; Johnston 2008; Cong 2011) and one used it as an outcome for heel lance or venipuncture (Akcan 2009). There was an MD of 0.04 (95% CI -1.14 to 1.23), reflecting no significant difference (Analysis 1.12).

1.13 PIPP following end of procedure

One report, Cong 2011 (two studies of 80 and 30 minutes SSC), followed PIPP scores beyond the time of the procedure. In both studies the PIPP scores favoured SSC, measured in 30 second blocks for two minutes following the procedure, by between 8.12 and 0.4 points on the PIPP. The closer to the end of the procedure the greater the difference was in scores.

1.14 Neonatal Facial Coding System (NFCS) during painful procedure

One study used the NFCS as an outcome for heel lance on preterm neonates (Castral 2008), and another used it as an outcome in full term neonates for intramuscular injection (Chermont 2009). In Castral 2008 there was a mean difference of 1.872 in favour of SSC (P < 0.001). There was no difference between skin-to-skin alone and the standard care control in Chermont 2009.

1.15 NFCS at recovery

Similarly, at recovery one study used the NFCS as an outcome for heel lance in preterm neonates (Castral 2008) and another for

intramuscular injection in full term neonates (Chermont 2009). Both studies favoured SSC.

1.16 Duration of crying after painful procedure

Four studies included cry duration as an outcome, which ranged from 19 seconds to 0.73 seconds but was not significantly different between the experimental and control groups (MD -0.93, 95% CI -2.28 to 0.42). This analysis was based on only two studies (Ludington-Hoe 2005; Kostandy 2008) since the other two studies did not provide enough information to include their results in the analysis (Gray 2000; Okan 2010).

1.17 Neonatal Infant Pain Scale (NIPS)

Chermont 2009, Saeidi 2011, Sajedi 2007 (as reported in the same study by Kashaninia 2008) used the NIPS as an outcome. In Chermont 2009, at the time of the actual intramuscular injection SSC alone was no better than control, but it was better at recovery. In Kashaninia 2008, the NIPS, a scale used to generate interval data, was reported as ordinal data and more infants in the SSC group were in the 'no pain to mild' category. Similarly, Saeidi 2011 reported results as the percentage of participants in each group having NIPS scores of 6 or 7 during the vaccination, which significantly favoured SSC with 96% of controls with a score of 7 versus only 70% in the SSC group.

1.18 Sleep and wake state

Four studies reported on sleep and wake state (Ludington-Hoe 2005; Sajedi 2007; Cong 2009; Cong 2012). Since this is a categorical or ordinal outcome, no analysis was performed. One study, Sajedi 2007, was conducted with full term neonates while the others were with preterm neonates. There were no differences in sleep and wake state at the time of the invasive procedure, although Cong 2012 reported more infants in the SSC group in quiet sleep during recovery following the procedure, as did Ludington-Hoe 2005 who reported that infants in SSC were more likely to be in deep sleep during baseline and heel warming. Kashaninia 2008 reported state as a dichotomous outcome, fussy or any other state, and reported a higher proportion of infants to be in a 'fussy' state in the control condition.

2. Effectiveness of skin-to-skin care (SSC) with different providers (Comparison 2)

Two studies compared different providers of SSC (Johnston 2011; Johnston 2012), although Johnston 2012 was reported only as a pilot study aimed at examining feasibility and effect size (Table 4). Since both studies examined preterm neonates undergoing heel lance and used PIPP scores at 30 second intervals over two minutes following the heel lance as well as heart rate recovery (defined as time for the heart rate to return to baseline levels) they were entered into a comparison. Differences in heart rate recovery were not significant (MD -32.58, 95% CI -92.43 to 27.26) in spite of the large mean difference in favour of the mother, due mostly to high variation. PIPP scores similarly had large mean differences favouring the mother but the variance was also large so that any difference was non-significant.

3. Effectiveness of skin-to-skin care (SSC): analysis by duration of SSC

Cong 2009 and Cong 2012 reported results from different durations of SSC, the first comparing 80 to 30 minutes SSC and the second comparing 30 to 15 minutes. Both studies examined preterm neonates undergoing heel lance and some physiological outcomes were the same so that an analysis was able to be performed.

4. Effectiveness of skin-to-skin care (SSC) compared to alternative treatments

There were no studies that could be combined for analysis. There were some interesting comparisons that are described below.

SSC versus sweet taste

The study by Chermont 2009 on full term newborns receiving an intramuscular injection compared SSC alone or in combination with dextrose to incubator controls. On the PIPP outcome, SSC was most effective with or without the addition of dextrose. On the NFCS and NIPS, SSC was favoured over dextrose or control, although the combination was most effective. Freire 2008 also compared SSC with sweet taste (glucose) to control in preterm neonates undergoing heel lance, with the PIPP score. Heart rate and oxygen saturation variability (not defined) were reported to significantly favour SSC over both control and glucose. This was also reported for the composite measure of these variables, the PIPP. All outcomes favoured SSC.

SSC versus breastfeeding

Okan 2010 compared SSC to breastfeeding or swaddled control in full term neonates undergoing heel lance. In all outcomes (heart rate, oxygen saturation, NFCS, and duration of crying) there were no differences between SSC or breastfeeding, but both were better than the swaddled control group.

SSC versus enhanced SSC

One study, Johnston 2009, examined PIPP scores in preterm neonates undergoing heel lance for differences between SSC and SSC enhanced by the mother rocking, singing and offering the infant a finger or pacifier for sucking. There were no differences between the conditions.

5. Effectiveness of skin-to-skin care (SSC): analysis by dose or duration of SSC

The range of time for SSC prior to the intervention was two minutes (Saeidi 2011) to three hours (Ludington-Hoe 2005). The only studies that compared times were Cong 2009 and Cong 2011. However, these studies used different outcomes and thus no analyses could be conducted. In Cong 2009, 80 minute SSC and 30 minute SSC were independently compared to control for the physiological variables of heart rate and heart rate variability. SSC was favoured only in the 30 minute condition. In Cong 2011, the PIPP was used as an outcome for SSC for 15 minutes, SSC for 30 minutes, or control. The 30 minute SSC was favoured over control and 15 minute SSC. Although these two studies, not directly compared, seemed to favour 30 minutes to either longer or shorter doses, other studies using different outcomes favoured (or did not favour) SSC for times longer and shorter than 30 minutes so no conclusion could be made.

6. Effectiveness of skin-to-skin care (SSC): analysis by postmenstrual age (PMA)

Outcomes of studies reporting different PMAs were different so that comparisons could not be made. Studies examined different times and some used the same outcomes (for example, PIPP) but the comparisons and painful procedures were different so that an effect size could not be estimated.

DISCUSSION

Summary of main results

In this first review of skin-to-skin care (SSC) for procedural pain in neonates, 19 studies were found that met the selection criteria of using SSC as an intervention to reduce pain. Most of the studies used the most common painful event of heel lance as the painful procedure, although venipuncture and intramuscular injections were also among the painful procedures. Very few studies could be compared due to variations in painful procedure, design, outcomes, or participants.

The most detailed information was found in studies with preterm neonates undergoing heel lance for SSC versus control with either heart rate, heart rate variability, or the composite measure PIPP as outcomes. The physiological outcomes of heart rate during or after the procedure or heart rate variability, low frequency, high frequency, or low/high frequency ratio spectra, were not significant for either SSC or control. The heterogeneity was small in these studies. The PIPP in the first 90 seconds favoured SSC but the heterogeneity was high.

Two studies examined different providers of SSC and were able to be entered into an analysis for the PIPP and heart rate recovery. The differences between mother provider and other provider were not significant.

No analyses could be conducted on the effect on outcomes of duration of SSC or different age groups of infants.

Overall completeness and applicability of evidence

These results were based on a small number of studies as there was wide variability in outcomes reported. Some outcomes could not be analysed. For example, Castral 2008 reported a significant difference in facial actions favouring SSC for heel lance, but there was not enough information to include it in an analysis. Although Chermont 2009 also used facial actions as an outcome, the painful procedure of that study was intramuscular injection. Both studies reported results favouring SSC but they could not be analysed together.

Although it would be of interest to know if there was a dose-response relationship, that is, did the number of minutes in SSC increase the effectiveness, we were not able to conduct that analysis. We were not even able to make a direct comparison of differences with 30 minutes as a cut-off point. Ludington-Hoe 2005 reported the longest duration of SSC prior to the painful event of three hours, and Saeidi 2011 reported the shortest duration of two minutes. Both of these studies reported results favouring SSC but no comparisons could be made. One study, Cong 2011, reported on two samples, one receiving 60 minutes of SSC and the other only 10 minutes, and both were compared to standard care. There were positive results only for the group receiving 10 minutes of SSC, reported as lower PIPP scores as well as lower serum and salivary cortisol levels.

The providers of SSC were compared in two studies, which showed mean differences in favour of the mother, but the variance was very large so there were no significant differences. Only three studies included full term neonates and one was for heel lance, for which standard deviations were not available (Gray 2000). The other two studies (Sajedi 2007; Chermont 2009) used intramuscular injection rather than heel lance so that a comparison between full term neonates and preterm neonates was not possible.

No studies reported any adverse events.

Quality of the evidence

The studies that were included were generally strong and free from bias. More than half (11/19) of the studies reported using adequate random allocation, and most reported low risk of bias related to incomplete data (15/19), selective reporting (16/19), and other forms of possible bias (12/19). Just under half of the studies (8/19) reported adequate allocation concealment and blinding (5/19). Thirteen of the studies did report measures such as blinded assessors using objective outcome measures and 'close up video

recording of infant faces', but few addressed the issue of whether the presence of the mother may have been detectable to the assessor. Little information was provided regarding the 'usual care' control, so in the first comparison of SSC versus no-treatment control we were uncertain precisely what the control condition was.

The degree of heterogeneity of the studies varied a great deal, but interestingly the more heterogeneous outcomes were physiological. There is a greater potential for bias in behavioural outcomes that require human judgement. Only a few studies reported how video recordings avoided identification of the condition. The conflicting results between physiological outcomes, mostly showing no differences, and composite or behavioural outcomes generally favouring SSC would suggest caution in interpretation. Further research is needed in order to solve the long standing confusion and controversy about which indicators are most appropriate.

Potential biases in the review process

Two of the authors of this review (CJ, MCY) authored studies that were reviewed (Johnston 2003; Johnston 2008; Johnston 2009; Johnston 2011; Johnston 2012). Another author (AF) studied SSC for her doctoral dissertation and a manuscript is under review. Inglis is a nurse manager who champions SSC in the nurseries at the IWK Health Centre.

Agreements and disagreements with other studies or reviews

There have been a few reviews of non-pharmacological interventions for procedural pain relief in neonates (Cignacco 2007; Yamanda 2008; Warnock 2010; Pillai Riddell 2011) and all support the practice of SSC (also known as Kangaroo Care (KC)). No studies or reviews were found that disagreed.

AUTHORS' CONCLUSIONS

Implications for practice

Only a few data sets could be pooled, thus not enabling an effect size to be determined on all but a few outcomes. Nevertheless studies comparing skin-to-skin care to standard care, which was rarely defined, favoured skin-to-skin care or were non-significant. No studies favoured standard care. In the two studies comparing skin-to-skin care to glucose, skin-to-skin care was more effective in one study and a possible synergistic effect was reported in the other. The addition of breastfeeding did not appear to increase the effectiveness of SSC. When skin-to-skin care was enhanced by the addition of the mother's voice or rocking, it had no additional benefit. There were no adverse events reported in any of the studies. Therefore, it would seem that for neonates who are able to be held in the skin-to-skin care paradigm, using it for the painful procedures of heel lance, venipuncture, and intramuscular injection is potentially beneficial and not harmful. However, the degree of benefit, although not estimable, may not be large.

Implications for research

There are numerous areas in this topic that require further research before definitive statements can be made. First of all, more studies are needed that use outcomes that are the same as the ones in this review so that an effect size can be estimated. Secondly, studies need to be more rigorous about randomisation, allocation concealment, and blinding. Thirdly, when wide age ranges are used, particularly when full term and preterm neonates are in the same study, results for each group should be reported separately. Although it seems as though a 'dose' as low as 10 minutes was effective, more studies testing different durations of the provision of skin-to-skin care might allow for a dose response analysis to be conducted. All the studies were conducted using skin-to-skin care for a single procedure. It would be interesting to determine if the effect changed with repeated use. Once more studies meet these criteria, studies on dose, that is, duration of skin-to-skin care, and other providers would be of interest. More fundamentally, it would be of interest to explore the underlying mechanism of the comforting effect of skin-to-skin care and its long-term impact.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akcan 2009

Methods	Randomised controlled trial
Participants	50 preterm infants (PMA 31.6 ± 2.0 weeks) Postnatal age, mean ± SD, days: 4.7 ± 4.4 (total), 4.9 ± 4.3 (intervention), 4.6 ± 4.5 (control) Birth weight, mean ± SD, grams: 1669 ± 530 (total), 1577± 491 (intervention), 1762 ± 561 (control) Painful procedure: heel lance or venepuncture Study period: February 2006 to December 2006
Interventions	Intervention: 45 minutes of uninterrupted skin-to-skin every day for 5 days, with the painful procedure carried out on the 5th day Control: standard care during painful procedure Provider: mother
Outcomes	PIPP score at 1st, 2nd, and 3rd minute of painful procedure PIPP score 1st and 2nd minute after painful procedure
Notes	Country: Turkey Power calculation: No

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The infants were chosen for the groups using a random method by drawing out of a thick, non-transparent envelope." (15/3/7) Random method was not clearly described
Allocation concealment (selection bias)	Unclear risk	"The infants were chosen for the groups using a random method by drawing out of a thick, non-transparent envelope." (15/3/7) It is unclear whether the envelopes were sealed or numbered sequentially and if each individual participant was given an envelope or if group assignment was drawn from one envelope
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The mothers put on a gown leaving the chest area open and the infant was placed between the mother's breasts with head upright to provide the greatest surface area for skin contact." (15/5/6) "The video recordings and monitor records of the infants in both groups were analysed by three experts (neonatol-

		ogy nurse, neonatologist and anaesthesiologist) who were totally blind to the study." (16/7/2) Not clear if camera recording focused only on infants' faces or if mothers' skin/breasts could be noted by researchers
Incomplete outcome data (attrition bias) All outcomes	Low risk	"A total of 100 infants dropped out of the study (91 discharged within 5 days of admission, mothers of 6 infants could not come to the unit regularly, and 3 mothers did not agree to implement KC). As a result, 50 infants comprised the sample, with 25 allocated to the KC group and the other 25 to the control group." (15/3/5-6) Data were presented for all participants assigned to intervention and control groups
Selective reporting (reporting bias)	Low risk	Methods section reported that infants' behavioral responses to pain and physiologic variables, such as heart rate and oxygen saturation, were monitored and recorded. Although these outcomes compose the PIPP score, they were not individually reported or mentioned in the discussion
Other bias	Low risk	"Method of delivery, sex, postmenstrual age, birth weight, receipt of oxygen support prior to the procedure, or PIPP scores before or after the invasive procedure were similar (P > 0.05) in both groups." (16/4/1) Study was apparently free from other sources of bias

Castral 2008

Methods	Randomised controlled trial
Participants	59 preterm infants (PMA 248 days (intervention), 254 days (control)) Birthweight, mean, grams: 1749 (intervention), 1846 (control) Painful procedure: Heel lance Study period: September 2005 to May 2006
Interventions	Intervention: 15 minutes of skin-to-skin care before, during and following heel prick Control: standard care during painful procedure Provider: mother
Outcomes	Neonatal Facial Coding System (NFCS) and heart rate at heel prick, heel squeezing, wound compression, and recovery
Notes	Country: Brazil Power calculation: No
Risk of bias	

Castral 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was achieved using a sequence of random numbers from a computer generated sequence." (465/6/3)
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment were not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Two trained coders, who were blinded to the purpose of the study, coded for change in facial action following protocols established by Grunau and Craig (1987)." (466/2/1) "The faces of all of the infants were continuously videorecorded throughout the seven study phases to capture change in facial action." (466/8/2) Not clear if camera recording focused only on infants' faces or if mothers' skin/breasts could be noted by researchers
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 62 mothers initially approached, three infants were not entered into the study because two mothers declined participation and another mother was under treatment for tuberculosis. The remaining 59 infants who met the inclusion criteria and whose parent agreed to their infant's or to their infant's and their own participation were randomly assigned into two study groups: skin-to-skin (n = 31) or to the regular crib/incubator care (n = 28)." (465/6/1-2) Data were presented for all participants assigned to intervention and control groups
Selective reporting (reporting bias)	Low risk	Outcomes listed in methods (facial action, behavioral state, crying and heart rate) were clearly presented in Tables 3, 4 and Figures 1, 2
Other bias	High risk	"The duration of heel puncture (heel cleaning to wound compression) was significantly shorter for the treatment group than it was for the control group (P = 0.014)." (467/4/1) The article stated that "measures were taken to minimize factors that could have led to group differences in duration. The same two trained nurses conducted all of the heel pricks using a standardized protocol" (470/1/1-2) . Study researchers, however, did not apparently control for differences in duration of heel puncture for the regression analysis

Chermont 2009

Methods	Randomised controlled trial
Participants	640 term infants (mean PMA 39 ± 1 weeks, for all groups); 4 groups - standard care, skin-to-skin, 25% dextrose, skin-to-skin + 25% dextrose Postnatal age, mean ± SD, hrs: 293 ± 13 (skin-to-skin care), 29 ± 15 (control), 29 ± 13 (25% dextrose), 27 ± 13 (skin-to-skin + 25% dextrose) Birth weight, mean ± SD, g: 3164 ± 371 (intervention); 3163 ± 418 (control); 3252 ± 389 (25% dextrose); 3240 ± 418 (skin-to-skin + 25% dextrose) Painful procedure: Intramuscular injection Study period: March 2006 to October 2007
Interventions	Intervention: skin-to-skin contact, initiated 2 minutes before injection and persisting throughout procedure Control: standard care during painful procedure Comparison 1: oral 25% dextrose treatment (1mL), given 2 minutes before injection Comparison 2: combination of oral dextrose treatment and skin-to-skin contact strategies Provider: mother provided skin-to-skin; oral dextrose provided by nurse or neonatologist
Outcomes	Neonatal Facial Coding System (NFCS) and Neonatal Infant Pain Scale (NIPS) score at baseline, cleansing, injection, and recovery; HR, O2 saturation
Notes	Country: Brazil Power calculation: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomization was performed by using 2 boxes, 1 for male infants and 1 for female infants." (e1102/6/1)
Allocation concealment (selection bias)	Unclear risk	"Each box was filled with 320 opaque sealed envelopes, corresponding to 80 envelopes for each analgesic procedure to be performed during immunization." (e1102/6/2) Envelopes should ideally be opaque, sealed and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	High risk	"Pain evaluators were aware of skin-to-skin contact but were blinded to whether the infant received water or dextrose." (e1103/5/5)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All randomly assigned patients completed the study, with no losses." (e1103/8/1)
Selective reporting (reporting bias)	High risk	Data for the primary outcomes (NFCS, NIPS and PIPP scores) were presented in Tables 2 & 3 and Figure 1. The trial registry lists heart rate and oxygen saturation as secondary outcomes. Although these outcomes were

Chermont 2009 (*Continued*)

		covered within the pain scales, no discussion of the results were found
Other bias	Low risk	The authors failed to report the number of patients assessed for eligibility

Cong 2009

Methods	Randomised cross-over trial
Participants	14 preterm infants (PMA 30-32 weeks); 13 intervention, 10 control Postnatal age, mean ± SD, days: 6 ± 1 Birth weight, mean ± SD, grams: 1775 ± 292 Weight on day of study, mean ± SD, grams: 1706 ± 293 Painful procedure: Heel lance Study period: Unclear
Interventions	Intervention: 60 minutes of skin-to-skin care before, during and following heel stick Control: standard care during painful procedure Provider: mother
Outcomes	Heart rate, low frequency (LF) and high frequency (HF) power, LF/HF power, and state at baseline, heel warming, heel stick, and recovery
Notes	Country: United States Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A prospective cross-over with random assignment by permuted block design was used. A statistician helped the investigator generate a list of randomisation codes using the SAS® procedure PLAN. The list of random codes consisted of the subject's number and the treatment assignment. According to random codes, infants were assigned to two groups..." (562/5/1-4)
Allocation concealment (selection bias)	Low risk	"A prospective cross-over with random assignment by permuted block design was used. A statistician helped the investigator generate a list of randomisation codes using the SAS® procedure PLAN. The list of random codes consisted of the subject's number and the treatment assignment. According to random codes, infants were assigned to two groups..." (562/5/1-4)

Cong 2009 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	"Movement and artefact were eliminated by comparing amplitude (height) of the R-wave to be included with the amplitude for the last acceptable R-wave. Waves of more or less than 38% deviance from the previous wave were automatically eliminated. The researcher or research assistant who extracted the HRV data was not blinded from the study conditions. Although the bias was likely minimal, still it is important. A proper blinded data extraction process would be necessary to guard against bias pertaining to knowledge of study conditions in the future study. " (563/7/7-12)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Heart rate and HRV data were available for all days except one KC and four IC days due to equipment problems. The pair wise deletion was used for missing data; therefore, the final data were from 13 observations in KC and 10 observations in IC." (564/3/1-2)
Selective reporting (reporting bias)	Low risk	Heart rate and variability (Low frequency, high frequency, and low/high frequency power frequency power ratio) were presented in Table 2 and Figure 2. The Anderson Behavioral State Scoring System (ABSS) were used to measure infant state. The outcomes are discussed (564/2) but are not presented in a table or figure
Other bias	Low risk	"The heel stick and subsequent blood draw were standardized and performed in accordance with the guidelines and step-by-step procedure developed by National Association of Neonatal Nurses." (563/3/3) "One consistent person, the neonatal unit phlebotomist, did all the heel sticks and blood draws." (563/3/5) "A 24-hour routine IC washout period was incorporated into the design for both groups. Twenty-four-hours was sufficient to allow any lingering effects of KC to dissipate. " (562/5/8-9)

Cong 2011

Methods	Randomised cross-over trial
Participants	28 preterm infants (PMA 30-32 weeks): 18 infants - 80 min SSC (Study a); 10 infants - 30 min SSC (Study b) Postnatal age, mean ± SD, days: 5 ± 1 (Study 1); 6 ± 2 (Study 2) Birth weight, mean ± SD, grams: 1779 ± 277 (Study 1); 1577 ± 327 (Study 2) Painful procedure: Heel lance Study period: Unclear

Cong 2011 (*Continued*)

Interventions	Intervention: (a) Study a: 60 minutes of skin-to-skin care before heel stick, with continued SSC during procedure, and followed by 20 minutes SSC post-procedure; (b) Study b: 10 minutes of skin-to-skin care before heel lance, with continued SSC during procedure, and followed by 20 minutes SSC post-procedure Control: standard care during painful procedure Provider: mother
Outcomes	PIPP score, salivary and serum cortisol at baseline, heel warming, heel stick and recovery
Notes	Country: United States Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"permuted block randomisation to determine the order of condition (KCH or IH first) was used. A list of randomisation codes with four subjects in each randomisation block using the SAS(R) procedure PLAN was developed by an independent statistician." (206/2/1-2)
Allocation concealment (selection bias)	Low risk	"The list of random codes consisted of the subject's number and assignment to groups; assignments were kept in sealed envelopes and opened in front of the mother after consent was obtained." (206/2/3)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"A video camera recorder was set up and focused on the infants' faces to record facial actions. The videotapes were independently scored by the researcher and one other certified PIPP scorer (trained to reliability by the PIPP creator), who was blind to the purpose of the study." (206/5/3-4) "Another limitation is that the PIPP scorers could not be blind to KCH because maternal respiratory movements moved the infant's face up and down in the video, as previously reported and acknowledged by other KC pain researchers." (212/4/2) Potential for bias as researcher coded videos and it is unknown if data was collected by the same individual
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were provided for all infants recruited in the study
Selective reporting (reporting bias)	Low risk	All outcomes were reported in Tables 1-2 and Figures 1-2

Cong 2011 (*Continued*)

Other bias	Low risk	"Standard incubator care for 24 hr was considered a sufficient "wash out" period because physiological and behavioural state effects of KC disappear within 3 hr of KC cessation." (206/2/5)

Cong 2012

Methods	Randomised cross-over trial
Participants	26 preterm infants (PMA 28 0/7 to 32 6/7 weeks): 22 infants - 30 min SSC (Study a); 25 infants - 15 min SSC (Study b); 23 infants control Postnatal age, mean ± SD, days: 14.5 ± 6.3 (Study a); 13.8 ± 5.6 (Study b); 13.5 ± 5.6 (control) Birth weight, mean ± SD, grams: 1444.6 ± 379.0 Painful procedure: Heel lance Study period: Unclear
Interventions	Intervention: (a) Study a: 30 minutes of skin-to-skin care before and throughout heel lance (b) Study b: 15 minutes of skin-to-skin care before and throughout heel lance Control: standard care during painful procedure Provider: mother
Outcomes	Heart rate, Heart rate variability (low frequency and high frequency power), LF/HF ratio, Infant behavioural state
Notes	Country: United States Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A list of randomisation codes with 4 subjects in each randomisation block was developed by the statistician (the third author). The list of random codes consisted of the subject's number and assignment to sequence." (638/1/1-2)
Allocation concealment (selection bias)	Low risk	"assignments were kept in sealed envelopes and opened in front of the mother after consent was obtained." (638/1/2)
Blinding (performance bias and detection bias) All outcomes	Low risk	"A video camera was mounted on a tripod and focused on the infant's face to record facial actions, and the videotapes were later reviewed and scored." (639/2/5) "In order to minimize bias, a research assistant who was blind to the purpose of the study helped analyse the data.

Cong 2012 (*Continued*)

		" (639/4/2)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were provided for all infants recruited in the study; dropout rates described (639/5/6)
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the Results section and Table 2
Other bias	Low risk	"A 24- to 72-hour washout period was applied between each study condition." (638/1/6)

Freire 2008

Methods	Randomised controlled trial with three groups (routine care; skin-to-skin; routine care + oral glucose)
Participants	95 preterm infants (PMA 28-36 weeks) Painful procedure: Heel lance Study period: Unclear
Interventions	Intervention: 10 minutes of skin-to-skin care before, during heel stick Control: standard care during painful procedure Comparison: Sweet taste 2 minutes before painful procedure Provider: mother
Outcomes	PIPP score
Notes	Country: Brazil Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The groups were selected at random by a nurse on duty using closed envelopes" (29/5/5) Not clear how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	"The groups were selected at random by a nurse on duty using closed envelopes" (29/5/5) Not clear whether the envelopes were opaque, sealed and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	"The examiner was blinded and trained to record any grimacing..." (29/7/1) "Only the newborn's face was filmed in

Freire 2008 (*Continued*)

		close-up with little surrounding area and minimal colour to reduce the possibility of unblinding by the research assistants who recorded the tapes". (29/6/6)
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 10 neonates excluded due to errors in the blinding of the video (30/Fig 1). Data were provided only for all other neonates
Selective reporting (reporting bias)	Low risk	All outcomes were clearly presented in Table 2
Other bias	Low risk	Study was apparently free of other sources of bias

Gray 2000

Methods	Randomised controlled trial
Participants	30 term infants (≥37 weeks) Postnatal age, range, hours: 33-55 Birth weight, mean (range), grams: 3300 (2600-3700) Painful procedure: Heel lance Study period: March 1998 to October 1998
Interventions	Intervention: 10-15 minutes of skin-to-skin care before heel stick Control: standard care during painful procedure Provider: mother
Outcomes	Heart rate and cry duration in seconds during blood collection, and grimacing during recovery period
Notes	Country: United States Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"They [healthy full-term newborns] were assigned randomly the morning of the study." (2/2/2)
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment were not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Their infant, wearing only a diaper, then was positioned on the mother so that skin-to-skin contact was maintained through her open gown. This arrangement left the

Gray 2000 (*Continued*)

		infant's face visible for filming from the side of the bed." (2/6/2-3) "After a 2-minute baseline period, during which the infant's face was filmed and heart rates were announced every 10 seconds from the monitor, the heel warmer was removed, and the heel was swabbed with alcohol." (2/7/1) "videotape evaluations of infant pain reactions were conducted by research assistants who were not aware of either the purpose of the study or the number of different groups." (2/9/1) "For grimacing, of course, knowledge of group assignment was unavoidable. The data obtained in these analyses were reliable among scorers." (2/9/5) Not clear if mothers' skin/breasts could be noted by researchers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were provided for all infants randomised except grimacing in 3 infants (all in the skin-to-skin contact group) where blood collection lasted >3 minutes. (3/Figure 2)
Selective reporting (reporting bias)	Low risk	Data were provided for all outcome measures listed in the methods section (Figures 2-4)
Other bias	Low risk	"Since L.G. conducted all heel sticks because of scheduling difficulties with the phlebotomists, a potential bias of differential treatment has been introduced. We are not concerned about this potential bias for a number of reasons. First, the duration of the procedure and apparent discomfort that it caused in control infants, expressed in crying, for example, was of the same order of magnitude as that caused by the phlebotomist in other studies conducted in our laboratory. Second, as indicated, mean blood collection times for both groups were not statistically different. Third, we went through a number of iterations...before a successful set of parameters was attained. It would seem to us that any systematic bias on the part of L.G. would have become manifest from the outset and not after a number of procedural changes." (2/9) Study is apparently free of other sources of bias

Johnston 2003

Methods	Randomised cross over trial
Participants	74 infants (32-36 weeks PMA) Postnatal age, range, days: 0-10 Birth weight, mean ± SD (range), grams: 2054 ± 406 (1320-3125) Painful procedure: Heel lance

Johnston 2003 (*Continued*)

	Study period: April 9, 2001, to June 28, 2002	
Interventions	Intervention: 30 minutes of skin-to-skin care before and during heel stick Control: standard care during painful procedure Provider: mother	
Outcomes	PIPP score at 30, 60, 90, and 120 minutes Secondary outcomes: heart rate and oxygen saturation	
Notes	Country: Canada Power calculation: Yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Ordering of conditions was determined randomly by a computer-generated program." (1085/4/2)
Allocation concealment (selection bias)	Low risk	Off site computer generated program (information obtained from authors)
Blinding (performance bias and detection bias) All outcomes	Low risk	"The camera was in close-up focus on the neonate's face, with little surrounding area, no sound, and minimal colour, and turned 60 degrees in the KC condition so as to decrease the possibility of unblinding by research assistants who scored the tapes. Research assistants, who were blinded to the purpose of the study by being told that the study was about neonatal facial actions, coded facial actions in the laboratory of the principal investigator." (1086/1/2-3)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were provided for all 74 neonates included in the study
Selective reporting (reporting bias)	Low risk	Data were provided for all outcome measures listed in the methods section (page 1087)
Other bias	Low risk	"There was a minimum of 24 hours and a maximum of 7 days between conditions, because the frequency of blood sampling was determined by clinical considerations." (1085/4/3) Study is apparently free of other sources of bias

Johnston 2008

Methods	Randomised cross-over trial
Participants	61 preterm infants (PMA 30.5 ± 1 weeks) Postnatal age, range, days: 1-14 Birth weight, mean ± SD, grams: 1421 ± 490 Painful procedure: Heel lance Study period: April 2003 to December 2005
Interventions	Intervention: 15 minutes of skin-to-skin care before and during heel stick Comparison: swaddling in incubator 15 minutes before painful procedure Provider: mother
Outcomes	PIPP score at 30, 60, 90 and 120 minutes Time to return to baseline heart rate
Notes	Country: Canada Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Ordering of conditions was determined randomly by a computer-generated program in the study centre and assignment was accessed on the web site by the site research nurse after consent was obtained." (3/2/3)
Allocation concealment (selection bias)	Low risk	"...assignment was accessed on the web site by the site research nurse after consent was obtained." (3/2/3)
Blinding (performance bias and detection bias) All outcomes	Low risk	"The camera was in close up focus on the infant's face with very little surrounding area, no sound, with minimal colour, and turned to an angle in the kangaroo condition as to mimic the prone position in order to decrease the possibility of unblinding by research assistants who scored the tapes. Research assistants, who were blinded to the purpose of the study by being told that the study was about infant facial actions, coded facial actions in the laboratory of the PI." (4/1/5-6)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes were clearly presented for all infants included in the study. Dropout rates were detailed in Figure 1
Selective reporting (reporting bias)	Low risk	Data were clearly reported for all outcome measures in Figures 2-5
Other bias	Low risk	Study was apparently free of other sources of bias

Johnston 2009

Methods	Randomised cross-over trial
Participants	90 preterm infants (PMA 32 0/7 to 36 0/7 weeks) Postnatal age, range, days: 1-14 Birth weight, mean ± SD, grams: 1968 ± 388 Painful procedure: Heel lance Study period: April 2003 to December 2006
Interventions	Intervention: 30 minutes of skin-to-skin care before and during heel stick Comparison: 30 minutes of enhanced skin-to-skin care (rocking, singing/talking to baby, offering finger/pacifier for baby to suck Provider: mother
Outcomes	PIPP score at 30, 60, 90, and 120 minutes
Notes	Country: Canada Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Ordering of conditions was determined randomly by a computer-generated program in the study center..." (52/3/3)
Allocation concealment (selection bias)	Low risk	"...assignment was accessed on the web site by the site research nurse after consent was obtained." (52/3/3)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Authors were contacted via email and stated that "Camera [was] zoomed on face." Not clear if mothers' skin/breasts could be noted by researchers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Of those 330 meeting the selection criteria, 187 were approached and 139 accepted to participate, giving a refusal rate of 26%." (53/3/2) Not clear of why only 187 were approached "Not all infants had complete data at each time block, due to movement artefacts or hand obscuring the face, but there were no more than seven missing data at any point in time and it was not the same infants, so the analyses were conducted with some cases missing." (53/3/6)
Selective reporting (reporting bias)	Low risk	Outcomes were clearly laid out in Figures 2 and 3
Other bias	Unclear risk	"Two of the three committees approved the two KMC conditions without sucrose. The other site required usual use of sucrose but this was not consistent. To accommo-

		date the study, if an infant received sucrose in the first session, then sucrose was administered for the second session and similarly, if sucrose was not administered in the first session, it was withheld in the second" (52/1/5). This implies inconsistent use of sucrose Study was apparently free of other sources of bias

Johnston 2011

Methods	Randomised cross-over trial
Participants	62 preterm infants (PMA 28 to 36 weeks) Postnatal age, mean, days: 5-10 Birth weight, mean ± SD, grams: 1565 ± 469 (father KC/mother KC); 1610 ± 494 (mother KC/father KC) Painful procedure: Heel lance Study period: January 16, 2008 to March 24, 2009
Interventions	Intervention: 30 minutes of skin-to-skin care before and during heel lance provided by mother Comparison: 30 minutes of skin-to-skin care before and during heel lance provided by father Provider: mother or father
Outcomes	PIPP score at 30, 60, 90, and 120 minutes, time for HR to return to baseline
Notes	Country: Canada Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"When clinical care required blood procurement, the research nurse went to the secure computer Web site for the order assignment that had been generated randomly in permutated blocks of 4 and 6." (793/7/1)
Allocation concealment (selection bias)	Low risk	"When clinical care required blood procurement, the research nurse went to the secure computer Web site for the order assignment that had been generated randomly in permutated blocks of 4 and 6. The parents were then contacted by the research nurse, informing them of which one was to provide KC for that procedure." (793/7/1-2)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Close-up video recordings of the infants' faces were made using a KS162 digital camera at 2 sites and a webcam at the third site." (793/8/5)

Johnston 2011 (*Continued*)

		Not clear if mothers' skin/breasts could be noted by researchers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"...there were 185 infants who were determined to be eligible from 3 university-affiliated level III neonatal intensive care units. A major reason for not being eligible was the unavailability of the father in the daytime. The refusal rate was 22%, mostly because one or the other parent did not want to do KC or particularly did not want to be videotaped, even though it was explained that the camera would be focused on the infant's face." (794/4/1-2) Unclear of the exact number of participants
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were clearly laid out in Table 2 and in the Results section
Other bias	Unclear risk	"Intrarater reliability was checked every 3 months, remaining more than 90%. When asked what they thought the study was about, the coders independently stated that it was about facial grimacing when infants were calm or crying." (793/10/6) Washout period not described

Johnston 2012

Methods	Randomised cross-over trial	
Participants	18 preterm infants (PMA 28 to 36 completed weeks) Postnatal age, range, days: within 10 days Birth weight, mean, grams: 2200 Painful procedure: Heel lance Study period: October 2007 to January 2010	
Interventions	Intervention: 30 minutes of skin-to-skin care before and during heel stick provided by the mother Comparison: 30 minutes of skin-to-skin care before and during heel lance provided by an unrelated woman Provider: mother or an unrelated woman	
Outcomes	PIPP score at 30, 60, 90, and 120 minutes	
Notes	Country: Canada Power calculation: No	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Johnston 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	Sequence generation not described in text. Author communication confirmed that an off site computer generated randomisation and sequentially numbered allocation program was used
Allocation concealment (selection bias)	Low risk	Allocation concealment not described. Author communication confirmed that an off site computer generated randomisation and sequentially numbered allocation program was used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Close-up video recordings of the infants' faces were made using a KS162 digital camera...or a webcam." (2/5/7) Not clear if mothers' skin/breasts could be noted by researchers
Incomplete outcome data (attrition bias) All outcomes	Low risk	"...of the 82 infants meeting the selection criteria, 21 initially refused at the time of asking, and another refused after condition order had been randomised. The main reason for refusal was not wanting another woman to provide kangaroo care with her baby." (2/9/1-2) Drop out rates clearly explained in Figure 1 and incomplete data accounted for
Selective reporting (reporting bias)	Low risk	Outcomes were clearly laid out in Figure 2
Other bias	Unclear risk	"All data were coded and analysed in the research laboratory at the off-site university. Faces were coded second-to- second on a stop frame system. Coders were trained on faces from similar studies, and inter-rater reliability was over 90%. Coders were from outside the unit and did not know the purpose of the study, because the camera was focused on the infant's face. Intrarater reliability was checked every 3 months and was maintained over 90%. " (2/7/1-4) Washout period not described

Kostandy 2008

Methods	Randomised cross-over trial
Participants	Only 10 infants (30-32 weeks PMA) enrolled Postnatal age, range, days: 2-9 Birth weight, mean ± SD, grams: 1577 ± 327.00 Painful procedure: Heel lance Study period: Unclear

Kostandy 2008 (*Continued*)

Interventions	Intervention: 30 minutes of skin-to-skin care before and during painful procedure Control: standard care during painful procedure Provider: mother provided skin-to-skin care
Outcomes	Cry duration at baseline, warming, heel stick, and recovery
Notes	Country: United States Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomization was by permuted block design to ensure highest possible equivalence among infants." (57/1/5) The system of randomisation is not mentioned
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Independent scorers of the videotapes were blind to the purpose and cross-over design of the study." (57/1/6) Not clear if mothers' skin/breasts could be noted by researchers
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All mothers who were approached agreed to participate. " (57/3/6)
Selective reporting (reporting bias)	Low risk	Outcomes listed in methods match those reported
Other bias	Low risk	"26 subjects were needed to detect moderate difference in crying time; however, funding permitted recruitment of only 10 subjects." (57/3/2) 24 hour between procedures - carry over effect: "Heel sticks were done by a consistent neonatal phlebotomist who used the National Association of Neonatal Nursing's standardized heel stick procedure with a Tenderfoot(TM) spring-loaded lancet." (57/6/1)

Ludington-Hoe 2005

Methods	Randomised cross-over trial
Participants	24 preterm infants (< 37 weeks PMA); results from 23 infants Postnatal age, mean ± SD, days: 22 ± 11.4 Painful procedure: Heel lance Study period: Unclear

Interventions	Intervention: 3 hours of skin-to-skin care before and during painful procedure Control: standard care during painful procedure Provider: mother
Outcomes	Heart rate, respiratory rate, oxygen saturation, cry duration, behavioural state
Notes	Country: El Salvador and USA Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The cross-over design controlled for all threats to internal validity except the interaction of selection and treatment, but assignment to group A or B independently and randomly by the Zellen technique insured balanced representation in both treatment sequences." (380/1/2)
Allocation concealment (selection bias)	Unclear risk	"Consenting mother-infant pairs were randomized by sealed envelope technique into 2 groups" It is not specified whether envelopes were sealed. opaque and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	High risk	"...the observers were not blind to treatment and group, a condition that is being corrected by having all data videotaped and computer-stored for scoring outside the clinical area in an ongoing study." (382/4/2)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates explained
Selective reporting (reporting bias)	Low risk	All outcomes are clearly presented in Tables 2, 3
Other bias	High risk	"Each infant was tested on one day using this cross-over design that controlled for intra- and inter-subject variability and provided the highest possible equivalence among subjects exposed to both conditions. The cross-over design controlled for all threats to internal validity except the interaction of selection and treatment, but assignment to group A or B independently and randomly by the Zellen technique insured balanced representation in both treatment sequences. Carry-over effects from one condition to the next is a concern with any cross-over design; previous KC research has shown that physiological and behavioral state effects of KC are not sustained long after KC is discontinued, making 3-4 hours sufficient to minimize carry-over effects." (380/1)

		In Zellen's technique, patients are randomised before consent occurs; therefore in theory, consent can be sought conditionally

Nimbalkar 2013

Methods	Randomised cross-over trial
Participants	47 preterm infants (PMA 32 0/7 to 36 6/7 weeks) Postnatal age, mean, days: within 10 days Birth weight, mean, grams: 1730 (intervention), unclear (control) Painful procedure: Heel lance Study period: April 1, 2009 to September 30, 2009
Interventions	Intervention: 15 minutes of skin-to-skin care before, during, and 15 minutes after heel lance Control: standard care during painful procedure Provider: mother
Outcomes	PIPP score
Notes	Country: India Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization of patients to give KMC or not for the first heel prick was done using graphpad.com (a web-based program)..." (2/7/1)
Allocation concealment (selection bias)	Unclear risk	"the random numbers were stored in opaque envelopes, which were opened once the patient entered study." (2/7/1) Envelopes should be opaque, sealed, and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	"The persons examining the video were unaware of the status of the neonate during analysis as the videography was done by focusing only on the baby's face and the surroundings were not visible, with the sound kept on mute." (2/7/2) "Mothers were asked to keep their hands clasped behind the neonate's back throughout the procedure and refrain from touching the neonate's head with her face and from vocalizing to the neonate during filming (to keep observers blind)." (2/10/5)

Nimbalkar 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop out rates were clearly explained in Figure 1
Selective reporting (reporting bias)	Low risk	Outcomes were clearly laid out in Figure 2 and Table 1
Other bias	Low risk	"There was a minimum of 24 h and a maximum of 7 d gap between the conditions. The heels were assessed for any signs of inflammation so as to remove it as a confounding factor." (3/2/10) "Only two staff nurses did the heel prick for these neonates to keep the procedure standardized and without bias." (3/2/5)

Okan 2010

Methods	Randomised controlled trial
Participants	107 full term infants (PMA 39.5 ± 0.6): Randomised to 3 groups: Skin-to-skin + breast feeding; skin-to-skin; and standard care Postnatal age, mean ± SD, days: 33.1 ± 5 Painful procedure: Heel lance Study period: Unclear
Interventions	Intervention: held in mother's arms with skin-to-skin contact 15 minutes before and during painful procedure Comparison: breastfed with skin-to-skin contact for 15 minutes before and during painful procedure Control: wrapped in blankets and lying on table before, during and after painful stimulus Provider: mother provided skin-to-skin care and breastfeeding
Outcomes	Neonatal Facial Coding System Scores (NFCS), physiological responses (heart rate and oxygen saturation changes) and behavioural responses (duration of crying and grimacing)
Notes	Country: Turkey Power calculation: Yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Study infants were assigned to one of three groups using a random number digits table" (121/1/3)
Allocation concealment (selection bias)	Unclear risk	"1200 (full-term infants) met all inclusion criteria. Every day, at least six such infants were in the maternity wards, only one of whom was studied. In the morning, the name of an infant who met the inclusion criteria was drawn form a bag by a nurse not involved in the study." (120/

Okan 2010 (*Continued*)

		7/1)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"this arrangement (skin-to-skin with mother) left the infants faces visible for recording from the side of the bed and simultaneously provided cover and comfort for the mothers." (121/3/4) "to minimise variability, the blood collection process was performed by the same nurse who was not aware of the purpose of the study, and the time spent squeezing the heel was recorded."(121/4/7) "observers of facial actions recognized the groups while evaluating the recordings. In order to minimise any errors caused by prejudice, the video records were evaluated by two persons who were unaware of each other's results." (127/3/2-3). Breastfeeding difficult to blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates explained
Selective reporting (reporting bias)	Low risk	Outcomes listed in methods match those reported
Other bias	Low risk	"All tests were performed...1-2 hours after breastfeeding. " (121/2/1) "to minimise variability, the blood collection process was performed by the same nurse who was not aware of the purpose of the study, and the time spent squeezing the heel was recorded." (121/4/7) "there were no significant differences between the groups in the clinical characteristics, pretest behavioural state score, and blood collection time." (122/5/3)

Saeidi 2011

Methods	Randomised controlled trial
Participants	60 full term infants (80% of case group and 73.3% of control group had 40 weeks GA) Birth weight, mean ± SD, grams: 3242 ± 306.6 (intervention), 3151 ± 331.5 (control) Painful procedure: Vaccination Study period: March to July 2006
Interventions	Intervention: 30 minutes skin to skin contact Control: standard care during painful procedure Provider: mother provided skin-to-skin care
Outcomes	Behavioural changes using the Neonatal/Infant Pain Scale (NIPS) 2 minutes before, during, and 3 minutes after intervention; heart rate and oxygen saturation
Notes	Country: Iran Power calculation: Unclear

Saeidi 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Samples were divided randomly into two groups." Unclear how the matching was done or how the sequence was generated. (100/6/2)
Allocation concealment (selection bias)	Unclear risk	Insufficient information available to judge
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Neonatal reactions to pain were video recorded." Unclear whether video recording was focused on face of infant. (100/7/1)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates not reported
Selective reporting (reporting bias)	Unclear risk	NIPS outcomes were clearly presented in Tables 1-3; O2 saturation presented clearly under results but specific HR and crying interval data not reported
Other bias	Unclear risk	Power calculation not done

Sajedi 2007

Methods	Randomised controlled trial
Participants	100 term neonates (PMA 39.4 ± 1.5 weeks (intervention), 39.1 ± 1.4 weeks (control) Birth weight, mean ± SD, grams: 3083 ± 258 (intervention), 3142 ± 242 (control) Painful procedure: Intramuscular injection Study period: Unclear "2-month observation period"
Interventions	Intervention: 10 minutes of skin-to-skin care before, during, and 3 minutes after painful procedure Control: standard care during painful procedure Provider: mother provided skin-to-skin care
Outcomes	Neonatal Infant Pain Scale (NIPS), behavioural outcomes (including facial expression, breathing pattern, state of arousal, arm movements, leg movements, and cry), heart rate and oxygen saturation before, during and after injection
Notes	Country: Iran Power calculation: No

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Sajedi 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"The neonates were randomly assigned to intervention and control groups by using randomized permuted blocks. Randomization was done by a well-trained nurse using a random numbers table." Unclear how the matching was done (276/4/4)
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment were not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	we filmed only the face of the neonate for evaluation of the duration of crying..." (277/6/2)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Table 4 data for 20 infants in the intervention group were reported and for 44 in the control group. Stated that 30 infants in the intervention group and 6 in the control group did not cry at all
Selective reporting (reporting bias)	Low risk	Data of all outcomes were clearly presented in Tables 2-4 (Kashaninia) and Tables 2-3 (Sajedi)
Other bias	High risk	Study is a combination of 2 studies (Sajedi 2007 and Kashaninia 2008)

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdel-Razek 2009	Inappropriate intervention (breastfeeding)
Arditi 2006	Inappropriate intervention (no skin-to-skin care)
Axelin 2009	Inappropriate intervention ("parental holding" which didn't include ventral skin contact)
Bellieni 2002	Inappropriate intervention (no isolated skin-to-skin care)
Bellieni 2007	Inappropriate intervention (no isolated skin-to-skin care)
Campbell-Yeo 2012	Inappropriate intervention (not consistently ventral contact)
Erlandsson 2007	Inappropriate participants (no painful procedure delivered by health care professionals)
Ferber 2008	Inappropriate outcome (NIDCAP has some behaviours associated with pain, but is not a measure of pain)
Gabriel 2010	Inappropriate participants (no painful procedure delivered by healthcare professionals)

(*Continued*)

Gazzolo 2000	Inappropriate participants (no painful procedure delivered by healthcare professionals)
Johnson 2007b	Inappropriate intervention (no skin-to-skin care)
Kashaninia 2008	Same data set as Sajedi 2007.
Miles 2006	Inappropriate participants (skin-to-skin care did not take place during painful procedure)
Mooncey 1997	Inappropriate participants (no painful procedure delivered by healthcare professionals)
Morelius 2005	Inappropriate participants (no painful procedure delivered by healthcare professional)
Reis 2003	Inappropriate intervention (no ventral skin contact)
Schlez 2011	Inappropriate participants (no painful procedure delivered by healthcare professionals)
Silva 2004	Inappropriate intervention (study focuses on understanding maternal experiences during first contact with child; no painful procedure implemented)
Uga 2008	Inappropriate intervention (breastfeeding)
Vivancos 2010	Inappropriate intervention: (skin-to-skin care did not occur during the painful procedure)

Characteristics of studies awaiting assessment *[ordered by study ID]*

Mahindre 2009

Methods	Cross-over trial
Participants	60 infants postmenstrual age: "30 infants between 28-32 weeks and 30 between 32-36 weeks" Painful procedure: "blood sampling"
Interventions	Intervention: "Kangaroo Mother Care" Control: "Conventional open care" Provider: Unclear
Outcomes	PIPP scores at 30, 60, 90 and 120 seconds; time required for heart rate and oxygen saturation to touch baseline
Notes	Country: India Power calculation: Unclear

DATA AND ANALYSES

Comparison 1. Skin-to-skin care versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart Rate during painful procedure	4	121	Mean Difference (IV, Fixed, 95% CI)	0.35 [-6.01, 6.71]
1.1 Heel lance	4	121	Mean Difference (IV, Fixed, 95% CI)	0.35 [-6.01, 6.71]
2 Heart rate following painful procedure	4	121	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-8.86, 1.39]
2.1 Heel lance	4	121	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-8.86, 1.39]
3 HRV during painful procedure - Low frequency power	2	38	Mean Difference (IV, Fixed, 95% CI)	-2.11 [-17.69, 13.47]
3.1 Heel lance	2	38	Mean Difference (IV, Fixed, 95% CI)	-2.11 [-17.69, 13.47]
4 HRV during painful procedure - High frequency power	2	38	Mean Difference (IV, Fixed, 95% CI)	-5.11 [-23.36, 13.14]
4.1 Heel lance	2	38	Mean Difference (IV, Fixed, 95% CI)	-5.11 [-23.36, 13.14]
5 HRV during painful procedure - Low frequency to high frequency ratio	2	38	Mean Difference (IV, Fixed, 95% CI)	2.33 [-2.94, 7.59]
5.1 Heel lance	2	38	Mean Difference (IV, Fixed, 95% CI)	2.33 [-2.94, 7.59]
6 HRV after painful procedure - Low frequency power	2	38	Mean Difference (IV, Fixed, 95% CI)	0.58 [-0.92, 2.07]
6.1 Heel lance	2	38	Mean Difference (IV, Fixed, 95% CI)	0.58 [-0.92, 2.07]
7 HRV after painful procedure - High frequency power	2	38	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.18, 0.29]
7.1 Heel lance	2	38	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.18, 0.29]
8 HRV during painful procedure - Low frequency to high frequency ratio	2	38	Mean Difference (IV, Fixed, 95% CI)	-3.77 [-13.69, 6.14]
8.1 Heel lance	2	38	Mean Difference (IV, Fixed, 95% CI)	-3.77 [-13.69, 6.14]
9 PIPP Score 30 seconds after painful procedure	5	268	Mean Difference (IV, Fixed, 95% CI)	-3.21 [-3.94, -2.48]
9.1 Heel lance	5	268	Mean Difference (IV, Fixed, 95% CI)	-3.21 [-3.94, -2.48]
10 PIPP Score 60 seconds after painful procedure	3	164	Mean Difference (IV, Fixed, 95% CI)	-1.85 [-3.03, -0.68]
10.1 Heel lance	3	164	Mean Difference (IV, Fixed, 95% CI)	-1.85 [-3.03, -0.68]
11 PIPP Score 90 seconds after painful procedure	3	163	Mean Difference (IV, Fixed, 95% CI)	-1.34 [-2.56, -0.13]
11.1 Heel lance	3	163	Mean Difference (IV, Fixed, 95% CI)	-1.34 [-2.56, -0.13]
12 PIPP Score 120 seconds after painful procedure	3	157	Mean Difference (IV, Fixed, 95% CI)	0.04 [-1.14, 1.23]
12.1 Heel lance	3	157	Mean Difference (IV, Fixed, 95% CI)	0.04 [-1.14, 1.23]

Comparison 2. Skin-to-skin care with different providers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart rate recovery	2	78	Mean Difference (IV, Fixed, 95% CI)	-32.97 [-94.52, 28.59]
1.1 Father	1	62	Mean Difference (IV, Fixed, 95% CI)	-26.0 [-91.34, 39.34]
1.2 Alternate Female	1	16	Mean Difference (IV, Fixed, 95% CI)	-88.0 [-271.66, 95.66]
2 PIPP Score 30 seconds	2	80	Mean Difference (IV, Fixed, 95% CI)	-1.29 [-2.73, 0.16]
2.1 Father	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.94 [-2.56, 0.68]
2.2 Alternate Female	1	18	Mean Difference (IV, Fixed, 95% CI)	-2.63 [-5.82, 0.56]
3 PIPP Score 60 seconds	2	80	Mean Difference (IV, Fixed, 95% CI)	0.79 [-0.75, 2.34]
3.1 Father	1	62	Mean Difference (IV, Fixed, 95% CI)	1.30 [-0.37, 2.97]
3.2 Alternate Female	1	18	Mean Difference (IV, Fixed, 95% CI)	-2.13 [-6.15, 1.89]
4 PIPP Score 90 seconds	2	80	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-2.05, 1.09]
4.1 Father	1	62	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.73, 1.73]
4.2 Alternate Female	1	18	Mean Difference (IV, Fixed, 95% CI)	-2.62 [-6.27, 1.03]
5 Pipp Score 120 Seconds	2	80	Mean Difference (IV, Fixed, 95% CI)	0.12 [-1.31, 1.55]
5.1 Father	1	62	Mean Difference (IV, Fixed, 95% CI)	0.61 [-0.93, 2.15]
5.2 Alternate Female	1	18	Mean Difference (IV, Fixed, 95% CI)	-2.88 [-6.70, 0.94]

Analysis 1.1. Comparison 1 Skin-to-skin care versus control, Outcome 1 Heart Rate during painful procedure.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

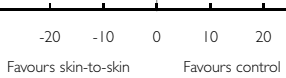
Outcome: 1 Heart Rate during painful procedure

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Castral 2008	31	175.5 (40.08)	28	173.2 (38.09)		10.2 %	2.30 [-17.65, 22.25]
Cong 2009	7	158.86 (12.36)	5	156.73 (15.35)		15.3 %	2.13 [-14.14, 18.40]
Cong 2012	17	164.24 (19.26)	9	166.77 (16.31)		20.5 %	-2.53 [-16.58, 11.52]
Ludington-Hoe 2005	12	171.43 (12.17)	12	170.86 (9.24)		54.1 %	0.57 [-8.08, 9.22]
Total (95% CI)	**67**		**54**			**100.0 %**	**0.35 [-6.01, 6.71]**

Heterogeneity: $Chi^2 = 0.25$, df = 3 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 0.11 (P = 0.91)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Skin-to-skin care versus control, Outcome 2 Heart rate following painful procedure.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

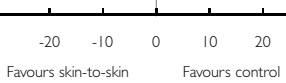
Outcome: 2 Heart rate following painful procedure

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Castral 2008	31	159.5 (33.49)	28	167.2 (31.83)		9.4 %	-7.70 [-24.37, 8.97]
Cong 2009	7	153.26 (6.33)	5	146.99 (16.86)		10.9 %	6.27 [-9.23, 21.77]
Cong 2012	17	152.69 (13.86)	9	155.42 (15.23)		18.4 %	-2.73 [-14.66, 9.20]
Ludington-Hoe 2005	12	161.14 (7.33)	12	166.35 (8.96)		61.2 %	-5.21 [-11.76, 1.34]
Total (95% CI)	**67**		**54**			**100.0 %**	**-3.73 [-8.86, 1.39]**

Heterogeneity: $Chi^2 = 2.04$, df = 3 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 1.43 (P = 0.15)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Skin-to-skin care versus control, Outcome 3 HRV during painful procedure - Low frequency power.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

Outcome: 3 HRV during painful procedure - Low frequency power

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2009	7	16.61 (16.51)	5	20.08 (16.71)		66.7 %	-3.47 [-22.55, 15.61]
Cong 2012	17	20.47 (41.33)	9	19.87 (28.3)		33.3 %	0.60 [-26.38, 27.58]
Total (95% CI)	**24**		**14**			**100.0 %**	**-2.11 [-17.69, 13.47]**

Heterogeneity: $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 0.27 (P = 0.79)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Skin-to-skin care versus control, Outcome 4 HRV during painful procedure - High frequency power.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

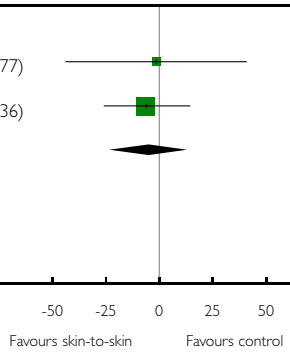
Outcome: 4 HRV during painful procedure - High frequency power

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2009	7	24.83 (26.99)	5	26.26 (42.77)		18.4 %	-1.43 [-43.92, 41.06]
Cong 2012	17	5.77 (13.36)	9	11.71 (29.36)		81.6 %	-5.94 [-26.15, 14.27]
Total (95% CI)	**24**		**14**			**100.0 %**	**-5.11 [-23.36, 13.14]**

Heterogeneity: $Chi^2 = 0.04$, df = 1 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 0.55 (P = 0.58)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Skin-to-skin care versus control, Outcome 5 HRV during painful procedure - Low frequency to high frequency ratio.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

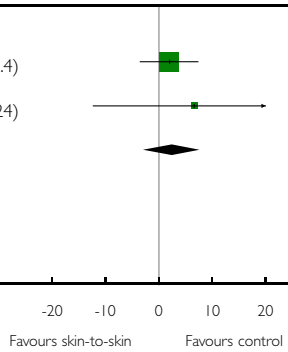
Outcome: 5 HRV during painful procedure - Low frequency to high frequency ratio

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2009	7	3.9 (6.83)	5	1.93 (2.4)		92.2 %	1.97 [-3.51, 7.45]
Cong 2012	17	30.49 (32.87)	9	23.93 (16.24)		7.8 %	6.56 [-12.33, 25.45]
Total (95% CI)	**24**		**14**			**100.0 %**	**2.33 [-2.94, 7.59]**

Heterogeneity: $Chi^2 = 0.21$, df = 1 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 0.87 (P = 0.39)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Skin-to-skin care versus control, Outcome 6 HRV after painful procedure - Low frequency power.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

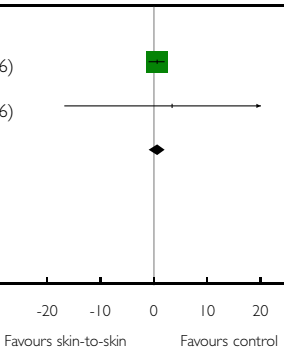
Outcome: 6 HRV after painful procedure - Low frequency power

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2009	7	2.79 (1.75)	5	2.23 (0.86)		99.5 %	0.56 [-0.94, 2.06]
Cong 2012	17	15.56 (35.73)	9	12.14 (16.76)		0.5 %	3.42 [-16.79, 23.63]
Total (95% CI)	**24**		**14**			**100.0 %**	**0.58 [-0.92, 2.07]**

Heterogeneity: $Chi^2 = 0.08$, df = 1 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Skin-to-skin care versus control, Outcome 7 HRV after painful procedure - High frequency power.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

Outcome: 7 HRV after painful procedure - High frequency power

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2009	7	0.3 (0.24)	5	0.25 (0.17)		99.9 %	0.05 [-0.18, 0.28]
Cong 2012	17	5.65 (15.27)	9	1.15 (1.89)		0.1 %	4.50 [-2.86, 11.86]
Total (95% CI)	**24**		**14**			**100.0 %**	**0.05 [-0.18, 0.29]**

Heterogeneity: Chi^2 = 1.40, df = 1 (P = 0.24); I^2 =29%

Test for overall effect: Z = 0.46 (P = 0.65)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Skin-to-skin care versus control, Outcome 8 HRV during painful procedure - Low frequency to high frequency ratio.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

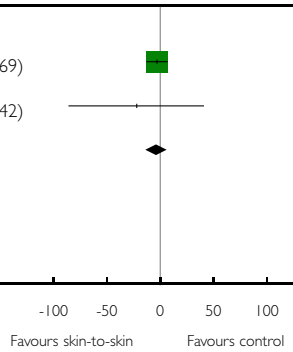
Outcome: 8 HRV during painful procedure - Low frequency to high frequency ratio

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2009	7	11.51 (4.86)	5	14.81 (10.69)		97.5 %	-3.30 [-13.34, 6.74]
Cong 2012	17	45.39 (77.61)	9	67.87 (78.42)		2.5 %	-22.48 [-85.61, 40.65]
Total (95% CI)	**24**		**14**			**100.0 %**	**-3.77 [-13.69, 6.14]**

Heterogeneity: $Chi^2 = 0.35$, df = 1 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 0.75 (P = 0.46)

Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1 Skin-to-skin care versus control, Outcome 9 PIPP Score 30 seconds after painful procedure.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

Outcome: 9 PIPP Score 30 seconds after painful procedure

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2011	7	13.29 (2.5)	10	13 (3.2)		7.3 %	0.29 [-2.42, 3.00]
Cong 2011	6	7.25 (1.9)	4	13.7 (5.2)		1.9 %	-6.45 [-11.77, -1.13]
Freire 2008	31	6 (2.6)	33	10.93 (2.46)		34.9 %	-4.93 [-6.17, -3.69]
Johnston 2003	34	9.71 (3.62)	34	11.74 (1.69)		29.8 %	-2.03 [-3.37, -0.69]
Johnston 2008	31	9 (3.59)	31	10.74 (3.63)		16.7 %	-1.74 [-3.54, 0.06]
Nimbalkar 2013	20	5.4 (3.87)	27	10.63 (4.47)		9.4 %	-5.23 [-7.62, -2.84]
Total (95% CI)	**129**		**139**			**100.0 %**	**-3.21 [-3.94, -2.48]**

Heterogeneity: Chi^2 = 23.46, df = 5 (P = 0.00028); I^2 =79%

Test for overall effect: Z = 8.57 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Skin-to-skin care versus control, Outcome 10 PIPP Score 60 seconds after painful procedure.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

Outcome: 10 PIPP Score 60 seconds after painful procedure

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2011	7	15 (1.63)	10	14.3 (3.56)		21.7 %	0.70 [-1.82, 3.22]
Cong 2011	7	7.5 (1.73)	10	12.8 (5.5)		10.4 %	-5.30 [-8.94, -1.66]
Johnston 2003	34	10.59 (4.07)	34	13.53 (3.2)		45.4 %	-2.94 [-4.68, -1.20]
Johnston 2008	31	9.48 (4.68)	31	10.03 (5.22)		22.6 %	-0.55 [-3.02, 1.92]
Total (95% CI)	**79**		**85**			**100.0 %**	**-1.85 [-3.03, -0.68]**

Heterogeneity: Chi^2 = 9.97, df = 3 (P = 0.02); I^2 =70%

Test for overall effect: Z = 3.10 (P = 0.0019)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Skin-to-skin care versus control, Outcome 11 PIPP Score 90 seconds after painful procedure.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

Outcome: 11 PIPP Score 90 seconds after painful procedure

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2011	7	15.86 (1.8)	10	14.4 (3.6)		21.8 %	1.46 [-1.14, 4.06]
Cong 2011	6	9 (3.6)	10	12.67 (6.1)		6.5 %	-3.67 [-8.42, 1.08]
Johnston 2003	34	9.71 (4.22)	34	12.5 (3.87)		39.9 %	-2.79 [-4.71, -0.87]
Johnston 2008	31	9.48 (4.32)	31	10.45 (4.34)		31.8 %	-0.97 [-3.13, 1.19]
Total (95% CI)	**78**		**85**			**100.0 %**	**-1.34 [-2.56, -0.13]**

Heterogeneity: Chi^2 = 7.67, df = 3 (P = 0.05); I^2 =61%

Test for overall effect: Z = 2.16 (P = 0.031)

Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 Skin-to-skin care versus control, Outcome 12 PIPP Score 120 seconds after painful procedure.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 1 Skin-to-skin care versus control

Outcome: 12 PIPP Score 120 seconds after painful procedure

Study or subgroup	Skin-to-skin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Heel lance							
Cong 2011	7	16.57 (1.3)	10	14.78 (2.59)		39.9 %	1.79 [-0.08, 3.66]
Cong 2011	6	7.75 (3)	4	10.33 (5.6)		3.9 %	-2.58 [-8.57, 3.41]
Johnston 2003	34	8.97 (3.83)	34	10.02 (4.08)		39.5 %	-1.05 [-2.93, 0.83]
Johnston 2008	31	9.65 (6.93)	31	10.58 (4.43)		16.7 %	-0.93 [-3.83, 1.97]
Total (95% CI)	**78**		**79**			**100.0 %**	**0.04 [-1.14, 1.23]**

Heterogeneity: $Chi^2 = 5.81$, df = 3 (P = 0.12); $I^2 = 48\%$

Test for overall effect: Z = 0.07 (P = 0.94)

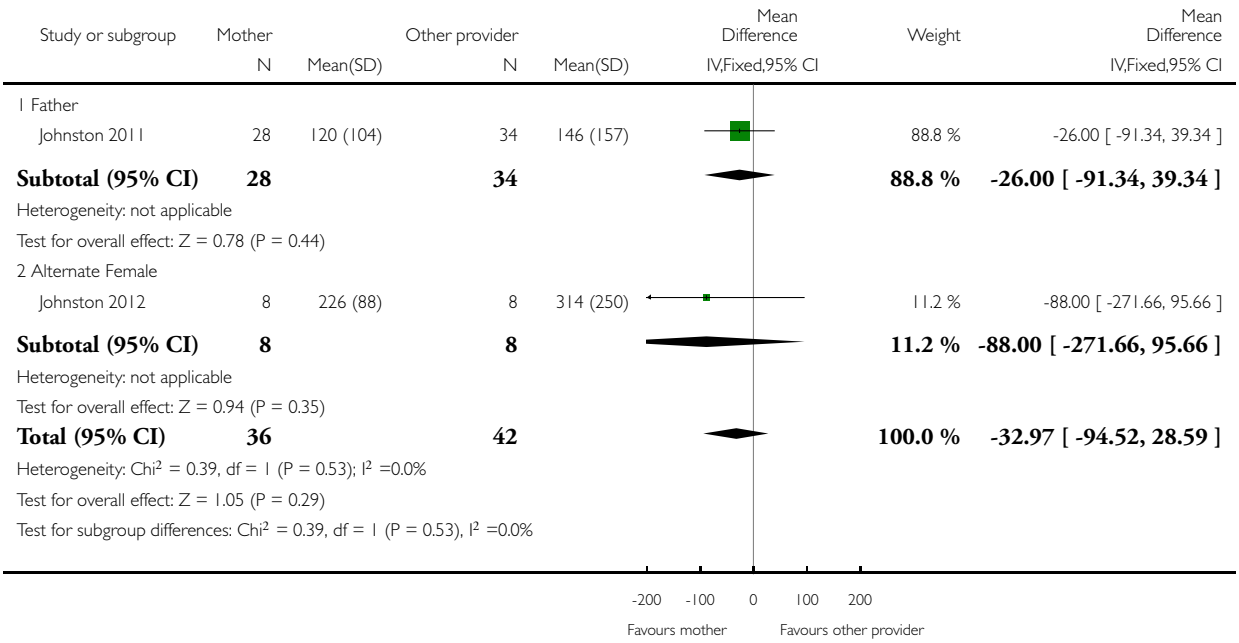
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Skin-to-skin care with different providers, Outcome 1 Heart rate recovery.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 2 Skin-to-skin care with different providers

Outcome: 1 Heart rate recovery

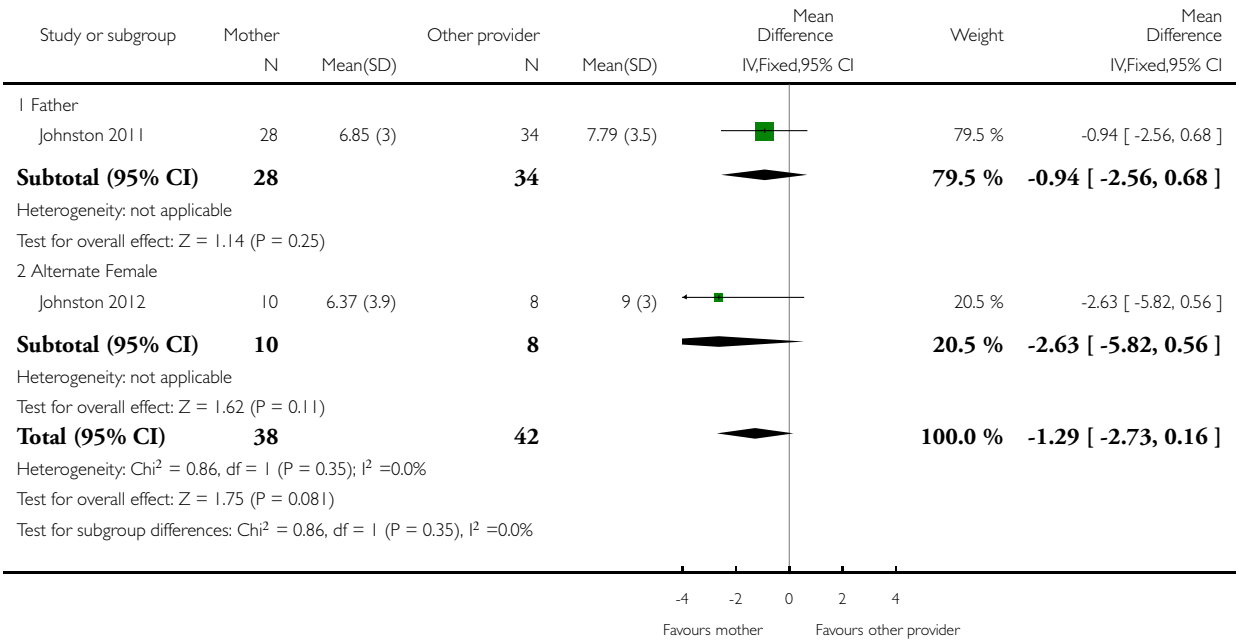


Analysis 2.2. Comparison 2 Skin-to-skin care with different providers, Outcome 2 PIPP Score 30 seconds.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 2 Skin-to-skin care with different providers

Outcome: 2 PIPP Score 30 seconds

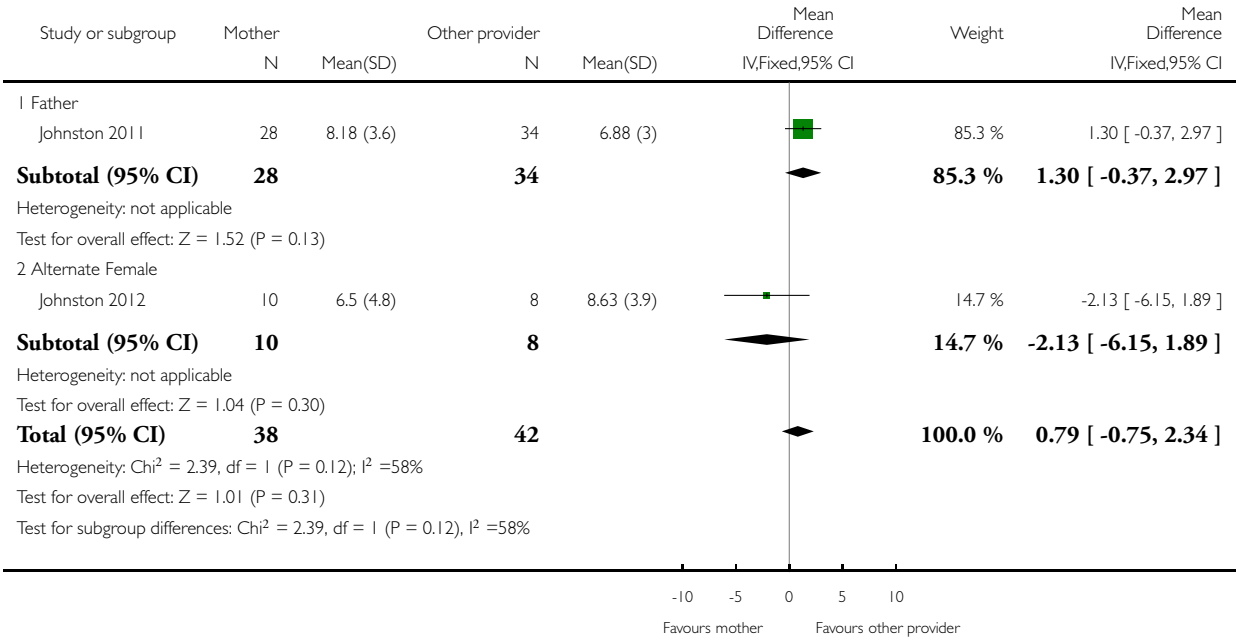


Analysis 2.3. Comparison 2 Skin-to-skin care with different providers, Outcome 3 PIPP Score 60 seconds.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 2 Skin-to-skin care with different providers

Outcome: 3 PIPP Score 60 seconds

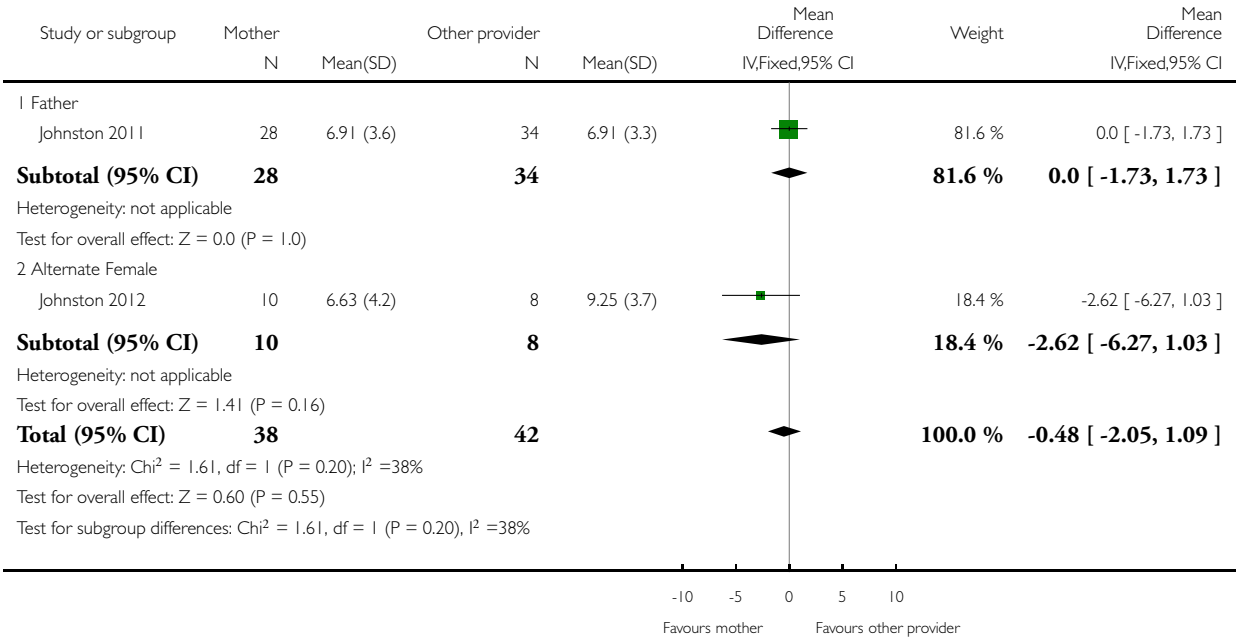


Analysis 2.4. Comparison 2 Skin-to-skin care with different providers, Outcome 4 PIPP Score 90 seconds.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 2 Skin-to-skin care with different providers

Outcome: 4 PIPP Score 90 seconds

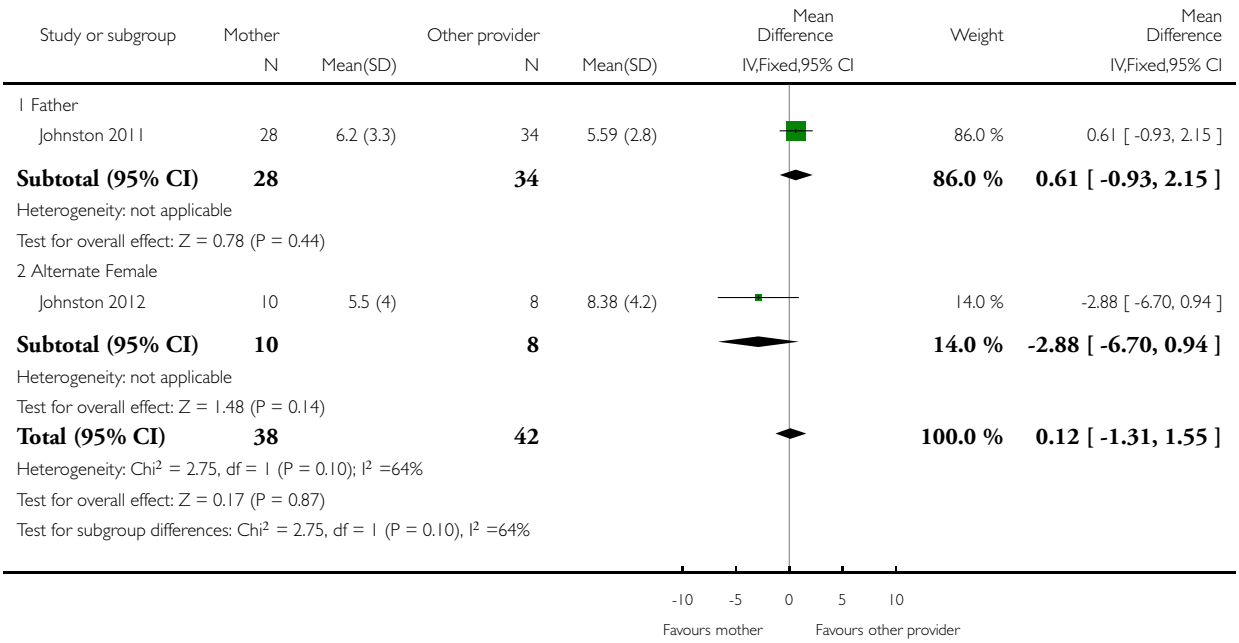


Analysis 2.5. Comparison 2 Skin-to-skin care with different providers, Outcome 5 Pipp Score 120 Seconds.

Review: Skin-to-skin care for procedural pain in neonates

Comparison: 2 Skin-to-skin care with different providers

Outcome: 5 Pipp Score 120 Seconds



ADDITIONAL TABLES

Table 1. Trials assessing pain during heel lance

Study	Design	Participants	Intervention	Outcome	Metrics Used	Results
Castral 2008	Randomised controlled trial	59 infants (31 intervention, 28 control) Postmenstrual age, mean, days: 248.3 (intervention), 254.4 (control) Birth weight, mean, grams: 1748. 8 (intervention),	Intervention: 15 minutes of skin-to-skin care before, during and following heel lance Control: standard care during heel lance Provider: mother	Neonatal Facial Coding System (NFCS) and heart rate at baseline, treatment, heel cleaning, heel lance, heel squeezing, wound compression, and recovery	Mean, mean difference (Treatment -control) Std. error, p-value, 95% confidence intervals	Statistically significant differences between treatment and control groups during puncture, heel squeeze and post phases of heel lance. Infants receiving skin-to-skin

Table 1. Trials assessing pain during heel lance (*Continued*)

		1846.2 (control)				contact more likely than infant controls to have significant lower NFCS scores for heel lance (p = . 023) and for heel squeeze. Both groups showed increased heart rate during puncture and heel squeeze although changes in these measures were less for treated infants (average increase of 19 bpm from baseline to heel puncture and squeezing in treatment group compared to average increase value of 23 bpm during puncture and 34 bpm during heel squeezing in control group) Means and standard deviations for NFCS scores and cry duration were obtained from the author
Cong 2009	Randomised cross-over	14 infants (13 intervention, 10 control) Postnatal age, mean ± SD, days: 6 ± 1 (total) Postmenstural age, range, weeks:30-32	Intervention: 60 minutes of skin-to-skin care before, during and following heel lance Control: standard care during heel lance	Heart rate, low frequency (LF) and high frequency (HF) power, LF/HF power, and state at baseline, heel warming, heel lance,	Not reported	HR significantly lower in the KC condition (146 ± 9 bpm) than in IC (152 ± 13 bpm) during BL period (p < .05) and HS period (KC 159 ± bpm

Table 1. Trials assessing pain during heel lance (*Continued*)

		Birth weight, mean ± SD, grams: 1775 ± 292 (total) Weight on day of study, mean ± SD, grams: 1706 ± 293 (total)	Provider: mother	and recovery		versus IC 165 ± 14 bpm, P < .05) . HR increased significantly during HS from the BL and HW periods in both KC (P < .05) and IC conditions (P < .001), and returned to BL values during RC in both conditions. LF was higher in KC at BL (P < .01) and HS (P < .001) and HF was higher in KC at BL than in IC condition (P < .05). LF/HF ratio fluctuated less across periods in KC than in IC condition and was significantly lower during RC in KC than in IC (P < . 001). LF and HF increased during HS from BL and HW, and dropped in the RC period in both KC (LF, P < .05 and HF, P < .01) and IC (LF, P < .01 and HF, P < .001) conditions. The LF/HF ratio was lower during HS than during BL, HW, and RC in both KC (P < . 01) and IC (P < . 001) conditions

Table 1. Trials assessing pain during heel lance (*Continued*)

Cong 2011	Prospective randomised cross-over	28 infants: 14 infants - 80 min SSC (Study 1); 10 infants - 30 min SSC (Study 2) Postnatal age, mean ± SD, days: 5 ± 1 (Study 1); 6 ± 2 (Study 2) Postmenstrual age, range, weeks: 30-32 Birth weight, mean ± SD, grams: 1779 ± 277 (Study 1) ; 1577 ± 327 (Study 2)	Intervention: (a) Study 1: 60 minutes of skin-to-skin care before heel lance, with continued SSC during procedure, and followed by 20 minutes SSC post-procedure; (b) Study 2: 10 minutes of skin-to-skin care before heel lance, with continued SSC during procedure, and followed by 20 minutes SSC post-heel lance Control: standard care during heel lance Provider: mother	PIPP score, salivary and serum cortisol at baseline, heel warming, heel lance and recovery	Mean, standard deviations	Study 2 showed lower PIPP scores at four time points during recovery (P < .05 to P < .001), lower salivary cortisol at the end of recovery (P < .05) and lower serum cortisol during heel lance for the kangaroo care heel lance condition (KCH) (P < .05) as swell as clinically lower PIPP scores in the KCH condition during heel lance
Cong 2012	Randomised cross-over	26 preterm infants (PMA 28 0/7 to 32 6/7 weeks): 22 infants - 30 min SSC (Study a); 25 infants - 15 min SSC (Study b); 23 infants control Postnatal age, mean ± SD, days: 14.5 ± 6.3 (Study a); 13.8 ± 5.6 (Study b) ; 13.5 ± 5.6 (control) Birth weight, mean ± SD, grams: 1444.6 ± 379.0	Intervention: (a) Study a: 30 minutes of skin-to-skin care before and throughout heel lance (b) Study b: 15 minutes of skin-to-skin care before and throughout heel lance Control: standard care during heel lance Provider: mother	Heart rate, Heart rate variability (low frequency and high frequency power), LF/HF ratio, Infant behavioural state	Mean, standard deviations	HR changes from Baseline to Heel Stick were significantly less in KC30 and KC15 than in IC, and more infants had HR decrease in IC than in 2 KC conditions. In IC, LF and HF significantly increased from Baseline to Heel Stick and dropped from Heel Stick to Recovery; in 2 KC conditions, no changes

Table 1. Trials assessing pain during heel lance (*Continued*)

						across study phases were found. During Heel Stick, LF and HF were significantly higher in IC than in KC30. In all 3 conditions, LF/HF ratio decreased from Baseline to Heel Stick and increased to Recovery; no differences were found between IC and two KC conditions. Both longer and shorter KC before and throughout heel stick can stabilize HR response in preterm infants, and longer KC significantly affected infants' sympathetic and parasympathetic responses during heel stick compared with incubator care
Freire 2008	Randomised controlled trial	95 infants (31 intervention, 33 control, 31 comparison) Postmenstrual age, range, weeks: 28-36	Intervention: 10 minutes of skin-to-skin care before, during heel lance Control: standard care during heel lance Comparison: Sweet taste 2 minutes before heel lance	PIPP score	Mean, standard deviations	Heart rate variation and oxygen saturation significantly lower in kangaroo group compared to incubator and glucose groups (p = 0.0001 and P = 0.0012, respectively). Shorter duration

Table 1. Trials assessing pain during heel lance (*Continued*)

			Provider: mother			of facial activity (brow bulge, eye squeeze and nasolabial furrowing) (P = 0.0001) and significantly lower PIPP score (P = 0.0001) observed in the kangaroo care method group Means and standard deviations for PIPP scores were obtained from the author
Gray 2000	Randomised controlled trial	30 infants (15 control, 15 intervention) Postnatal age, range, hours: 33-55 Postmenstrual age, weeks: ≥37 Birth weight, mean (range) , grams: 3300 (2600-3700)	Intervention: 10-15 minutes of skin-to-skin care before heel lance Control: standard care during heel lance Provider: mother	Heart rate during blood collection, cry duration and grimacing during recovery period	Mean	Infants held by mother in skin-to-skin contact, cried and grimaced for an average of 1 and 2 seconds, respectively, for entire recovery period. Control infants cried for a mean of 32 seconds and grimaced for a mean of 30 seconds of the 3-minute recovery period (P < .0001). Heart rate of skin-to-skin infants increased by about 8 to 10 bpm during blood collection whereas control infants heart rate rose by 36 to 38 bpm to an asymptote of 160bpm

Table 1. Trials assessing pain during heel lance (*Continued*)

Johnston 2003	Randomised cross-over	74 infants Postnatal age, range, days: 0-10 Postmenstrual age, mean ± SD (range), weeks: 33.7 ± 1.1 (32.0-36.0) Birth weight, mean ± SD (range), grams: 2054 ± 406 (1320-3125)	Intervention: 30 minutes of skin-to-skin care before and during heel lance Control: standard care during heel lance Provider: mother	PIPP score at 30, 60, 90, and 120 minutes	Mean, 95% confidence interval	Significantly lower PIPP scores in KC condition at 30 seconds (difference, 1.5 points; P = .04), 60 seconds (difference, 2.2 points; P=.002), and 90 seconds (difference, 0.6 point; P=.37) after heel-lancing procedure. Heart rate and oxygen saturation similar in both conditions. Facial actions contributed significantly to total pain score (.000<P<.005), with facial actions averaging 20% greater in control versus KC condition Means and standard deviations for heart rate were obtained from the author
Johnston 2008	Randomised cross-over	61 infants Postmenstrual age, mean ± SD, weeks: 30.5 ± 1 Birth weight, mean ± SD, grams: 1421 ± 490	Intervention: 15 minutes of skin-to-skin care before and during heel lance Comparison: swaddling in incubator 15 minutes before heel lance Provider: mother	PIPP score at 30, 60, 90, and 120 minutes Time to return to baseline Heart rate	Mean	Mean PIPP scores not significantly lower in KMC condition 30 and 60 seconds post-heel lance Significant difference by 90 seconds post-heel lance (KMC 8.871 (95%CI 7.852-

Table 1. Trials assessing pain during heel lance (*Continued*)

						9.889) versus Incubator 10. 677 (95%CI 9. 563-11.792) P < .001). Insignificant difference continued to 120 seconds (8. 855 (95%CI 7.447-10.262) versus 10.210 (95%CI 9.030-11.389) P = . 145). Significant difference in time returning to baseline heart rate at end of blood sampling (123 seconds (95%CI 103-142) for the KMC and 193 seconds for incubator (95% CI 158-227) (F (61,1) = 13. 6, P < .0000) . Facial actions significantly lower in KMC than incubator throughout phases. Maximum heart rate significantly lower at 30, 60 and 90 seconds. Minimum oxygen saturation levels significantly higher at 60 and 90 seconds Means

Table 1. Trials assessing pain during heel lance (*Continued*)

						and standard deviations for PIPP scores were obtained from the author
Johnston 2009	Randomised cross-over	90 infants Postnatal age, range, days: 1-14 Postmenstrual age, mean ± SD, weeks: 33.4 ± 1.1 Birth weight, mean ± SD, grams: 1968 ± 388	Intervention: 30 minutes of skin-to-skin care before and during heel lance Comparison: 30 minutes of enhanced skin-to-skin care (rocking, singing/talking to baby, offering finger/pacifier for baby to suck Provider: mother	PIPP score at 30, 60, 90, and 120 minutes	Mean	Mean PIPP scores not significantly different between conditions for any of the 30s blocks of time. No difference in condition for examining time for heart rate to return to baseline Means and standard deviations for PIPP scores were obtained from the author
Johnston 2011	Randomised cross-over	62 preterm infants (PMA 28 to 36 weeks) Postnatal age, mean, days: 5-10 Birth weight, mean ± SD, grams: 1565 ± 469 (father KC/mother KC); 1610 ± 494 (mother KC/father KC)	Intervention: 30 minutes of skin-to-skin care before and during heel lance provided by mother Comparison: 30 minutes of skin-to-skin care before and during heel lance provided by father Provider: mother or father	PIPP score at 30, 60, 90, and 120 minutes, time for HR to return to baseline	Mean difference, 95% confidence interval	Infants in maternal KC displayed significantly lower scores on the PIPP at 30 and 60 seconds after the heel lance than when in paternal KC (30 seconds mean difference 1.435 (95% confidence interval, 0.232-2.632); 60 seconds mean difference 1.548 (95% confidence interval, 0.069-3.027)). No differences at 90 and 120 seconds The difference in time to return

Table 1. Trials assessing pain during heel lance (*Continued*)

						to KC heart rate before the heel lance was significant, with the time in maternal KC being 204 seconds and in paternal KC, 246 seconds (mean difference, 42 seconds (95% confidence interval 5.16-81.06 seconds)
Johnston 2012	Randomised cross-over	18 preterm infants (PMA 28 to 36 completed weeks) Postnatal age, range, days: within 10 days Birth weight, mean, grams: 2200	Intervention: 30 minutes of skin-to-skin care before and during heel stick provided by the mother Comparison: 30 minutes of skin-to-skin care before and during heel lance provided by an unrelated woman Provider: mother or an unrelated woman	PIPP score at 30, 60, 90, and 120 minutes	Estimate of effect size (based Cohen's formula, based on mean differences divided by the standard deviation)	The effect sizes on the pain scores (PIPP) were small, ranging from 1.1 to 1.7. The effect size at 30 sec was 0.23, at 60 sec was .24, at 90 sec was 0.43 and at 120 sec was 0.37 There was a 48% participation rate, with only 40 of 82 eligible cases having maternal consent. The main reason for refusal was discomfort with another woman providing kangaroo care
Kostandy 2008	Randomised cross-over	10 infants Postmenstrual age, range, weeks: 30-32 Birth weight, mean ± SD, grams: 1577 ± 327.00	Intervention: 30 minutes of skin-to-skin care before and during heel lance Control: standard care during heel lance Provider: mother	Cry duration at baseline, warming, heel lance, and recovery	Mean, standard deviation	Significant difference in crying time between study phases on both days ($F(1, 8) = 10.25$, $P < 0.001$). When in KC as compared to the incubator,

Table 1. Trials assessing pain during heel lance (*Continued*)

						crying time was less during the heel lance (P = 0.001) and Recovery (P = 0.01) phases
Ludington-Hoe 2005	Randomised cross-over	23 preterm infants (< 37 weeks PMA) Postnatal age, mean ± SD, days: 22 ± 11.4 Postmenstrual age, mean ± SD, weeks: 31.4 ± 2.7	Intervention: 3 hours of skin-to-skin care before and during heel lance Control: standard care during heel lance Provider: mother	Heart rate, respiratory rate, oxygen saturation, cry duration, behavioural state	Mean, standard deviation	Heart rate and length of crying in response to pain significantly reduced during KC and the KC heel lance as compared to when infants were in the warmer and had a heel lance in the warmer. Significant main effects were found for heart rate (F[1,32] = 3.54, P = .042) and cry length (F[1, 32] = 5.20; P = .01). Mean rise in heart rate from baseline to heel lance was less in the KC condition than in the warmer condition (F[1,32] = 3.01, P = .047). Crying length during KC heel lance significantly less than during warmer heel lance (F[1, 32] = 7.38, P = .003) and post-lance period (P = .02)
Nimbalkar 2012	Randomised cross-over	47 preterm infants (PMA 32	Intervention: 15 minutes of skin-	PIPP score	Mean, standard deviation	Heart rate, behaviour and fa-

Table 1. Trials assessing pain during heel lance (*Continued*)

		0/7 to 36 6/7 weeks) Postnatal age, mean, days: within 10 days Birth weight, mean, grams: 1730 (intervention), unclear (control)	to-skin care before, during, and 15 minutes after heel lance Control: standard care during heel lance Provider: mother			cial scores were statistically significant and lower in KMC group. But there was no statistically significant difference in oxygen saturation (SpO2. The difference (4.85) in PIPP score was clinically and statistically significant (P < 0.0001)
Okan 2010	Prospective randomised controlled trial	107 infants (35 treatment, 36 control, 36 comparison) Postnatal age, mean ± SD, days: 33.1± 5 Postmenstrual age, mean ± SD, days: 39.5 ± 0.6	Intervention: 15 min of skin-to-skin care before and during heel lance Control: standard care during heel lance Comparison: skin-to-skin care and breastfeeding before and during heel lance Provider: mother	Crying time after painful stimulus Change in heart rate Change in SaO2 NFCS	Median, 25-75% IQR	Heart rate, oxygen saturation changes and length of crying were significantly reduced in treatment and comparison groups compared with control (P < 0.001) . No difference found between treatment and comparison group Length of crying - Intervention: 65 (50-133); Control: 184 (107-281); Comparison: 48 (40-98) Means and standard deviations for NFCS scores, heart rate and oxygen saturation were obtained from the author

units: heart rate - beats/minute (bpm); crying time - seconds

Table 2. Trials assessing pain during intramuscular injection

Study	Design	Participants	Intervention	Outcome	Metrics Used	Results
Chermont 2009	RCT	640 infants (160 skin-to-skin care, 160 control, 160 comparison1, 160 comparison2) Post-natal age, mean ± SD, hrs: 293 ± 13 (skin-to-skin care) , 29 ± 15 (control) , 29 ± 13 (comparison1), 27 ± 13 (comparison2) postmenstrual age, mean ± SD, wk: 39 ± 1 (for all groups) Birth weight, mean ± SD, g: 3164 ± 371 (intervention); 3163 ± 418 (control); 3252 ± 389 (comparison1); 3240 ± 418 (comparison2)	Intervention: skin-to-skin contact, initiated 2 minutes before injection and persisting throughout procedure Control: standard care during injection Comparison1: oral 25% dextrose treatment (1mL), given 2 minutes before injection Comparison2: combination of oral dextrose treatment and skin-to-skin contact strategies Provider: mother provided skin-to-skin; oral dextrose provided by nurse or neonatologist	Neonatal Facial Coding System (NFCS) , Neonatal Infant Pain Scale (NIPS) , and Premature Infant Pain Profile (PIPP) scores at baseline, cleansing, injection, and recovery	Mean, standard error	NFCS and NIPS scores for the 4 groups at the 4 study times showed that main effect of time and analgesic procedures were statistically significant (P<.001), as was interaction between time and procedure (P<.001). Either skin-to-skin contact or 25% dextrose treatment alone did not significantly affect pain scores during injection, but the combination of both significantly decreased these scores during the invasive procedure. Mean PIPP scores showed significant differences among groups (P<.001). PIPP scores were lower when IM vaccine injections were given to healthy neonates during skin-to-skin contact with their mothers, regardless of

Table 2. Trials assessing pain during intramuscular injection (*Continued*)

						whether oral 25% dextrose treatment was administered. Isolated use of the sweetener did not decrease PIPP scores, compared with standard care. Heart rate and oxygen saturation variability (not defined) were reported significantly to favour of SSC over both control and sucrose
Saeidi 2010	RCT	60 full term infants (80% of case group and 73.3% of control group had 40 weeks GA) Birth weight, mean ± SD, grams: 3242 ± 306.6 (intervention), 3151 ± 331.5 (control)	Intervention: 30 minutes skin to skin contact Control: standard care during injection Provider: mother provided skin-to-skin care	Behavioural changes using the Neonatal/Infant Pain Scale (NIPS) 2 minutes before, during, and 3 minutes after intervention heart rate oxygen saturation	NIPS: number (%) O2 saturation: mean, SD HR and crying interval: P-values	Mean pain intensity during the intervention was significantly lower in the case group (P<0. 006). Mean pain intensity 3 minutes after intervention was also significantly lower in the case group (P<0. 021). Mean duration of crying was significantly lower in the case group as well (P<0.001)
Sajedi 2007	RCT	100 infants (50 intervention, 50 control) Postmenstrual age, mean ± SD, weeks: 39.36 ± 1.45 (intervention), 39.12 ± 1.42 (control) Birth weight, mean ± SD, grams: 3083. 2 ± 258.33 (inter-	Intervention: 10 minutes of skin-to-skin care before and during painful procedure, and 3 minutes after injection Control: standard care during injection Provider: mother provided skin-to-	Neonatal Infant Pain Scale (NIPS) , Behavioural responses (facial expression, breathing pattern, state of arousal, arm and leg movements, and cry), heart rate and oxygen saturation before, during and	Mean, standard deviations, chi-squared, degrees of freedom	Significantly more severe behavioral responses immediately after injection in control than intervention group (p < .001). NIPS scores immediately after injection significantly higher in control than in-

Table 2. Trials assessing pain during intramuscular injection (*Continued*)

		vention), 3142.2 ± 242.3 (control)	skin care	after injection		tervention group (P < .001). Duration of crying post-injection significantly longer in control than intervention group (P = .001). No significant difference in mean heart rate before injection (P = 0.4) but during (P < 0.001), and after (P < 0.001) injection, favouring the KC group. No significant difference in the blood oxygen saturation before (P = 0.7) but during (P < 0.001) and after (P < 0.001) injection between the 2 groups, favouring the KC group

Table 3. Trials assessing pain during heel lance and venepuncture

Study	Design	Participants	Intervention	Outcome	Metrics Used	Results
Akcan 2009	RCT	50 preterm infants (25 SSC, 25 control), PMA 31.6 ± 2.0 weeks, Birth weight 1669 ± 530 (total)	Intervention: 45 minutes of uninterrupted skin-to-skin every day for 5 days, with the painful procedure carried out on the 5th day Control: standard care during painful procedure Provider: mother	Premature Infant Pain Profile (PIPP) scores at baseline, the 1st, 2nd, and 3rd minute of the painful procedure, and the 1st and 2nd minute after the painful procedure	Means, 95% CI chi-square	SSC was found to be effective in decreasing pain during and after invasive procedure in premature infants. PIPP scores were significantly lower at each measurement in infants in the SSC group (P < 0.001, P = 0.001, P = 0.047, respectively). PIPP scores at the 1st and 2nd minute af-

Table 3. Trials assessing pain during heel lance and venepuncture (*Continued*)

						ter painful procedure were 4 and 4 in infants in KC and 12.5 and 7 in infants in the control group, respectively. PIPP scores soon after the invasive procedure were significantly lower in infants in the KC group compared to the control group (P < 0.001, P = 0.023, respectively)

Table 4. Trials assessing pain with different skin-to-skin providers

Study	Design	Participants	Intervention	Outcome	Metrics Used	Results
Johnston 2011	Randomised cross-over	62 preterm infants (PMA 28 to 36 weeks) Postnatal age, mean, days: 5-10 Birth weight, mean ± SD, grams: 1565 ± 469 (father KC/mother KC); 1610 ± 494 (mother KC/father KC)	Intervention: 30 minutes of skin-to-skin care before and during heel lance provided by mother Comparison: 30 minutes of skin-to-skin care before and during heel lance provided by father Provider: mother or father	PIPP score at 30, 60, 90, and 120 minutes, time for HR to return to baseline	Mean difference, 95% confidence interval	Infants in maternal KC displayed significantly lower scores on the PIPP at 30 and 60 seconds after the heel lance than when in paternal KC (30 seconds mean difference 1.435 (95% confidence interval 0.232-2.632); 60 seconds mean difference, 1.548 (95% confidence interval 0.069-3.027). No differences at 90 and 120 seconds The difference in time to return to KC heart rate before the heel lance was signif-

Table 4. Trials assessing pain with different skin-to-skin providers (*Continued*)

						icant, with the time in maternal KC being 204 seconds and in paternal KC, 246 seconds (mean difference 42 seconds (95% confidence interval 5.16-81.06 seconds)
Johnston 2012	Randomised cross-over	18 preterm infants (PMA 28 to 36 completed weeks) Postnatal age, range, days: within 10 days Birth weight, mean, grams: 2200	Intervention: 30 minutes of skin-to-skin care before and during heel stick provided by the mother Comparison: 30 minutes of skin-to-skin care before and during heel lance provided by an unrelated woman Provider: mother or an unrelated woman	PIPP score at 30, 60, 90, and 120 minutes	Estimate of effect size (based on Cohen's formula, based on mean differences divided by the standard deviation)	The effect sizes on the pain scores (PIPP) were small, ranging from 1.1 to 1. 7. The effect size at 30 sec was 0. 23, at 60 sec was .24, at 90 sec was 0.43 and at 120 sec was 0.37 There was a 48% participation rate, with only 40 of 82 eligible cases having maternal consent. The main reason for refusal was discomfort with another woman providing kangaroo care

CONTRIBUTIONS OF AUTHORS

CJ oversaw the process and arbitrated disputes between other reviewers, and wrote narrative. MCY and RZ contributed to content and editing of narrative.

MCY, AF, DI, RZ reviewed articles and rated them according to criteria.

DS served as methodological expert and advised about statistics.

DECLARATIONS OF INTEREST

The authors have nothing to declare.

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INDEX TERMS

Medical Subject Headings (MeSH)

Breast Feeding; Heart Rate [physiology]; Hydrocortisone [analysis]; Infant, Premature; Injections, Intramuscular [*adverse effects]; Kangaroo-Mother Care Method [*methods]; Oxygen Consumption [physiology]; Pain Management [*methods]; Phlebotomy [*adverse effects]; Punctures [*adverse effects]; Randomized Controlled Trials as Topic; Saliva [chemistry]; Term Birth

MeSH check words

Humans; Infant, Newborn