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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), often referred to 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 compared to no intervention, sucrose or other analgesics, or additions to simple SSC such as rocking; and to determine the effects of the amount of SSC (duration in minutes), method of administration (e.g. who provided the SSC) of SSC in reducing pain from medical or nursing procedures in neonates

The secondary objectives were to determine the safety of SSC care for relieving procedural pain in infants; and to compare the SSC effect in different postmenstrual age subgroups of infants.

Search methods

For this update, we used the standard search strategy of the Cochrane Neonatal Review group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 1); MEDLINE via PubMed (1966 to 25 February 2016); Embase (1980 to 25 February 2016); and CINAHL (1982 to 25 February 2016). We also searched clinical trials' databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials.

Selection criteria

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

Data collection and analysis

The main outcome measures were physiological or behavioural pain indicators and composite pain scores. A mean difference (MD) 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.

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

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Main results

Twenty-five studies (n = 2001 infants) were included. Nineteen studies (n = 1065) used heel lance as the painful procedure, one study combined venepuncture and heel stick (n = 50), three used intramuscular injection (n = 776), one used 'vaccination' (n = 60), and one used tape removal (n = 50). The studies were generally strong and had low or uncertain risk of bias. Blinding of the intervention was not possible, making them subject to high risk, depending on the method of scoring outcomes.

Seventeen studies (n = 810) compared SSC to a no-treatment control. Although 15 studies measured heart rate during painful procedures, data from only five studies (n = 161) could be combined for a mean difference (MD) of -10.78 beats per minute (95% CI -13.63 to -7.93) favouring SSC. Meta-analysis of four studies (n = 120) showed no difference in heart rate following the painful procedure (MD 0.08, 95% CI -4.39 to 4.55). Two studies (n = 38) reported heart rate variability with no significant differences. Two studies (n = 101) in a meta-analysis on oxygen saturation at 30 and 60 seconds following the painful procedure did not show a difference. Duration of crying meta-analysis was performed on four studies (n = 133): two (n = 33) investigated response to heel lance (MD = -34.16, 95% CI -42.86 to -25.45), and two (n = 100) following IM injection (MD = -8.83, 95% CI -14.63 to -3.02), favouring SSC. Five studies, one consisting of two substudies (n = 267), used the Premature Infant Pain Profile (PIPP) as a primary outcome, which favoured SSC at 30 seconds (MD -3.21, 95% CI -3.94 to -2.47), at 60 seconds (3 studies; n = 156) (MD -1.64, 95% CI -2.86 to -0.43), and at 90 seconds (n = 156) (MD -1.28, 95% CI -2.53 to -0.04); but at 120 seconds there was no difference (n = 156) (MD 0.07, 95% CI -1.11 to 1.25). No studies on return of heart rate to baseline level, cortisol levels, and facial actions could be combined for meta-analysis findings.

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 (father, another female) 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 (n = 640) 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 (n = 95). SSC either in combination with breastfeeding or alone was favoured over a no-treatment control, but not different to breastfeeding. One study compared SSC alone and in combination with both sucrose and breastfeeding on heart rate (HR), NIPS scores, and crying time (n = 127). The combinations were more effective than SSC alone for NIPS and crying. Expressed breast milk was compared to SSC in one study (n = 50) and found both equally effective on PIPP scores. 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 with both physiological and behavioural indicators and, independently, using heart rate and crying time; and safe for a single painful procedure. Purely behavioural indicators tended to favour SSC but with facial actions there is greater possibility of observers not being blinded. Physiological indicators were mixed although the common measure of heart rate favoured SSC. 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. Studies examining optimal duration of SSC, gestational age groups, repeated use, and long-term effects of SSC are needed. Of interest would be to study synergistic effects of SSC with other interventions.

PLAIN LANGUAGE SUMMARY

Skin-to-skin care with newborns cuts down procedural pain

Review question: Is skin-to-skin care effective in cutting down pain from procedures in newborns? Are there any safety issues?

Background: 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 a Neonatal Intensive Care Unit, must have various tests and procedures as part of their care, for example heel stick, venous puncture, and injections. Giving analgesic drugs for these procedures can often pose problems so that alternatives to drugs must be found.

Study characteristics: Twenty-eight studies in which newborn babies who were by chance in the kangaroo care group or condition were included from an extensive search of the literature. Skin-to-skin care was clearly defined and could have been compared to no pain-reducing strategies or other pain-reducing strategies such as sweet taste. Studies were examined which examined well-established

signs of pain, both physiological and behavioural, as well as a combination of physiological and behavioural signs. Different providers of skin-to-skin care other than the mother were included.

Key results: Kangaroo care appears to reduce the pain response to, and recovery from, these frequent procedures, although few studies could be combined to provide strong evidence. As far as it has been reported, skin-to-skin care is safe. Although it appears that skin-to-skin care is effective, the size of the benefit remains uncertain.

Quality of evidence: The quality of evidence in these studies was generally low for the response to the actual procedure but was moderate for recovery from the procedure.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Studies examining Skin-to-skin care vs no treatment control						
Patient or population: procedural pain in neonates Setting: Multiple Intervention: Skin-to-skin care Comparison: control						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with Skin-to-skin care				
Heart rate during painful procedure		The mean heart rate during painful procedure in the intervention group was 10.78 fewer (13.63 fewer to 7.93 fewer)	-	161 (5 RCTs)	⊕○○○ VERY LOW ¹²³	
Heart rate following painful procedure		The mean heart rate following painful procedure in the intervention group was 0.08 more (4.39 fewer to 4.55 more)	-	120 (4 RCTs)	⊕⊕⊕⊕ HIGH	
PIPP Score 30 seconds after painful procedure		The mean PIPP Score 30 seconds after painful procedure in the intervention group was 3.2 fewer (3.94 fewer to 2.47 fewer)	-	268 (5 RCTs)	⊕⊕⊕○ MODERATE ⁴	

NIPS - Proportion of infants in low or no pain during procedure	Study population	not estimable	480 (3 RCTs)	⊕○○○ VERY LOW ²³⁵	
	46 per 1,000	0 per 1,000 (0 to 0)			
	Moderate				
	20 per 1,000	0 per 1,000 (0 to 0)			
NIPS - Infants in no pain during recovery	Study population	not estimable	380 (2 RCTs)	⊕⊕⊕○ MODERATE ⁵	
	316 per 1,000	0 per 1,000 (0 to 0)			
	Moderate				
	485 per 1,000	0 per 1,000 (0 to 0)			
Duration of cry (seconds) following heel lance		The mean duration of cry (seconds) following heel lance in the intervention group was 34.16 fewer (42.86 fewer to 25.45 fewer)	-	33 (2 RCTs)	⊕⊕⊕○ MODERATE ⁵
Duration of cry (seconds) following IM injection		The mean duration of cry (seconds) following IM injection in the intervention group was 8.83 fewer (14.63 fewer to 3.02 fewer)	-	100 (2 RCTs)	⊕⊕⊕○ MODERATE ³

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹ Pooled effect significantly influenced by a single high RoB study

² Large heterogeneity statistics

³ Confidence interval crosses MID threshold

⁴ Intervention is less effective against active control

⁵ All studies in analysis were assessed as having high RoB

BACKGROUND

Description of the condition

The preterm neonate frequently spends the first days or weeks of life in a Neonatal Intensive Care Unit (NICU), where numerous painful procedures are part of routine care (Johnston 1997; Simons 2003; Stevens 2003; Johnston 2008; Johnston 2011b; Cruz 2016). There is substantial evidence that long-term blunting of behavioural, autonomic, and hormonal responses - and even brain and cognitive development - result from early untreated exposure to pain in preterm neonates (Johnston 1996; Oberlander 2000; Grunau 2007a; Grunau 2007b; Brummele 2012; Vinall 2014). 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 1999a). Sucrose has been shown to be effective (Stevens 2013); 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 (Pillai Riddell 2015), with non-nutritive sucking having a significant effect even in very preterm neonates (Campos 1994; Corff 1995; Stevens 1999b; 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 less 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, 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-Poë 1997; Ko 1998). In the above study of NICU parents, 87% stated that they would wish to participate in managing their infant's pain (Franck 2002). In a study of mothers engaged in kangaroo care (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). A recent study examining NICU staff nurse beliefs surrounding the use of SSC for pain management found that while neonatal staff nurses also positively viewed SSC as an effective pain-relieving intervention, they noted contextual challenges such as heavy nurse-workload and lack of maternal presence prevented its utilization (Benoit 2016).

Skin-to-skin care, referred to as kangaroo care 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°, 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

Several recent reviews have been published that report on the positive outcomes associated with SSC (Campbell-Yeo 2015; Boundy 2016). A review of clinical trials of SSC on targeted infant outcomes of breastfeeding, behaviour, and physiological adaptation in healthy neonates found 30 studies that met the inclusion criteria, four being with late preterm infants (Moore 2012). They reported evidence supporting SSC for success and duration of breastfeeding (Carfoot 2003; Johnson 2006; Moore 2012). Physiological stability and temperature control have been consistently reported as improved during SSC (de Leeuw 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 (de Leeuw 1991; Ludington-Hoe 1992; Michelsson 1996; Feldman 2002; Erlandsson 2007; Kostandy 2008). For example, a randomized 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 2014). Given that SSC promotes autonomic stability 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 painful stimuli includes autonomic arousal and crying, in addition to its advantage of giving mothers back their comforting role.

Why it is important to do this review

The American Pediatric Society and Canadian Paediatric Society's Fetus and Newborn Committee incorporated SSC as a recommended intervention. However, no systematic review with the rigour of The Cochrane Collaboration had been conducted until the first review (Johnston, 2014). 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, which did favour SSC over usual care controls for infections and weight gain (Conde-Agudelo 2014).

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 SSC effect in different postmenstrual age subgroups of infants: 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 randomized controlled trials, randomized 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 or tape removal (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 an invasive procedure, 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; audible crying time as a proportion of total procedure time; 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 2010). 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.

vi) Douleur Aiguë du Nouveau-né (DAN) (Carbajal 1997). The scale scores pain with a range from 0 to 10 with three items: facial expression, limb movements, and vocal expression with ratings per item ranging from 0 to 4, 0 to 3 and 0 to 3, respectively.

All of these indicators yield continuous data, although the NIPS was reported as proportion of infants in low, moderate, or severe pain and was analyzed as risk ratio, not mean difference.

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

was analyzed.

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

For the 2016 update we conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 1) in the Cochrane Library; MEDLINE via PubMed (1966 to 25 February 2016); Embase (1980 to 25 February 2016); and CINAHL (1982 to 25 February 2016) using the following search terms: ((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)), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We did not apply language restrictions.

We searched clinical trials' registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform www.who.int/ictrp/search/en/; and the [ISRCTN Registry](http://www.isrctn.com)).

For the previous review, these databases were searched in August 2013: 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).

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, and the 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 in our search, except with author response. 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 us to make decisions 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, TD, BB) 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 Review Manager (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 MCY).

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 during the selection process.

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 randomization, 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 (pharmacological and non-pharmacological).
- 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 Cochrane tool for assessing risk of bias, *Cochrane Handbook for Systematic Reviews of Interventions*, Table 8.5.a (Higgins 2011). 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, TD, BB) independently scored each study for quality, with verification by CJ .

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 randomized 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 fixed-effect meta-analysis was based on the clinical decision regarding the appropriateness of combining trials and outcomes (Erez 1996; Hedges 1998; Overton 1998; Field 2003). Heterogeneity was explored using the I^2 statistic.

The statistical analysis was performed using RevMan 5 software, which is provided by Cochrane. 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 mean difference (MD) 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, we pooled data and analyzed it together. We computed mean differences. Data were entered into RevMan via the table of means and standard deviations per group in order to develop a forest plot.

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: heart rate during painful procedure, heart rate following painful procedure, PIPP score 30

seconds after painful procedure, NIPS - proportion of infants in low or no pain during procedure, NIPS - infants in no pain during recovery, duration of cry following heel lance, duration of cry following intramuscular (IM) injection.

Two authors independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from randomized controlled trials as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias); consistency across studies; directness of the evidence; precision of estimates; and presence of publication bias. We used the [GRADEpro 2014](#) Guideline Development Tool to create a [Summary of findings for the main comparison](#) to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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

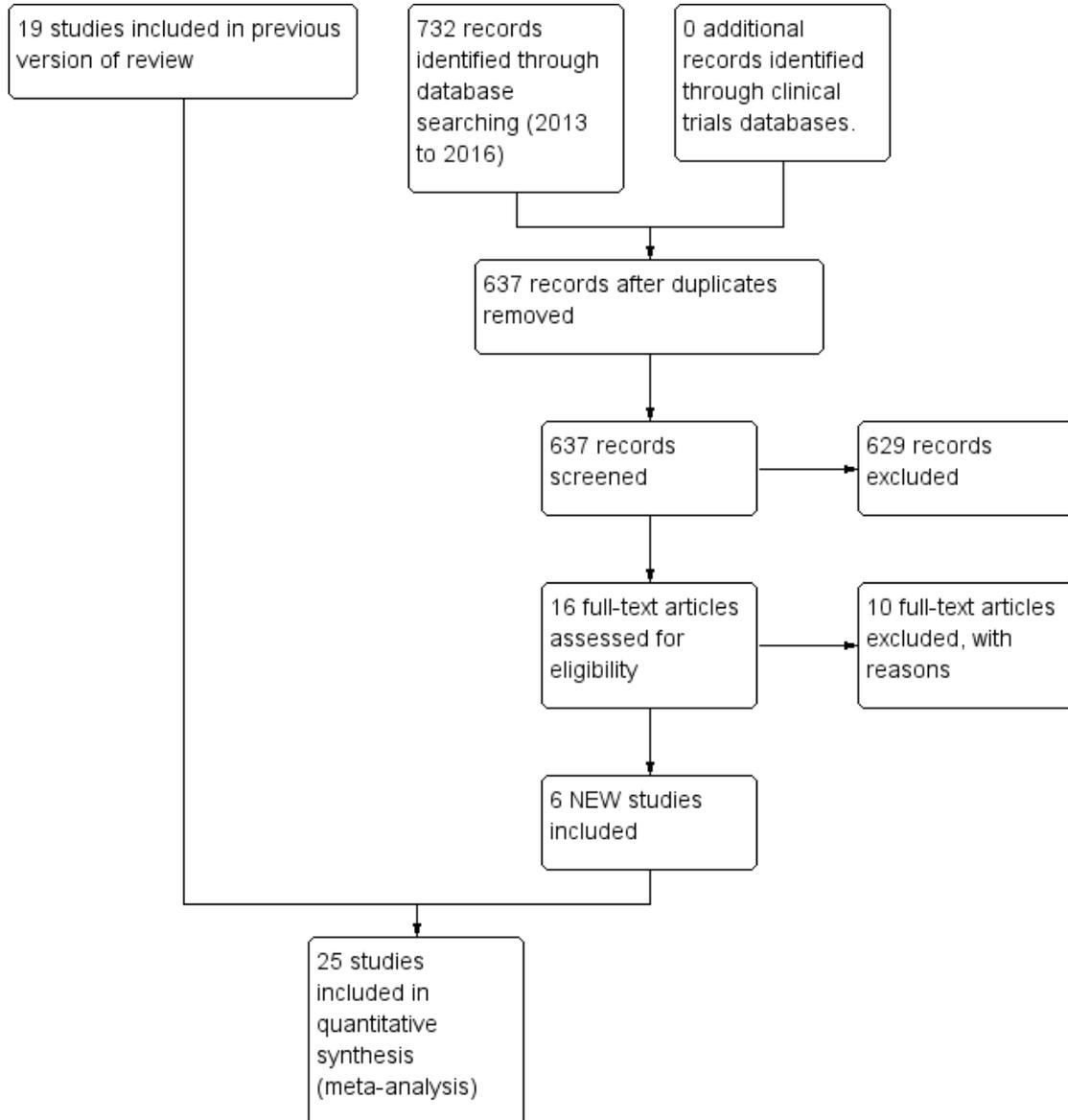
Description of studies

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#) below.

Results of the search

Two authors identified 16 additional studies for possible inclusion in this 2016 update. Of these 16 additional studies, ten were excluded leaving a total of 6 new studies for inclusion in the updated review for a total of 25 unique studies (Figure 1). Two reports were of the same study, so that only one was included and it counted as one of the 25 unique studies (Sajedi 2007; Kashaninia 2008).

Figure 1. Study flow diagram: review update



Included studies

The 25 included studies reported on a total of 2001 infants. Among the included studies, seven were with full-term neonates (Gray 2000; Sajedi 2007; Chermont 2009; Saeidi 2011; Gabriel 2013; Kostandy 2013; Liu 2015); and the remaining 18 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; Nanavati 2013; Nimbalkar 2013; Mosayebi 2014; Gao 2015). Details of each study are outlined in the tables under [Characteristics of included studies](#).

Most (19) of the included studies examined responses to the painful procedure of heel lance (Gray 2000; Johnston 2003; Ludington-Hoe 2005; Castral 2008; Freire 2008; Johnston 2008; Kostandy 2008; Cong 2009; Johnston 2009; Okan 2010; Cong 2011; Johnston 2011; Cong 2012; Johnston 2012; Gabriel 2013; Nimbalkar 2013; Mosayebi 2014; Gao 2015; Liu 2015) and are shown in Table 1. Four studies examined the response to intramuscular injection (Table 2) (Sajedi 2007; Chermont 2009; Saeidi 2011; Kostandy 2013); one study included both venipuncture and heel lance (Table 3) (Akcan 2009); three studies examined different providers (Table 4); and one study examined response to tape removal (Table 5) (Nanavati 2013).

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; Freire 2008; Johnston 2008; Cong 2009; Okan 2010; Saeidi 2011; Cong 2012; Gabriel 2013; Kostandy 2013; Nimbalkar 2013; Gao 2015; Liu 2015) and after the painful procedure (Gray 2000; Ludington-Hoe 2005; Sajedi 2007; Castral 2008; Johnston 2008; Cong 2009; Cong 2012; Gabriel 2013; Liu 2015); heart rate recovery (time to return to baseline levels post-procedure (Johnston 2008; Johnston 2009; Johnston 2011; Johnston 2012; Kostandy 2013; Gao 2015); 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; Liu 2015); 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 seven studies (Gray 2000; Ludington-Hoe 2005; Kostandy 2008; Okan 2010;

Saeidi 2011; Gabriel 2013; Kostandy 2013). Facial grimacing, not according to a validated measure, was used in three studies (Gray 2000; Okan 2010; Gao 2015), while in three others the validated Neonatal Facial Coding Scale (NFCSS) was used (Castral 2008; Chermont 2009; Okan 2010). Validated composite pain measures that included both physiological and behavioural indicators were used in 17 studies. The Premature Infant Pain Profile (PIPP) was used in 12 studies (Johnston 2003; Freire 2008; Johnston 2008; Akcan 2009; Chermont 2009; Johnston 2009; Cong 2011; Johnston 2011; Johnston 2012; Nanavati 2013; Nimbalkar 2013; Mosayebi 2014), the Neonatal Infant Pain Scale (NIPS) was used in four studies (Sajedi 2007; Chermont 2009; Saeidi 2011; Gabriel 2013) and the Douleur Aiguë du Nouveau-né (DAN) for one Liu 2015.

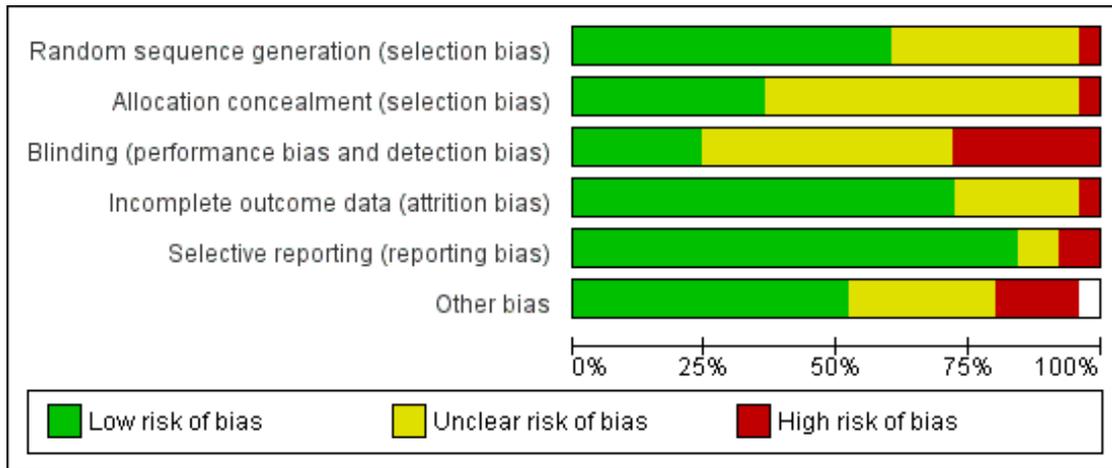
Excluded studies

Of the 29 studies that were excluded, three focused on breastfeeding (Uga 2008; Abdel-Razek 2009; Obeidat 2015), four did not have SSC as defined in this review (Bellieni 2002; Arditì 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). One had skin-to-skin contact but not during the procedure (Mitchell 2013). Maternal interview was the focus of one study (Silva 2004); and maternal mood and stress the focus of another with no comparison group (Castral 2015). Three studies did not randomize (Chidambaram 2014; Choudhary 2015; Olsson 2015). 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, Khashaninia 2008, was a duplicate of another (Sajedi 2007). One was a protocol of an ongoing study (Campbell-Yeo 2013). One study used diaper change as procedure, which is not within our definition of being tissue damaging or painful (Lyngstad 2014). Finally, seven studies reported on SSC alone without implementation of a painful procedure (Mooncey 1997; Gazzolo 2000; Mörelius 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 2.

Figure 2. 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 16 studies. Allocation concealment, another source of selection bias, was deemed adequate for 10 studies.

Blinding

Blinding to avoid performance or detection bias by definition is impossible to achieve given the nature of the intervention. Clearly reported blinding of assessors was adequate in only nine of the studies. Although 12 of the remaining trials did institute measures to overcome detection bias, there was some uncertainty that the video recordings were made in such a way that the SSC provider could not be identified. Only two studies specifically mentioned how they dealt with blinding the observers.

Incomplete outcome data

Incomplete outcome data were rated above low risk in 19 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

Fifteen studies had low risk of other biases. There were three individual cases of high 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 randomization. Seven 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 two studies, and the washout period was not described in the 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, $I^2 = 94%$.

Effects of interventions

See: [Summary of findings for the main comparison Skin-to-Skin care for procedural pain in neonates - summary of findings](#)

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.

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

1.1 Heart rate response

Fifteen 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; Gabriel 2013; Nimbalkar 2013; Gao 2015; Liu 2015) or IM injection (Kostandy 2013). Only five studies could be combined in an analysis (Ludington-Hoe 2005; Castral 2008; Cong 2009; Cong 2012; Liu 2015) with all but Liu 2015 (who compared SSC to swaddled in incubator) comparing SSC to incubator. 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, not all crossover studies could be included in the meta-analysis. One study - Gao 2015 - reported mean scores over three heel lances, but we were not able to get data for only one. 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 averaged over two minutes during intramuscular injection and reported lower scores, that is, in favour of SSC. 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. Johnston 2003 reported no overall differences; nor did Gao 2015, who compared heart rate over three heel lances. Kostandy 2013 did not find any differences between groups.

The meta-analysis across the five studies of heel lance versus incubator control (one with additional swaddling) showed differences between the experimental and control groups ranging from 0.57 to 13.53 beats per minute with a significant MD of -10.78 (95% CI -13.63 to -7.93) beats per minute (Analysis 1.1). One study, with additional swaddling (Liu 2015), made the difference of whether effect was significant. This effect was based on very low level evidence.

1.2 Heart rate recovery

Heart rate following the painful procedure was reported in seven articles, but only four could be entered into the analysis (Ludington-Hoe 2005; Castral 2008; Cong 2009; Cong 2012). The MD was not statistically significant with MD 0.08 (95% CI -4.39 to 4.55) (Analysis 1.2). The level of evidence for this effect was high. Findings from Gray 2000 favoured SSC, but Kostandy 2013 found no difference. 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; $F(61, 1) = 13.6$, $P < 0.001$).

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. Low frequency was not significant (MD -2.11 , 95% CI -17.69 to 13.47) (Analysis 1.3); nor was high frequency (MD -5.11 , CI -23.36 to 13.14) (Analysis 1.4); nor was the low frequency/high frequency (LF/HF) ratio significantly different (MD -3.77 , -13.69 to 6.14) (Analysis 1.8). 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 not significantly different among the conditions. The level of evidence for the effect of SSC on heart rate variability (LF, HF, and LF/HF ratio) during painful procedure was low, whereas the level of evidence for the effect of SSC on heart rate variability LF and HF following painful procedure was high. The effect of SSC on heart rate variability LF/HF ratio after painful procedure is supported by low-level evidence.

1.4 Oxygen saturation during painful procedure

Four studies used oxygen saturation as an outcome (Ludington-Hoe 2005; Sajedi 2007; Johnston 2008; Liu 2015), however only the latter two could be combined for analysis as they specified 30-second intervals. The MD at both 30 and 60 seconds was not significant: at 30 seconds, MD was 1.73 (95% CI -0.53 to 3.99) (Analysis 1.9); and at 60 seconds MD was 2.17 (95% CI -0.12 to 4.46) (Analysis 1.10). Sajedi 2007 examined full-term neonates receiving intramuscular injection. Sajedi 2007 reported an almost 4% lower oxygen saturation ($P < 0.001$) in the control group, favouring SSC. Ludington-Hoe 2005 did not find significant differences between SSC and incubator care. The effect of SSC on oxygen saturation at 30 seconds is supported by low-level evidence and the effect at 60 seconds is supported by very low level evidence.

1.5 Oxygen saturation after painful procedure

Two of 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 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 \pm SD: 0.19 \pm 0.10) than the standard care control group (mean \pm SD: 0.15 \pm 0.06), $P < 0.05$. Conversely, salivary cortisol levels were lower in the 30-minute SSC group (mean \pm SD: 0.21 \pm 0.12) than the standard care control group (mean \pm SD: 0.57 \pm 0.61), $P < 0.05$ (Table 1).

1.8 Premature Infant Pain Profile (PIPP) at 30 seconds

Six studies used the PIPP as the outcome for heel lance (Johnston 2003; Freire 2008; Johnston 2008; Cong 2011 (Study 1 and 2) Mosayebi 2014) or IM injection (Chermont 2009). Cong 2011 was analyzed for the two amounts of time of SSC so that the first study of 80-minute 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 moderate-level evidence of a significant effect in favour of SSC (MD -3.21 , 95% CI -3.94 to -2.47), although Cong 2011 (study 1) and Johnston 2008 did not find a significant difference (Analysis 1.11). Mosayebi 2014 used the PIPP but changed the scoring to an ordinal scale which could not be entered into the analysis, although the results favoured SSC. The means and standard deviations are reported in the text, but not separated between first and second condition and the authors did not forward us those separated data.

1.9 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 -1.64 , 95% CI -2.86 to -0.43). This effect is supported by low-level evidence. Johnston 2008 and Cong 2011 (Study 1) did not find a significant difference (Analysis 1.12); while Akcan 2009 did (SSC = 7.0, Control = 15.0, $P < 0.001$).

1.10 PIPP at 90 seconds

There was a significant difference in favour of SSC with three studies for the PIPP score at 90 seconds (MD -1.28 , 95% CI -2.53 to -0.04) (Analysis 1.13) (Johnston 2003; Johnston 2008;

Cong 2011 (Study 2)). This effect is supported by moderate level evidence.

1.11 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 0.07 (95% CI -1.11 to 1.25), reflecting no significant difference (Analysis 1.14). This effect is supported by moderate level evidence. Akcan 2009 reported PIPP of 4 in the SSC group compared to 15.5 in control group ($P = 0.001$).

1.12 PIPP following end of procedure

Two studies, Cong 2011 (two studies of 80 and 30 minutes SSC) and Akcan 2009, followed PIPP scores beyond the time of the procedure. In both Cong 2011 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. In the first and second minute following end of procedure, Akcan 2009 reported PIPPs of 4 and 4 in infants in KC and 12.5 and 7 in infants in the control group ($P < 0.001$, $P = 0.023$, respectively).

1.13 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 1.87 in favour of SSC ($P < 0.001$). There was no difference between skin-to-skin alone and the standard care control in Chermont 2009.

1.14 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.

1.15 Duration of crying after painful procedure

Six studies included cry duration as an outcome. Meta-analysis was conducted including two studies investigating response to heel lance (MD -34.16 , 95% CI -42.86 to -25.45) (Analysis 1.19) (Ludington-Hoe 2005; Kostandy 2008); and two following IM injection (MD -8.83 , 95% CI -14.63 to -3.02) with results favouring SSC (Analysis 1.20) (Kostandy 2013; Sajedi 2007). The level of evidence for the effect of SSC on duration of cry was moderate. The other two studies did not provide enough information to include their results in the analysis (Gray 2000; Okan 2010).

Gray 2000 reported that infants held by mother in skin-to-skin contact cried an average of 1 second while control infants cried for a mean of 32 seconds of the 3-minute recovery period ($P < 0.001$). Similarly Okan 2010 found reduced length of crying in SSC (mean 65 seconds vs 184 seconds in control, $P < 0.001$).

1.16 Neonatal Infant Pain Scale (NIPS)

Chermont 2009, Saeidi 2011, Sajedi 2007 used the NIPS as an ordinal outcome and these were able to be entered into an analysis. There was a significant difference in proportion of infants in no pain (Risk Difference (RD) 0.10, 95% CI 0.06 to 0.15) versus severe pain (RD -0.16 , 95% CI -0.22 to -0.10) in favour of SSC during the painful procedure. The level of evidence for this effect was very low. Similarly during recovery, there was a significant relative risk in favour of SSC of those with no pain (RD 0.35, 95% CI 0.26 to 0.44) and those with severe pain (RD -0.23 , 95% CI -0.31 to -0.15). The level of evidence in favour of SSC for the proportion of infants in no pain during recovery was moderate. Gabriel 2013 used NIPS and reported results comparing interventions in median scores, but had only active comparisons with no control group.

1.17 Serum cortisol

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

1.18 Douleur Aiguë du Nouveau-né (DAN) Scale

One study used the DAN as an outcome measure and found significant differences in favour of the SSC group, although the report does not include specific values, only significance levels (Liu 2015).

1.19 Sleep and wake state

Five studies reported on sleep and wake state (Ludington-Hoe 2005; Sajedi 2007; Kashaninia 2008; 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. That study 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. 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 -94.52 to 28.59) in spite of the large mean difference in favour of the mother, due mostly to high variation. The level of evidence for the effect on heart rate recovery was low. PIPP scores similarly had large mean differences favouring the mother but the variance was also large so that any difference was non-significant (Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5). The level of evidence for the effect on PIPP 30 at 30, 60, and 90 seconds following painful procedure was moderate, and at 120 seconds following painful procedure was high.

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

Cong 2011 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 in that report, favouring 30 minutes. No comparisons could be made between other reports.

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.

4.1 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.

[Gabriel 2013](#) compared SSC alone and in combination with both sucrose and breastfeeding on heart rate, NIPS scores, and crying time. The combinations were both more effective than SSC alone for NIPS and crying.

4.2 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. [Gabriel 2013](#), as above, compared SSC alone and in combination with both sucrose and breastfeeding on heart rate, NIPS scores, and crying time. The combinations were both more effective than SSC alone for NIPS and crying.

4.3 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.

4.4 SSC versus Expressed Breastmilk

One study, [Nanavati 2013](#), comparing SSC with expressed breast milk for adhesive tape removal, found both interventions equally effective in diminishing pain.

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 2011](#) and [Cong 2012](#). However, these studies used different outcomes and thus no analyses could be conducted. In [Cong 2011](#), 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 2012](#), 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 revision of the first review of skin-to-skin care (SSC) for procedural pain in neonates, 25 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. A small proportion of studies could be compared due to variations in design or outcomes. Even if the outcome measures were the same, they were often used differently enough that they could not be combined.

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 and NIPS as outcomes. With the addition of six studies from the first review to this revision, meta-analyses of heart rate, crying time, and composite measures of pain PIPP and NIPS were significantly favouring SSC. Oxygen saturation, and heart rate variability differences were not significant.

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

Although most of the studies used heel lance as the painful procedure, several used injections, including ones found for this newer review, such that we included both procedures in some analyses. The data analyses tables separate out the procedures, but we report the overall values which include both sessions.

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 2012](#), reported on two samples, one receiving 30 minutes of SSC and the other only 15 minutes, and both were compared to standard care. There were positive results only for the group receiving 30 minutes of SSC, reported 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 used intramuscular injection rather than heel lance so that a comparison between full-term neonates and preterm neonates was not possible ([Sajedi 2007](#); [Chermont 2009](#)).

No studies reported any adverse events.

Quality of the evidence

The studies that were included were generally strongly designed and free from bias. More than half (15/25) of the studies reported using adequate random allocation, and most reported low risk of bias related to incomplete data (19/25), selective reporting (20/25), and other forms of possible bias (13/25). Under half the studies (10/25) reported adequate allocation concealment and just under a quarter reported adequate blinding (6/25). Sixteen of the studies did report measures such as blinded assessors using objective outcome measures and/or '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 quality of the evidence varied. The quality of the evidence for heart rate in response to the painful procedure was low, but in recovery from the procedure, it was high. It is important to note that the significant effect size found in heart rate during procedure was due to a single trial ([Liu 2015](#)), with the remaining four studies finding no effect. While this was the only trial to compare SSC to a swaddled control (vs no treatment), it is unlikely that this is the source of the variation as swaddling would be expected to support regulation of heart rate ([Pillai Riddell 2015](#)) and reduce the comparative effectiveness of SSC. The quality of evidence regarding heart rate variability during the procedure was low. Following the procedure for HF and LF, quality of evidence was moderate, but for LF/HF it was low. Oxygen saturation studies had low or very

low quality of evidence for SSC. The PIPP at 30 and 90 seconds for SSC was supported by moderate quality of evidence but at 60 seconds this was low. Cry duration following the tissue-damaging part of the procedure as an indicator of effectiveness of SSC was of moderate quality. The NIPS studies for SSC had very low quality of evidence during the procedure; but after the procedure, the quality was moderate. In summary, in spite of the range of quality, it seems as though there is better evidence for SSC in recovery from a painful procedure than during it.

The degree of heterogeneity of the studies varied a great deal, but interestingly the more heterogeneous outcomes were physiological, even though 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 ([Pillai Riddell 2016](#)). The numerical analyses are very limited, i.e. of the 25 included studies (N = 2001), only up to six provided data for the primary outcomes. This is a potential source of bias as it may be that authors chose not to report statistically insignificant findings.

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. DI is the manager of the Neonatal Intensive Care Unit of the IWK Health Centre and champions SSC as a practice of family-centred care as well as for procedural pain management.

Agreements and disagreements with other studies or reviews

There have been a few reviews of non-pharmacological interventions for procedural pain relief in neonates and all support the practice of SSC ([Cignacco 2007](#); [Yamanda 2008](#); [Warnock 2010](#); [Pillai Riddell 2015](#)). No studies or reviews were found that disagreed.

AUTHORS' CONCLUSIONS

Implications for practice

Only a maximum of six data sets could be pooled, which did not enable us to determine an effect size on all 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 three studies comparing skin-to-skin care to sweet solution, skin-to-skin care was more effective in two studies and a possible synergistic effect was reported in the other. The addition of breastfeeding did not appear to increase the effectiveness of SSC in one study, but did in another. 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 randomization, 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. One cross-over study that was excluded due to lack of randomisation found that SSC reduced haemodynamic brain response to venepuncture measured using near-infrared spectroscopy (Olsson 2015); however, more rigorous studies are needed to elucidate such neurologic mechanisms.

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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	Randomized 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." 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." 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." "The video recordings and monitor records of the infants in both groups were analyzed by three experts (neona-

Akcan 2009 (Continued)

		<p>tology nurse, neonatologist and anaesthesiologist) who were totally blind to the study.”</p> <p>Not clear if camera recording focused only on infants’ faces or if mothers’ skin/breasts could be noted by researchers</p>
<p>Incomplete outcome data (attrition bias) All outcomes</p>	<p>Unclear risk</p>	<p>“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.”</p> <p>Data were presented for all participants assigned to intervention and control groups</p> <p>There is variability in the length of procedure (mean 1 minute for heel lance, 2.5 minutes for venepuncture) and authors do not report how this is addressed in analysis (e.g. number of infants in each time point, adjustment for procedure duration)</p>
<p>Selective reporting (reporting bias)</p>	<p>Low risk</p>	<p>Methods section reported that infants’ behavioural 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</p>
<p>Other bias</p>	<p>Low risk</p>	<p>“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.”</p> <p>Study was apparently free from other sources of bias</p>

Castral 2008

<p>Methods</p>	<p>Randomized controlled trial</p>
<p>Participants</p>	<p>59 preterm infants (PMA 248 days (intervention), 254 days (control))</p> <p>Birthweight, mean, grams: 1749 (intervention), 1846 (control)</p> <p>Painful procedure: heel lance</p> <p>Study period: September 2005 to May 2006</p>
<p>Interventions</p>	<p>Intervention: 15 minutes of skin-to-skin care before, during and following heel prick</p> <p>Control: standard care during painful procedure</p> <p>Provider: mother</p>
<p>Outcomes</p>	<p>Neonatal Facial Coding System (NFCS) and heart rate at heel prick, heel squeezing, wound compression, and recovery</p>

Notes	Country: Brazil Power calculation: no	
Risk of bias		
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."
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)." "The faces of all of the infants were continuously video-recorded throughout the seven study phases to capture change in facial action." 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)." 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)." 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". Study researchers, however, did not apparently control for differences in duration of heel puncture for the regression analysis

Chermont 2009

Methods	Randomized 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 (1 mL), 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, O ₂ 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."
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." 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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All randomly assigned patients completed the study, with no losses."
Selective reporting (reporting bias)	High risk	Data for the primary outcomes (NFCS, NIPS and PIPP scores) were presented in Tables 2 & 3 and Figure 2 . The trial registry lists heart rate and oxygen saturation as secondary outcomes. Although these outcomes were covered within the pain scales, no discussion of the results

Chermont 2009 (Continued)

		were found
Other bias	Unclear risk	The authors failed to report the number of patients assessed for eligibility

Cong 2009

Methods	Randomized cross-over trial
Participants	14 preterm infants (PMA 30-32 weeks); 13 intervention, 10 control Postnatal age, mean \pm SD, days: 6 ± 1 Birth weight, mean \pm SD, grams: 1775 ± 292 Weight on day of study, mean \pm 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 randomization 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..."
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 randomization 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..."

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.”
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.”
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 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.” “One consistent person, the neonatal unit phlebotomist, did all the heel sticks and blood draws.” “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.”

Cong 2011

Methods	Randomized 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

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 randomization to determine the order of condition (KCH or IH first) was used. A list of randomization codes with four subjects in each randomization block using the SAS(R) procedure PLAN was developed by an independent statistician."
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."
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." "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." Potential for bias as researcher coded videos and it is unknown if data were 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.”
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Cong 2012

Methods	Randomized 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 randomization codes with 4 subjects in each randomization block was developed by the statistician (the third author). The list of random codes consisted of the subject's number and assignment to sequence.”
Allocation concealment (selection bias)	Low risk	“assignments were kept in sealed envelopes and opened in front of the mother after consent was obtained.”
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.” “In order to minimize bias, a research assistant who was blind to the purpose of the study helped analyse the data.”

Cong 2012 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were provided for all infants recruited in the study; dropout rates described
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.”

Freire 2008

Methods	Randomized controlled trial with three groups (routine care; skin-to-skin; routine care + oral glucose)
Participants	95 preterm infants (PMA 28 to 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” 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” 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...” “Only the newborn's face was filmed in close-up with little surrounding area and minimal colour to reduce the possibility of unblinding by the research assistants who recorded the tapes”

Freire 2008 (Continued)

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

Gabriel 2013

Methods	Randomized controlled trial
Participants	136 term infants (127 in analysis) (37 to 42 weeks GA); 4 groups: skin-to-skin, sucrose, sucrose + skin-to-skin, skin-to-skin + breastfeeding Postnatal age - N/A Birth weight, mean (SD N/A), g: 3359 (skin-to-skin); 3215 (sucrose); 3349 (sucrose + skin-to-skin); 3289 (sucrose + breastfeeding) Painful procedure: heel lance Study period: unclear
Interventions	Group 1 - Skin-to-skin five minutes before and during heel lance Group 2 - 2 mL of 24% oral sucrose two minutes before heel lance Group 3 - Skin-to-skin five minutes before and during heel lance + 2 mL; 24% sucrose two minutes before heel lance Group 4 - Breastfeeding 5 minutes before heel lance
Outcomes	Crying time (seconds), % of crying during blood sampling, heart rate, NIPS
Notes	Trial terminated after planned mid-point analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The authors indicate that they mixed together groups of envelopes that had the different intervention groups on them together and then allowed the parents to select an envelope. They thus did not use a method to generate the sequence that is approved in the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> making this method at high risk of bias.
Allocation concealment (selection bias)	High risk	The authors indicate the envelopes utilized were opaque; however, they were not sequentially numbered and the parents who consented to take part in the study were

Gabriel 2013 (Continued)

		the ones who selected the envelope. Additionally, there is no mention as to whether or not the participant information was written on the envelope prior to opening, which would be an additional requirement to make this method low risk of bias as per the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> .
Blinding (performance bias and detection bias) All outcomes	High risk	The authors report that there were three outcome assessors for this study who all coded the NIPS. However, they report that they only reported on the data coded by a single outcome assessor for the study (as a result of good interclass correlation coefficient) out of the three individuals who were completing the coding. Therefore, as a single individual coded the outcome data across all of the intervention groups, there was no attempt to blind the outcome assessor to the interventions received. The authors provide no description of attempts to blind the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	The main reasons that the authors noted for missing outcome data in the BF group was non-effective breastfeeding (n = 3), non-correct SSC (n = 2) and technical problems (n = 1). While the authors followed an intention-to-treat protocol and noted that the missing data were greater in the breastfeeding group compared to the other groups, they have unexplained missing heart rate data, hence an assignment of high risk of bias. Authors report that "correct" heart rate was only obtained in a proportion of participants in each of the intervention conditions but do not specify the reason for inability to obtain correct heart rate in the remaining participants
Selective reporting (reporting bias)	Low risk	It appears that authors report on all outcomes for which, in the Methods section of the paper, they indicate they are collecting data . We looked for a study protocol on line; however, there does not appear to be one available
Other bias	Unclear risk	The authors do not report on provision of any training of NIPS coders, simply report an ICC of > 0.6 between the three coders for the study and they go on to indicate that because of high ICC they only utilized the data coded by one of the observers. They also do not report any data on intra-rater reliability

Methods	Randomized Controlled Trial	
Participants	80 preterm infants (75 in analysis) (27 to 37 weeks GA); 2 groups - skin-to-skin, incubator control Postnatal age - N/A Birth weight, mean (SD N/A), g: 2017.8 (skin-to-skin); 2030 (incubator) Painful procedure: heel lance Study period: unclear	
Interventions	First heel lance: both groups in incubator Next three heel lances: Treatment: Skin-to-skin: 30 minutes pre-procedure Control: Prone in incubator: 30 minutes pre-procedure	
Outcomes	Crying time (seconds), grimacing time (seconds), heart rate	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors report that they randomly assigned the infants in the study to either the KMC or incubator condition using a "random table format". This statement does not provide enough information about the randomisation sequence and how it was generated and therefore has an unclear risk of bias
Allocation concealment (selection bias)	Unclear risk	The authors report that they used a random table format to assign the infants in the study to the intervention conditions; however, they do not provide information regarding who had access to that table, who completed the randomisation, and any steps that were taken to conceal the allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Recordings were assessed by blind reviewers. Camera was focused on face with little surrounding area with no sound, low colour
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors had some loss to follow-up, but they provide rationale for the reasons that participants were lost, making this low risk of bias
Selective reporting (reporting bias)	Low risk	The authors report on all outcomes and provide complete within- and between-group analyses to show differences between groups and across time

Gao 2015 (Continued)

Other bias	Low risk	There does not appear to be concerning issues related to other sources of bias. The authors provide detailed descriptions of how inter- and intra-rater reliability were maintained for the behavioural outcomes reported
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Gray 2000

Methods	Randomized controlled trial
Participants	30 term infants (≥ 37 weeks) Postnatal age, range, hours: 33 to 55 Birth weight, mean (range), grams: 3300 (2600 to 3700) Painful procedure: heel lance Study period: March 1998 to October 1998
Interventions	Intervention: 10 to 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."
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 infant's face visible for filming from the side of the bed." "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." "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." "For grimacing, of course, knowledge of group assign-

Gray 2000 (Continued)

		ment was unavoidable. The data obtained in these analyses were reliable among scorers.” 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 randomized 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.” Study is apparently free of other sources of bias

Johnston 2003

Methods	Randomized cross over trial
Participants	74 infants (32 to 36 weeks PMA) Postnatal age, range, days: 0 to 10 Birth weight, mean ± SD (range), grams: 2054 ± 406 (1320-3125) Painful procedure: heel lance Study period: 9 April 2001 to 28 June 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

Johnston 2003 (Continued)

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."
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."
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
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." Study is apparently free of other sources of bias

Johnston 2008

Methods	Randomized cross-over trial
Participants	61 preterm infants (PMA 30.5 ± 1 weeks) Postnatal age, range, days: 1 to 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

Johnston 2008 (Continued)

Outcomes	PIPP score at 30, 60, 90 and 120 minutes Time to return to baseline heart rate	
Notes	Country: Canada Power calculation: yes	
<i>Risk of bias</i>		
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."
Allocation concealment (selection bias)	Low risk	"...assignment was accessed on the web site by the site research nurse after consent was obtained."
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."
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 2
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	Randomized cross-over trial
Participants	90 preterm infants (PMA 32 0/7 to 36 0/7 weeks) Postnatal age, range, days: 1 to 14 Birth weight, mean ± SD, grams: 1968 ± 388 Painful procedure: heel lance Study period: April 2003 to December 2006

Johnston 2009 (Continued)

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..."
Allocation concealment (selection bias)	Low risk	"...assignment was accessed on the web site by the site research nurse after consent was obtained."
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%." 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."
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 accommodate 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". This implies inconsistent use of sucrose Study was apparently free of other sources of bias

Johnston 2011

Methods	Randomized cross-over trial
Participants	62 preterm infants (PMA 28 to 36 weeks) Postnatal age, mean, days: 5 to 10 Birth weight, mean \pm SD, grams: 1565 \pm 469 (father KC/mother KC); 1610 \pm 494 (mother KC/father KC) Painful procedure: heel lance Study period: 16 January 2008 to 24 March 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 permuted blocks of 4 and 6."
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 permuted 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."
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." 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

Johnston 2011 (Continued)

		would be focused on the infant's face." 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." Washout period not described

Johnston 2012

Methods	Randomized 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
Random sequence generation (selection bias)	Low risk	Sequence generation not described in text. Author communication confirmed that an off-site computer-generated randomization 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 randomization and sequentially numbered allocation program was used

Johnston 2012 (Continued)

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.” 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 randomized. The main reason for refusal was not wanting another woman to provide kangaroo care with her baby.” Drop out rates clearly explained in Figure 2 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 analyzed 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%.” Washout period not described

Kostandy 2008

Methods	Randomized cross-over trial	
Participants	Only 10 infants (30 to 32 weeks’ PMA) enrolled Postnatal age, range, days: 2 to 9 Birth weight, mean ± SD, grams: 1577 ± 327.00 Painful procedure: heel lance Study period: unclear	
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	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Kostandy 2008 (Continued)

Random sequence generation (selection bias)	Unclear risk	“randomisation was by permuted block design to ensure highest possible equivalence among infants.” The system of randomization 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.” 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.”
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.” 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.”

Kostandy 2013

Methods	Randomized Controlled Trial	
Participants	36 term infants (GA 28 to 36 completed weeks) Birth weight, mean, ± SD, grams: 3358.25 (skin-to-skin: 3389.7 ± 333.3; Control: 3326.8 ± 324.08) Painful procedure: IM Injection Study period: July 2002 to December 2002	
Interventions	Skin-to-skin: 10 to 15 minutes prior to, and during, heel lance Control: infant supine in bassinet 10-15 minutes prior to heel lance	
Outcomes	Cry time (seconds), Anderson Behavioural State Scale, heart rate	
Notes	Country: United States Power calculation: yes	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Kostandy 2013 (Continued)

Random sequence generation (selection bias)	Low risk	Each mother-neonate dyad was randomly assigned using the computerized minimization method
Allocation concealment (selection bias)	Low risk	Randomization was completed for each participant, using a minimization method calculated by a computer program. Staff could not access this information prior to group assignment
Blinding (performance bias and detection bias) All outcomes	High risk	The nature of the intervention makes blinding study staff and participants impossible, no blinding of outcomes assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All dyads completed the study
Selective reporting (reporting bias)	Low risk	All mothers and neonates enrolled in the study completed the protocol, all outcomes were reported

Liu 2015

Methods	Randomized Controlled Trial	
Participants	40 term infants (mean = 39.3 weeks GA) Birth weight, mean, \pm SD, grams: Skin-to-skin: 3337 \pm 409.1; Control: 3740 \pm 298.9) Painful procedure: heel lance Study period: April 2010 to December 2010	
Interventions	Intervention: skin-to-skin 15 mins pre heel lance, during, 1 minute after Control: post bath, swaddled during and 1 minute after	
Outcomes	Douleur Aiguë du Nouveau-né (DAN), cry time (seconds), pain facial expression (seconds), oxygen saturation, heart rate	
Notes	Power calculation: N/A Country: United States	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table method was used to generate the sequence
Allocation concealment (selection bias)	Unclear risk	No information was provided regarding who had access to the number table used to allocate the intervention. It would be feasible to predict the nurse recruiting participants had access to this table; however, information

Liu 2015 (Continued)

		as to who had access is not provided
Blinding (performance bias and detection bias) All outcomes	High risk	Impossible to blind personnel and participants to group assignment, no attempt to blind outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors indicate that they selected 40 infants (intervention n = 20; intervention n = 20), however, they do not provide numbers for each of the individual outcomes (only for the final number of infants included in the sample, which was 40). Therefore, it is unclear if there was incomplete data for any particular outcome
Selective reporting (reporting bias)	High risk	The authors do not report if there was a statistically significant difference between the intervention and control group on the DAN - they only report on the duration of facial expression and crying times. They do not report the DAN scores whatsoever in their results section
Other bias	High risk	The authors do not discuss training of personal to complete facial coding for the scoring of the DAN

Ludington-Hoe 2005

Methods	Randomized 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	
<i>Risk of bias</i>		
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

Ludington-Hoe 2005 (Continued)

		randomly by the Zellen technique insured balanced representation in both treatment sequences.”
Allocation concealment (selection bias) All outcomes	Unclear risk	“Consenting mother-infant pairs were randomised 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.”
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.” In Zellen’s technique, patients are randomized before consent occurs; therefore in theory, consent can be sought conditionally

Mosayebi 2014

Methods	Randomized Crossover Trial
Participants	64 preterm infants (mean ± SD: 33 ± 1.95 weeks) Postnatal age, mean ± SD, days: 7.28, ± 3.65 Birthweight, mean ± SD, grams: 2095.85 ± 672.27 Painful procedure: heel lance Study period: June 2012 to October 2012
Interventions	Intervention: skin-to-skin 15 min pre, during, and 2 minutes post heel lance Control: Proned in incubator 15 min pre, during, and 2 minutes post heel lance

Mosayebi 2014 (Continued)

Outcomes	Premature Infant Pain Profile (PIPP)	
Notes	Country: Iran Power calculation: no	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization of neonates to give MC or incubator for the first heel lance was done by drawing out a thick, nontransparent envelope
Allocation concealment (selection bias)	Unclear risk	No mention of envelopes being sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Impossible to blind bedside nurses or participants, no discussion of whether the mother's skin or breasts were visible, single assessor scored both conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition among consented participants. Complete data for all reported outcomes
Selective reporting (reporting bias)	Low risk	All outcomes outlined in trial registry reported in final publication
Other bias	Unclear risk	No report on the effect of treatment order

Nanavati 2013

Methods	Randomized Controlled Trial
Participants	50 preterm infants (< 37 weeks GA) Gestational age, mean ± SD, weeks: skin-to-skin: 32.72 ± 2.03; control: 32.4 ± 2.16 Postnatal age, mean ± SD, days: skin-to-skin: 7.12 ± 6.64; control: 5.4 ± 3.65 Painful procedure: tape removal Study period: June 2012 to October 2012
Interventions	Intervention: skin-to-skin 15 minutes before, and during tape removal Control: EBM soaked swab 2 minutes before, and during tape removal
Outcomes	Premature Infant Pain Profile
Notes	Country: India Power Calculation: yes
<i>Risk of bias</i>	

Nanavati 2013 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The babies were randomised to receive either KMC or EBM. A computer-generated randomisation sequence was used to assign infants to two treatment groups in 1:1 ratio."
Allocation concealment (selection bias)	Unclear risk	"Treatment allocations were inserted in sequentially numbered opaque envelopes and were sealed. Just prior to adhesive tape removal, a neonatal research nurse opened the sequentially numbered"
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of participants and personnel impossible as a result of treatment characteristics, there did not appear to be any effort to blind outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Figure 2 provides an overview of all participants
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	

Nimbalkar 2013

Methods	Randomized 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: 1 April 2009 to 30 September 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	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Nimbalkar 2013 (Continued)

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)...”
Allocation concealment (selection bias)	Unclear risk	“the random numbers were stored in opaque envelopes, which were opened once the patient entered study.” 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.” “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).”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates were clearly explained in Figure 2
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.” “Only two staff nurses did the heel prick for these neonates to keep the procedure standardized and without bias.”

Okan 2010

Methods	Randomized controlled trial
Participants	107 full term infants (PMA 39.5 ± 0.6): Randomized 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: breast fed 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	
<i>Risk of bias</i>		
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"
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 from a bag by a nurse not involved in the study."
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." "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." "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." 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." "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." "there were no significant differences between the groups in the clinical characteristics, pretest behavioural state score, and blood collection time."

Saeidi 2011

Methods	Randomized controlled trial
Participants	60 full term infants (80% of case group and 73.3% of control group had 40 weeks GA) Birth weight, mean \pm SD, grams: 3242 \pm 306.6 (intervention), 3151 \pm 331.5 (control) Painful procedure: vaccination Study period: March to July 2006
Interventions	Intervention: skin to skin contact 2 minutes before vaccination through 3 minutes after 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

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
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
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; O ₂ 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	Randomized controlled trial
Participants	100 term neonates (PMA 39.4 \pm 1.5 weeks (intervention), 39.1 \pm 1.4 weeks (control)) Birth weight, mean \pm SD, grams: 3083 \pm 258 (intervention), 3142 \pm 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
Random sequence generation (selection bias)	Unclear risk	"The neonates were randomly assigned to intervention and control groups by using randomised permuted blocks. Randomization was done by a well-trained nurse using a random numbers table." Unclear how the matching was done
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..."
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)

BF = breastfeeding
GA = gestational age
HR = heart rate
PMA = postmenstrual age

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)
Campbell-Yeo 2013	Protocol only. No results.
Castral 2015	Inappropriate design (no comparison group).
Chidambaram 2014	Design unclear. Author confirmed case-control design, no random crossover. PIPP used at times outside guidelines for use
Choudhary 2015	No randomisation.
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)
Gazzolo 2000	Inappropriate participants (no painful procedure delivered by healthcare professionals)
Johnston 2007	Inappropriate intervention (no skin-to-skin care)
Kashaninia 2008	Same data set as Sajedi 2007 .
Lyngstad 2014	Inappropriate design (diaper change not a painful procedure)
Miles 2006	Inappropriate participants (skin-to-skin care did not take place during painful procedure)
Mitchell 2013	Innapropriate intervention (no skin-to-skin during procedure)
Mooncey 1997	Inappropriate participants (no painful procedure delivered by healthcare professionals)
Möreljus 2005	Inappropriate participants (no painful procedure delivered by healthcare professional)
Obeidat 2015	Innapropriate intervention (no skin-to-skin during procedure)

(Continued)

Olsson 2015	Subjects not randomized
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

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

[IRCT2014120217972N4](#)

Trial name or title	Paternal vs Maternal Kangaroo and routine care for pain relief in preterm neonates
Methods	Randomized crossover trial
Participants	240 infants 28 to 36 6/7 weeks GA
Interventions	Paternal Kangaroo Care, Maternal Kangaroo Care, Control (incubator)
Outcomes	Premature Infant Pain Profile, change in heart rate, change in O ₂ saturation

IRCT2014120217972N4 (Continued)

Starting date	23 September 2014
Contact information	Zahra Godarzi School of Nursing and Midwifery, Tehran University of Medical Sciences Nusrat Sharghi street, Tohid square Tehran Tehran Iran, Islamic Republic Of Phone: 00982161054407 Fax: 00982166904252 godarziz@tums.ac.ir
Notes	

IRCT201505142639N16

Trial name or title	Efficacy of kangaroo mother care, breastfeeding and swaddling on BCG vaccine pain score in neonates
Methods	RCT
Participants	Inclusion criteria: Inclusion criteria: term neonates (gestation age of 37-42 weeks); birth weight of 2500 to 4000 g; product of normal vaginal delivery; without systemic illness and with healthy medical condition Exclusion criteria: birth asphyxia; severe congenital malformation; receiving sedative hypnotic drugs within the past 24 hours Exclusion criteria: Age minimum: 0 Age maximum: 0 Gender: both male and female
Interventions	Intervention 1: breast feeding two minutes before vaccination until one minute after BCG vaccination . Intervention 2: kangaroo mother care of neonate with close contact of thorax and abdomen skin of mother ten minutes before vaccination until one minute after BCG vaccination. Intervention 3: swaddling of neonate ten minutes before vaccination until one minute after BCG vaccination
Outcomes	Obtaining of pain score of less than four during BCG vaccine injection. Timepoint: during BCG vaccine injection. Method of measurement: Neonatal/Infant Pain Scale Pain score of BCG vaccine injection. Timepoint: before, during, one minute and two minutes after BCG vaccine injection. Method of measurement: Neonatal/Infant Pain Scale Duration of neonate crying during BCG vaccine injection. Timepoint: every 10 seconds after vaccine injection until stopping of crying. Method of measurement: By chronometer
Starting date	24 April 2015
Contact information	Name: Dr. Raziieh Fallah Address: Pediatric Ward, Shahid Sadoughi Hospital, Ebn - Sina BLVD, Shahid Ghandi BLVD, Yazd, I.R.Iran Yazd Iran, Islamic Republic Of Telephone: 00983538224000

IRCT201505142639N16 (Continued)

	Email: dr.raziehfallah@yahoo.com Affiliation: Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Notes	

IRCT2015052914251N3

Trial name or title	Effect of neonate's massage and kangaroo mother care on neonates' pain
Methods	RCT
Participants	Inclusion criteria: lack of symptoms of severe disease or congenital abnormality that prevents neonates to exit from incubator; lack of any CNS abnormalities; lack of any obstetric or medical problems in mother; neonates who will be born in 32 to 37 weeks of age based on the age as recorded in the medical record; lack of intubation or connecting to ventilator in neonates; approve of haemodynamic stability and allow to neonates participate in the study and exit from incubator by physician. Exclusion criteria: existence or occurrence of any kind of medical or obstetric problems for the mother; neonate dies during the study; any situation which does not allow neonates to exit the incubator Exclusion criteria: Age minimum: 0 Age maximum: 0 Gender: both male and female
Interventions	Intervention 1: First intervention group: neonates will place on the mother's chest based on kangaroo mother method for 15 minutes before and 15 minutes after invasive procedures. Intervention 2: Second intervention group: neonates' leg will be massaged by mother for 15 minutes before and 15 minutes after invasive procedures. Intervention 3: Control group: neonate, whilst connected to pulse oximetry in supine position, will be put in incubator without any touching and changes in position.
Outcomes	Pain. Timepoint: before, during and after invasive procedures. Method of measurement: pain scale and pulse oximetry Heart rate. Timepoint: before, during and after invasive procedures. Method of measurement: pulse oximetry Oxygen saturation . Timepoint: before, during and after invasive procedures. Method of measurement: pulse oximetry
Starting date	1 April 2015
Contact information	Maryam Valimalayeri Faculty of Nursing and Midwifery, Hamadan University of Medical Sciences, Shaheed Fahmideh avenue Hamadan, Iran, Islamic Republic Of 00988138330641 valimalayeri@gmail.com Department of Pediatrics, Faculty of Nursing and Midwifery, Hamadan University of Medical Sciences
Notes	

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	5	161	Mean Difference (IV, Fixed, 95% CI)	-10.78 [-13.63, -7.93]
1.1 Heel lance - No treatment control	4	121	Mean Difference (IV, Fixed, 95% CI)	0.35 [-6.06, 6.76]
1.2 Heel lance - Swaddled control	1	40	Mean Difference (IV, Fixed, 95% CI)	-13.53 [-16.72, -10.34]
2 Heart rate following painful procedure	4	120	Mean Difference (IV, Fixed, 95% CI)	0.08 [-4.39, 4.55]
2.1 Heel lance - No treatment control	4	120	Mean Difference (IV, Fixed, 95% CI)	0.08 [-4.39, 4.55]
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 - No treatment control	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 - No treatment control	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 - No treatment control	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 - No treatment control	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 - No treatment control	2	38	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.18, 0.29]
8 HRV after 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 - No treatment control	2	38	Mean Difference (IV, Fixed, 95% CI)	-3.77 [-13.69, 6.14]
9 Oxygen saturation 30 seconds after painful procedure	2	101	Mean Difference (IV, Fixed, 95% CI)	1.73 [-0.53, 3.99]
9.1 Heel lance - Swaddled control	2	101	Mean Difference (IV, Fixed, 95% CI)	1.73 [-0.53, 3.99]
10 Oxygen saturation 60 seconds after painful procedure	2	101	Mean Difference (IV, Fixed, 95% CI)	2.17 [-0.12, 4.46]

10.1 Heel lance - Swaddled control	2	101	Mean Difference (IV, Fixed, 95% CI)	2.17 [-0.12, 4.46]
11 PIPP Score 30 seconds after painful procedure	5	267	Mean Difference (IV, Fixed, 95% CI)	-3.21 [-3.94, -2.47]
11.1 Heel lance - No treatment control	2	91	Mean Difference (IV, Fixed, 95% CI)	-4.12 [-5.22, -3.01]
11.2 Heel lance - Swaddled control	3	176	Mean Difference (IV, Fixed, 95% CI)	-2.49 [-3.47, -1.50]
12 PIPP Score 60 seconds after painful procedure	3	156	Mean Difference (IV, Fixed, 95% CI)	-1.64 [-2.86, -0.43]
12.1 Heel lance - No treatment control	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-2.62, 1.97]
12.2 Heel lance - Swaddled control	2	129	Mean Difference (IV, Fixed, 95% CI)	-2.16 [-3.58, -0.73]
13 PIPP Score 90 seconds after painful procedure	3	156	Mean Difference (IV, Fixed, 95% CI)	-1.28 [-2.53, -0.04]
13.1 Heel lance - No treatment control	1	27	Mean Difference (IV, Fixed, 95% CI)	0.77 [-1.69, 3.22]
13.2 Heel lance - Swaddled control	2	129	Mean Difference (IV, Fixed, 95% CI)	-1.99 [-3.43, -0.55]
14 PIPP Score 120 seconds after painful procedure	3	156	Mean Difference (IV, Fixed, 95% CI)	0.07 [-1.11, 1.25]
14.1 Heel lance - No treatment control	1	27	Mean Difference (IV, Fixed, 95% CI)	1.41 [-0.37, 3.19]
14.2 Heel lance - Swaddled control	2	129	Mean Difference (IV, Fixed, 95% CI)	-0.99 [-2.56, 0.59]
15 NIPS - Proportion of infants in low or no pain during procedure	3	480	Risk Difference (M-H, Fixed, 95% CI)	0.10 [0.06, 0.15]
15.1 IM Injection - No treatment control	1	320	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.08, 0.01]
15.2 IM Injection - Swaddled control	2	160	Risk Difference (M-H, Fixed, 95% CI)	0.38 [0.28, 0.47]
16 NIPS - Infants in severe pain following procedure	3	480	Risk Difference (M-H, Fixed, 95% CI)	-0.16 [-0.22, -0.10]
16.1 IM Injection - No treatment control	1	320	Risk Difference (M-H, Fixed, 95% CI)	-0.07 [-0.14, 0.01]
16.2 IM Injection - Swaddled control	2	160	Risk Difference (M-H, Fixed, 95% CI)	-0.35 [-0.44, -0.26]
17 NIPS - Infants in no pain during recovery	2	380	Risk Difference (M-H, Fixed, 95% CI)	0.35 [0.26, 0.44]
17.1 IM Injection - No treatment control	1	320	Risk Difference (M-H, Fixed, 95% CI)	0.38 [0.27, 0.48]
17.2 IM Injection - Swaddled control	1	60	Risk Difference (M-H, Fixed, 95% CI)	0.20 [0.02, 0.38]
18 NIPS - Infants in severe pain during recovery	2	380	Risk Difference (M-H, Fixed, 95% CI)	-0.23 [-0.31, -0.15]
18.1 IM Injection - No treatment control	1	320	Risk Difference (M-H, Fixed, 95% CI)	-0.23 [-0.32, -0.14]
18.2 IM Injection - Swaddled control	1	60	Risk Difference (M-H, Fixed, 95% CI)	-0.2 [-0.38, -0.02]

19 Duration of cry (seconds) following heel lance	2	33	Mean Difference (IV, Random, 95% CI)	-34.16 [-42.86, -25.45]
19.1 Heel lance - No treatment control	1	10	Mean Difference (IV, Random, 95% CI)	-33.5 [-134.66, 67.66]
19.2 Heel lance - Swaddled control	1	23	Mean Difference (IV, Random, 95% CI)	-34.16 [-42.90, -25.42]
20 Duration of cry (seconds) following IM injection	2	100	Mean Difference (IV, Fixed, 95% CI)	-8.83 [-14.63, -3.02]
20.1 IM injection - Swaddled control	1	64	Mean Difference (IV, Fixed, 95% CI)	-10.06 [-20.07, -0.05]
20.2 IM injection - No treatment control	1	36	Mean Difference (IV, Fixed, 95% CI)	-8.20 [-15.32, -1.08]

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

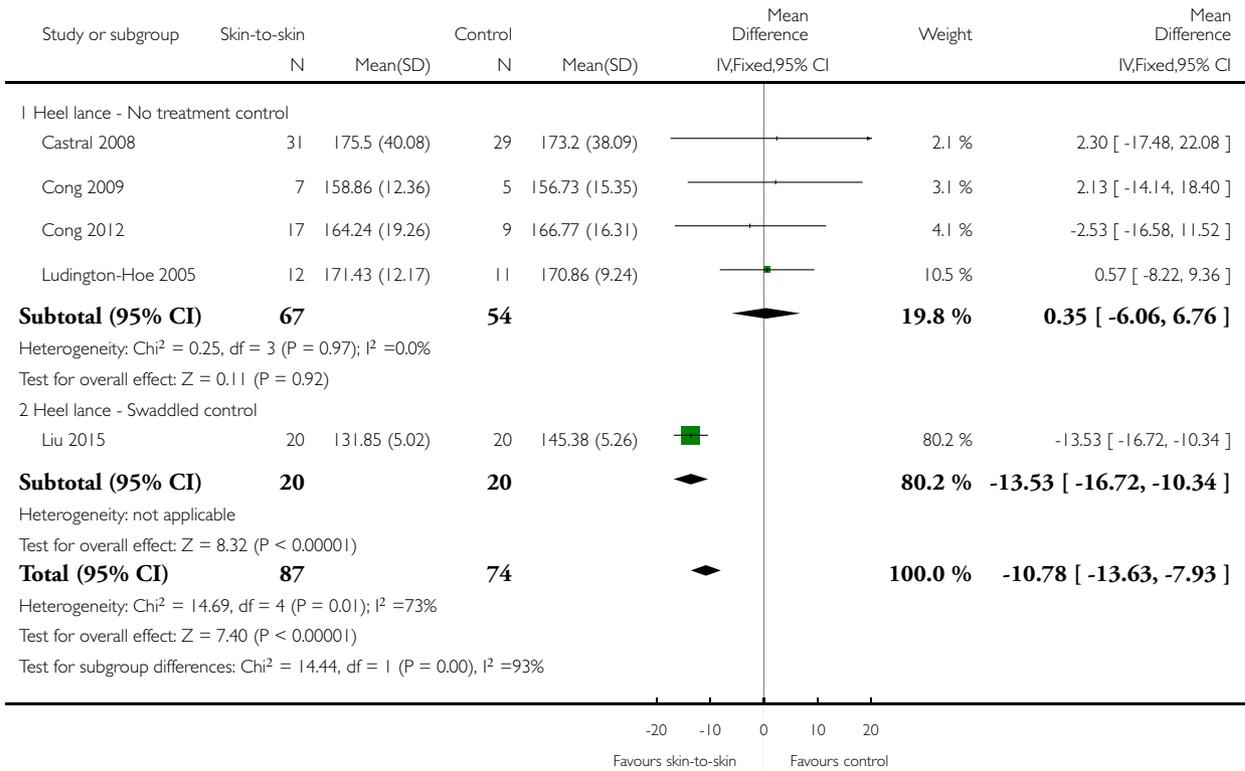
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart rate recovery	2	78	Mean Difference (IV, Random, 95% CI)	-32.97 [-94.52, 28.59]
1.1 Father	1	62	Mean Difference (IV, Random, 95% CI)	-26.0 [-91.34, 39.34]
1.2 Alternate Female	1	16	Mean Difference (IV, Random, 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)	-1.42 [-2.97, 0.12]
3.1 Father	1	62	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-2.97, 0.37]
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

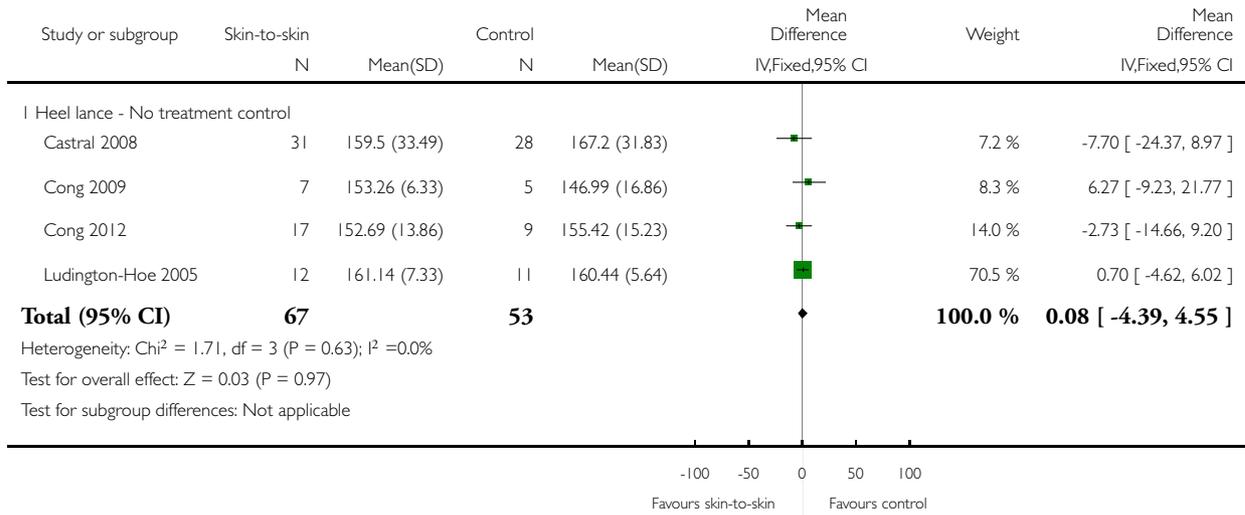


Analysis 1.2. Comparison 1 Skin-to-skin care versus control, Outcome 2 Heart rate following painful procedure.

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

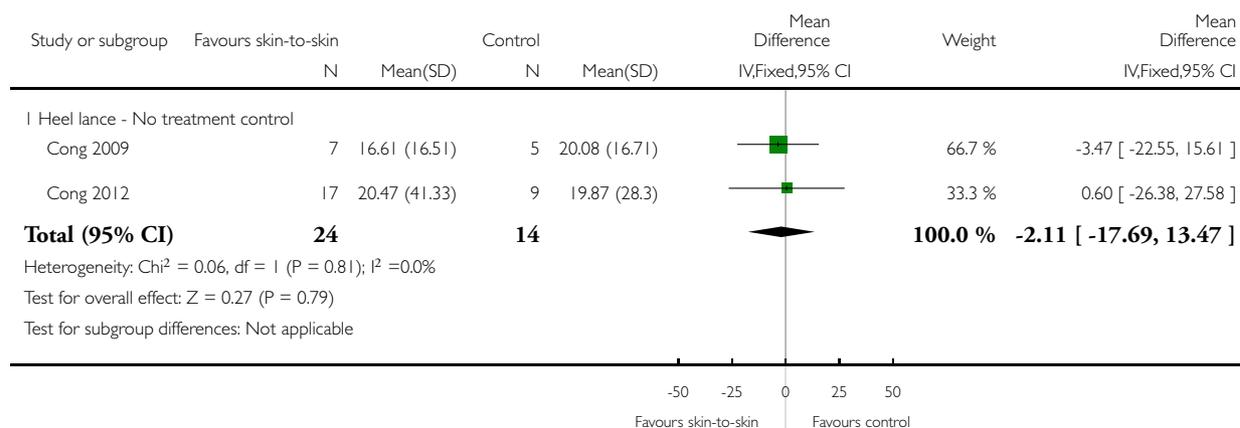


Analysis 1.3. Comparison 1 Skin-to-skin care versus control, Outcome 3 HRV during painful procedure - Low frequency power.

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

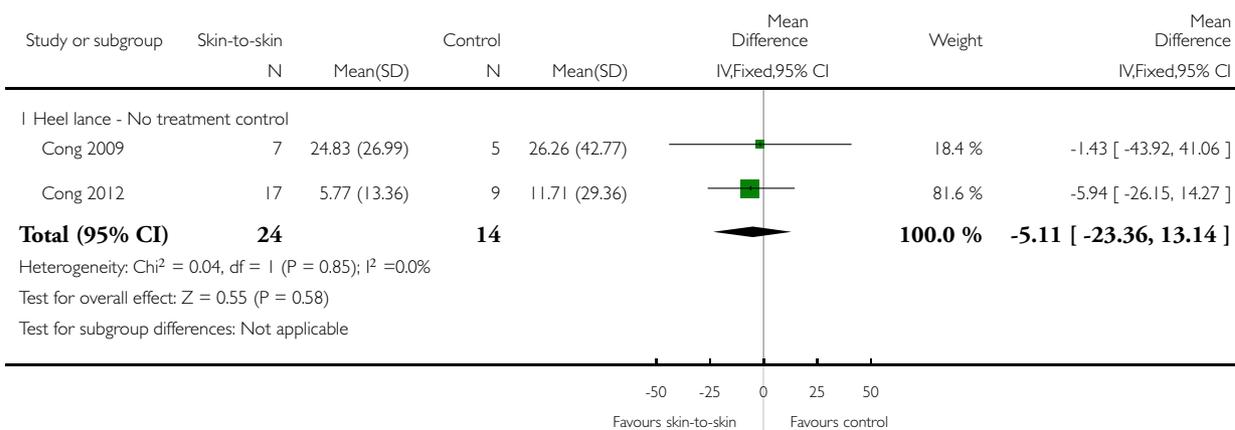


Analysis 1.4. Comparison 1 Skin-to-skin care versus control, Outcome 4 HRV during painful procedure - High frequency power.

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

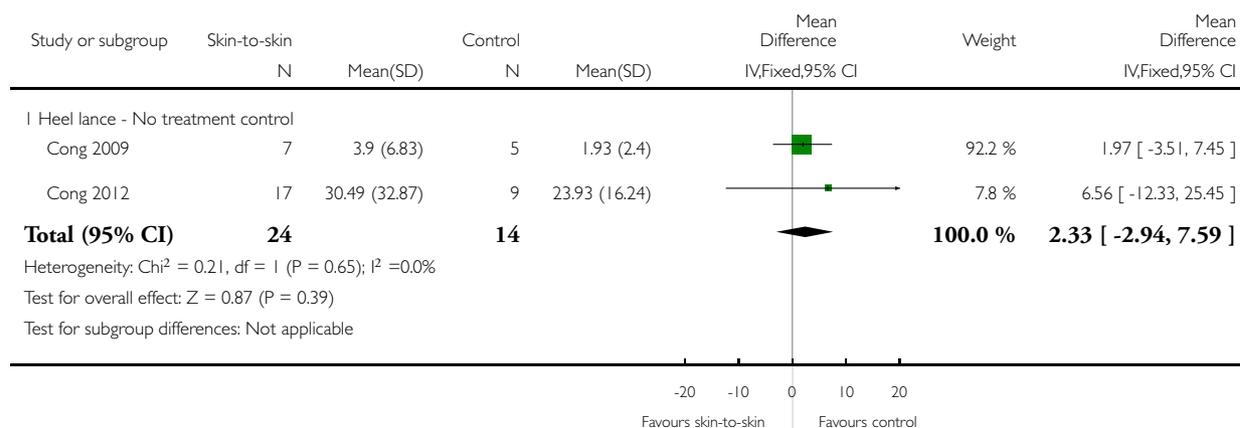


Analysis 1.5. Comparison 1 Skin-to-skin care versus control, Outcome 5 HRV during painful procedure - Low frequency to high frequency ratio.

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

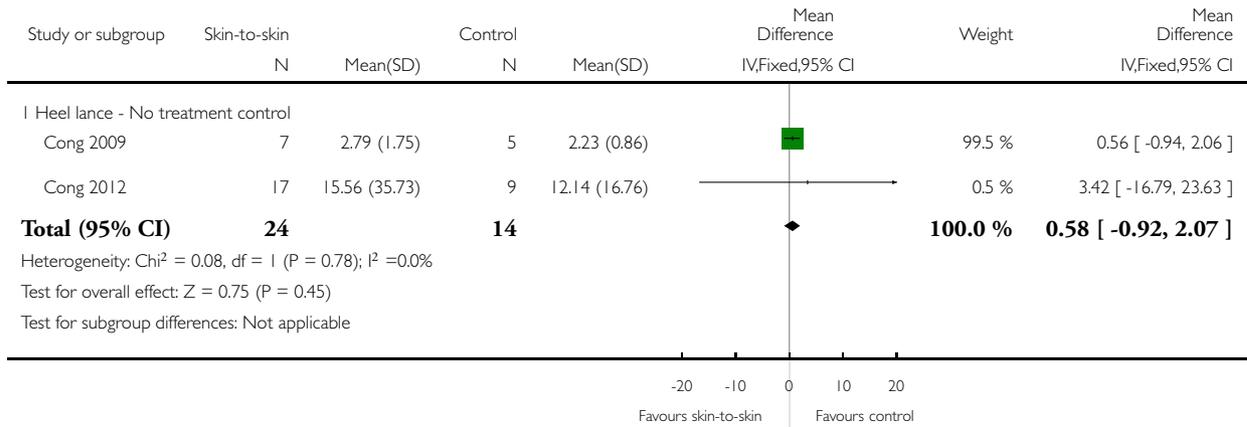


Analysis 1.6. Comparison 1 Skin-to-skin care versus control, Outcome 6 HRV after painful procedure - Low frequency power.

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

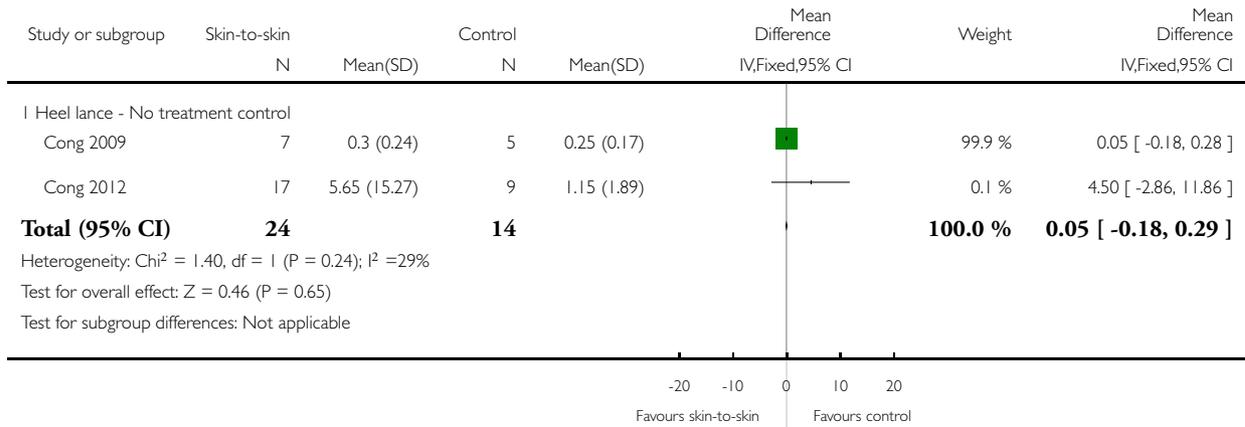


Analysis 1.7. Comparison 1 Skin-to-skin care versus control, Outcome 7 HRV after painful procedure - High frequency power.

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

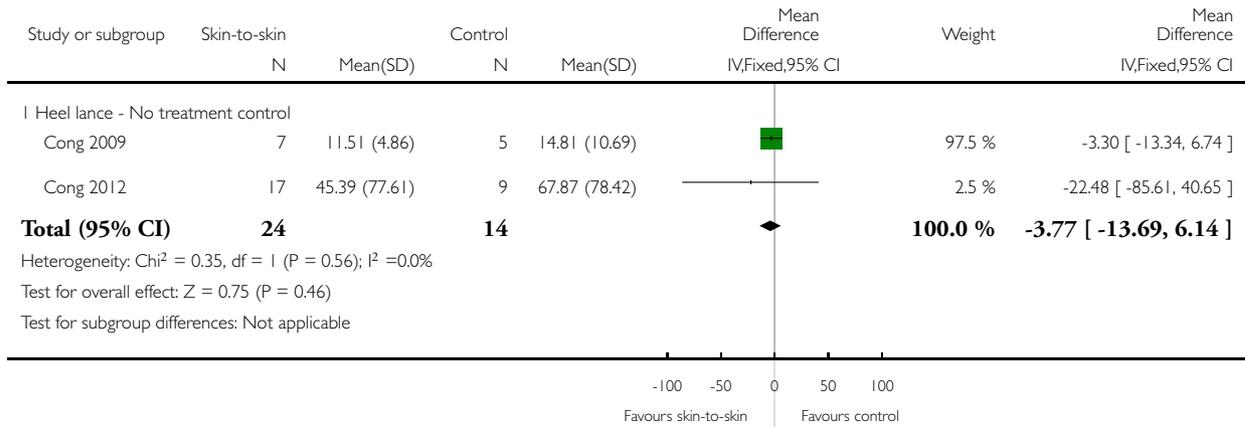


Analysis 1.8. Comparison 1 Skin-to-skin care versus control, Outcome 8 HRV after painful procedure - Low frequency to high frequency ratio.

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

Comparison: 1 Skin-to-skin care versus control

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

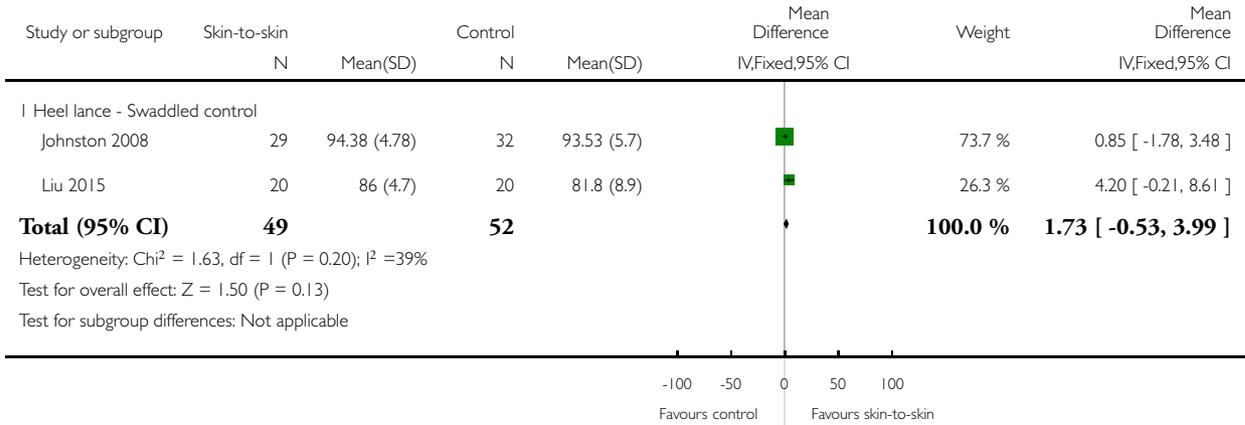


Analysis 1.9. Comparison 1 Skin-to-skin care versus control, Outcome 9 Oxygen saturation 30 seconds after painful procedure.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 9 Oxygen saturation 30 seconds after painful procedure

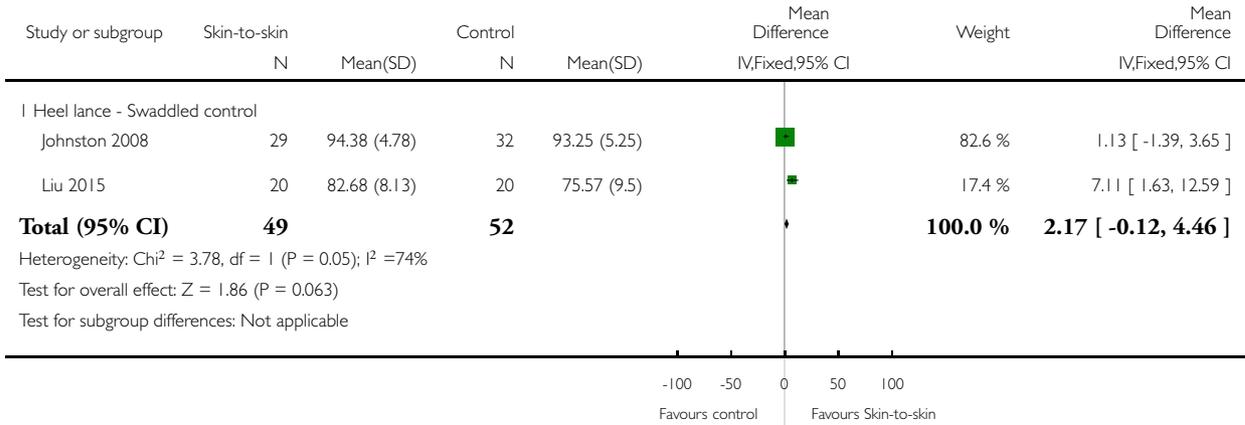


Analysis 1.10. Comparison 1 Skin-to-skin care versus control, Outcome 10 Oxygen saturation 60 seconds after painful procedure.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 10 Oxygen saturation 60 seconds after painful procedure

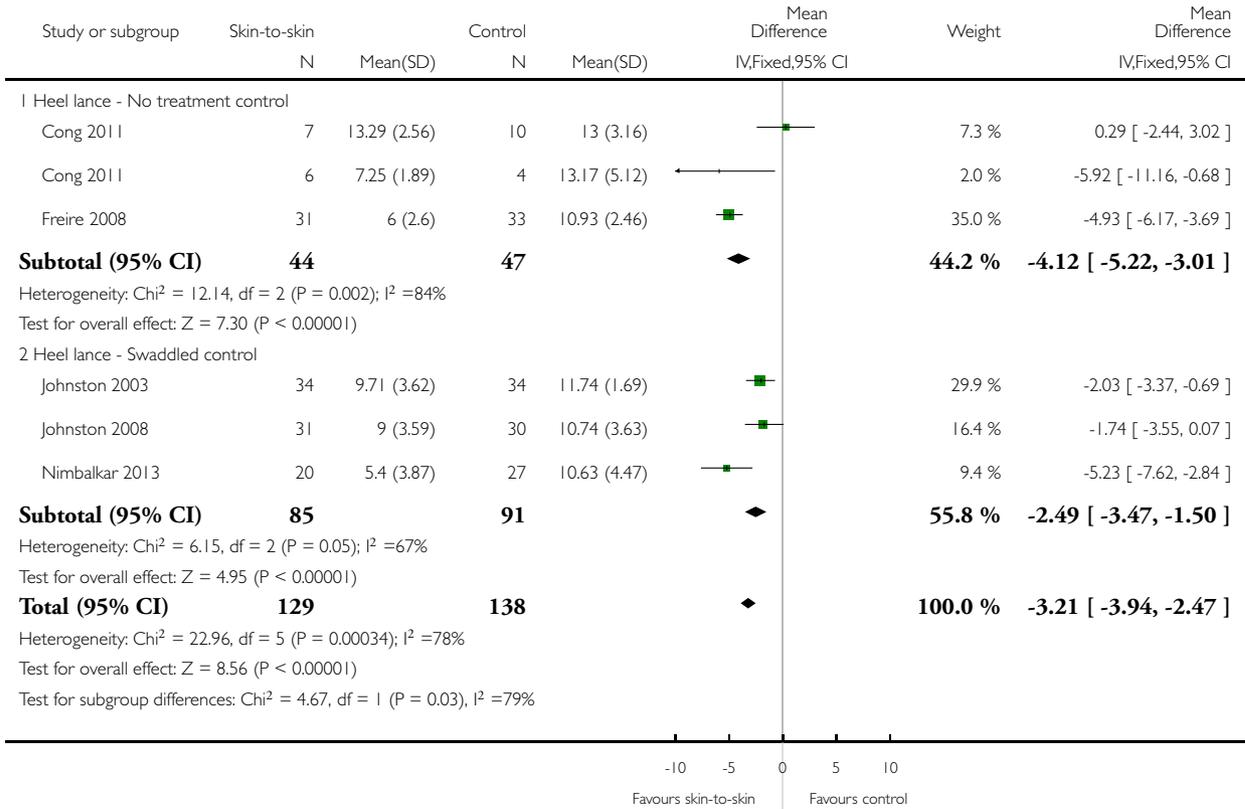


Analysis 1.11. Comparison 1 Skin-to-skin care versus control, Outcome 11 PIPP Score 30 seconds after painful procedure.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 11 PIPP Score 30 seconds after painful procedure

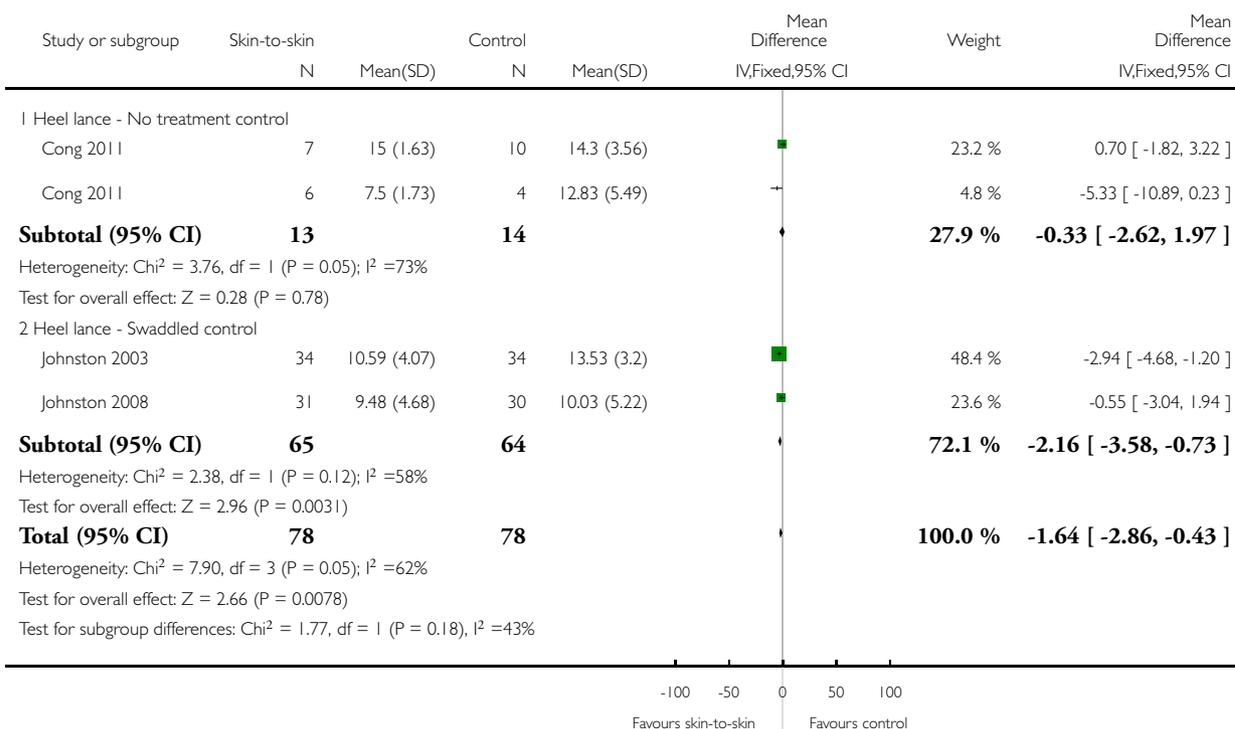


Analysis 1.12. Comparison 1 Skin-to-skin care versus control, Outcome 12 PIPP Score 60 seconds after painful procedure.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 12 PIPP Score 60 seconds after painful procedure

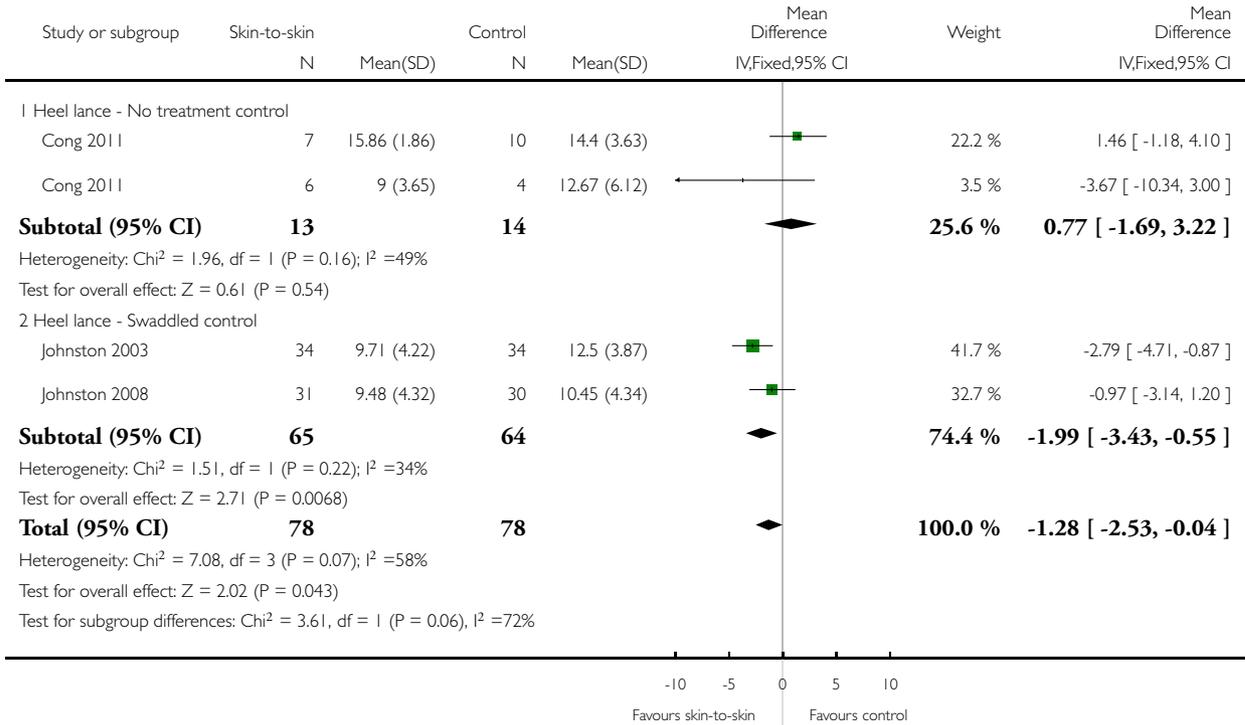


Analysis 1.13. Comparison 1 Skin-to-skin care versus control, Outcome 13 PIPP Score 90 seconds after painful procedure.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 13 PIPP Score 90 seconds after painful procedure

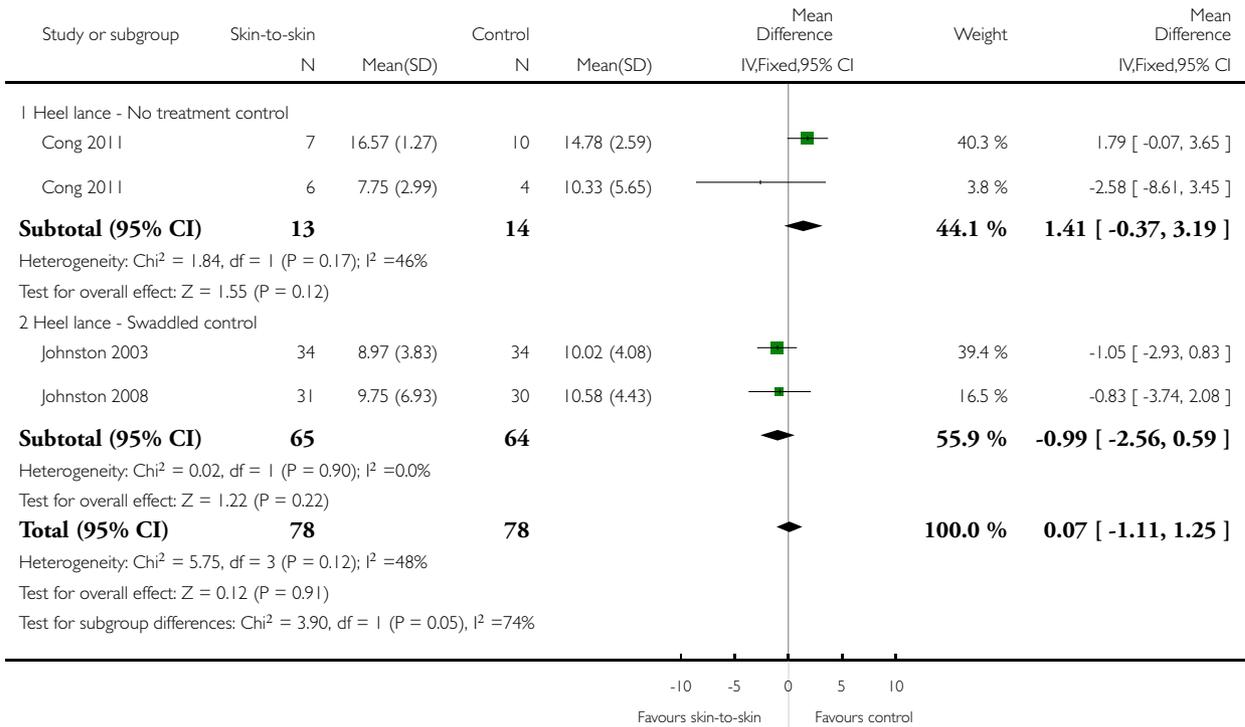


Analysis 1.14. Comparison 1 Skin-to-skin care versus control, Outcome 14 PIPP Score 120 seconds after painful procedure.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 14 PIPP Score 120 seconds after painful procedure

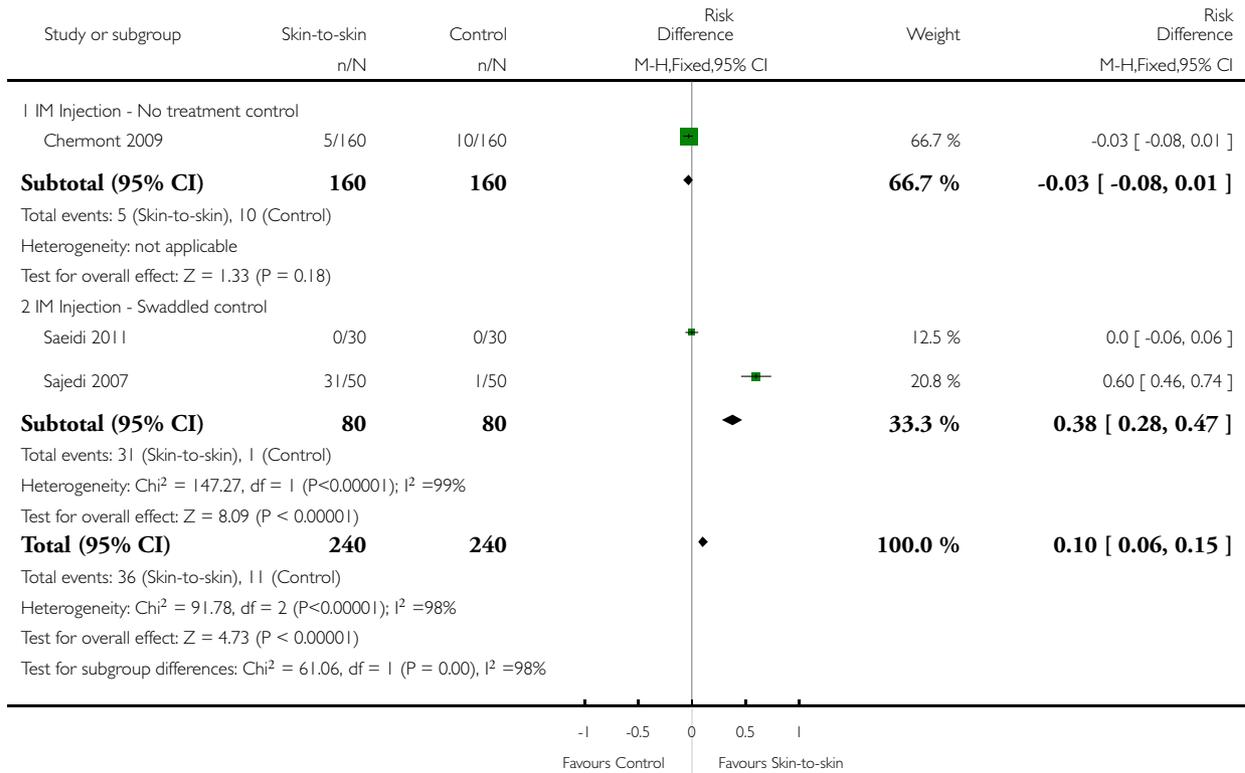


Analysis 1.15. Comparison 1 Skin-to-skin care versus control, Outcome 15 NIPS - Proportion of infants in low or no pain during procedure.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 15 NIPS - Proportion of infants in low or no pain during procedure

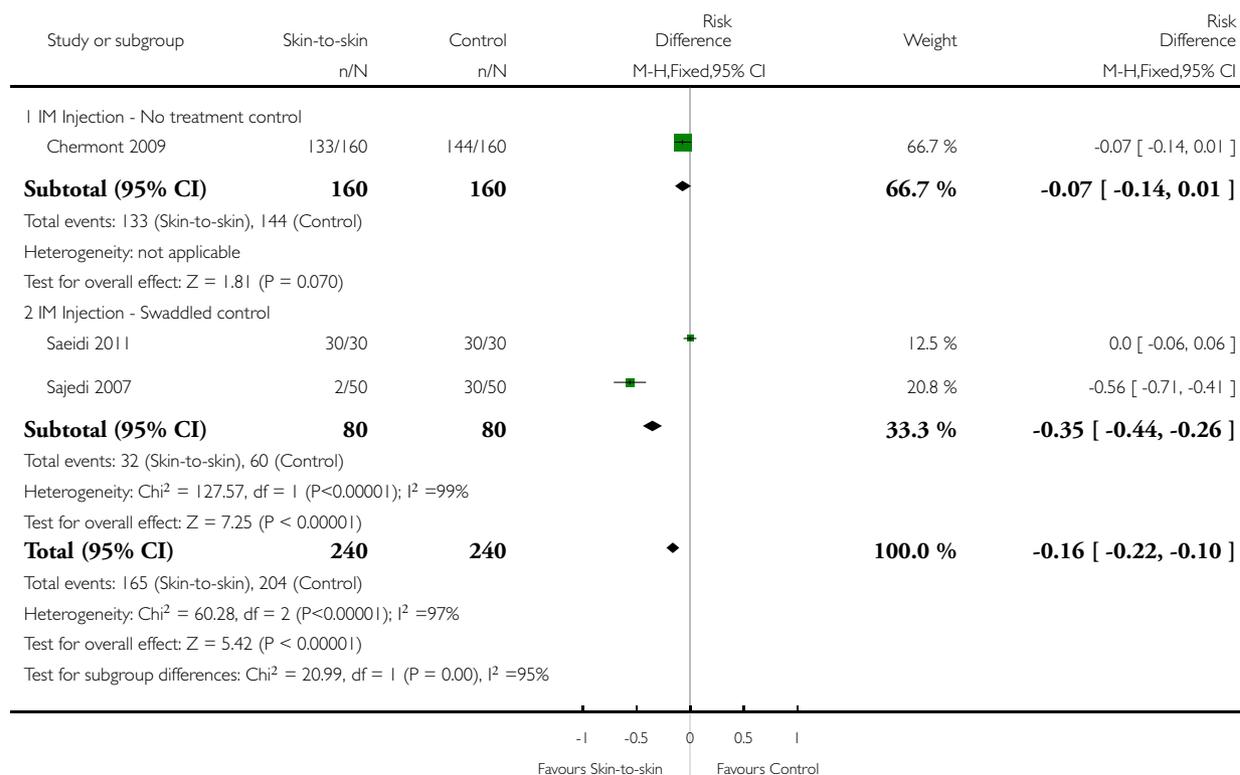


Analysis 1.16. Comparison 1 Skin-to-skin care versus control, Outcome 16 NIPS - Infants in severe pain following procedure.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 16 NIPS - Infants in severe pain following procedure

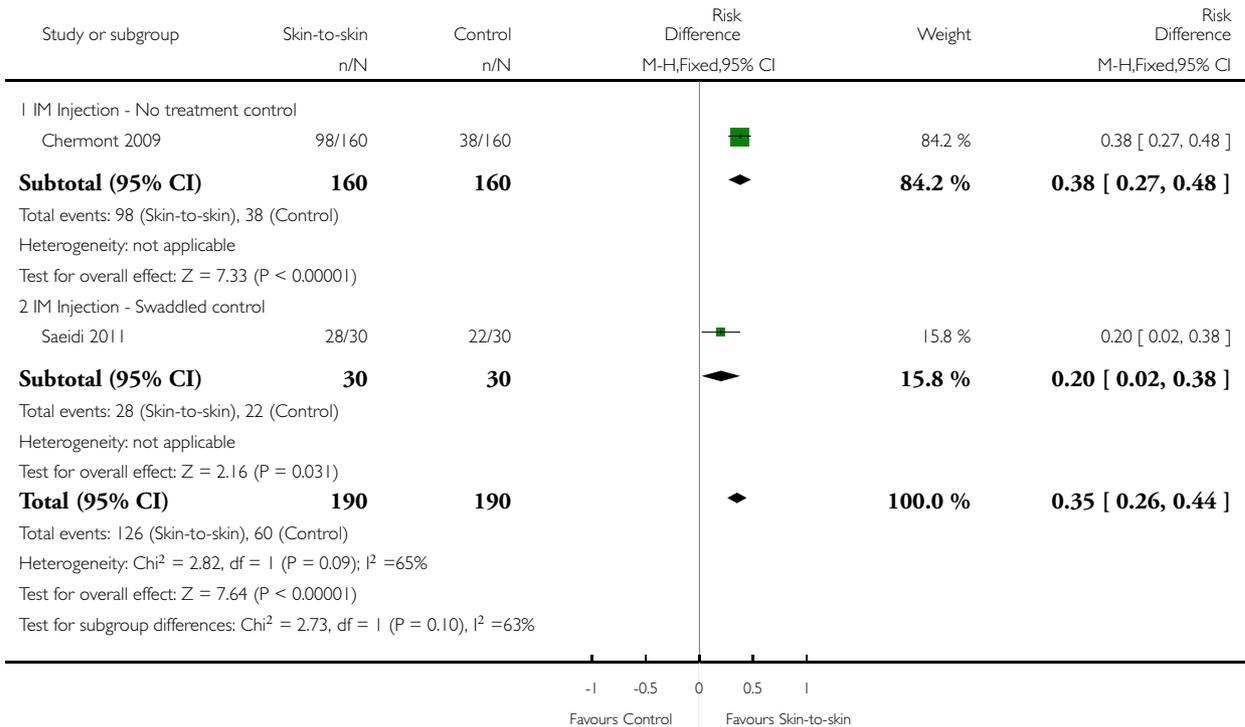


Analysis 1.17. Comparison 1 Skin-to-skin care versus control, Outcome 17 NIPS - Infants in no pain during recovery.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 17 NIPS - Infants in no pain during recovery

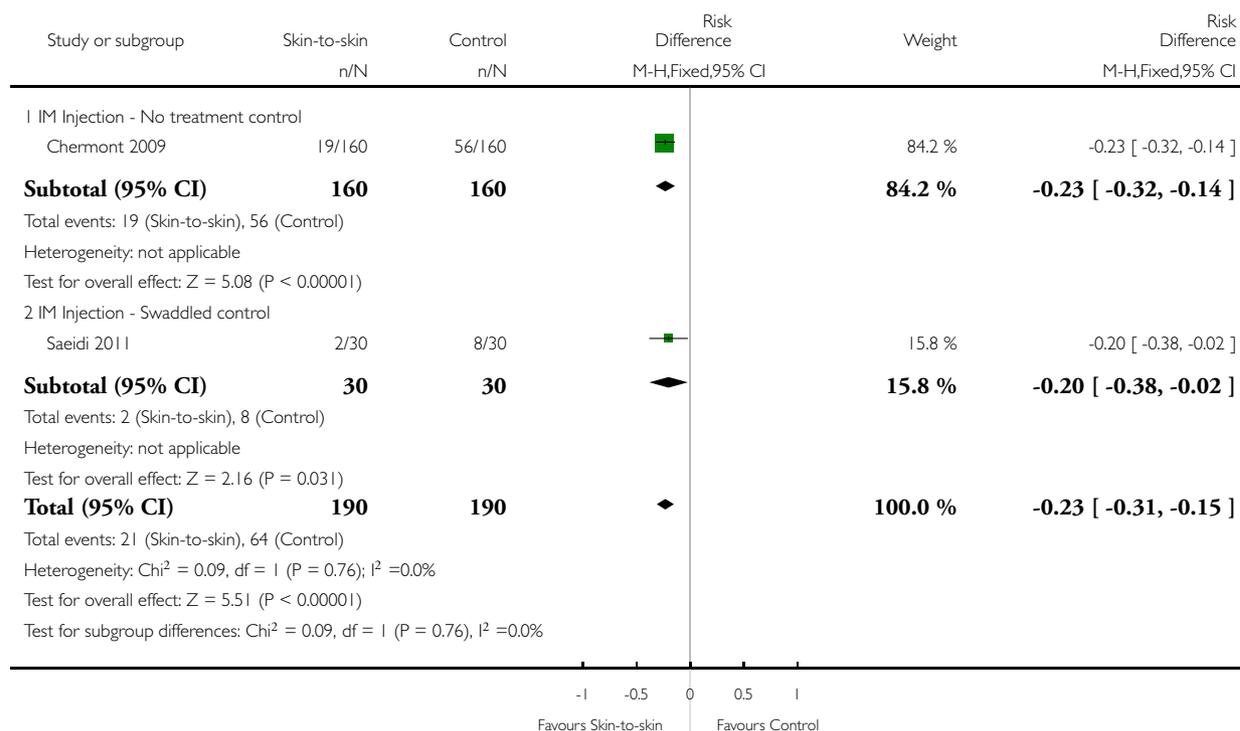


Analysis 1.18. Comparison 1 Skin-to-skin care versus control, Outcome 18 NIPS - Infants in severe pain during recovery.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 18 NIPS - Infants in severe pain during recovery

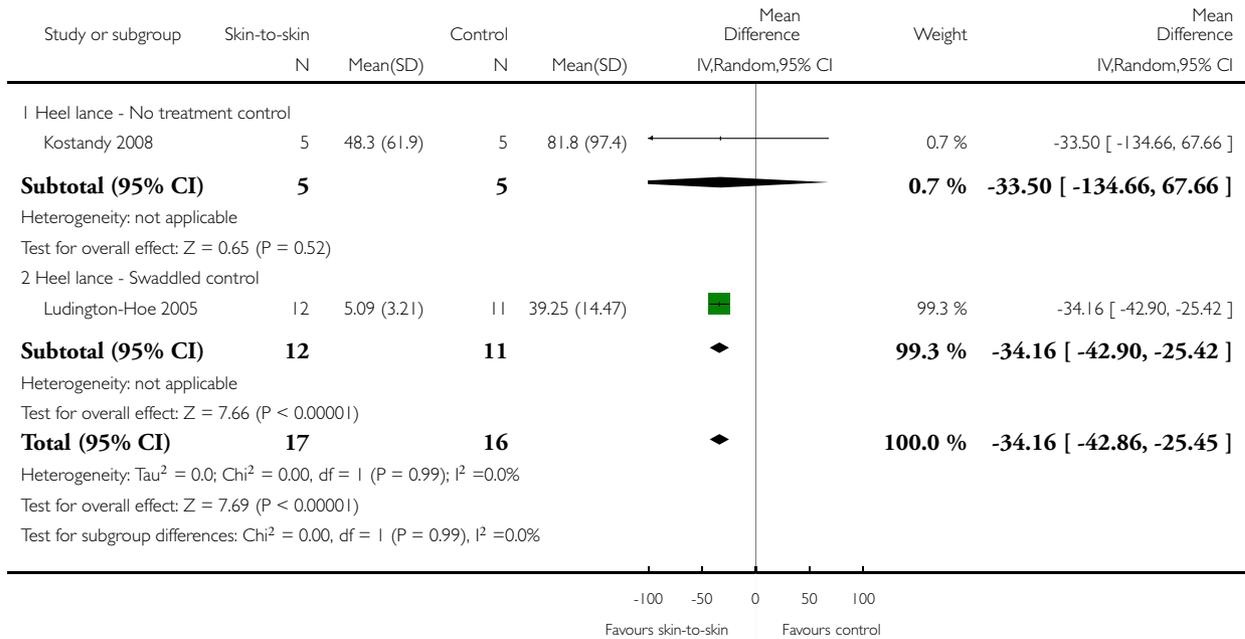


Analysis 1.19. Comparison 1 Skin-to-skin care versus control, Outcome 19 Duration of cry (seconds) following heel lance.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 19 Duration of cry (seconds) following heel lance

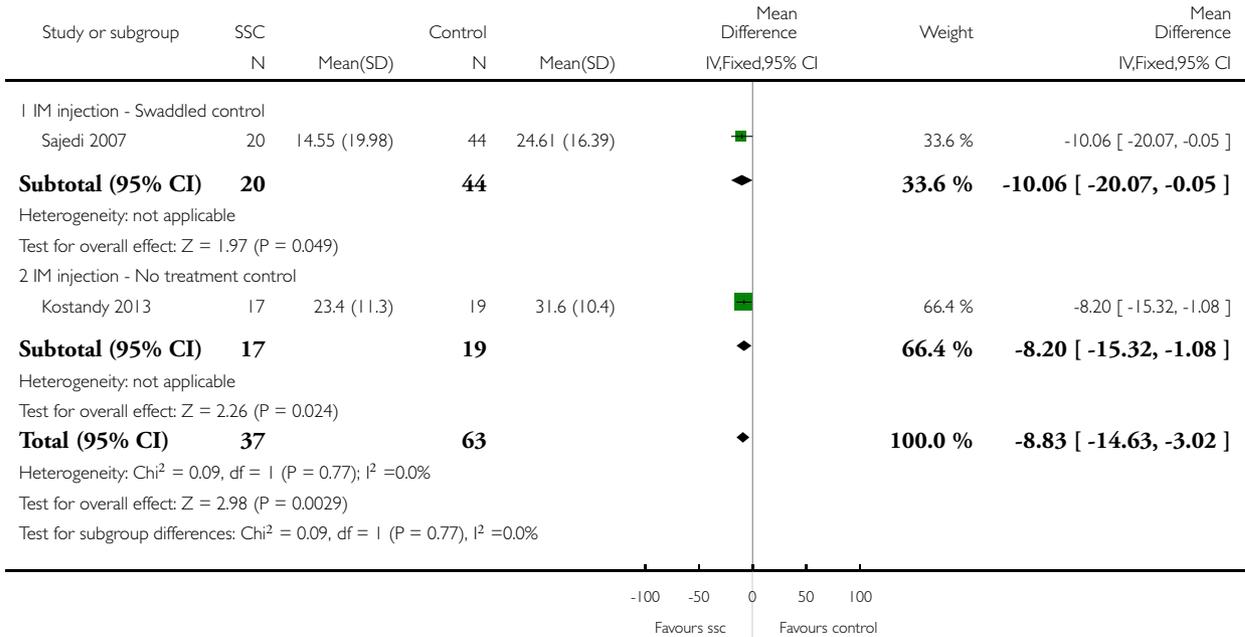


Analysis 1.20. Comparison 1 Skin-to-skin care versus control, Outcome 20 Duration of cry (seconds) following IM injection.

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

Comparison: 1 Skin-to-skin care versus control

Outcome: 20 Duration of cry (seconds) following IM injection

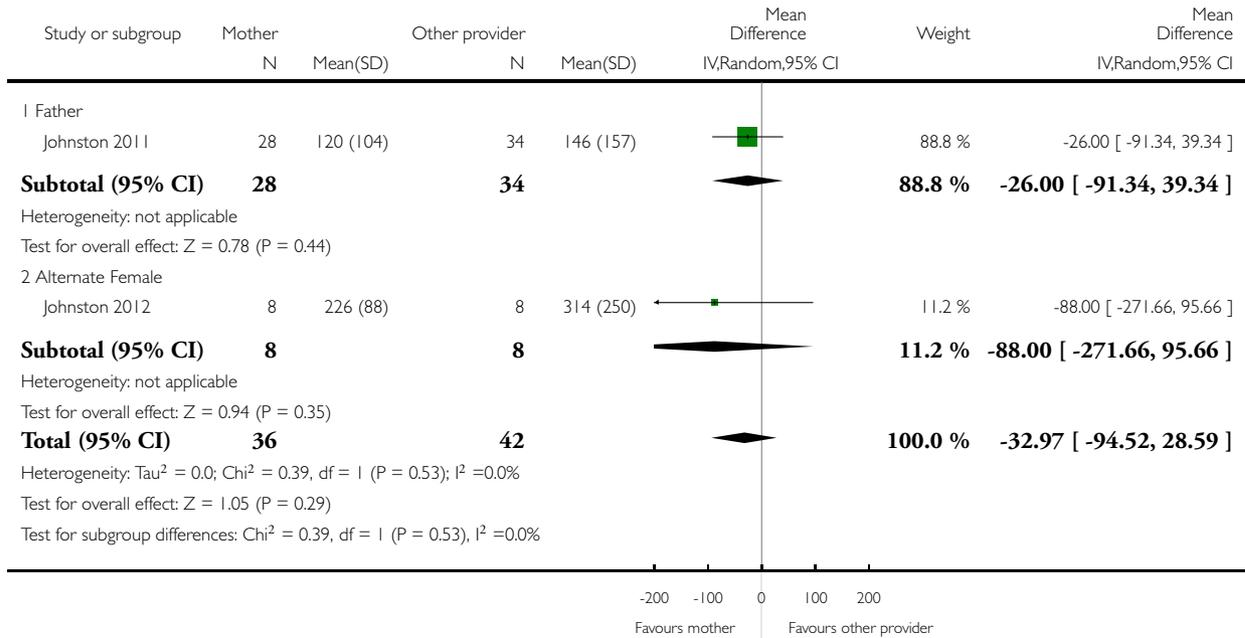


Analysis 2.1. Comparison 2 Skin-to-skin care with different providers, Outcome 1 Heart rate recovery.

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

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

Outcome: 1 Heart rate recovery

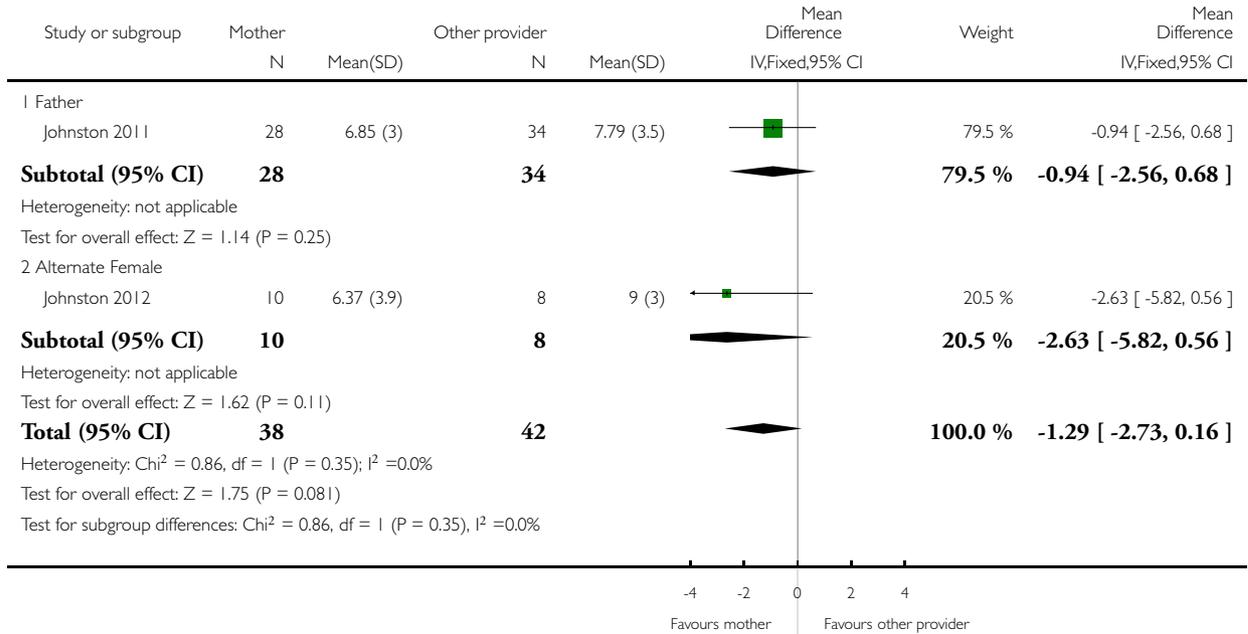


Analysis 2.2. Comparison 2 Skin-to-skin care with different providers, Outcome 2 PIPP Score 30 seconds.

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

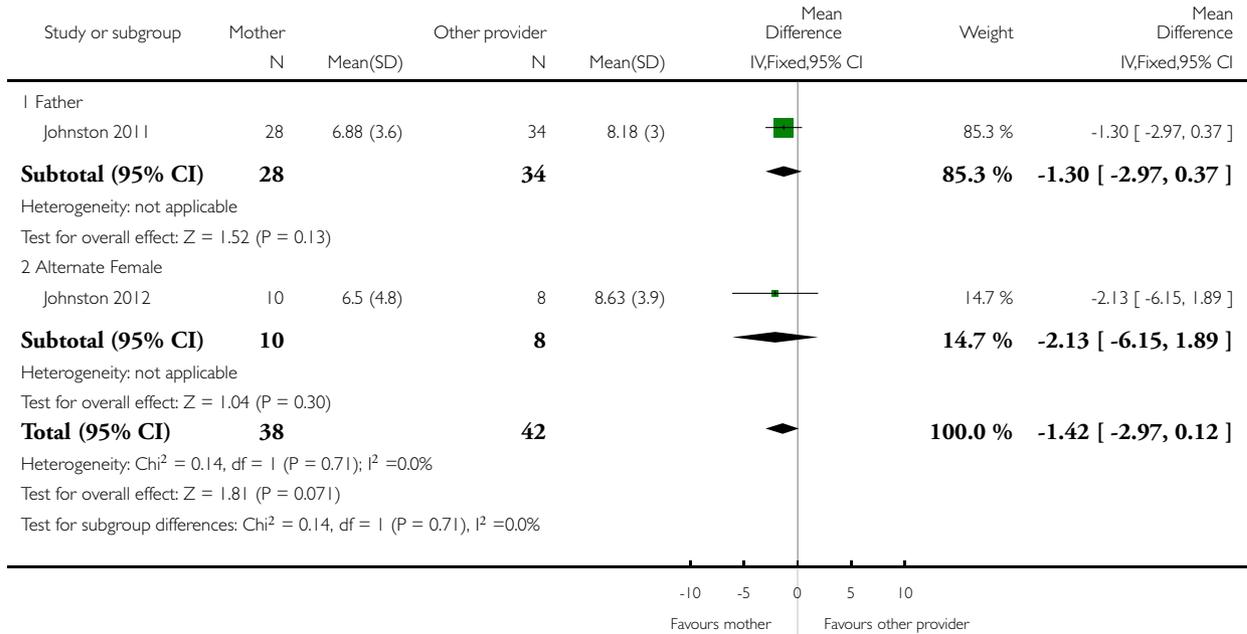


Analysis 2.3. Comparison 2 Skin-to-skin care with different providers, Outcome 3 PIPP Score 60 seconds.

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

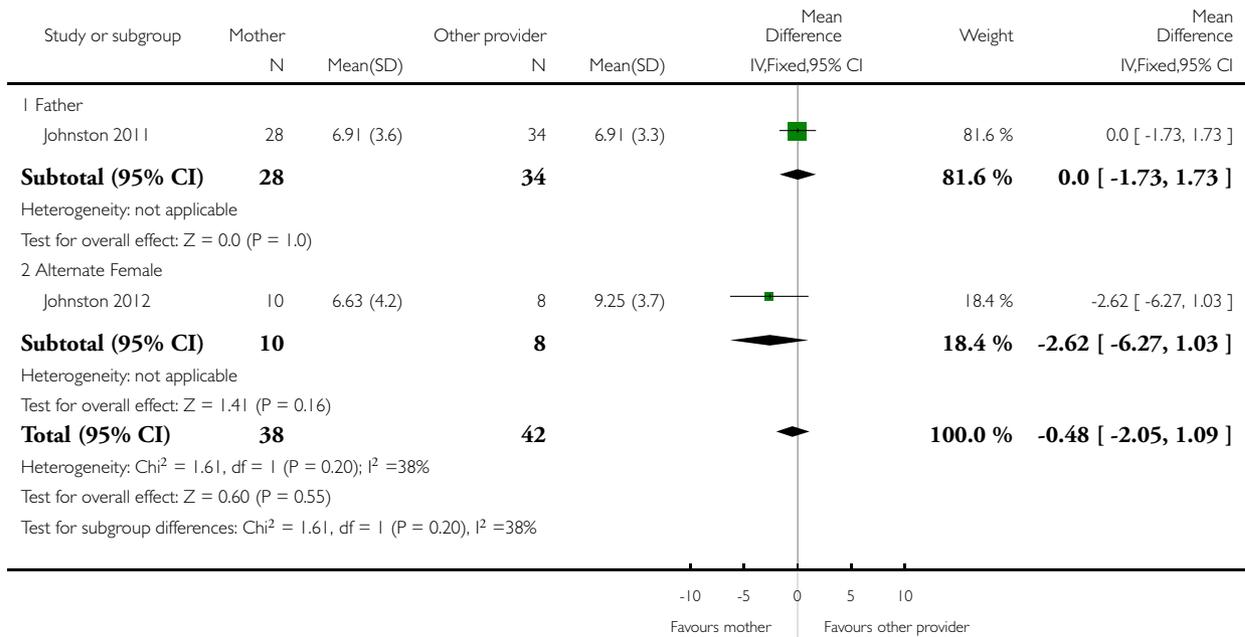


Analysis 2.4. Comparison 2 Skin-to-skin care with different providers, Outcome 4 PIPP Score 90 seconds.

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

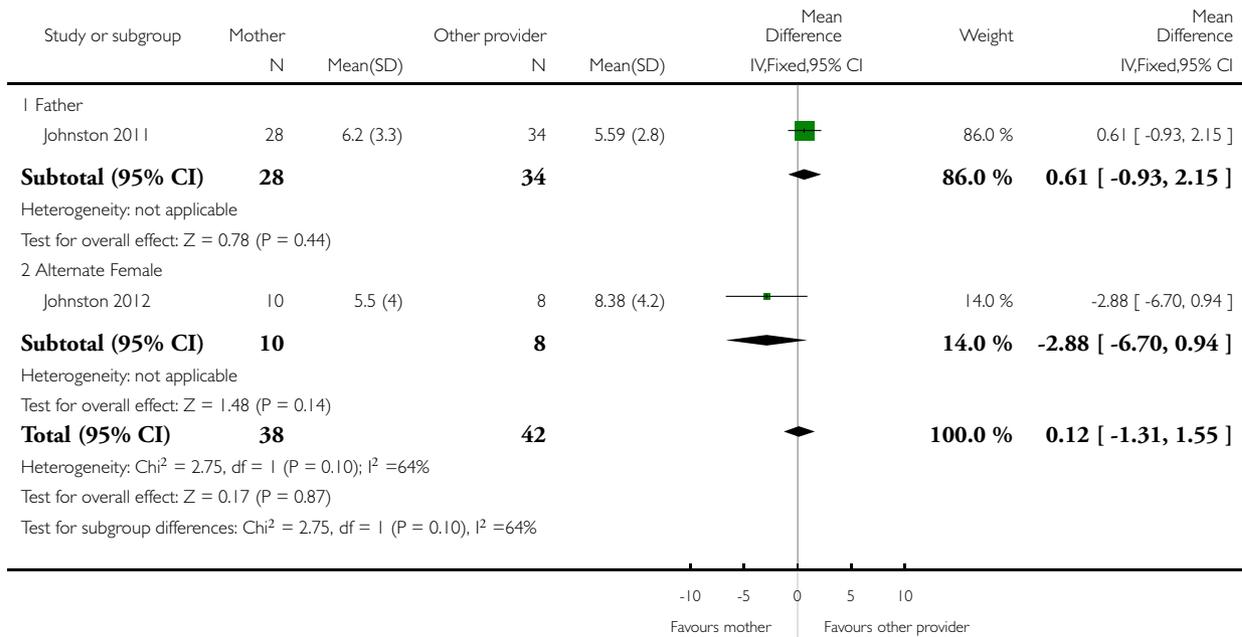


Analysis 2.5. Comparison 2 Skin-to-skin care with different providers, Outcome 5 PIPP Score 120 Seconds.

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	Randomized 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 con-

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

		1846.2 (control)				tact more likely than infant controls to have significantly lower NFCS scores for heel lance (P = 0.023) 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	Randomized cross-over	14 infants (13 intervention, 10 control) Postnatal age, mean ± SD, days: 6 ± 1 (total) Postmenstrual 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 < 0.05) and HS period (KC

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

		<p>Birth weight, mean \pm SD, grams: 1775 \pm 292 (total)</p> <p>Weight on day of study, mean \pm SD, grams: 1706 \pm 293 (total)</p>	<p>Provider: mother</p>	<p>and recovery</p>		<p>159 \pm bpm versus IC 165 \pm 14 bpm, $P < 0.05$) . HR increased significantly during HS from the BL and HW periods in both KC ($P < 0.05$) and IC conditions ($P < 0.001$), and returned to BL values during RC in both conditions. LF was higher in KC at BL ($P < 0.01$) and HS ($P < 0.001$) and HF was higher in KC at BL than in IC condition ($P < 0.05$). LF/HF ratio fluctuated less across periods in KC than in IC condition and was significantly lower during RC in KC than in IC ($P < 0.001$). LF and HF increased during HS from BL and HW, and dropped in the RC period in both KC (LF, $P < 0.05$ and HF, $P < 0.01$) and IC (LF, $P < 0.01$ and HF, $P < 0.001$) conditions. The LF/HF ratio was lower during HS than during BL,</p>
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Table 1. Trials assessing pain during heel lance (Continued)

						HW, and RC in both KC (P < 0.01) and IC (P < 0.001) conditions
Cong 2011	Prospective randomized cross-over	28 infants: 14 infants - 80 min SSC (Study 1); 10 infants - 30 min SSC (Study 2) Post-natal 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 < 0.05 to P < 0.001), lower salivary cortisol at the end of recovery (P < 0.05) and lower serum cortisol during heel lance for the kangaroo care heel lance condition (KCH) (P < 0.05) as well as clinically lower PIPP scores in the KCH condition during heel lance
Cong 2012	Randomized 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 Post-natal age, mean ± SD, days: 14.5 ± 6.3 (Study a); 13.8 ± 5.6 (Study b) ; 13.5 ± 5.6 (control)	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

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

		Birth weight, mean \pm SD, grams: 1444.6 \pm 379.0				dropped from heel stick to recovery; in 2 KC conditions, no changes 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	Randomized 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	PIPP score	Mean, standard deviations	Heart rate variation and oxygen saturation significantly lower in kangaroo group compared to incubator and glu-

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

			heel lance Compar- ison: Sweet taste 2 minutes before heel lance Provider: mother			cose groups (P = 0.0001 and P = 0.0012, respectively). Shorter duration 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
Gabriel 2013	Randomized controlled trial	136 infants (127 in analysis)(33/31 skin-to-skin, 33/32 sucrose, 35/35 sucrose + ssc, 35/29 skin-to-skin + breastfeeding) Gestational age, range, median, weeks: skin-to-skin: 37 to 41, 39; sucrose: 37 to 41, 39; sucrose + skin-to-skin: 37 to 41, 40; sucrose + breastfeeding: 37 to 42, 40 Birth weight, range, mean, grams: skin-to-skin: 2832 to 3900, 3359; sucrose: 1945 to 4176, 3215; sucrose + skin-to-	Group 1: 5 minutes of skin-to-skin care before, during heel lance Group 2: 2 mL of 24% sucrose 2 minutes before heel lance Group 3: 5 minutes of skin-to-skin care before, during heel lance + 2 mL of 24% sucrose 2 minutes before heel lance Group 4: 5 minutes of breastfeeding with skin-to-skin before, during heel lance Provider: skin-to-skin care and breastfeeding	Crying time, % of crying in blood sampling, heart rate, NIPS	median and IQR (crying time, % of crying during blood sample, NIPS), mean and standard deviations (heart rate)	Breastfeeding + skin-to-skin group lower median NIPS score during heel stick (P < 0.01). NIPS scores in sucrose + skin-to-skin group lower than sucrose alone group 2 minutes after procedure (P = 0.02). Percentage of neonates with moderate-to-severe pain lowest in breastfeeding + skin-to-skin group, breastfeeding + skin-to-skin and sucrose + skin-to-skin

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

		skin: 2340 to 4108, 3349; sucrose + breastfeeding: 2266 to 4338, 3289	provided by the mother. Sucrose administered by a nurse			had lower percentage of crying time compared to skin-to-skin alone
Gao 2015	Randomized controlled trial	80 infants (75 in analysis) (40/38 in skin-to-skin, 40/37 in control) Gestational age, range, weeks: 27 to 37 Postnatal age, mean \pm SD, days (heel stick 1,2,3, 4): Skin-to-skin: 3.5 \pm 0.3, 4.3 \pm 0.8, 5.3 \pm 0.6, 6.7 \pm 0.8 Control: 3.6 \pm 0.4, 4.2 \pm 0.8, 5.2 \pm 0.7, 6.8 \pm 0.8 Birth weight, mean \pm SD, grams: Intervention: 2017.8 \pm 154.7; Control: 2030 \pm 135.6	Intervention: Prone in incubator for 1 heel lance, Skin-to-skin 30 minutes pre-heel lance for three consecutive procedures Control: prone in incubator \times 4 heel lances Provider: mother	Crying time(seconds), grimacing time (seconds), heart rate	mean, standard deviations	Between group: Crying (P < 0.001), Grimacing (P < 0.001), HR (P < 0.001) significantly lower in skin-to-skin group Within group: No loss in efficacy of skin-to-skin over time
Gray 2000	Randomized controlled trial	30 infants (15 control, 15 intervention) Postnatal age, range, hours: 33 to 55 Postmenstrual age, weeks: \geq 37 Birth weight, mean (range), grams: 3300 (2600 to 3700)	Intervention: 10 to 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

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

						period ($P < 0.001$). 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
Johnston 2003	Randomized cross-over	74 infants Postnatal age, range, days: 0 to 10 Postmenstrual age, mean \pm SD (range), weeks: 33.7 ± 1.1 (32.0 to 36.0) Birth weight, mean \pm SD (range), grams: 2054 ± 406 (1320 to 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; $P = 0.04$), 60 seconds (difference, 2.2 points; $P = 0.002$), and 90 seconds (difference, 0.6 point; $P = 0.37$) after heel-lancing procedure. Heart rate and oxygen saturation similar in both conditions. Facial actions contributed significantly to total pain score ($0.0 < P < 0.005$), with facial actions averaging 20% greater in control versus KC condition Means and standard de-

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

						viations for heart rate were obtained from the author
Johnston 2008	Randomized cross-over	61 infants Postmenstrual age, mean \pm SD, weeks: 30.5 \pm 1 Birth weight, mean \pm SD, grams: 1421 \pm 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 7.85 to 9.89) versus Incubator 10.677 (95% CI 9.56 to 11.79) P < 0.001). Insignificant difference continued to 120 seconds (8.86 (95% CI 7.48 to 10.26) versus 10.21 (95% CI 9.03 to 11.39) P = 0.145). Significant difference in time returning to baseline heart rate at end of blood sampling (123 seconds (95% CI 103 to 142) for the KMC and 193 seconds for incubator (95% CI 158 to 227) (F (61,1) = 13.6, P < 0.0000). Facial actions sig-

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

						nificantly 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 and standard deviations for PIPP scores were obtained from the author
Johnston 2009	Randomized cross-over	90 infants Postnatal age, range, days: 1 to 14 Postmenstrual age, mean \pm SD, weeks: 33.4 \pm 1.1 Birth weight, mean \pm SD, grams: 1968 \pm 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 30 s 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	Randomized cross-over	62 preterm infants (PMA 28 to 36 weeks) Postnatal age, mean, days: 5 to 10 Birth weight, mean \pm	Intervention: 30 minutes of skin-to-skin care before and during heel lance provided by mother Comparison: 30 minutes of skin-	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

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

		SD, grams: 1565 ± 469 (father KC/mother KC); 1610 ± 494 (mother KC/father KC)	to-skin care before and during heel lance provided by father Provider: mother or father			when in paternal KC (30 seconds mean difference 1.44 (95% CI 0.23 to 2.63); 60 seconds mean difference 1.55 (95% CI, 0.07 to 3.03). No differences at 90 and 120 seconds The difference in time to return 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% CI 5.16 to 81.06 seconds))
Johnston 2012	Randomized 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 0.24, 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

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

						another woman providing kangaroo care
Kostandy 2008	Randomized cross-over	10 infants Postmenstrual age, range, weeks: 30 to 32 Birth weight, mean \pm SD, grams: 1577 \pm 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, crying time was less during the heel lance (P = 0.001) and recovery (P = 0.01) phases
Liu 2015	Randomized controlled trial	40 infants Gestational age, mean \pm SD, weeks: Intervention: 39.3 \pm 0.94; Control: 39.36 \pm 0.63 Birth weight, mean \pm SD, grams: Intervention: 3337g \pm 409.1; Control: 3740g \pm 298.9	Intervention: Skin-to-skin care 15 minutes pre, during, and one minute after heel lance Control: Post bath, swaddled during and 1 min after heel lance Provider: mother	DAN score, crying time, pain facial expression duration, SpO ₂ , HR	Mean, standard deviations	Decreased heart rate (P < 0.01), pain facial expression time (P = 0.041), crying time (P = 0.033), and DAN score (P < 0.01); increased oxygen saturation (P < 0.05) in skin-to-skin group
Ludington-Hoe 2005	Randomized cross-over	23 preterm infants (< 37 weeks PMA) Postnatal age, mean \pm SD, days: 22 \pm 11.4 Postmenstrual age, mean \pm SD, weeks: 31.4 \pm 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

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

						the warmer. Significant main effects were found for heart rate ($F(1,32) = 3.54, P = 0.042$) and cry length ($F(1,32) = 5.20; P = 0.01$). Mean rise in heart rate from baseline to heel lance was less in the KC condition than in the warmer condition ($F(1, 32) = 3.01, P = 0.047$). Crying length during KC heel lance significantly less than during warmer heel lance ($F(1, 32) = 7.38, P = 0.003$) and post-lance period ($P = 0.02$)
Mosayebi 2014	Randomized Crossover	64 preterm infants (GA range, mean, weeks \pm SD = 30 to 36, 33 ± 1.95) Postnatal age, range, mean \pm SD, days: 3 to 14, 7.28 ± 3.65 Birth weight range, mean \pm SD: 1000 to 3500, 2095.85 ± 672.27	Intervention: 15 minutes of skin-to-skin care before, during, and two-minutes post heel lance Control: 15 minutes prone and swaddled in an incubator before heel lance Provider: mother	PIPP	mean, standard deviations	Mean score during and two minutes after intervention lower in skin-to-skin condition ($P < 0.0$)
Nimbalkar 2013	Randomized cross-over	47 preterm infants (PMA 32 0/7 to 36 6/7 weeks) Postnatal age, mean, days:	Intervention: 15 minutes of skin-to-skin care before, during, and 15 minutes after heel lance	PIPP score	Mean, standard deviation	Heart rate, behaviour and facial scores were statistically significant and lower

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

		within 10 days Birth weight, mean, grams: 1730 (intervention), unclear (control)	Control: standard care during heel lance Provider: mother			in KMC group. But there was no statistically significant difference in oxygen saturation (SpO ₂) . The difference (4.85) in PIPP score was clinically and statistically significant (P < 0.001)
Okon 2010	Prospective randomized 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 SaO ₂ : NFCS	Median, 25% to 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 to 133); Control: 184 (107 to 281); Comparison: 48 (40 to 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; postmenstrual age (PMA); Douleur Aigue Neonatal (DAN); Neonatal Facial Coding Scale (NFCS); Premature Infant Pain Profile (PIPP)

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) Postnatal age, mean \pm SD, hrs: 293 \pm 13 (skin-to-skin care), 29 \pm 15 (control), 29 \pm 13 (comparison1), 27 \pm 13 (comparison2) postmenstrual age, mean \pm SD, wk: 39 \pm 1 (for all groups) Birth weight, mean \pm SD, g: 3164 \pm 371 (intervention); 3163 \pm 418 (control); 3252 \pm 389 (comparison1); 3240 \pm 418 (comparison2)	In- tervention: skin-to-skin contact, initiated 2 minutes before injection and persisting throughout procedure Control: standard care during injection Comparison1: oral 25% dextrose treatment (1 mL), 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 ($P < 0.001$), as was interaction between time and procedure ($P < 0.001$). 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 ($P < 0.001$). PIPP scores were lower when IM vaccine injections were given to healthy neonates during skin-to-skin contact with

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

						<p>their mothers, regardless of 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</p>
Kostandy 2013	Randomized controlled trial	<p>36 term infants (Gestational Age, mean, weeks = 39.6) Postnatal age, mean, hours = Intervention: 24.29; Control: 28.35 Birth weight mean \pm SD, grams: Intervention: 3389.7 \pm 333.3; Control: 3326.8 \pm 324.08</p>	<p>Intervention: skin-to-skin for 10-15 minutes before, and during IM injection Control: supine in bassinet 10 to 15 minutes before IM injection Provider: mother</p>	<p>Cry time, behavioural state, heart rate</p>	<p>means, standard deviations</p>	<p>neonates in skin-to-skin group had shorter cry time during recovery (16 vs 72 seconds, $P = 0.007$), calmer behavioural state (2.82 vs 6.47 time points to reach non-crying state $P = 0.005$)</p>
Saeidi 2010	RCT	<p>60 full-term infants (80% of case group and 73.3% of control group had 40 weeks GA) Birth weight, mean \pm SD, grams: 3242</p>	<p>Intervention: 30 minutes skin to skin contact Control: standard care during injection Provider: mother provided skin-to-skin care</p>	<p>Behavioural changes using the Neonatal/Infant Pain Scale (NIPS) 2 minutes before, during, and 3 minutes after intervention</p>	<p>NIPS: number (%) O₂ saturation: mean, SD HR and crying interval: P values</p>	<p>Mean pain intensity during the intervention was significantly lower in the case group ($P < 0.006$). Mean pain intensity 3 minutes after inter-</p>

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

		± 306.6 (intervention), 3151 ± 331.5 (control)		heart rate oxygen saturation		vention 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 (intervention), 3142.2 ± 242.3 (control)	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-skin care	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 after injection	Mean, standard deviations, Chi ² , degrees of freedom	Significantly more severe behavioural responses immediately after injection in control than intervention group (P < 0.001). NIPS scores immediately after injection significantly higher in control than intervention group (P < 0.001). Duration of crying post-injection significantly longer in control than intervention group (P = 0.001). 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

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

Study	Design	Participants	Intervention	Outcome	Metrics Used	Results
Johnston 2011	Randomized cross-over	62 preterm infants (PMA 28 to 36 weeks) Postnatal age, mean, days: 5 to 10 Birth weight, mean \pm SD, grams: 1565 \pm 469 (father KC/mother KC); 1610 \pm 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% CI	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 0.23 to 2.63); 60 seconds mean difference, 1.548 (95% CI 0.07 to 3.03). No differences at 90 and 120 seconds The difference in time to return 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% CI 5.16 to 81.06 seconds))
Johnston 2012	Randomized 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	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 0.24, at 90 sec was 0.43 and at 120 sec was 0.37

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

			heel lance provided by an unrelated woman Provider: mother or an unrelated woman			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
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Table 5. Trials assessing pain during tape removal

Study	Design	Participants	Intervention	Outcome	Metrics Used	Results
Nanavati 2013	Randomized controlled trial	50 preterm neonates (Gestational age, mean \pm SD weeks: Intervention: 32.72 \pm 2.03; Control: 32.4 \pm 2.16) Post-natal age, mean \pm SD, days: Intervention: 7.12 \pm 6.64; Control: 5.4 \pm 3.65) Birth weight, mean \pm SD, grams: Intervention: 1352.76 \pm 150.12, Control: 1235.48 \pm 169.12	Intervention: skin-to-skin care 15 minutes before, and during tape removal Control: swab soaked with expressed breast milk inserted in infants mouth 2 minutes before, and during tape removal Provider: mother	PIPP	mean, standard deviation	Post intervention PIPP score was no significantly different between groups (P = 0.62)

APPENDICES

Appendix I. Standard search methodology

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

WHAT'S NEW

Date	Event	Description
26 February 2016	New citation required and conclusions have changed	It was found that the physiological indicator of heart rate also favours Skin-to-skin contact, as well as in earlier review, behavioural and composite indicators of pain, although only one study contributed to this change
13 January 2016	New search has been performed	Six more trials were found in the updated searching and included in the meta-analysis

CONTRIBUTIONS OF AUTHORS

CJ oversaw the process and arbitrated disputes between other reviewers, and wrote narrative. MCY, TD, BB, and RZ contributed to content and editing of narrative. MCY, TD, BB, AF, RZ reviewed articles and rated them according to criteria. DS served as methodological expert. All authors reviewed and approved the final submission.

DECLARATIONS OF INTEREST

The authors have nothing to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the methodology and plan for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol or in the previous review.

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