Pain relief for neonatal circumcision (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

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[Intervention Review]

Pain relief for neonatal circumcision

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Editorial group: Cochrane Neonatal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.
Review content assessed as up-to-date: 2 August 2005.

Citation: Brady-Fryer B, Wiebe N, Lander JA. Pain relief for neonatal circumcision. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD004217. DOI: 10.1002/14651858.CD004217.pub2.

ABSTRACT

Background

Circumcision is a painful procedure that many newborn males undergo in the first few days after birth. Interventions are available to reduce pain at circumcision; however, many newborns are circumcised without pain management.

Objectives

The objective of this review was to assess the effectiveness and safety of interventions for reducing pain at neonatal circumcision.

Search methods

We searched Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004), MEDLINE (1966 - April 2004), EMBASE (1988 - 2004 week 19), CINAHL (1982 - May week 1 2004), Dissertation Abstracts (1986 - May 2004), Proceedings of the World Congress on Pain (1993 - 1999), and reference lists of articles. Language restrictions were not imposed.

Selection criteria

Randomised controlled trials comparing pain interventions with placebo or no treatment or comparing two active pain interventions in male term or preterm infants undergoing circumcision.

Data collection and analysis

Two independent reviewers assessed trial quality and extracted data. Ten authors were contacted for additional information. Adverse effects information was obtained from the trial reports. For meta-analysis, data on a continuous scale were reported as weighted mean difference (WMD) or, when the units were not compatible, as standardized mean difference.

Main results

Thirty-five trials involving 1,997 newborns were included. Thirty-three trials enrolled healthy, full term neonates, and two enrolled infants born preterm.

Fourteen trials involving 592 newborns compared dorsal penile nerve block (DPNB) with placebo or no treatment. Compared to placebo/no treatment, DPNB demonstrated significantly lower heart rate [WMD -35 bpm, 95% CI -41 to -30], decreased time crying [WMD -54 %, 95% CI -64 to -44], and increased oxygen saturation [WMD 3.7 %, 95% CI 2.7 to 3.7]. Six trials involving 200

newborns compared eutectic mixture of analgesics (EMLA) with placebo. EMLA demonstrated significantly lower facial action scores [WMD -46.5, 95% CI -80.4 to -12.6], decreased time crying [WMD - 15.2 %, 95% CI -21 to -9.3] and lower heart rate [WMD -15 bpm, 95% CI -19 to -10]. DPNB, compared with EMLA in three trials involving 139 newborns (133 of whom were included in the analysis), demonstrated significantly lower heart rate [WMD -17 bpm, 95% CI -23 to -11] and pain scores. When compared with sucrose in two trials involving 127 newborns, DPNB demonstrated less time crying [MD -166 s, 95% CI -211 to -121], and lower heart rate [WMD -27 bpm, 95% CI -33 to -20]. Results obtained for trials comparing oral sucrose and oral analgesics to placebo, and trials of environmental modification were either inconsistent or were not significantly different.

Adverse effects included gagging, choking, and emesis in placebo/untreated groups. Minor bleeding, swelling and hematoma were reported with DPNB. Erythema and mild skin pallor were observed with the use of EMLA. Methaemoglobin levels were evaluated in two trials of EMLA, and results were within normal limits.

Authors' conclusions

DPNB was the most frequently studied intervention and was the most effective for circumcision pain. Compared to placebo, EMLA was also effective, but was not as effective as DPNB. Both interventions appear to be safe for use in newborns. None of the studied interventions completely eliminated the pain response to circumcision.

PLAIN LANGUAGE SUMMARY

Pain relief for neonatal circumcision

Circumcision is a painful procedure frequently performed on newborn baby boys without using pain relief. Available treatments include dorsal penile nerve block (DPNB), which involves injecting anesthetic at the base of the penis. Ring block is another form of penile block. Locally applied anesthetic creams include EMLA, a water-based cream including lidocaine and prilocaine. Based on 35 clinical trials involving 1,997 newborns, it can be concluded that DPNB and EMLA do not eliminate circumcision pain, but are both more effective than placebo or no treatment in diminishing it. Compared head to head, DPNB is substantially more effective than EMLA cream. Ring block and lidocaine creams other than EMLA also reduced pain but did not eliminate it. Trials of oral acetaminophen, sugar solutions, pacifiers, music, and other environmental modifications to reduce circumcision pain did not prove them effective. DPNB can cause minor bruising, bleeding, or swelling at the injection site. EMLA and other lidocaine creams can cause skin color changes or local skin irritation. There is a rare risk with lidocaine creams of causing methaemoglobinaemia (blue-baby syndrome, where the baby's blood lacks sufficient oxygen). However, two trials of EMLA for circumcision pain relief measured methaemoglobin levels and found them normal. The circumcision procedure itself, especially without pain relief, can cause short term effects such as choking, gagging, and vomiting. Long term effects of circumcision without pain relief are not well understood. Strict comparability between trials was rare. Trials used a variety of indicators to measure baby's pain. Crying time, facial expression, and sweating palms can indicate infant pain, as can increased heart rate, breathing rate, and blood pressure. Levels of chemical indicators that can be part of a pain or stress response and are present in the blood or saliva are another gauge of pain levels. Also, procedures were not generally performed in just the same way in different trials. Type of clamp used (8sing a Mogen clamp can shorten the duration of the procedure), length of wait time after injection or application of anesthetic and procedure techniques varied.

BACKGROUND

Neither the American Academy of Pediatrics nor the Canadian Paediatric Society recommends routine or elective circumcision of the male newborn. Nevertheless, elective circumcision of male newborns is commonly performed in the first few days after birth. Approximately 1.2 million newborn males are circumcised in the United States annually at a cost of 150 to 270 million dollars (AAP 1999). Precise Canadian data are not available because the procedure has been delisted in many provinces, but it is estimated that 48% of male neonates born in Canada are circumcised (CPS 1996). The practice of male neonatal circumcision is not limited to North America; it is performed worldwide for religious and cultural reasons.

As an invasive, painful procedure, unanaesthetized circumcision elicits systemic stress responses in the vulnerable newborn which negatively affect major body systems. Documented physiological and behavioral responses include increased output of adrenal corticoids (Gunnar 1981; Talbert 1976), increased heart rate and respiratory rate, decreased arterial oxygen (Rawlings 1980), skin flushing, vomiting and cyanosis (Poma 1980), changes in sleep/wake state, increased crying (Anders 1974; Gunnar 1981), and diminished responsiveness to parents (Dixon 1984). Unanaesthetized circumcision has also been linked with complications such as apnea and choking (Lander 1997), gastric rupture (Connelly 1992), and recurrence of pneumothorax (Auerbach 1978). Infants circumcised without anaesthesia exhibit stronger pain responses to routine immunizations during the first six months of life than infants who were not circumcised (Taddio 1997b), suggesting that circumcision pain may exert long term effects on infant behavior.

INTERVENTIONS FOR CIRCUMCISION PAIN

Numerous interventions to prevent or reduce circumcision pain have been examined. These include penile blocks, topical anaesthetics, oral analgesia and sucrose administration, non-nutritive sucking, music and other environmental interventions.

The technique of dorsal penile nerve block (DPNB) for newborn circumcision was first described in 1978 (Kirya 1978), and it has since been extensively evaluated. More recently, subpubic (Dalens 1989) and penile ring block techniques (Hardwick Smith 1998; Lander 1997) have been examined. Adverse effects of penile blocks appear to be limited to bruising and slight bleeding at the injection site (Snellman 1995). Of note, the rapidity of onset of the anaesthetic used for penile blocks (generally 1% lidocaine without epinephrine) is intermediate and a "wait time" of 5 minutes is recommended to achieve anaesthesia (Taddio 2001). Wait time is a concern for clinicians because it increases the total time required for the circumcision surgery; however, inadequate "wait time" influences anaesthetic effect (Kharasch 2003).

Several types of topical anaesthetics have been used for neonatal circumcision, including eutectic mixture of local anaesthetics (EMLA) and 4 to 30% lidocaine creams. EMLA is a water-based cream that contains 2.5% lidocaine and 2.5% prilocaine. Compared with placebo, EMLA attenuates the pain responses of increased heart rate, facial activity and crying, and decreased oxygen saturation (Lander 1997; Taddio 1997). A meta-analysis of three studies examining this intervention indicated that the use of EMLA results in a significantly lower increase in heart rate (from baseline) and less crying during the various phases of circumcision surgery compared to placebo. In two of the included studies, lower facial action scores suggested less pain in the EMLA treated groups compared to placebo (Taddio 2002).

Potential difficulties with drug administration and the presurgical wait time may limit the feasibility of topical anaesthesia as a pain intervention for circumcision in many settings (Lander 1997). Considerable technical skill is required to apply the drug, and to secure the occlusive dressing needed to keep it in place. For adequate absorption, EMLA must be applied for at least 60 minutes prior to surgery (Taddio 1998), and must be reapplied if the infant voids during the wait time.

Methaemoglobinaemia (MetHb), caused by oxidation of haemoglobin by the metabolites of prilocaine, is a serious but relatively rare risk associated with EMLA use in infants less than 12 months of age. A recent systematic review of the use of EMLA for acute pain in infants demonstrated that the risk of significant MetHb is low with single dose applications of 0.5 to 2g applied for 10 - 180 minutes for full term neonates, and 0.5 to 1.25g applied for 3 to 180 minutes for preterm neonates (Taddio 1998). Local skin reactions, such as blanching, erythema, and edema of the skin have been reported with the use of EMLA , but these are usually transient and not considered serious.

Sucrose or other sugar solutions alone or in combination with non-nutritive sucking have recently been recommended as interventions for procedural pain management (Mitchell 2000). Oral sucrose is thought to activate central endogenous pathways, and may stimulate release of endorphins from the hypothalamus. Non nutritive sucking (NNS) is also thought to have an analgesic-like effect through stimulation of orotactile and mechanoreceptor mechanisms (Gibbons 2001; Mitchell 2003). The sensations created by NNS may deflect attention away from pain and facilitate self regulation because the infant is in control of the sucking. Sucrose and NNS appear to operate synergistically when offered in combination, and may provide more effective pain relief (Carbajal 1999; Gibbons 2001; Gibbons 2002). The analgesic effect of sucrose is activated within two minutes, and lasts for three to five minutes (Haouari 1999; Mitchell 2003). Although sucrose in a wide variety of dosages (concentrations from 12 to 24%, and volumes from 0.05 to 2.0 ml) has generally been found to decrease acute, procedural pain responses in neonates (Mitchell 2000; Stevens 1997), the optimal dose has not yet been identified. Meta-analyses results indicate that a 0.24g dose is effective to reduce pain responses in term infants, and higher doses do not appear to increase effectiveness (Stevens 1997). In comparison, relatively small doses (0.01 to 0.02g) appear to be effective for preterm infants (Johnston 1997). Interest in sucrose or other sugar solutions as a single or adjunctive intervention for circumcision pain is reflected in the design of recent research (e.g. Kass 2001; Kaufman 2002).

Acetaminophen is the most frequently prescribed non-opioid oral analgesic used to treat mild to moderate pain in pediatric populations (Berde 2002; McGrath 1990). Acetaminophen is safe and effective for neonates and can be administered orally or rectally (Stevens 1999). Acetaminophen has been used as an intervention for circumcision pain (Howard 1994).

A variety of non-pharmacological interventions have been evalu-

ated for treatment of acute procedural pain in neonates. In theory, these interventions provide nonpainful stimuli that compete with painful stimuli for the neonate's attention, and thus may blunt the perception of pain (Bellieni 2002). Interventions such as rocking, massage, facilitated tucking, and cuddling reduce pain responses during invasive procedures (Campos 1994; Corff 1995; Gray 2000). Music and other sounds (intrauterine, heartbeat) provide an auditory stimulus which may modulate pain perception and these have been evaluated as interventions for circumcision pain (Marchette 1989; Marchette 1991).

NEONATAL PAIN RESPONSES

It is difficult to evaluate the effectiveness of interventions for circumcision pain because newborns are non-verbal and display stereotypic responses to a variety of painful and non-painful stimuli. To maximize the validity of pain assessment in newborn populations three classes of pain indicators or outcomes, biochemical, physiological, and behavioural, are generally employed for research. Salivary and serum cortisol, the most frequently measured biochemical indicators, serve as markers of the stress response to pain because hormones of the hypothalamic-pituitary-adrenal axis are assayed. Physiological indicators include heart rate, respiratory rate, blood pressure, transcutaneous oxygen saturation (Tc pO2), transcutaneous carbon dioxide (Tc pCO2), oxygen saturation (SaO2), palmar sweat, intracranial pressure (ICP) and vagal tone. In newborn populations, heart rate is the most frequently studied physiological indicator (Sweet 1998). Behavioral indicators include facial expression, cry, gross motor movement, and changes in behavioral state. Facial expression (Grunau 1987) is the most comprehensively studied behavioral indicator for neonatal pain.

Multidimensional measurement tools that employ more than one parameter usually contain physiological and behavioral indicators, and occasionally add contextual information to obtain an overall pain score. The Neonatal Infant Pain Scale (NIPS) (Lawrence 1993) and the Premature Infant Pain Profile (PIPP) (Stevens 1996) are multidimensional tools frequently utilized as outcome measures for investigation of acute procedural pain in term and preterm neonates. Although a number of pain measures are available for use with neonatal populations, no single measure has proven to be the best for all situations. Accordingly, all outcomes evaluated in the included studies as measures of neonatal pain were included in this review.

SUMMARY

The substantial amount of research conducted to date suggests a willingness to address the problem of circumcision pain. However, the majority of neonates are circumcised without interventions for pain (Myron 1991; Ryan 1994; Snellman 1995; Wellington 1993). This situation persists despite growing awareness that newborns may perceive pain more intensely than older children or adults (Anand 2001; Fitzgerald 1993) and can be significantly compromised by it.

It has been suggested that training to manage circumcision pain is inadequate to promote consistent use of available interventions (Howard 1998). Recent surveys indicate that significant numbers of obstetricians (75%), family practitioners (44%), and pediatricians (29%) do not use analgesia/anaesthesia for circumcision because of concerns about adverse drug effects or because they believe that the procedure does not require pain management (Maxwell 1999; Stang 1991; Stang 1998).

Although a wide variety of interventions for circumcision pain have been examined, the individual and relative effectiveness of each has not been systematically assessed. Thus, the apparent reluctance of practitioners to adopt the regular use of pain interventions for circumcision may reflect beliefs that the findings of research conducted to date are collectively un-interpretable. At the same time, negative perceptions of the technical and practical difficulties associated with pain interventions may diminish clinician motivation to implement their regular use.

A systematic review of the research in this area was needed to summarize and identify implications arising from the existing evidence, and to provide an informed basis for practice and to identify gaps in knowledge which require further investigation. This review adds to knowledge gained from a previous systematic review which examined the efficacy of a single intervention for circumcision pain (Taddio 2002) by evaluating the efficacy and safety of all interventions for reducing pain at neonatal circumcision.

OBJECTIVES

To determine the safety and effectiveness of interventions to relieve pain associated with neonatal circumcision. Subgroup analyses were prespecified according to wait time (after anaesthetic administration and prior to start of surgery) for penile blocks, and for dose delivered for sucrose interventions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). Studies reported only as abstracts were included if relevant.

Types of participants

Male term or preterm neonates undergoing circumcision during the neonatal period (with postnatal age maximum of 28 days after reaching 40 weeks corrected gestational age).

Types of interventions

Any intervention intended to relieve pain during the circumcision procedure, for example, penile blocks, topical anaesthetics, oral sucrose administration, oral analgesics, surgical devices or techniques, or environmental manipulation such as music therapy or special restraints. This review included trials of interventions for circumcision pain in which any intervention was compared with placebo, no treatment, or with another active intervention.

Types of outcome measures

The primary outcome was pain as assessed by:
1. Physiological variables, such as heart rate (HR), respiratory rate (RR), oxygen saturation, or blood pressure (whether reported as change in, mean or absolute values)
2. Biochemical variables, such as salivary or serum cortisol levels (whether reported as pre- and post- measures or as change from baseline values)
3. Cry variables, for example, latency and duration of first cry, total cry duration, and/or percentage of time crying during the circumcision procedure
4. Validated pain measures, for example:
- Neonatal Infant Pain Score (Lawrence 1993);
- Neonatal Facial Action Coding System (Grunau 1987);
- Premature Infant Pain Profile (Stevens 1996);
- Other pain measures.
Secondary outcomes:
Complications of pain interventions were assessed as secondary outcomes. The outcomes included but were not limited to:
1) occurrence/incidence of methaemoglobinaemia (topical anaesthesia)
2) blanching and local skin irritations (topical anaesthesia)
3) bleeding, bruising and hematoma formation (penile blocks)
4) behavioral responses such a choking, spitting up, etc. during circumcision (all interventions)
Difficulties encountered in implementation of pain interventions, as reported by researchers, were noted.

Search methods for identification of studies

Standard methods as per the guidelines of the Cochrane Neonatal Review Group (CNRG) were utilized.
1. CIRCUMCISION/exp
2. circumcision surgery.mp
3. newborn circumcision.mp
4. 1 OR 2 OR 3
5. local anaesthes*
6. penile block.mp/exp
7. dorsal penile nerve block.mp/exp
8. ring block.mp/exp
9. 5 OR 6 OR 7 OR 8
10. eutectic mixture of local anaesthetics.mp/exp
11. EMLA.mp/exp
12. LIDOCAINE.mp/exp
13. 10 OR 11 OR 12
14. acetaminophen.mp/ OR paracetamol.mp/exp
15. sucrose.mp
16. pacifiers.mp
17. music therapy.mp
18. Gomco clamp.mp
19. Mogen clamp.mp
20. 9 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. 4 AND 20
22. HUMAN
23. MALE
24. 22 and 23
25. infant, newborn
26. neonat*
27. 25 OR 26
28. 24 AND 27
29. 21 AND 28
30. clinical trial
31. 29 AND 30
Databases searched included: Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004; MEDLINE 1966 - April 2004; EMBASE 1988 - 2004 week 19; CINAHL 1982 - May week 1 2004; PubMed 1966 - May 2004; Web of Science 1975 - May 2004; Dissertation Abstracts 1986 - May 2004. Keywords and (MeSH) terms included infant/newborn, male, circumcision, penile blocks, sucrose, lidocaine, EMLA, acetaminophen. Abstracts of the World Congress on Pain were searched for the years 1993 - 1999 inclusive. Reference lists of all articles were screened to identify any additional studies. Language restrictions were not imposed.

Data collection and analysis

Study Selection
The titles and abstracts of all reports identified through the electronic and other searches were scanned independently by two reviewers and full study reports were obtained for those that appeared to meet the inclusion criteria. Study reports were then evaluated independently by two reviewers for possible inclusion in the review. Disagreements were resolved by consensus. Studies rejected at this stage were included in the Table of Excluded Studies.

Quality Assessment

Assessment of the quality of all included studies was undertaken independently by two reviewers as a component of the data extraction process. Standard methods of the CNRG were used to assess: 1) the randomisation procedure, 2) concealment of allocation/blinding of randomisation, 3) blinding of intervention, 4) subject attrition and follow-up, and 5) blinding of outcome measurement. As per the CNRG guidelines, an overall quality score was not assigned. Reviewers were not blind to trial authors or institutions during the study selection or quality assessment processes.

Data Extraction

Data were extracted from included studies by two independent reviewers using a data extraction form designed specifically for this review. The data extraction form was developed in a draft format and piloted on several studies and modified as required before use. The reviewers abstracted data independently, compared results and resolved differences.

Sixteen trials included in this review either did not report outcome data, or did not report data in a format that could be analysed in this review (Arnett 1990; Benini 1993; Blass 1991 A; Holliday 1999; Holve 1983, Joyce 2001; Kass 2001; Marchette 1989; Marchette 1991; Maxwell 1987; Mohan 1998; Mudge 1989; Spencer 1992; Williamson 1997; Zahorodny 1998; Zahorodny 1999). Additional information was sought from ten authors and means and standard deviations were subsequently obtained for three trials (Benini 1993; Joyce 2001; Kass 2001). Where means and standard deviations were not available, data were imputed or derived from graphs contained in the reports (Arnett 1990; Benini 1993; Blass 1991 A; Holliday 1999; Maxwell 1987; Mohan 1998; Mudge 1989; Taddio 1997). Missing standard deviations were either calculated from other summary statistics or imputed using singular or mean standard deviations from similar trials.

Several authors reported total sample size only and information about the number of subjects per group was obtained from the authors (Benini 1993; Joyce 2001). When additional information about sample size could not be obtained from the authors, we assumed equal distribution to study groups in our data analyses (Blass 1991 A; Zahorodny 1998; Zahorodny 1999).

Data Analysis

The outcomes presented in this review were reported as results obtained during the whole circumcision procedure. Usually, the circumcision surgery was described as commencing with application of forceps to the dorsal foreskin of the penis (referred to as dorsal or lateral clamping) and ending with removal of the surgical clamp (the Gomco, Mogen, or Plastibell surgical device, also referred to as a clamp). Some authors reported a single numerical outcome result for the entire circumcision procedure (e.g. Butler O'Hara 1998; Howard 1999; Maxwell 1987; Taddio 1997). Others reported numerical results by procedure phase or step (e.g. dorsal foreskin grasped with forceps, adhesion lysis, dorsal incision, surgical clamp application, foreskin amputation, surgical clamp removal) (Benini 1993; Lander 1997; Woodman 1999). For the latter studies, depending on the outcome, we calculated either the arithmetic mean (e.g. heart rate) or total (e.g. time crying) across the phases or steps of the circumcision (as defined by the authors), and did not include the baseline or recovery phase data. Variance formulae for these arithmetic means and these totals were derived according to the general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)). We assumed a correlation of 0.5 as proposed by Follmann 1992. Additional Tables 1 - 7 (Table 1; Table 2; Table 3; Table 4; Table 5; Table 6; Table 7) provide specific details on summary estimate extractions from the included studies.

Data were analysed using the statistical package (RevMan 4.2) provided by the Cochrane Collaboration. When two or more studies were identified that examined the same comparison and clinically similar outcomes, data were pooled using fixed effects. Random effects accounting for inter-study heterogeneity were considered in sensitivity analyses. Studies that compared an active intervention with placebo were analysed separately from those that compared the same active intervention with no treatment.

Continuous data summaries are reported as weighted mean differences (WMD) when the units provided were compatible. When the units were not compatible, the standardized mean difference (SMD) is reported. The SMD describes the difference between the treatments in terms of units of standard deviations (SDs). To improve interpretability, we also report estimates of WMDs derived from the estimated SMDs. To derive the WMDs from the SMDs, we selected either the unit used in the majority of the trials or the most clinically relevant unit under a particular comparison and pooled the available SDs from the trials that used that unit. We then multiplied this pooled SD by the SMD to obtain an estimate of the WMD. The WMDs thus derived are reported along side the SMDs in the results. An example of how a SMD was converted to a WMD is provided in Figure 1.

Figure 1.

DPNB versus placebo
Cry time in % (Metagraph 01.02)

Studies	DPNB		Placebo	
	n	SD	n	SD
Kurtis 1999 A	24	38.5	24	16.80
Lander 1997	14	29.97	12	14.32
Stang 1988 A	10	33.98	20	31.75
Stang 1988 B	10	33.98	20	34.88
Williamson 1983	20	40.30	10	15.30
Pooled SD		**36.53**		**25.61**
Final Pooled SD				**31.07**

The DPNB pooled SD is calculated in this way:

$$\sqrt{\frac{38.5^2\cdot(24-1)+29.97^2\cdot(14-1)+33.98^2\cdot(10-1)+33.98^2\cdot(10-1)+40.3^2\cdot(20-1)}{(24-1)+(14-1)+(10-1)+(10-1)+(20-1)}}=36.53\%$$

The placebo pooled SD is calculated in a similar way.

The final pooled SD was simply averaged in this way:

$$\frac{36.53+25.61}{2}=31.07\%$$

Then, an estimated WMD is derived in this way:

$$SMD\cdot SD_{final\,pooled}=-1.74*31.07\%=-54\%$$

Individual study outcomes were reported as both final values (FVs) and change from baseline values (CVs). It is appropriate to combine FVs and CVs when combining mean differences to calculate a WMD. However, it is not appropriate, generally, to combine FVs and CVs when combining SMD to calculate an overall SMD. CVs often have smaller standard errors (SEs) than FVs since some of the intra-patient variation is removed from their SEs. Thus the individual study CV SMD tend to be in smaller SD units than the individual study FV SMD. However, in this systematic review, many of the SEs for CVs were either within the range of the FV SEs or they were larger, which is counterintuitive to the argument presented here. Hence, some of the SMD calculated in this review do combine CVs and FVs (Metagraphs 01.03; 01.08; 01.09; 03.02). Additional Tables 1 - 7 (Table 1; Table 2; Table 3; Table 4; Table 5; Table 6; Table 7) provide specific details on summary estimate extractions from the included studies.

Heterogeneity was assessed quantitatively with the I-squared statistic (Higgins 2003). The I-squared statistic indicates the percent variability due to between study (or inter-study) variability as opposed to within study (or intra-study) variability. An I-squared greater than 50% may be considered large. Only non-null heterogeneity statistics are presented here. Too few studies under a single comparison did not allow for any assessment of publication bias nor extensive sub-group or sensitivity analyses. However, post-hoc, we selected heart rate (the most frequently reported outcome) for between-study subgroup analyses using a chi-square method proposed by Deeks 2001. We selected the following subgroup analyses a priori: for penile block interventions, "wait time" from anaesthesia administration to start of the circumcision procedure were considered by the following three categories: no wait time reported, wait time </= 5 minutes, wait time >/= 5 minutes; for sucrose administration interventions, dose of sucrose administered was to be considered but could not be due to the lack of information provided in the reports. Surgical clamp type, use of pacifiers as a co-intervention, and choice of control group were selected for consideration post-hoc.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

210 unique references were identified through search of the electronic databases. The full text of forty-two potentially relevant articles were obtained and reviewed for possible inclusion in this review. Six studies were excluded (see Table - Characteristics of Excluded Studies). In two excluded studies, subjects were not randomised and the intervention was chosen by the attending physician (Malnory 2003; Olson 1998). Two of the excluded studies had no comparison group (Mintz 1989, Russell 1996). One study

was a cohort design and the outcome data for the control group was obtained from a previously conducted trial (Taddio 2000), and one (Taeusch 2002) was a head to head comparison of surgical clamps used for the circumcision procedure rather than a direct comparison of interventions for pain relief.

Thirty-five studies (thirty-six reports) were included in this systematic review. Details of each are given in the Table - Characteristics of Included Studies. Two reports outlined different outcome data from the same trial (Dixon 1984, Holve 1983). Two trials were reported as abstracts only (Zahorodny 1998, Zahorodny 1999) and we were unable to obtain additional information from the authors. One unpublished report of Master's thesis research was included (Zolnoski 1993).

Thirty-three of the thirty-five included studies enrolled healthy, full term neonates. One trial included infants born preterm (and less than 28 days age after reaching 40 weeks corrected gestational age) who were ready for discharge from the neonatal intensive care unit (NICU) at the time of circumcision (Butler O'Hara 1998), and one trial enrolled infants born preterm and weighing 1600 - 2500g at the time of circumcision (Holliday 1999).

Nineteen trials examined the effectiveness of penile blocks (Arnett 1990; Butler O'Hara 1998; Hardwick Smith 1998; Herschel 1998; Holliday 1999; Holve 1983; Howard 1999; Kass 2001; Kurtis 1999 A; Lander 1997; Masciello 1990; Maxwell 1987; Newton 1999; Spencer 1992; Stang 1988 A; Stang 1997; Williamson 1983; Williamson 1986; Williamson 1997). Twelve trials assessed topical anaesthetics (EMLA, lidocaine creams) (Benini 1993; Butler O'Hara 1998; Holliday 1999; Howard 1999; Joyce 2001; Lander 1997; Mohan 1998; Mudge 1989; Taddio 1997; Weatherstone 1993; Woodman 1999; Zahorodny 1998), and nine evaluated oral sucrose in a variety of concentrations and doses (Blass 1991 A; Herschel 1998; Kass 2001; Kaufman 2002; Mohan 1998; Stang 1997; Zahorodny 1998; Zahorodny 1999; Zolnoski 1993). In two trials, subjects received an oral analgesic (acetaminophen) (Howard 1994; Macke 2001). Three trials evaluated forms of environmental manipulation (e.g. music, intrauterine sounds) (Joyce 2001; Marchette 1989; Marchette 1991). For trial details see Table - Characteristics of Included Studies.

In the trials, the interventions were compared with placebo/sham treatments (e.g. saline penile block or inactive topical cream), no treatment, or with other active interventions. In several trials, all subjects received an active baseline intervention (e.g. EMLA cream or DPNB) prior to administration of the study intervention (Butler O'Hara 1998; Kaufman 2002; Stang 1997).

Risk of bias in included studies

All of the studies included in this systematic review were described as RCTs. However, fifteen of the study reports provided insufficient information or described inadequate procedures for assurance of blinding of randomisation (see Table - Characteristics of Included Studies). Nine were double-blind for delivery of all interventions (Howard 1994; Howard 1999; Joyce 2001; Macke 2001; Mudge 1989; Taddio 1997; Weatherstone 1993; Woodman 1999; Zolnoski 1993). Some studies compared interventions which could not be masked, for example, block techniques (Masciello 1990; Newton 1999; Spencer 1992). Partial blinding was achieved in several trials through inclusion of a sham or placebo group (Arnett 1990; Blass 1991 A; Holve 1983; Kass 2001; Kaufman 2002; Lander 1997; Stang 1988 A; Stang 1997). Blinding was occasionally achieved on a temporary basis during baseline assessments (Butler O'Hara 1998; Holliday 1999).

There was considerable methodologic diversity between the included studies. For example, there was variation between all of the trials as to what constituted the circumcision "procedure". In one trial (Williamson 1983), outcome data were reported for an undefined three minute "dissection period". In other trials, data were reported for each of multiple steps of a standardized procedure (Benini 1993; Hardwick Smith 1998; Herschel 1998; Lander 1997; Woodman 1999), or reported as a single summary statistic for the entire procedure (Taddio 1997). Other authors did not describe any details of the circumcision procedure followed for the trial (Blass 1991 A; Holliday 1999; Maxwell 1987; Stang 1988 A; Weatherstone 1993). In general, not enough information was provided by authors to be certain that outcome results were directly comparable across studies, as the events that constituted the procedure may not have been equivalent.

There were differences within the group of trials of DPNB (the most frequently studied intervention) in length of time fasting prior to surgery, anaesthetic dose, wait time after anaesthetic administration, and in type of surgical clamp used. In some cases, a single operator performed all circumcisions (Butler O'Hara 1998; Hardwick Smith 1998; Howard 1994), in others, the circumcisions were performed by a number of different operators (Howard 1999; Macke 2001; Stang 1997). Differences in operator technique or in the circumcision procedure could have effected outcome results. For most of the trials, subjects were required to fast prior to the surgery, however, the fasting period varied between trials from 30 - 90 minutes (Arnett 1990; Blass 1991 A; Herschel 1998; Kurtis 1999 A; Maxwell 1987) to 2 - 4 hours (Butler O'Hara 1998; Howard 1994; Kaufman 2002; Masciello 1990). Hunger could have influenced outcomes such as duration of infant crying or other behavioral responses. In a number of studies, subjects were offered pacifiers (Holliday 1999; Howard 1994; Howard 1999; Kurtis 1999 A; Mohan 1998; Spencer 1992; Stang 1997) although pacifiers were not the study intervention. In one trial, all subjects were offered sugar pacifiers (Butler O'Hara 1998). The potential effect of NNS on the outcomes measured in the trials providing pacifiers was not addressed in the reports.

Effects of interventions

ACTIVE VERSUS PLACEBO OR NO TREATMENT COM-

PARISONS

- Penile block interventions

Dorsal penile nerve block

Fourteen trials compared dorsal penile nerve block (DPNB) to no treatment or placebo (sham injection). A total of 592 infants were included. Three trials employed pain scores (Metagraph 01.01) as an outcome measure (Arnett 1990; Holliday 1999; Kass 2001). These trials were not combined for meta-analysis of effect on pain because the scores used are not similar in conceptual development or measurement technique. However, outcomes significantly favoured DPNB using all four scores reported: infant irritability score [MD -1.8, 95% CI -2.4 to -1.2], modified behavioral pain scale (MBPS) [MD -3.2 , 95% CI -4.5 to -1.9], Holliday's behaviour score [MD -8.8, 95% CI -11.1 to -6.5], and the crying component of the same behavioral score [MD -9.8, 95% CI -13 to -6.6]. Another behavioral measure, time crying, also significantly favoured the DPNB group [WMD -54 %, 95% CI -64 to -44; SMD -1.74, 95% CI -2.1 to -1.4; Metagraph 01.02; SMD displayed, WMD derived from SMD; data not shown].

Among the physiological measures, heart rate significantly favoured DPNB [WMD - 35 bpm, 95% CI -41 to -30; SMD -1.6, 95% CI -1.8 to -1.3; I^2 = 73%; Metagraph 01.03; ; SMD displayed, WMD derived from SMD; data not shown]. Oxygen saturation results also significantly favoured DPNB [WMD 3.2 %, 95% CI 2.7 to 3.7; I^2 = 97%; Metagraph 01.06]. Results were heterogeneous, and one author reported the loss of large amounts of data (Herschel 1998). A single trial (Williamson 1983) reported results for transcutaneous oxygen saturation that also significantly favoured DPNB [MD 9.3 torr, 95% CI 1.8 to 16.9; Metagraph 01.07].

Respiratory rate (Metagraph 01.08) and serum B-endorphin (Metagraph 01.12) were not significantly different. Systolic blood pressure was reported in two studies. The combined result was significant and favoured DPNB [WMD -9 mmHg, 95% CI -16 to -2; SMD -0.66, 95% CI -1.18 to -0.13; I^2 =92%; Metagraph 01.09; SMD displayed, WMD derived from SMD; data not shown] but the effect was not significant in the random effects model or when Maxwell 1987 was removed. The populations for these two trials were different. Maxwell 1987 recruited healthy newborns in the first few days of life, while Holliday 1999 enrolled low birthweight preterm infants. The preterm infants were cared for NICU and experience with other invasive procedures prior to circumcision may have affected their pain responses.

Serum cortisol (Metagraph 01.10) outcomes were reported in mg/dL, ug/dL and nmol/dL. Results were converted to nmol/dL using standard conversion factors and the outcomes expressed in these units were combined but were not significantly different. A single study (Kurtis 1999 A) reported salivary cortisol results and these were not significantly different.

In two studies (comparing DPNB to no treatment), authors did not report means and SDs. Williamson 1997 found significantly lower oxygen saturation and higher heart rates in the no treatment group during adhesion lysis and application of the surgical clamp ($p< 0.001$). There was a significant difference in duration of crying between the groups ($p <0.001$) with the DPNB group crying less. The second study found that the mean increase in heart rate and percent of time crying during circumcision was 50% less for infants in the DPNB group ($p< 0.01$) (Holve 1983). The DPNB group infants were more attentive to stimuli following circumcision, and were better able to quiet themselves when disturbed (Dixon 1984).

Ring block

Two trials compared ring block to no treatment and included 65 subjects (Hardwick Smith 1998; Lander 1997). Percent time crying was significantly reduced in the ring block group [WMD -26.3%, 95% CI -38 to -15, SMD -1.25, 95% CI -1.82 to -0.69; I^2 = 68%; Metagraph 02.01; SMD displayed, WMD derived from SMD; data not shown]. Only single studies reported other measures. In one (Lander 1997) heart rate significantly favoured the ring block group [MD -29 bpm, 95% CI -52 to - 7; Metagraph 02.02]. Oxygen saturation (Metagraph 02.03) and respiratory rate (Metagraph 02.04) were reported by Hardwick Smith 1998 and were not significantly different.

- Topical anaesthetics

EMLA

Six studies compared EMLA to placebo for a total 200 patients (Benini 1993; Joyce 2001; Lander 1997; Taddio 1997; Woodman 1999; Zahorodny 1998). Two studies measured infant behavioral responses using the same pain score, the Neonatal Facial Coding System (Grunau 1987). The trials used the same measure, but the researchers scored a different set of facial actions (see Additional Table 1), and calculated the summary pain score differently. In both summation techniques, a lower score indicated less facial action and less pain. When combined, the results significantly favoured EMLA [WMD -46.5, 95% CI -80.4 to -12.6; SMD -0.6, 95% CI -1.0 to -0.2; Metagraph 03.01; SMD displayed, WMD derived from SMD; data not shown].

Cry time was also significantly decreased with EMLA treatment [WMD - 15.2 %, 95% CI -21 to - 9.3; SMD -0.78, 95% CI -1.08 to - 0.48; Metagraph 03.02; SMD displayed, WMD derived from SMD; data not shown]. One study (Joyce 2001) did not favour the EMLA treatment, but for this study cry time was measured from the start of circumcision until crying stopped or until 30 minutes elapsed. The other studies measured cry time by phases of the procedure or gave a summary value for the procedure and thus only time spent crying during circumcision surgery could be calculated.

Heart rate was significantly decreased for infants treated with EMLA [WMD -15 bpm, 95% CI -19 to -10; Metagraph 03.03]. The effect on oxygen saturation was not significant [WMD 0.9%, 95% CI -0.2 to 2.0; Metagraph 03.04], and heterogeneity was large (I^2= 86%). Respiratory rate, systolic and diastolic blood pressure (Metagraphs 03.05, 03.06, 03.07) were not significantly different.

Lidocaine cream

Three trials compared topical lidocaine to placebo and included 115 patients (Mudge 1989; Weatherstone 1993; Woodman 1999). One study measured percentage of time spent in Brazelton behavioral state 6 (full cry) as a proxy for pain (Weatherstone 1993) and the results were insignificant [MD -8, 95% CI -23 to 7; Metagraph 04.01]. Cry time was significantly reduced [WMD -60 s, 95% CI -99 to -20; Metagraph 04.02] and favoured lidocaine. Heart rate was also significantly reduced [WMD -9 bpm, 95% CI -14 to - 4; I^2=12%; Metagraph 04.03]. A single study examined *B*-endorphin levels, and these were significantly reduced for the group treated with lidocaine [MD -49 pg/mL, 95% CI -89 to -9; Metagraph 04.06]. One study (Mudge 1989) did not report standard deviations for oxygen saturation (Metagraph 04.04) and respiratory rate (Metagraph 04.05) and these could not be calculated from the information available. However, the direction of results favoured treatment with lidocaine. Oxygen saturation results for another study (Woodman 1999) were not significantly different.

- Oral sucrose/dextrose

Eight trials compared sugar solutions to water and/or no treatment and included 360 subjects (Blass 1991 A; Herschel 1998; Kass 2001; Kaufman 2002; Stang 1997; Zahorodny 1998; Zahorodny 1999; Zolnoski 1993). A variety of concentrations (24 to 50%) and volumes (1.5 to 10 ml) of sucrose or dextrose were tested. Two studies measured pain scores (Kass 2001; Stang 1997). The results were not combined because the measures are not similar in conceptual development or measurement technique. For example, distress scores (Stang 1997) ranging from 0 to 3 indicated no crying to sustained cry respectively. The modified behavioral pain scale (MBPS) scores (Kass 2001) ranged from 0 to 10 and incorporated ratings for facial expression, crying and body movements. Results using the behavioral distress score significantly favoured sucrose [MD -0.7 units, 95% CI -1.1 to -0.3], while the MBPS results were not significantly different (Metagraph 05.01).

Cry time results were not significantly different overall [WMD -1.3 %, 95% CI -5.8 to -8.3; SMD 0.07, 95% CI -0.31 to 0.44; I^2 = 78%; Metagraph 05.02; SMD displayed, WMD derived from SMD; data not shown]. Individual results from five trials were inconsistent in direction. Zahorodny 1998 reported means only and SDs were substituted from another study using the same intervention and same outcome measure. One study (Kaufman 2002) reported a different measure of cry time. They averaged time spent crying in 10 second intervals, then took the cumulative average of that for each group. In this study, cry time was statistically significant and favoured the sucrose group (56 vs 86 s; P=0.0001). Zahorodny 1999 did not report means or standard deviations, but did report that both the sucrose and the water group cried much less than the no treatment group (p<0.001), and that subjects receiving the sucrose pacifier cried the least (p<.03). The sucrose and water groups in this trial also had smaller increases in heart rate compared to those receiving no intervention (p<.017). These authors did not comment on any differences between the sucrose group and the water group.

The effect on heart rate was not significant [WMD -4 bpm, 95% CI -9 to 2; Metagraph 05.03] overall in three trials. Heterogeneity was large (I^2=55%) with two trials favouring the water treatment and one trial favouring the sucrose treatment. In two trials (Herschel 1998; Kass 2001) oxygen saturation was significantly greater in the sucrose group [WMD 1.8%, 95% CI 0.5 to 3.1; Metagraph 05.04] although heterogeneity was again large (I^2= 88%) and the random effects estimate was not significant [WMD 1.3%, 95% CI -2.7 to 5.2]. Serum cortisol (Metagraph 05.05) was measured in a single study (Stang 1997) and results were not significant.

The inconsistent results in these trials may be related to the volume and concentration of sucrose provided and to the sucrose delivery method. For example, in two studies the treatment group received a dose of 10 ml of 50% sucrose as the treatment intervention (Herschel 1998; Zahorodny 1999), while in two other studies, the treatment group received 2 ml of 50% sucrose (Kass 2001; Zahorodny 1998). The treatment groups in the other trials received 1.5 ml (Blass 1991 A), 2.3 ml (Zolnoski 1993) or an unspecified volume of 24% sucrose (Kaufman 2002; Stang 1997) respectively. The delivery method for the sugar solution also varied between studies. Five administered the sugar/water solution via a nipple/pacifier (Blass 1991 A; Herschel 1998; Kaufman 2002; Stang 1997; Zahorodny 1999) thus providing the opportunity for non-nutritive sucking. In one trial (Herschel 1998), the sucrose group had a nipple (and the opportunity for non-nutritive sucking throughout the circumcision procedure), while the no treatment control group did not receive a pacifier at all. In two studies, the sugar solution was delivered using oral syringes (Kass 2001; Zolnoski 1993). In one trial, the method of delivery was not specified (Zahorodny 1998).

- Oral analgesics

Acetaminophen

Two trials compared acetaminophen to placebo with a total of 104 patients (Howard 1994; Macke 2001). The studies employed two different pain scales, and the results were not combined because the measures are not similar in conceptual development or measurement technique. Howard 1994 used a comfort score that measures 10 behaviours (sleep, facial expression, motor activity, tone, etc.) to arrive at a composite score of 0 to 20. The lower the score, the more uncomfortable the infant. Macke 2001 used the Nursing Child Assessment Feeding Scale (NCAFS) which measures mother-infant feeding interactions using 76 behavioral items based on the concepts of synchronism and adaptation. Lower scores on the NCAFS indicate less positive responses on the part of the infant. Results using the post-operative comfort score were not significant, but the total infant scores on the NCAFS were significant and favoured acetaminophen [MD 4.0, 95% CI 1.0 to 7.1; Metagraph 06.01]. All other outcomes (cry time, heart rate, respiratory rate Metagraphs 06.02, 06.03, 06.04) were not statistically significant.

ACTIVE VERSUS ACTIVE TREATMENT COMPARISONS

- DPNB versus EMLA

Three studies compared DPNB to EMLA for a total of 139 patients (Butler O'Hara 1998; Howard 1999; Lander 1997). Two studies measured different pain scores (Metagraph 07.01). The results were not combined because of conceptual and measurement differences between the scales. The Neonatal Infant Pain Scale (NIPS) consists of 6 behavioral components with a composite score of 0 to 6 based on facial expression, crying, breathing pattern, body movement and arousal. The behavioral distress score measures crying on a scale of 0 (no crying) to 3 (sustained crying). Lower scores indicate less pain for both measures. Results using both scales were statistically significant and favoured DPNB; NIPS [MD -2.5, 95% CI -3.3 to -1.7]; behavioral distress score [MD -0.3, 95% CI -0.5 to -0.03].

Cry time was measured in a single study and was not significantly different [MD -10%, 95% CI -30 to 10; Metagraph 07.02]. Heart rate was significantly reduced for the DPNB group [WMD -17 bpm, 95% CI -23 to -11; Metagraph 07.03] but heterogeneity was large (I^2=93%). The random effects estimate was not statistically significant. Butler O'Hara 1998 had a large mean difference [MD -40 bpm, 95% CI -51 to -29]; when this study was removed, heterogeneity was absent and the overall fixed effects WMD was no longer significant [WMD -7 bpm, 95% CI -14 to 0.5]. The large heterogeneity may be related to differences in the characteristics of the study subjects. Infants enrolled in the Butler O'Hara 1998 trial were born prematurely and hospitalised in the neonatal intensive care unit (NICU). Postnatal age was 3 - 105 days by the time of circumcision (but less than 28 days after reaching 40 weeks corrected gestational age). Exposure to invasive treatments during their NICU stay may have caused the infants to become sensitized and thus respond differently than infants in the other two trials who were healthy newborns in the first few days of life. Respiratory rate (Metagraph 07.05), measured by a single study, was not significantly different.

- DPNB versus sucrose

Two trials compared DPNB to sucrose for 127 patients. In one trial, pain was measured using the modified behavioral pain scale (MPBS) (Kass 2001) and the results significantly favoured DPNB [MD -3.2, 95% CI -4.7 to -1.8; Metagraph 08.01]. Cry time was measured in one trial and significantly favoured the DPNB group [MD -166 s, 95% CI -211 to -121; Metagraph 08.02]. Heart rate also significantly favoured DPNB [WMD -27 bpm, 95% CI -33 to -20; Metagraph 08.03]. Heterogeneity was large (I^2=94%) however, both trials measuring heart rate favoured the DPNB group. The effect on oxygen saturation (Metagraph 08.04) was not significant, heterogeneity was large (I^2=96%), and the individual trial estimates were not consistent in direction of effect. The authors of one study (Herschel 1998) reported that a significant amount of oxygen saturation data (measured using pulse oximetry) was lost due to excessive motion. Also of note, the dose and delivery method of the sugar solution differed between the two studies. In one study (Kass 2001) subjects received 2 ml of 50% dextrose by oral syringe. In the other (Herschel 1998), subjects received up to 10 ml of 50% sucrose by nipple and had a pacifier throughout the procedure.

- DPNB versus ring block

One trial compared DPNB to ring block (Lander 1997) and included 27 patients. Results for cry time and heart rate were not significantly different between the groups (Metagraphs 09.01, 09.02).

- DPNB versus local block

A single trial compared DPNB to local block using 1% lidocaine (Masciello 1990) and included 20 patients. Local block was performed by injecting lidocaine subcutaneously into the foreskin at the 10 and 2 o'clock positions at the level of the corona. Results for serum cortisol significantly favoured the local block administration group [MD 306 nmol/dL, 95% CI 141 to 471; Metagraph 10.01].

- Ring block versus EMLA

Ring block was compared to EMLA in a single trial that included 28 patients (Lander 1997). Results for heart rate [MD -3 bpm, 95% CI -20 to 14; Metagraph 11.01] and cry time [MD -16 %, CI -36 to 3; Metagraph 11.02] were not significantly different between the groups.

- Buffered lidocaine DPNB versus lidocaine DPNB

Two trials compared buffered lidocaine DPNB to lidocaine DPNB and included 234 patients (Newton 1999; Stang 1997). In clinical trials with adult subjects, buffering lidocaine with sodium bicarbonate had shown potential to decrease the burning sensation of injection, and enhance the speed of anaesthesia. The results for all outcomes measured (behavioral distress score, cry time, heart rate, oxygen saturation and serum cortisol; Metagraphs 12.01, 12.02, 12.03, 12.04, 12.05) were not significantly different between the groups.

- EMLA versus topical lidocaine

One trial compared EMLA to 30% topical lidocaine, and included 40 patients (Woodman 1999). Cry time and oxygen saturation (Metagraphs 13.01, 13.03) were not significantly different. Heart rate was significant and favoured EMLA [MD -12 bpm, 95% CI -19 to -4; Metagraph 13.02].

- EMLA versus sucrose

Two studies (Mohan 1998; Zahorodny 1998) compared EMLA to sucrose (67 patients). Cry time, heart rate, oxygen saturation (Metagraphs 14.01, 14.02, 14.03) were not significant. Systolic and diastolic blood pressures mean differences could not be calculated because no standard deviations were provided (Metagraphs 14.04, 14.05), but both means were larger in the sucrose group, indicating higher mean blood pressure.

- EMLA versus music

A small pilot study (Joyce 2001) compared EMLA to music, and included 12 patients. None of the outcome results (cry time, heart rate, oxygen saturation, respiratory rate; Metagraphs 15.01, 15.02, 15.03, 15.04) were significantly different.

ENVIRONMENTAL COMPARISONS

- Music versus no treatment

Three studies compared the provision of music or other soothing sounds during the circumcision procedure (Joyce 2001; Marchette 1989; Marchette 1991). In one trial that included 12 patients (Joyce 2001) the effect of the intervention on the outcomes of cry time, heart rate, oxygen saturation and respiratory rate (Metagraphs 16.01, 16.02, 16.03, 16.04) was not significant. In a second study, music was compared with intrauterine sounds and no treatment (Marchette 1989). Although 103 infants were randomised, 45 records were deleted from analysis due to missing data or prolonged circumcisions related to physician training. The researchers did not report standard deviations, but they did report that during all steps of the circumcision procedure in which infants were touched with surgical instruments the interventions did not offset pain as indicated by heart rate, systolic blood pressure, facial expression, and behavioral state outcomes. In the third study (Marchette 1991) 121 infants were randomised to six groups and received either classical music, intrauterine sounds, a pacifier, music and a pacifier, intrauterine sounds and a pacifier, or no treatment. The researchers did not report means and standard deviations but they did state that the interventions tested did not greatly reduce circumcision pain as assessed by heart rate, blood pressure, transcutaneous oxygen saturation, and time crying.

COMPLICATIONS/ADVERSE EFFECTS

Ten studies reported adverse effects (see Additional Tables - Table 8). Adverse effects including gagging, choking, and emesis were reported in untreated groups, while DPNB groups exhibited minor bleeding, swelling and hematoma at the block injection site post-circumcision. EMLA use was associated with erythema and minor skin pallor. In one study (Holliday 1999), two subjects who received EMLA had redness and blistering of the foreskin, leading to closure of the EMLA arm of the study. Methaemoglobin levels were measured in two trials of EMLA and found to be within normal limits (Lander 1997; Taddio 1997). All adverse effects of pain interventions were reported to be transient in nature and were not considered serious. Several authors reported on the questionable clinical utility of topical anaesthetic interventions (Herschel 1998; Howard 1999; Lander 1997) given the dexterity required to apply the creams properly and the lengthy application time.

SUBGROUP AND SENSITIVITY ANALYSES

We examined two subgroups: length of wait time after penile block interventions (a priori) and choice of clamp for all procedures (post-hoc) on the most frequently reported outcome heart rate. One study compared different lengths of wait time and two anaesthetics (Spencer 1992) but did not report means and SDs. The authors did report that DPNB groups that received either anaesthetic exhibited decreased pain responses compared to the control group. We made indirect (or between study) comparisons. Six trials comparing DPNB to no treatment prescribed and reported wait times. The trials with the longer wait time (>5 minutes) did not perform significantly better than short wait time trials (</= 5 minutes) [Metagraph 01.04]. In fact, the probability under the null hypothesis was close to significant (P=0.09 vs P=0.65) when Maxwell 1987 was removed and favoured shorter wait times. A similar and statistically significant result was calculated when comparing wait times in DPNB vs EMLA (P=0.04; Metagraph 07.04). Using an indirect comparison, the Mogen clamp trial performed significantly better on reducing heart rate compared to the Gomco clamp trials when Maxwell 1987 was again removed (P=0.05 vs P=0.07) under the DPNB versus no treatment comparison (Metagraph 01.05). Sucrose dose (a priori) was not analysed because there were too few studies under the same comparison and not enough information was provided.

Post-hoc, we considered two other potential treatment effect size modifiers: control intervention and choice of pacifiers. For ethical considerations, use of saline DPNB in pain research was generally abandoned since the early 1990's. Among the included studies for this review, three used both saline DPNB treatment (sham) and no treatment control arms (Arnett 1990, Holve 1983, Stang 1988 A). In one study saline DPNB was used to blind comparison of lidocaine DPNB with another active intervention (Howard 1999). The researchers wanted to control for the effects of the injection and fluid volume compression on penile sensation. None of the studies found statistical differences between these control arms. In our review, the two control arms were displayed separately in the metagraphs when the data were reported separately in the referenced study (Stang 1988 A). Visually, we also see no difference. Other concerns for blinding involve placebo creams. One study (Mohan 1998) did not use a placebo cream and one study (Benini 1993) reported using petroleum jelly as a placebo for EMLA cream.

In nine trials pacifiers were made available to all patients (Butler O'Hara 1998; Holliday 1999; Howard 1994; Howard 1999; Kurtis 1999 A; Mohan 1998; Spencer 1992; Stang 1988 A; Stang 1997). In one (Butler O'Hara 1998) all infants were provided with sugar pacifiers although sucrose was not the intervention under study and its use may have affected results obtained on outcome measures. In another (Herschel 1998) only one out of the three study groups received a pacifier because it was used to deliver a sucrose intervention. At least two studies (Kass 2001; Zolnoski 1993) strictly prohibited the use of pacifiers and used oral syringes to deliver the sucrose intervention. The remaining studies did not report pacifier use. There were too few studies to compare within outcomes, and we could not identify obvious deviations with use or non-use of pacifiers. Of mention, Blass 1991 A and Zahorodny 1999 both found that in a water via pacifier group, cry time was significantly reduced compared with the no treatment control group

(P<0.001; P<0.001).

DISCUSSION

This systematic review incorporates data from 35 trials enrolling 1997 neonates to examine a variety of interventions for circumcision pain relief. Although the results are generally applicable to current practice, the review identified a number of important limitations of the primary studies included in the review and thus the results should be interpreted with some caution. Sample size in the majority of the trials was small (total sample size was < or = to 80 in 32 out of 35 trials), and there were some differences in the characteristics of the study subjects. Butler O'Hara 1998 enrolled neonates from an NICU that were between 3 and 105 days postnatal age at the time of circumcision (although still less than 28 days after reaching 40 weeks corrected gestational age). Holliday 1999 enrolled low birthweight neonates aged 25 - 27 days at circumcision. Each of these groups of subjects could have experienced numerous painful or invasive treatments during their stay in NICU prior to circumcision. Accordingly, their responses during circumcision, regardless of the intervention, could have been different from those of the healthy newborns that were recruited for the remainder of the trials.

All of the studies included in this review were described as randomised, but 15 of the trial reports did not include sufficient information or describe adequate procedures for assurance of blinding of randomisation. Nine of the trials were double-blind for all interventions, but some interventions such as block technique could not be blinded. In six trials of DPNB, a standardized approach to the circumcision procedure was not described in the reports, making it impossible to tell whether every infant underwent exactly the same surgical process. The impact of this could be intensified within individual trials where more than one operator performed the circumcisions (e.g. Howard 1999, Macke 2001). Other differences that may have affected outcome results between trials of the same comparison include the variability in wait time after block administration, length of fasting prior to circumcision, provision of pacifiers or other non-study interventions, and use of different surgical clamps. Finally, differences between trials in the structure of pain interventions were evident, especially in trials of oral sucrose where the dose and method of delivery varied substantially.

The studies included in this review reported on measurement of a variety of pain outcomes (physiological, behavioral, biochemical). Techniques and methods for measurement of outcomes were more dissimilar than similar across the trials, even within a single outcome variable (e.g. heart rate), and this presented significant challenges to combining outcome results. In particular, the dissimilarity in outcome measures severely limited the feasibility of combining pain scores across the included studies. None of the reports included in this review offered a definition of pain, and in general, the reports did not differentiate between the painful versus the distressing/stressful aspects of the circumcision procedure (e.g. removal of foreskin versus application of restraints). Reasons for selection of pain scores as outcome measures were not articulated in most cases, and among the included studies, a variety were used that differed in conceptual development and in measurement technique. Some pain scores were author-devised measures with no reported psychometric testing (Arnett 1990; Holliday 1999; Weatherstone 1993), while others measured behavioral indicators that were not conceptually linked to the neonate's experience of pain (Dixon 1984; Macke 2001; Newton 1999; Stang 1988 A). Others were subjective in their measurement technique (Howard 1999; Stang 1997). In six trials, researchers employed validated pain scales developed specifically to measure neonatal pain (Benini 1993; Butler O'Hara 1998; Howard 1994; Joyce 2001; Kass 2001; Taddio 1997).

Sixteen trials included in this review either did not report outcome data, or did not report data in a format that could be analysed in this review. One of the strengths of this review was that we were able to obtain additional information for three trials. Where means and standard deviations were not available, data were imputed or derived from graphs contained in the reports, and missing standard deviations were either calculated from other summary statistics or substituted with singular or mean standard deviations from similar trials allowing us to maximize the data included under each comparison.

DPNB was identified as the most effective intervention and demonstrated decreases in time crying and heart rate that were statistically and clinically significant (time crying 54% less, heart rate 30 beats per minute less) when compared with placebo or no treatment. EMLA also reduced pain responses when compared with placebo but the differences in time crying (15% less) and heart rate (15 beats per minutes less) were not as large as those observed with DPNB. Topical lidocaine demonstrated statistically significant decreases in time crying (60 seconds less), heart rate (9 beats per minute less) and serum B-endorphin levels (49 pg/ml less) compared to placebo. The issue of the statistical versus clinical significance of the outcome results was not discussed in any of the study reports, and no author identified a threshold for clinically significant (as opposed to statistically significant) intervention effects. It should be emphasized that none of the interventions examined in these trials completely eliminated pain responses to circumcision.

Ease of administration of the pain interventions will influence the applicability of the results of this review to current clinical practice. The relative ease of establishing the different penile blocks was not systematically evaluated, but it was suggested that the ring block technique is easier and safer because it eliminates the risk of injection of lidocaine into the dorsal vessels (Hardwick Smith 1998). A single study reported on use of local penile block (Masciello 1990) which appears to be similar in technique to ring block. Few

adverse effects were reported with use of any of the penile blocks. EMLA and lidocaine topical anaesthetics are effective for circumcision pain when compared with placebo or no treatment, but their use may be precluded because of difficulties in application and the time required for maximum anaesthetic effect. Adverse effects such as transient skin reactions were reported but not considered serious, and methaemoglobin levels, when measured, were within normal range.

AUTHORS' CONCLUSIONS

Implications for practice

Circumcision is a painful procedure and routine or elective newborn circumcision is not recommended by either the American Academy of Pediatrics or the Canadian Paediatric Society. However, if circumcision is performed, the results of this review show that DPNB, RB and the topical anaesthetics EMLA and lidocaine cream can be recommended over no treatment for attenuation of circumcision pain. DPNB demonstrated the most consistent results, has been the most comprehensively studied, and was the most effective in terms of clinically significant reductions in pain responses. RB is also effective to reduce circumcision pain compared with placebo. The RB technique may be easier and safer to use because it eliminates the risk of injection of lidocaine into the dorsal vessels.

EMLA and lidocaine topical anaesthetics are effective for circumcision pain when compared with placebo or no treatment, but their use may be precluded because of difficulties in application and the time required for maximum anaesthetic effect. Adverse effects with EMLA use such as transient skin reactions were reported but not considered serious, and methaemoglobin levels, when measured, were within normal range. Topical anaesthetics are a less effective alternative to no treatment when expertise with penile blocks is not readily available.

Results for oral sucrose, oral analgesics and environmental modification interventions were either inconsistent or did not produce significantly different outcome results. These therapies cannot be recommended as treatments for circumcision pain.

None of the studied interventions completely eliminated the pain response to circumcision.

Circumcisions performed using the Mogen clamp take less time than is required using Gomco clamps. Shorter procedure time may reduce the total amount of pain experienced during circumcision, and may be important in terms of practitioner time to do the surgery.

Implications for research

Future studies should compare two or more active interventions for pain relief - a placebo or no-treatment control group is no longer acceptable. The impact of different "wait times" on the effectiveness of penile blocks and the relative acceptability and ease of administration of DPNB versus RB for practitioners should be systematically investigated. Use of the Mogen clamp in combination DPNB and RB should be investigated further to identify an optimal target time for circumcision surgery and to maximize anaesthetic effect. Although sucrose cannot be recommended as an intervention for circumcision pain at this time, research to determine the optimal dose and delivery method and the effect of combining oral sucrose with other interventions and comfort measures (e.g. nonnutritive sucking) should be pursued.

Lidocaine block and topical anaesthetic interventions could be useful in other situations where neonates undergo acute procedural pain. The pain associated with chest tube insertion, lumbar puncture, insertion of percutaneous central lines and other procedures commonly performed on high risk neonates may be significantly reduced with use of an appropriately adapted lidocaine block technique or topical anaesthetics. Further research should be pursued to identify situations where this potential can be examined.

ACKNOWLEDGEMENTS

We are grateful to Dr. J. R Holman, Dr. C Johnston, and Dr. J. F. Keck for their willingness to provide us with additional data from their studies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arnett 1990

Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	52 male NB; FT; BW > 2000 g; 5 min Apgar scores >/= 6
Interventions	0.4 ml lidocaine DPNB (n=23) 0.4 ml saline DPNB (n=22) no treatment control (n=7) WT not reported; mean length for entire procedure was 4.4 minutes
Outcomes	HR, infant irritability, O2sat
Notes	- no treatment control group added after study start; results for saline DPNB group and no treatment group were combined for analysis (n=29) - data missing for 3 subjects (1 in each group) and cases deleted from analysis - procedure not standardized - lower dose lidocaine used (0.4 ml total) - subjects fasted 90 minutes prior to circumcision - Gomco clamp - adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Benini 1993

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - yes
Participants	28 male NB; FT; BW > 2500g; 5 min Apgar > 7; < 7 d age

Benini 1993 (*Continued*)

Interventions	0.5 ml (0.5g) LP cream (n=14) 0.5 ml (0.5 g) petroleum jelly (n=14) applied and covered with occlusive dressing 45 - 60 min prior
Outcomes	HR, O2sat, % time crying, facial action
Notes	- 1 withdrawal from placebo group because infant not FT - procedure standardized to 9 phases - Gomco clamp - no adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Blass 1991 A

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - partial Complete follow-up - can't tell Blinding of outcome measurement - yes
Participants	30 male NB, FT; 28 - 54 h age; Apgars > 8
Interventions	1.5 ml 24% sucrose by nipple 1.5 ml water by nipple no treatment control *comparison is sucrose versus water (placebo) number subjects per group not specified 3 min WT after intervention
Outcomes	% time crying
Notes	- assumed distribution was equal (10/group) for data analysis - procedure not standardized - infants fasted for at least 1 hr prior - Gomco clamp

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Blass 1991 B

Methods	see Blass A
Participants	see Blass A
Interventions	* comparison is sucrose versus no treatment
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Butler O'Hara 1998

Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - yes
Participants	50 male infants in NICU; >/= 34.5 weeks (post-menstrual) at time of circumcision and stable for discharge participants were 3 -105 days age at time of circumcision
Interventions	0.5 ml (0.5g) LP cream (n=25) 0.7 - 1.0 ml lidocaine DPNB + placebo cream (n=25) creams applied 60 min prior and covered with occlusive dressing 3 min WT after DPNB
Outcomes	HR; RR; NIPS score (primary outcome)
Notes	- non-randomized, no treatment group (n=20) also had data collected - outcome data for 6 subjects (4 LP cream, 2 DPNB) lost due to technical difficulties - infants fasted for 2 to 3 hours before circumcision - all subjects had sugar pacifiers during procedure - procedure standardized - Plastibell clamp - adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Dixon 1984

Methods	RCT Blinding of randomization - yes Blinding of intervention - can't tell Complete follow-up - yes Blinding of outcome measurement - partial
Participants	31 male NB, FT, AGA, < 7 days age, > 2500 gm, 5 min Apgar > 7
Interventions	0.8 ml lidocaine DPNB (n=15) 0.8 ml saline DPNB (n=8) no treatment control (n=8) 4 - 5 min WT
Outcomes	Brazelton Neonatal Assessment Scale
Notes	- Holve 1983 is primary study report - circumcision procedure not standardized - all circumcisions performed by single physician - Gomco clamp - adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hardwick Smith 1998

Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - can't tell Blinding of outcome measurement - no
Participants	40 male NB; FT; Apgar >/= 7; 6 hr - 5 days age; fasting 30 -120 min prior; normal exam
Interventions	1.0 ml 5% lidocaine RB (n=20) no treatment control (n=20) 3 min WT
Outcomes	HR; RR; O2sat; behavioral state; cry time
Notes	- O2sat not recorded in up to 50% of infants - single operator performed all circumcisions - Gomco clamp - no adverse effects reported

Hardwick Smith 1998 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Herschel 1998

Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - yes
Participants	120 male NB; FT; > 2500g; Apgar >/= 8 at 5 min; >/= 12 hr age
Interventions	0.8 ml 1% lidocaine DPNB (n=40) 10 ml 50% oral sucrose via nipple (n=40) no treatment control (n=40) 3 min WT for DPNB; 2 min WT for sucrose group
Outcomes	HR; O2sat (%)
Notes	- 1 withdrawal from sucrose group, circumcision contraindicated - O2 sat data missing - 31% intervals control, 10% intervals DPNB, 8% sucrose - infants fasted 30 min prior to circumcision - sucrose group had nipple throughout procedure, other groups did not have pacifier - Gomco clamp

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Holliday 1999

Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	50 male preterm/low birthweight NICU patients, subjects weighed 1600 to 2500g at time of circumcision 25-27 days age, 36 week GA at circumcision

Holliday 1999 (*Continued*)

Interventions	0.8 ml 1% lidocaine DPNB + placebo cream (n= 19) LP cream (n=12) (group enrollment stopped, excluded from data analyses) placebo cream (n=19) DPNB 5 min WT cream applied 1 hr prior and covered with occlusive dressing
Outcomes	HR, RR, O2sat, systolic BP, behavioral score, serum B-endorphin
Notes	- LP cream group discontinued due to redness and blistering of foreskin in 2 infants - procedure not standardized - all circumcisions performed by single operator - pacifiers provided - Gomco clamp - no adverse effects reported for DPNB group

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Holve 1983

Methods	RCT Blinding of randomization - yes Blinding of intervention - partial Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	31 male NB; FT, < 7 days age, > 2500 gm, 5 min Apgar > 7
Interventions	0.8 ml 1% lidocaine DPNB (n=15) 0.8 ml saline DPNB (n=8) no treatment control (n=8) 4-5 min WT
Outcomes	HR; % time crying per interval; clinical observation of anesthesia effectiveness (good, fair, poor)
Notes	- procedure standardized - Gomco clamp - adverse effects reported

Risk of bias

Item	Authors' judgement	Description

Holve 1983 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Howard 1994

Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - yes
Participants	44 male NB, healthy, AGA, FT, Apgars > 7, >/= 24 h age
Interventions	acetaminophen 15 mg/kg/dose (n= 23) placebo (n= 21) given 2 hr prior and q 6H X 24 hr following
Outcomes	HR; RR; cry time; post-operative comfort score; feeding behavior pre/post
Notes	- infants fasted 2 - 3 h prior to circumcision - all had pacifiers - procedure standardized - single operator performed all circumcisions - Gomco clamp - no adverse effects reported

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Howard 1999

Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - unclear Blinding of outcome measurement - yes
Participants	62 male NB; healthy; AGA; FT
Interventions	1g LP cream + 0.8 ml saline DPNB (n=31) 0.8 ml 1% lidocaine DPNB + 1g placebo cream (n=31) 4 min WT for DPNB creams applied 1 hr prior and covered with occlusive dressing

Howard 1999 (*Continued*)

Outcomes	HR; RR; behavioral distress score
Notes	- 2 infants withdrawn (1 tachypnea, 1 parents withdrew consent) - procedure standardized - 3 operators performed the circumcisions - all subjects had pacifiers - Gomco clamp - no adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Joyce 2001

Methods	RCT; Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - yes
Participants	23 male NB, FT; 5 min Apgar > 7; BW > 2500 g; age < 7 d
Interventions	LP cream (1 - 2 g) + music (n=6) LP cream + no music (n=5) placebo cream + music (n=7) placebo cream + no music (n=5) cream applied 1 hr prior and covered with occlusive dressing music started just prior to procedure and continued to 10 min post procedure
Outcomes	HR, O2sat, cry duration; RR, Riley Infant pain scale, salivary cortisol, infant state
Notes	- pilot study - no adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Kass 2001

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - no Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	71 healthy male NB
Interventions	lidocaine DPNB (n=24) 2ml D50W orally (n=23) 2 ml H2O orally (n=24) WT 2 to 6 min
Outcomes	time cry (primary outcome); HR; O2sat ; modified behavioral pain scale
Notes	- additional data obtained from authors - no pacifiers used - Gomco clamp

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kaufman 2002

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - partial Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	57 NB; healthy; male; FT; Apgar > 7 at 5 min
Interventions	Mogen + water pacifier (15) Mogen + 24% sucrose pacifier (n=14) Gomco+ water pacifier (n=14) Gomco + 24% sucrose pacifier (n=14)
Outcomes	time crying; grimacing, procedure length
Notes	- all subjects had EMLA cream applied between 1 and 3 hr before procedure - single operator performed all circumcisions -procedure standardized - infants fasted from 15 min to 4 hr before procedure - no adverse effects reported

Kaufman 2002 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Kurtis 1999 A

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - no Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	48 male NB; FT; 5 min Apgar >/= 7
Interventions	Mogen clamp and 0.8 ml 1% lidocaine DPNB (n=16) Mogen clamp and no DPNB (n=16) Gomco clamp and 0.8 mL 1% lidocaine DPNB (n=8) Gomco clamp and no DPNB (n=8) 5 minute WT
Outcomes	time crying, HR, O2sat, salivary cortisol, RR
Notes	- all subjects had pacifiers - infants fasted 1 - 2 hr before procedure - Mogen = 8 procedural steps; Gomco = 13 procedural steps

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Kurtis 1999 B

Methods	see Kurtis 1999 A
Participants	see Kurtis 1999 A
Interventions	comparison is Mogen versus Gomco for patients receiving no DPNB
Outcomes	
Notes	

Risk of bias

Kurtis 1999 B (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Lander 1997

Methods	RCT Blinding of randomization - yes Blinding of intervention - partial Complete follow-up - no Blinding of outcome measurement - yes
Participants	54 male NB; FT; AGA; 1-3 d age
Interventions	2g LP cream (n=15) placebo cream (n=12) 0.8 ml 1% lidocaine DPNB (n=14) 0.8 ml 1% lidocaine RB (n=13) - penile blocks 8 min WT; creams applied 90 min prior and covered with occlusive dressing
Outcomes	HR; time cry; O2 sat, RR, palmar sweat, metHgb level
Notes	- 2 withdrawals, 1 in placebo group, 1 in RB group (1 parents unable to remain in hospital, 1 required phototherapy) - procedure standardized - Gomco clamp - adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Macke 2001

Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - yes
Participants	60 male NB; FT; Apgar >/= 8
Interventions	acetaminophen 10 mg/kg (n=29) placebo (n=31) given 1 hr prior to circumcision

Macke 2001 (*Continued*)

Outcomes	HR , Nursing Child Assessment Feeding Scale, cry time, infant state
Notes	- 12 operators performed circumcisions in analgesia group, 21 performed circumcisions in placebo group - Gomco clamp

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Marchette 1989

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - can't tell Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	103 male NB; Apgar >/= 8
Interventions	classical music (n=25) intrauterine sounds (n=15) control (no nurse present) (n=18)
Outcomes	HR; heart rhythm; BP; TcpO2; MDFMCS; BNAS
Notes	- 103 subjects randomized, 45 cases deleted due to missing data or prolonged circumcisions - procedure standardized - Gomco clamp

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Marchette 1991

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - can't tell Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	121 male NB; Apgar =/> 6; normal delivery; 2 - 9 days age
Interventions	taped music (n=20) intrauterine sounds (n=20) pacifier (n=20) music and pacifier (n=20) intrauterine sounds and pacifier (n=20) control - no treatment (n=21)
Outcomes	HR, rhythm, BP; tcPO2; rate pressure product, BNAS; crying
Notes	- cases excluded if circumcision longer than 15 min or if bleeding - Gomco clamp

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Masciello 1990

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	30 male NB, healthy, FT
Interventions	0.8 ml 1% lidocaine DPNB (n=10) 0.8 ml 1% lidocaine local block (n=10) no treatment control (n=10) 5 min WT
Outcomes	plasma cortisol, HR, O2sat, cry
Notes	- cortisol levels obtained for first 3 cases lost (1 in each group) - all fasted for at least 3 hours prior - procedure standardized - single operator performed all circumcisions - Gomco clamp

Masciello 1990 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Maxwell 1987

Methods	RCT; Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	30 male NB; FT; healthy
Interventions	0.8 ml 1% lidocaine DPNB (n=20) no treatment control (n=10) 5 min WT
Outcomes	HR, O2sat, BP, plasma lidocaine
Notes	- subjects fasted for 2 hr prior - procedure not standardized - Gomco clamp - no adverse effects observed

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mohan 1998

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - can't tell Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	60 male NB; FT; BW>/= 2500 g; 5 min Apgar >/= 7; < 5 days age
Interventions	5 g LP cream + 2 ml 24% sucrose via pacifier (n=19) 5 g LP cream + water via pacifier (n=20) 2 ml 24% sucrose via pacifier (n=21) water via pacifier (n=19) - non-randomized control

Mohan 1998 (*Continued*)

	- cream applied 45-60 min prior, covered with occlusive dressing
Outcomes	HR; O2sat; BP; cry duration
Notes	- control group not randomized - all received pacifiers - procedure standardized - Gomco clamp - no adverse effects reported

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Mudge 1989

Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	44 male NB; 5 min Apgar > 7; BW 2.5 - 4.5 kg; FT; age 12 - 72 h
Interventions	4% lidocaine cream (n=20) placebo cream (n=24) cream applied 2 hr prior covered with occlusive dressing
Outcomes	HR, RR, O2sat, cry time, behavior
Notes	- Gomco clamp - procedure standardized

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Newton 1999

Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - no Blinding of outcome measurement - can't tell
Participants	194 male NB; healthy
Interventions	0.8 ml 1% lidocaine DPNB (n=92) 0.8 ml 1% buffered lidocaine (n=102)
Outcomes	HR (primary outcome variable); O2sat; number crying/phase; modified BNAS
Notes	- complete data on crying for 165 subjects; complete data on BNAS for 194 - complete data on HR, O2 sat for 143 subjects due to technical difficulties - procedure standardized - Mogen clamp - adverse effects reported

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Spencer 1992

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - can't tell Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	75 male NB; BW 2500 - 4500 g; >12 hr age; 5 min Apgar > 6; normal exam
Interventions	lidocaine DPNB - 5 min WT (n=15) lidocaine DPNB with 2 min WT (n=15) 1% chloroprocaine DPNB with 3 min WT (n=15) 1% chloroprocaine DPNB with 5 min WT (n=15) no treatment control (n=15)
Outcomes	cry duration, O2Sat, HR, BNAS
Notes	- all received pacifiers - fed 60 to 90 min prior to circumcision - procedure standardized - Gomco clamp

Spencer 1992 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Stang 1988 A

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - partial Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	60 male NB; > 24 hr age; BW > 3000 g; 5 min Apgar > 7; uncomplicated delivery
Interventions	0.8 ml 1% lidocaine DPNB (n=20) saline DPNB (n=20) no treatment control (n=20) 5 min WT *comparison is DPNB versus no treatment
Outcomes	% time cry, modal behavior state, plasma cortisol
Notes	- all handling avoided for 2 hr prior - 1/2 had blood sample for cortisol at 30 min, 1/2 at 90 min - all received pacifiers and continuously soothed - procedure standardized to 3 periods - Gomco and Plastibell used at operator's discretion - adverse effects reported

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Stang 1988 B

Methods	see Stang A
Participants	see Stang A
Interventions	*comparison is DPNB versus sham (saline) treatment
Outcomes	see Stang A

Stang 1988 B (*Continued*)

Notes	see Stang A	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Stang 1997

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - partial Complete follow-up - can't tell Blinding of outcome measurement - can't tell	
Participants	83 male NB, > 20 hr age; BW 3000 - 4000 gm; 5 min Apgar >/= 8; FT	
Interventions	group 1 = 0.8 ml 1% lidocaine DPNB, padded restraint , water via pacifier (n=20) group 2 = 0.8 ml 1% lidocaine DPNB, regular restraint, 24% sucrose via pacifier (n=20) group 3 = 0.8 ml 1% buffered lidocaine DPNB, regular restraint, water via pacifier (n=20) group 4 = 0.8 ml 1% lidocaine DPNB, regular restraint, water via pacifier (n=20) (control) 5 min WT	
Outcomes	behavioral distress scale, plasma cortisol 30 min post-circ	
Notes	- 5th arm of study (24% sucrose only) abandoned due to high behavioral distress scores - no forced preoperative fasting period - all handling avoided for 1 hr prior - procedure standardized - all given pacifiers - Gomco and Plastibell methods used	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Taddio 1997

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - yes Complete follow-up - no Blinding of outcome measurement - yes
Participants	68 male NB, BW >/= 2500 g; FT; no jaundice or metHgb
Interventions	1 g (1ml) LP cream (n=38) 1 g (1ml) placebo cream (n=30) creams covered with occlusive dressing for 60 - 80 min prior
Outcomes	HR, time cry, NFCS, systolic/diastolic BP, metHgb
Notes	- 68 subjects randomized, 8 in the LP group included in safety analysis only, 59 subjects in the efficacy analysis - 1 withdrawal - procedure standardized - Gomco clamp - adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Weatherstone 1993

Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - yes
Participants	30 male NB; BW >/= 2500 g; FT; Apgar >/= 7; 6-72 hr age
Interventions	0.5 g 30% lidocaine cream (n=15) placebo cream (n=15) applied 20 min prior to circumcision and covered with occlusive dressing
Outcomes	HR, RR, O2 sat, BP, Newborn Pain Behavior Scale, serum B-endophin (15 min post), serum lidocaine
Notes	- procedure not standardized - Gomco and Plastibell clamps - no adverse effects reported

Risk of bias

Weatherstone 1993 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Williamson 1983

Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	30 male NB; BW = 2500 - 4000 g; 24 - 72 hr age; FT; Apgar score > 7; systolic BP > 40 mm Hg
Interventions	0.6 to 0.8 1% ml lidocaine DPNB (n=20) no treatment control (n=10) 4 min WT
Outcomes	TcpO2, time cry; HR, RR
Notes	- fasted at least 2 hr prior - PI performed all circumcisions - Gomco clamp

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Williamson 1986

Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	24 male NB; Apgar > 7; BW 2500 - 4500 g; FT; 24 - 72 hr age; normal physical exam
Interventions	lidocaine DPNB (n= 11) no treatment control (n=13) 5 min WT
Outcomes	plasma cortisol pre and 30 min post circumcision

Williamson 1986 (*Continued*)

Notes	- 6 additional infants circumcised after study completed to serve as controls for blood sampling/injections - all circumcisions done by PI - Gomco clamp

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Williamson 1997

Methods	RCT Blinding of randomization - yes Blinding of intervention - no Complete follow-up - yes Blinding of outcome measurement - yes
Participants	30 male NB; FT; >/= 24 hr age; BW 2500- 4500g; Apgar > 7
Interventions	lidocaine DPNB (n=20) no treatment control (n=10)
Outcomes	TcPO2, RR, HR, cardiac rhythm, cry time and type
Notes	- procedure standardized - fasting at least 2 hr prior - Gomco clamp - adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Woodman 1999

Methods	RCT Blinding of randomization - yes Blinding of intervention - yes Complete follow-up - yes Blinding of outcome measurement - can't tell
Participants	61 male NB; Apgar > 7; FT; BW > 2500 g; 6-72 hr age

Woodman 1999 (*Continued*)

Interventions	1 g (1 ml) LP cream (n=20) 30% lidocaine cream (n=20) placebo cream (n=21) creams applied 1 hr prior and covered with occlusive dressing
Outcomes	HR; time crying; O2sat
Notes	- all subjects fasted for at least 1 hr prior - procedure standardized - all circumcisions performed by same operator - Gomco clamp

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Zahorodny 1998

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - yes Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	53 healthy male NB
Interventions	1g LP cream + 2 ml 50% sucrose 1g LP cream + 2 ml H2O 1g placebo cream + 2 ml 50% sucrose 1g placebo cream + 2mL H2O creams applied 1 hr prior; sucrose or H2O oral 2 min prior total n=53, allocation not clear
Outcomes	time cry
Notes	abstract only, number of subjects per group not reported assumed equal distribution to groups unable to obtain additional data

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Zahorodny 1999

Methods	RCT Blinding of randomization - can't tell Blinding of intervention - yes Complete follow-up - can't tell Blinding of outcome measurement - can't tell
Participants	61; healthy male NB
Interventions	10 ml 50% sucrose via pacifier 10 ml H2O via pacifier no treatment control total n=61, allocation not clear
Outcomes	HR, time cry
Notes	abstract only, unable to obtain additional data assumed equal distribution to groups

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Zolnoski 1993

Methods	RCT Blinding of randomization - yes Blinding of intervention - can't tell Complete follow-up - yes Blinding of outcome measurement - yes
Participants	20 male NB, 8 - 120 hr age, FT; no maternal medication, BW > 2700 g, 5 min Apgar >/= 7
Interventions	2.4 ml 24% sucrose (n=10) 2.4 ml water via syringe (n=10) given 3 min prior
Outcomes	cry time, HR
Notes	- pilot study - Master's thesis - procedure standardized - Gomco clamp

Risk of bias

Item	Authors' judgement	Description

Zolnoski 1993 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Participant Characteristics: NB = newborn; AGA = growth appropriate for gestational age; BW = birthweight; FT = full-term >/= 37 weeks gestation; NICU - neonatal intensive care unit;
Interventions: DPNB = dorsal penile nerve block as described in Kirya (1978) using 1% lidocaine without epinephrine; RB = ring block following the procedure outlined by Broadman (1987); local block = local anesthesia performed by injecting 0.4 ml of 1% lidocaine without epinephrine subcutaneously into two positions on the foreskin at the level of the corona; LP cream = a lidocaine-prilocaine cream commonly known as EMLA (eutectic mixture of local anesthetics); D50W = 50% dextrose oral solution; control/no treatment group = group receiving no intervention for pain; placebo group = group receiving sham intervention which mimics active interventions; WT = the time from completion of administration of pain relief intervention to the start of circumcision procedure;
Scales: NIPS = Neonatal Infant Pain Scale consisting of six behavioral components with a composite score of 0 to 7 (Lawrence, 1993); NFCS score = evaluates the presence or absence of 10 discrete facial actions at outlined in Grunau (1987), scored from videotape in 2 sec intervals for the first 20 sec of each circumcision phase; BNAS = Brazelton Neonatal Behavioral Assessment Scale; MDFMCS = Maximally Discriminative Facial Movement Coding System for coding facial movements of three facial regions to determine emotions demonstrated; NCAFS = Nursing Child Assessment Feeding Scale measures mother-infant interaction using 76 behavioral items grouped into six subscales based on concepts of adaptation and synchronism - mother and infant are observed during natural feeding session; MBPS = modified behavioral pain scale;
Physiological measures: HR= heart rate in beats/minute (bpm); TcpO2 = transcutaneous oxygen saturation; O2sat = % oxygen saturation in the blood; BP = blood pressure; RR = respiratory rate in breaths/minute;
Biochemical measures: [PC] = plasma cortisol concentration; metHgb = methemoglobin

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

Study	Reason for exclusion
Malnory 2003	Study subjects not randomized to treatment groups, intervention chosen by physician
Mintz 1989	Not a clinical trial, no comparison between groups
Olson 1998	Study subjects not randomized to treatment groups, intervention chosen by physician
Russell 1996	Not a clinical trial, all subjects received EMLA, Plastibell technique
Taddio 2000	Cohort design with two study groups; all recruited subjects assigned to Group 1; Group 2 data obtained from previously conducted RCT
Taeusch 2002	Trial of head to head comparison of surgical devices (clamps) used for circumcision procedure, procedural differences have indirect effect on circumcision pain

DATA AND ANALYSES

Comparison 1. DPNB versus no treatment or sham

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 infant irritability score	1	49	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-2.41, -1.19]
1.2 modified behavioral pain scale (MBPS)	1	48	Mean Difference (IV, Fixed, 95% CI)	-3.23 [-4.54, -1.92]
1.3 author-created behavioural score	1	38	Mean Difference (IV, Fixed, 95% CI)	-8.80 [-11.08, -6.52]
1.4 crying component of behavioural score	1	38	Mean Difference (IV, Fixed, 95% CI)	-9.80 [-12.98, -6.62]
2 Cry time (by unit)	6	211	Std. Mean Difference (IV, Fixed, 95% CI)	-1.73 [-2.06, -1.40]
2.1 in %	5	163	Std. Mean Difference (IV, Fixed, 95% CI)	-1.67 [-2.04, -1.29]
2.2 in seconds	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	-1.97 [-2.67, -1.27]
3 Heart rate (by unit)	8	348	Std. Mean Difference (IV, Fixed, 95% CI)	-1.64 [-1.89, -1.38]
3.1 in bpm	3	135	Std. Mean Difference (IV, Fixed, 95% CI)	-1.60 [0.00, -1.21]
3.2 in bpm change-from-baseline	3	135	Std. Mean Difference (IV, Fixed, 95% CI)	-1.47 [-1.87, -1.08]
3.3 in % change-from-baseline	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-2.11 [-2.72, -1.50]
4 Heart rate (by wait time)	7		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 wait time after anesthetic administration </= 5 min	3	158	Std. Mean Difference (IV, Fixed, 95% CI)	-1.64 [-2.01, -1.27]
4.2 wait time after anesthetic administration > 5 min	3	93	Std. Mean Difference (IV, Fixed, 95% CI)	-1.50 [-2.01, -0.99]
4.3 wait time after anesthetic administration - other wait time reported	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	-1.98 [-2.69, -1.28]
5 Heart rate (by clamp)	9		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Gomco	8	316	Std. Mean Difference (IV, Fixed, 95% CI)	-1.60 [-1.87, -1.34]
5.2 Mogen	1	32	Std. Mean Difference (IV, Fixed, 95% CI)	-2.51 [-3.46, -1.56]
6 Oxygen saturation (by unit)	6	293	Mean Difference (IV, Fixed, 95% CI)	3.21 [2.69, 3.73]
6.1 in %	4	165	Mean Difference (IV, Fixed, 95% CI)	5.48 [4.73, 6.23]
6.2 in % change-from-baseline	2	128	Mean Difference (IV, Fixed, 95% CI)	1.12 [0.40, 1.84]
7 Transcutaneous oxygen saturation - change from baseline	1	30	Mean Difference (IV, Fixed, 95% CI)	9.3 [1.75, 16.85]
7.1 torr (TcpO2)	1	30	Mean Difference (IV, Fixed, 95% CI)	9.3 [1.75, 16.85]
8 Respiratory rate (by unit)	3	86	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.50, 0.36]
8.1 rpm	1	38	Std. Mean Difference (IV, Fixed, 95% CI)	-0.66 [-1.32, -0.01]
8.2 in % change-from-baseline	2	48	Std. Mean Difference (IV, Fixed, 95% CI)	0.39 [-0.19, 0.96]
9 Systolic blood pressure (by unit)	2	68	Std. Mean Difference (IV, Fixed, 95% CI)	-0.66 [-1.18, -0.13]
9.1 in mmHg	1	38	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.66, 0.61]
9.2 in % change-from-baseline	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	-2.03 [-2.97, -1.09]
10 Serum cortisol (nmol/dL) 30 min post	4	102	Mean Difference (IV, Fixed, 95% CI)	-70.11 [-142.12, 1.91]

11 Salivary cortisol increase (ug/dL) from baseline to 30 min post	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-1.08, -0.00]
12 B-endorphin (pmol/L)	1	38	Mean Difference (IV, Fixed, 95% CI)	21.0 [-73.45, 115.45]

Comparison 2. Ring block versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cry time (by unit)	2	63	Std. Mean Difference (IV, Fixed, 95% CI)	-1.25 [-1.80, -0.69]
1.1 in %	1	23	Std. Mean Difference (IV, Fixed, 95% CI)	-2.01 [-3.05, -0.98]
1.2 in seconds	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.94 [-1.60, -0.29]
2 Heart rate (bpm) change-from-baseline	1	23	Mean Difference (IV, Fixed, 95% CI)	-29.27 [-52.94, -5.60]
3 Oxygen saturation (%) change-from-baseline	1	40	Mean Difference (IV, Fixed, 95% CI)	3.84 [-0.94, 8.62]
4 Respiratory rate (rpm) change-from-baseline	1	40	Mean Difference (IV, Fixed, 95% CI)	-5.69 [-16.02, 4.64]

Comparison 3. EMLA versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	2	86	Std. Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.02, -0.16]
1.1 neonatal facial coding system (NFCS)	1	27	Std. Mean Difference (IV, Fixed, 95% CI)	-0.82 [-1.61, -0.03]
1.2 NFCS - author-devised summary score	1	59	Std. Mean Difference (IV, Fixed, 95% CI)	-0.49 [-1.01, 0.03]
2 Cry time (by unit)	6	189	Std. Mean Difference (IV, Fixed, 95% CI)	-0.78 [-1.08, -0.48]
2.1 in %	3	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.27, -0.33]
2.2 in minutes	2	51	Std. Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.13, -0.01]
2.3 percent increase in time crying	1	59	Std. Mean Difference (IV, Fixed, 95% CI)	-0.95 [-1.49, -0.41]
3 Heart rate (by unit)	5	143	Mean Difference (IV, Fixed, 95% CI)	-14.59 [-19.34, -9.84]
3.1 in bpm	3	78	Mean Difference (IV, Fixed, 95% CI)	-15.80 [-21.50, -10.10]
3.2 in bpm change-from-baseline	2	65	Mean Difference (IV, Fixed, 95% CI)	-11.83 [-20.42, -3.23]
4 Oxygen saturation (%)	3	78	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.19, 2.00]
5 Respiratory rate (rpm)	1	10	Mean Difference (IV, Fixed, 95% CI)	-4.31 [-20.79, 12.17]

6 Systolic blood pressure (mmHg) change-from-baseline	1	38	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-15.50, 9.50]
7 Diastolic blood pressure (mmHg) change-from-baseline	1	38	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-23.60, 13.60]

Comparison 4. Topical lidocaine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 % change- from-baseline in time spent in Brazelton state 6 (full cry)	1	25	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-22.90, 6.90]
2 Cry time (s)	2	85	Mean Difference (IV, Fixed, 95% CI)	-59.75 [-99.14, -20.36]
3 Heart rate (bpm)	2	85	Mean Difference (IV, Fixed, 95% CI)	-9.20 [-14.32, -4.07]
4 Oxygen saturation (%)	2	85	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.75, 0.75]
5 Respiratory rate (rpm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 B-endorphin (pg/mL)	1	30	Mean Difference (IV, Fixed, 95% CI)	-49.0 [-88.73, -9.27]

Comparison 5. Sucrose versus water or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 behavioral distress score	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.08, -0.26]
1.2 modified behavioral pain scale (MBPS)	1	47	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Cry time (by unit)	5	123	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.31, 0.44]
2.1 in %	3	56	Std. Mean Difference (IV, Fixed, 95% CI)	-0.63 [-1.22, -0.05]
2.2 in seconds	2	67	Std. Mean Difference (IV, Fixed, 95% CI)	0.56 [0.07, 1.04]
3 Heart rate (by unit)	3	146	Mean Difference (IV, Fixed, 95% CI)	-3.46 [-8.98, 2.07]
3.1 in bpm	2	67	Mean Difference (IV, Fixed, 95% CI)	2.16 [-5.45, 9.78]
3.2 in bpm change-from-baseline	1	79	Mean Difference (IV, Fixed, 95% CI)	-9.70 [-17.72, -1.68]
4 Oxygen saturation (by unit)	2	126	Mean Difference (IV, Fixed, 95% CI)	1.82 [0.51, 3.13]
4.1 in %	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.83 [-3.07, 1.41]
4.2 in % change-from-baseline	1	79	Mean Difference (IV, Fixed, 95% CI)	3.2 [1.59, 4.81]
5 Serum cortisol (nmol/dL) 30 min post	1	40	Mean Difference (IV, Fixed, 95% CI)	68.90 [-53.93, 191.73]

Comparison 6. Acetaminophen versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain / behavior score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 comfort score - change from baseline score at 30 min post	1	44	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.23, 1.63]
1.2 Nursing Child Assessment Feeding Scale (NCAFS) - total infant score	1	60	Mean Difference (IV, Fixed, 95% CI)	4.00 [0.95, 7.05]
2 Cry time (%)	2	104	Mean Difference (IV, Fixed, 95% CI)	-1.76 [-8.26, 4.74]
3 Heart rate (bpm)	2	104	Mean Difference (IV, Fixed, 95% CI)	2.27 [-2.89, 7.44]
4 Respiratory rate (rpm)	1	44	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-9.00, 3.54]

Comparison 7. DPNB versus EMLA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 neonatal infant pain scale (NIPS)	1	44	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-3.29, -1.71]
1.2 behavioral distress score	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.53, -0.03]
2 Cry time (%)	1	29	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-29.74, 9.74]
3 Heart rate (by unit)	3	133	Mean Difference (IV, Fixed, 95% CI)	-16.85 [-22.69, -11.00]
3.1 in bpm	1	60	Mean Difference (IV, Fixed, 95% CI)	-7.90 [-15.52, -0.28]
3.2 in bpm change-from-baseline	2	73	Mean Difference (IV, Fixed, 95% CI)	-29.61 [-38.71, -20.51]
4 Heart rate by wait time	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 wait time after anesthetic administration </= 5 min	2	104	Std. Mean Difference (IV, Fixed, 95% CI)	-1.05 [-1.48, -0.62]
4.2 wait time after anesthetic administration > 5 min	1	29	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.68, 0.78]
5 Respiratory rate (rpm)	1	60	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-7.47, 1.67]

Comparison 8. DPNB versus sucrose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	1	47	Mean Difference (IV, Fixed, 95% CI)	-3.23 [-4.65, -1.81]
1.1 modified behavioral pain scale	1	47	Mean Difference (IV, Fixed, 95% CI)	-3.23 [-4.65, -1.81]
2 Cry time (s)	1	47	Mean Difference (IV, Fixed, 95% CI)	-166.00 [-210.54, -121.46]
3 Heart rate (by unit)	2	126	Mean Difference (IV, Fixed, 95% CI)	-26.56 [-33.36, -19.76]
3.1 in bpm	1	47	Mean Difference (IV, Fixed, 95% CI)	-49.08 [-61.72, -36.44]
3.2 in bpm change-from-baseline	1	79	Mean Difference (IV, Fixed, 95% CI)	-17.40 [-25.47, -9.33]
4 Oxygen saturation (by unit)	2	126	Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.78, 1.27]
4.1 in %	1	47	Mean Difference (IV, Fixed, 95% CI)	3.85 [2.06, 5.64]
4.2 in % change-from-baseline	1	79	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-2.75, -0.25]

Comparison 9. DPNB versus ring block

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cry time (%)	1	26	Mean Difference (IV, Fixed, 95% CI)	6.33 [-15.94, 28.60]
2 Heart rate (bpm) change-from-baseline	1	26	Mean Difference (IV, Fixed, 95% CI)	4.43 [-14.42, 23.28]

Comparison 10. DPNB versus local block

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum cortisol (nmol/dL) 30 min post	1	18	Mean Difference (IV, Fixed, 95% CI)	306.27 [141.33, 471.21]

Comparison 11. Ring block versus EMLA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart rate (bpm) change-from-baseline	1	27	Mean Difference (IV, Fixed, 95% CI)	-3.17 [-20.84, 14.50]
2 Cry time (%)	1	27	Mean Difference (IV, Fixed, 95% CI)	-16.33 [-36.15, 3.49]

Comparison 12. Buffered lidocaine DPNB versus plain lidocaine DPNB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 behavioral distress score	1	40	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.30, 0.50]
2 Cry time (%)	1	194	Mean Difference (IV, Fixed, 95% CI)	9.0 [-11.71, 29.71]
3 Heart rate (bpm)	1	194	Mean Difference (IV, Fixed, 95% CI)	-4.20 [-10.51, 2.11]
4 Oxygen saturation (%)	1	194	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.87, 1.87]
5 Serum cortisol (nmol/dL) 30 min post	1	40	Mean Difference (IV, Fixed, 95% CI)	35.80 [-105.62, 177.22]

Comparison 13. EMLA versus 30% topical lidocaine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cry time (s)	1	40	Mean Difference (IV, Fixed, 95% CI)	-17.0 [-75.00, 41.00]
2 Heart rate (bpm)	1	40	Mean Difference (IV, Fixed, 95% CI)	-11.88 [-19.40, -4.36]
3 Oxygen saturation (%)	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-1.44, 1.10]

Comparison 14. EMLA versus sucrose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cry time (%)	1	26	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-26.74, 6.74]
2 Heart rate (bpm)	1	41	Mean Difference (IV, Fixed, 95% CI)	-9.35 [-20.08, 1.38]
3 Oxygen saturation (%)	1	41	Mean Difference (IV, Fixed, 95% CI)	-0.82 [-2.63, 0.99]
4 Systolic blood pressure (mmHg)	1	41	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Diastolic blood pressure (mmHg)	1	41	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 15. EMLA versus music

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cry time (min)	1	12	Mean Difference (IV, Fixed, 95% CI)	0.38 [-3.68, 4.44]
2 Heart rate (bpm)	1	12	Mean Difference (IV, Fixed, 95% CI)	2.31 [-15.99, 20.61]
3 Oxygen saturation (%)	1	12	Mean Difference (IV, Fixed, 95% CI)	0.19 [-3.56, 3.94]
4 Respiratory rate (rpm)	1	12	Mean Difference (IV, Fixed, 95% CI)	1.52 [-13.60, 16.64]

Comparison 16. Music versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cry time (min)	1	12	Mean Difference (IV, Fixed, 95% CI)	-1.58 [-5.81, 2.65]
2 Heart rate (bpm)	1	12	Mean Difference (IV, Fixed, 95% CI)	-7.89 [-41.37, 25.59]
3 Oxygen saturation (%)	1	12	Mean Difference (IV, Fixed, 95% CI)	2.51 [-0.62, 5.64]
4 Respiratory rate (rpm)	1	12	Mean Difference (IV, Fixed, 95% CI)	-5.83 [-21.41, 9.75]

Analysis 1.1. Comparison 1 DPNB versus no treatment or sham, Outcome 1 Pain score.

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 1 Pain score

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 infant irritability score							
Arnett 1990	22	2.4 (1.2)	27	4.2 (0.9)		100.0 %	-1.80 [-2.41, -1.19]
Subtotal (95% CI)	**22**		**27**			**100.0 %**	**-1.80 [-2.41, -1.19]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.83 (P < 0.00001)							
2 modified behavioral pain scale (MBPS)							
Kass 2001	24	4.4 (2.8)	24	7.63 (1.71)		100.0 %	-3.23 [-4.54, -1.92]
Subtotal (95% CI)	**24**		**24**			**100.0 %**	**-3.23 [-4.54, -1.92]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.82 (P < 0.00001)							
3 author-created behavioural score							
Holliday 1999	19	14.1 (4.1)	19	22.9 (3)		100.0 %	-8.80 [-11.08, -6.52]
Subtotal (95% CI)	**19**		**19**			**100.0 %**	**-8.80 [-11.08, -6.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.55 (P < 0.00001)							
4 crying component of behavioural score							
Holliday 1999	19	6.9 (6.1)	19	16.7 (3.6)		100.0 %	-9.80 [-12.98, -6.62]
Subtotal (95% CI)	**19**		**19**			**100.0 %**	**-9.80 [-12.98, -6.62]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.03 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 55.51, df = 3 (P = 0.00), I^2 =95%							

Analysis 1.2. Comparison 1 DPNB versus no treatment or sham, Outcome 2 Cry time (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 2 Cry time (by unit)

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 in %							
Kurtis 1999 A	24	34.8 (38.5)	24	91 (16.8)		23.0 %	-1.86 [-2.55, -1.17]
Lander 1997	14	47.33 (29.97)	11	88 (14.32)		12.6 %	-1.61 [-2.54, -0.68]
Stang 1988 A	10	23 (33.98)	20	71.1 (31.75)		14.9 %	-1.44 [-2.29, -0.59]
Stang 1988 B	10	23 (33.98)	20	68 (34.88)		15.6 %	-1.27 [-2.10, -0.43]
Williamson 1983	20	16.7 (40.3)	10	93.1 (15.3)		11.8 %	-2.17 [-3.13, -1.21]
Subtotal (95% CI)	**78**		**85**			**77.8 %**	**-1.67 [-2.04, -1.29]**
Heterogeneity: Chi² = 2.52, df = 4 (P = 0.64); I² =0.0%							
Test for overall effect: Z = 8.75 (P < 0.00001)							
2 in seconds							
Kass 2001	24	90 (87)	24	225 (39)		22.2 %	-1.97 [-2.67, -1.27]
Subtotal (95% CI)	**24**		**24**			**22.2 %**	**-1.97 [-2.67, -1.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.52 (P < 0.00001)							
Total (95% CI)	**102**		**109**			**100.0 %**	**-1.73 [-2.06, -1.40]**
Heterogeneity: Chi² = 3.08, df = 5 (P = 0.69); I² =0.0%							
Test for overall effect: Z = 10.32 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.45), I² =0.0%							

Analysis 1.3. Comparison 1 DPNB versus no treatment or sham, Outcome 3 Heart rate (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 3 Heart rate (by unit)

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 in bpm							
Arnett 1990	22	131.45 (19.41)	27	156.75 (12.98)		15.3 %	-1.54 [-2.19, -0.89]
Holliday 1999	19	159.46 (15.37)	19	180.77 (16.77)		12.8 %	-1.30 [-2.00, -0.59]
Kass 2001	24	133.03 (22.19)	24	178.76 (23.14)		13.0 %	-1.98 [-2.69, -1.28]
Subtotal (95% CI)	**65**		**70**			**41.0 %**	**-1.60 [-2.00, -1.21]**
Heterogeneity: Chi^2 = 1.89, df = 2 (P = 0.39); I^2 =0.0%							
Test for overall effect: Z = 7.97 (P < 0.00001)							
2 in bpm change-from-baseline							
Herschel 1998	40	9.7 (17.3)	40	36.8 (17.1)		25.2 %	-1.56 [-2.06, -1.06]
Lander 1997	14	21.86 (26.04)	11	46.7 (33.47)		9.3 %	-0.81 [-1.64, 0.01]
Williamson 1983	20	3.4 (26.9)	10	54.1 (17.8)		7.3 %	-2.03 [-2.96, -1.09]
Subtotal (95% CI)	**74**		**61**			**41.8 %**	**-1.47 [-1.87, -1.08]**
Heterogeneity: Chi^2 = 3.89, df = 2 (P = 0.14); I^2 =49%							
Test for overall effect: Z = 7.39 (P < 0.00001)							
3 in % change-from-baseline							
Kurtis 1999 A	24	13.3 (12.3)	24	32.1 (10.9)		14.8 %	-1.59 [-2.25, -0.94]
Maxwell 1987	20	3.1 (4.05)	10	33.3 (7.75)		2.4 %	-5.33 [-6.96, -3.69]
Subtotal (95% CI)	**44**		**34**			**17.2 %**	**-2.11 [-2.72, -1.50]**
Heterogeneity: Chi^2 = 17.30, df = 1 (P = 0.00003); I^2 =94%							
Test for overall effect: Z = 6.79 (P < 0.00001)							
Total (95% CI)	**183**		**165**			**100.0 %**	**-1.64 [-1.89, -1.38]**
Heterogeneity: Chi^2 = 26.09, df = 7 (P = 0.00049); I^2 =73%							
Test for overall effect: Z = 12.70 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.01, df = 2 (P = 0.22), I^2 =34%							

Analysis 1.4. Comparison 1 DPNB versus no treatment or sham, Outcome 4 Heart rate (by wait time).

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 4 Heart rate (by wait time)

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 wait time after anesthetic administration </= 5 min							
Herschel 1998	40	9.7 (17.3)	40	36.8 (17.1)		53.3 %	-1.56 [-2.06, -1.06]
Kurtis 1999 A	24	13.3 (12.3)	24	32.1 (10.9)		31.4 %	-1.59 [-2.25, -0.94]
Williamson 1983	20	3.4 (26.9)	10	54.1 (17.8)		15.4 %	-2.03 [-2.96, -1.09]
Subtotal (95% CI)	**84**		**74**			**100.0 %**	**-1.64 [-2.01, -1.27]**
Heterogeneity: Chi^2 = 0.77, df = 2 (P = 0.68); I^2 =0.0%							
Test for overall effect: Z = 8.76 (P < 0.00001)							
2 wait time after anesthetic administration > 5 min							
Holliday 1999	19	159.46 (15.37)	19	180.77 (16.77)		52.8 %	-1.30 [-2.00, -0.59]
Lander 1997	14	21.86 (26.04)	11	46.7 (33.47)		38.5 %	-0.81 [-1.64, 0.01]
Maxwell 1987	20	3.1 (4.05)	10	33.3 (6.75)		8.7 %	-5.79 [-7.53, -4.04]
Subtotal (95% CI)	**53**		**40**			**100.0 %**	**-1.50 [-2.01, -0.99]**
Heterogeneity: Chi^2 = 26.15, df = 2 (P<0.00001); I^2 =92%							
Test for overall effect: Z = 5.72 (P < 0.00001)							
3 wait time after anesthetic administration - other wait time reported							
Kass 2001	24	133.03 (22.19)	24	178.76 (23.14)		100.0 %	-1.98 [-2.69, -1.28]
Subtotal (95% CI)	**24**		**24**			**100.0 %**	**-1.98 [-2.69, -1.28]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.55 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 1.20, df = 2 (P = 0.55), I^2 =0.0%							

Analysis 1.5. Comparison 1 DPNB versus no treatment or sham, Outcome 5 Heart rate (by clamp).

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 5 Heart rate (by clamp)

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Gomco							
Arnett 1990	22	131.45 (19.41)	27	156.75 (12.98)		16.9 %	-1.54 [-2.19, -0.89]
Herschel 1998	40	9.7 (17.3)	40	36.8 (17.1)		27.8 %	-1.56 [-2.06, -1.06]
Holliday 1999	19	159.46 (15.37)	19	180.77 (16.77)		14.1 %	-1.30 [-2.00, -0.59]
Kass 2001	24	133.03 (22.19)	24	178.76 (23.14)		14.3 %	-1.98 [-2.69, -1.28]
Kurtis 1999 B	8	23.7 (13.9)	8	37.9 (12.6)		6.3 %	-1.01 [-2.07, 0.05]
Lander 1997	14	21.86 (26.04)	11	46.7 (33.47)		10.3 %	-0.81 [-1.64, 0.01]
Maxwell 1987	20	3.1 (4.05)	10	33.3 (6.75)		2.3 %	-5.79 [-7.53, -4.04]
Williamson 1983	20	3.4 (26.9)	10	54.1 (17.8)		8.0 %	-2.03 [-2.96, -1.09]
Subtotal (95% CI)	**167**		**149**			**100.0 %**	**-1.60 [-1.87, -1.34]**
Heterogeneity: Chi^2 = 29.48, df = 7 (P = 0.00012); I^2 =76%							
Test for overall effect: Z = 11.85 (P < 0.00001)							
2 Mogen							
Kurtis 1999 A	16	8 (7.3)	16	29.1 (9)		100.0 %	-2.51 [-3.46, -1.56]
Subtotal (95% CI)	**16**		**16**			**100.0 %**	**-2.51 [-3.46, -1.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.15 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.21, df = 1 (P = 0.07), I^2 =69%							

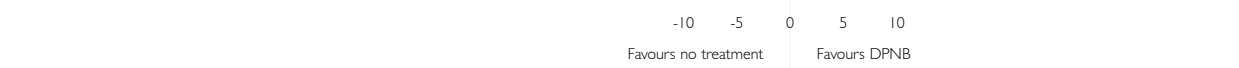
Analysis 1.6. Comparison 1 DPNB versus no treatment or sham, Outcome 6 Oxygen saturation (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 6 Oxygen saturation (by unit)

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 in %							
Arnett 1990	22	96.18 (2.54)	27	93.55 (3.44)		9.6 %	2.63 [0.95, 4.31]
Holliday 1999	19	97.8 (2)	19	95.3 (2.9)		10.7 %	2.50 [0.92, 4.08]
Kass 2001	24	98.2 (2.24)	24	95.18 (4.02)		7.9 %	3.02 [1.18, 4.86]
Maxwell 1987	20	91.7 (1.3)	10	82.2 (1.65)		19.6 %	9.50 [8.33, 10.67]
Subtotal (95% CI)	**85**		**80**			**47.9 %**	**5.48 [4.73, 6.23]**
Heterogeneity: Chi^2 = 76.86, df = 3 (P<0.00001); I^2 =96%							
Test for overall effect: Z = 14.33 (P < 0.00001)							
2 in % change-from-baseline							
Herschel 1998	40	-0.8 (2.1)	40	-2.5 (3.9)		14.3 %	1.70 [0.33, 3.07]
Kurtis 1999 A	24	-1 (1.1)	24	-1.9 (1.8)		37.8 %	0.90 [0.06, 1.74]
Subtotal (95% CI)	**64**		**64**			**52.1 %**	**1.12 [0.40, 1.84]**
Heterogeneity: Chi^2 = 0.95, df = 1 (P = 0.33); I^2 =0.0%							
Test for overall effect: Z = 3.05 (P = 0.0023)							
Total (95% CI)	**149**		**144**			**100.0 %**	**3.21 [2.69, 3.73]**
Heterogeneity: Chi^2 = 145.60, df = 5 (P<0.00001); I^2 =97%							
Test for overall effect: Z = 12.12 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 67.80, df = 1 (P = 0.00), I^2 =99%							



Analysis 1.7. Comparison 1 DPNB versus no treatment or sham, Outcome 7 Transcutaneous oxygen saturation - change from baseline.

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

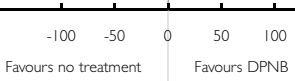
Outcome: 7 Transcutaneous oxygen saturation - change from baseline

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 torr (TcpO2)							
Williamson 1983	20	4.6 (8.5)	10	-4.7 (10.6)		100.0 %	9.30 [1.75, 16.85]
Total (95% CI)	**20**		**10**			**100.0 %**	**9.30 [1.75, 16.85]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.41 (P = 0.016)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 DPNB versus no treatment or sham, Outcome 8 Respiratory rate (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 8 Respiratory rate (by unit)

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 rpm							
Holliday 1999	19	53.6 (19.91)	19	64.43 (10.83)		43.5 %	-0.66 [-1.32, -0.01]
Subtotal (95% CI)	**19**		**19**			**43.5 %**	**-0.66 [-1.32, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.98 (P = 0.048)							
2 in % change-from-baseline							
Kurtis 1999 A	16	0.4 (6.7)	16	-4.5 (9.5)		37.1 %	0.58 [-0.13, 1.29]
Kurtis 1999 B	8	5.1 (5.5)	8	5 (10.5)		19.4 %	0.01 [-0.97, 0.99]
Subtotal (95% CI)	**24**		**24**			**56.5 %**	**0.39 [-0.19, 0.96]**
Heterogeneity: Chi^2 = 0.85, df = 1 (P = 0.36); I^2 =0.0%							
Test for overall effect: Z = 1.31 (P = 0.19)							
Total (95% CI)	**43**		**43**			**100.0 %**	**-0.07 [-0.50, 0.36]**
Heterogeneity: Chi^2 = 6.40, df = 2 (P = 0.04); I^2 =69%							
Test for overall effect: Z = 0.32 (P = 0.75)							
Test for subgroup differences: Chi^2 = 5.54, df = 1 (P = 0.02), I^2 =82%							

Analysis 1.9. Comparison 1 DPNB versus no treatment or sham, Outcome 9 Systolic blood pressure (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 9 Systolic blood pressure (by unit)

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 in mmHg							
Holliday 1999	19	89.59 (13.97)	19	89.95 (13.28)		68.5 %	-0.03 [-0.66, 0.61]
Subtotal (95% CI)	**19**		**19**			**68.5 %**	**-0.03 [-0.66, 0.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.08 (P = 0.94)							
2 in % change-from-baseline							
Maxwell 1987	20	5.4 (3.75)	10	15 (6)		31.5 %	-2.03 [-2.97, -1.09]
Subtotal (95% CI)	**20**		**10**			**31.5 %**	**-2.03 [-2.97, -1.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.25 (P = 0.000022)							
Total (95% CI)	**39**		**29**			**100.0 %**	**-0.66 [-1.18, -0.13]**
Heterogeneity: Chi^2 = 12.04, df = 1 (P = 0.00052); I^2 =92%							
Test for overall effect: Z = 2.45 (P = 0.014)							
Test for subgroup differences: Chi^2 = 12.04, df = 1 (P = 0.00), I^2 =92%							

Analysis 1.10. Comparison 1 DPNB versus no treatment or sham, Outcome 10 Serum cortisol (nmol/dL) 30 min post.

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 10 Serum cortisol (nmol/dL) 30 min post

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Masciello 1990	9	549.04 (121.39)	9	532.48 (209.68)		20.7 %	16.56 [-141.73, 174.85]
Stang 1988 A	10	386 (160.99)	20	461 (125.21)		40.0 %	-75.00 [-188.87, 38.87]
Stang 1988 B	10	386 (160.99)	20	532 (196.77)		29.8 %	-146.00 [-277.88, -14.12]
Williamson 1986	11	631.81 (256.03)	13	631.81 (328.04)		9.5 %	0.0 [-233.86, 233.86]
Total (95% CI)	**40**		**62**			**100.0 %**	**-70.11 [-142.12, 1.91]**

Heterogeneity: Chi^2 = 2.78, df = 3 (P = 0.43); I^2 =0.0%

Test for overall effect: Z = 1.91 (P = 0.056)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 DPNB versus no treatment or sham, Outcome 11 Salivary cortisol increase (ug/dL) from baseline to 30 min post.

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

Outcome: 11 Salivary cortisol increase (ug/dL) from baseline to 30 min post

Study or subgroup	DPNB N	Mean(SD)	No treatment or sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kurtis 1999 A	24	0.52 (0.98)	24	1.06 (0.92)		100.0 %	-0.54 [-1.08, 0.00]
Total (95% CI)	**24**		**24**			**100.0 %**	**-0.54 [-1.08, 0.00]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.97 (P = 0.049)

Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 DPNB versus no treatment or sham, Outcome 12 B-endorphin (pmol/L).

Review: Pain relief for neonatal circumcision

Comparison: 1 DPNB versus no treatment or sham

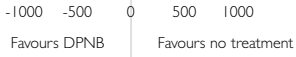
Outcome: 12 B-endorphin (pmol/L)

Study or subgroup	DPNB N	Mean(SD)	no treatment or sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Holliday 1999	19	326 (165)	19	305 (130)		100.0 %	21.00 [-73.45, 115.45]
Total (95% CI)	**19**		**19**			**100.0 %**	**21.00 [-73.45, 115.45]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Ring block versus no treatment, Outcome 1 Cry time (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 2 Ring block versus no treatment

Outcome: 1 Cry time (by unit)

Study or subgroup	Ring block N	Mean(SD)	No treatment N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 in %							
Lander 1997	12	41 (27.91)	11	88 (14.32)		28.6 %	-2.01 [-3.05, -0.98]
Subtotal (95% CI)	**12**		**11**			**28.6 %**	**-2.01 [-3.05, -0.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.80 (P = 0.00014)							
2 in seconds							
Hardwick Smith 1998	20	258.6 (115.8)	20	377.4 (130.8)		71.4 %	-0.94 [-1.60, -0.29]
Subtotal (95% CI)	**20**		**20**			**71.4 %**	**-0.94 [-1.60, -0.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.81 (P = 0.0049)							
Total (95% CI)	**32**		**31**			**100.0 %**	**-1.25 [-1.80, -0.69]**

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Study or subgroup	Ring block N	Mean(SD)	No treatment N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI

Heterogeneity: $Chi^2 = 2.92$, df = 1 (P = 0.09); $I^2 = 66\%$

Test for overall effect: Z = 4.41 (P = 0.000010)

Test for subgroup differences: $Chi^2 = 2.92$, df = 1 (P = 0.09), $I^2 = 66\%$

Analysis 2.2. Comparison 2 Ring block versus no treatment, Outcome 2 Heart rate (bpm) change-from-baseline.

Review: Pain relief for neonatal circumcision

Comparison: 2 Ring block versus no treatment

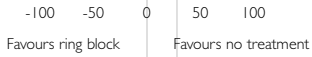
Outcome: 2 Heart rate (bpm) change-from-baseline

Study or subgroup	Ring block N	Mean(SD)	No treament N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Lander 1997	12	17.43 (22.99)	11	46.7 (33.47)		100.0 %	-29.27 [-52.94, -5.60]
Total (95% CI)	**12**		**11**			**100.0 %**	**-29.27 [-52.94, -5.60]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.42 (P = 0.015)

Test for subgroup differences: Not applicable

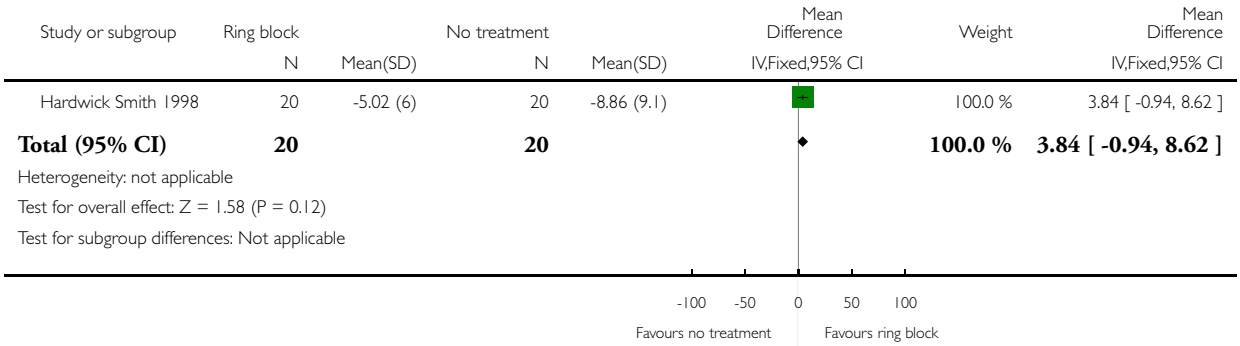


Analysis 2.3. Comparison 2 Ring block versus no treatment, Outcome 3 Oxygen saturation (%) change-from-baseline.

Review: Pain relief for neonatal circumcision

Comparison: 2 Ring block versus no treatment

Outcome: 3 Oxygen saturation (%) change-from-baseline

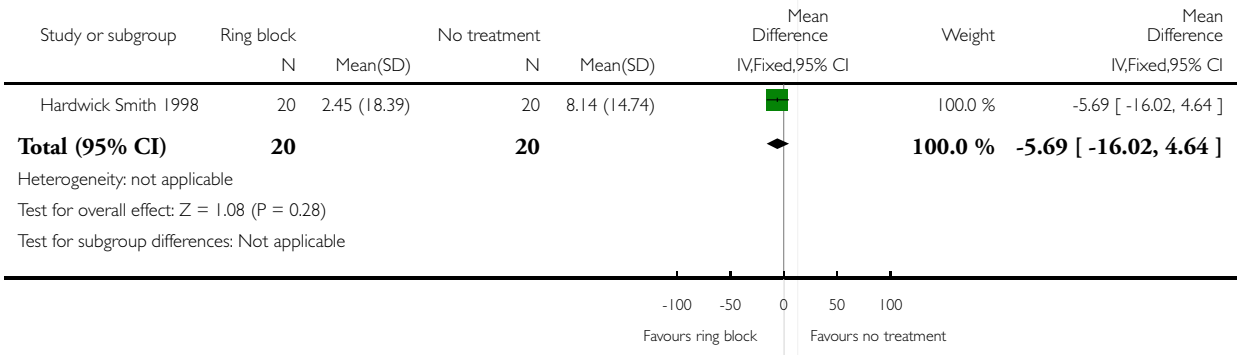


Analysis 2.4. Comparison 2 Ring block versus no treatment, Outcome 4 Respiratory rate (rpm) change-from-baseline.

Review: Pain relief for neonatal circumcision

Comparison: 2 Ring block versus no treatment

Outcome: 4 Respiratory rate (rpm) change-from-baseline



Analysis 3.1. Comparison 3 EMLA versus placebo or no treatment, Outcome 1 Pain score.

Review: Pain relief for neonatal circumcision

Comparison: 3 EMLA versus placebo or no treatment

Outcome: 1 Pain score

Study or subgroup	EMLA N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 neonatal facial coding system (NFCS)							
Benini 1993	14	356.75 (86.98)	13	423.86 (70.69)		30.1 %	-0.82 [-1.61, -0.03]
Subtotal (95% CI)	**14**		**13**			**30.1 %**	**-0.82 [-1.61, -0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.03 (P = 0.043)							
2 NFCS - author-devised summary score							
Taddio 1997	29	0.86 (0.47)	30	1.06 (0.32)		69.9 %	-0.49 [-1.01, 0.03]
Subtotal (95% CI)	**29**		**30**			**69.9 %**	**-0.49 [-1.01, 0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.86 (P = 0.063)							
Total (95% CI)	**43**		**43**			**100.0 %**	**-0.59 [-1.02, -0.16]**
Heterogeneity: Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%							
Test for overall effect: Z = 2.67 (P = 0.0076)							
Test for subgroup differences: Chi^2 = 0.45, df = 1 (P = 0.50), I^2 =0.0%							

Analysis 3.2. Comparison 3 EMLA versus placebo or no treatment, Outcome 2 Cry time (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 3 EMLA versus placebo or no treatment

Outcome: 2 Cry time (by unit)

Study or subgroup	EMLA N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 in %							
Benini 1993	14	77.07 (19.86)	13	88.33 (12.32)		14.8 %	-0.65 [-1.43, 0.12]
Lander 1997	15	57.33 (23.66)	11	88 (14.32)		11.3 %	-1.46 [-2.35, -0.57]
Zahorodny 1998	13	66 (24.5)	13	76 (20.57)		14.8 %	-0.43 [-1.21, 0.35]
Subtotal (95% CI)	**42**		**37**			**40.9 %**	**-0.80 [-1.27, -0.33]**
Heterogeneity: Chi^2 = 3.14, df = 2 (P = 0.21); I^2 =36%							
Test for overall effect: Z = 3.34 (P = 0.00085)							
2 in minutes							
Joyce 2001	5	7.8 (2.77)	5	9 (3.08)		5.7 %	-0.37 [-1.63, 0.89]
Woodman 1999	20	2.58 (1.75)	21	3.7 (1.8)		22.7 %	-0.62 [-1.25, 0.01]
Subtotal (95% CI)	**25**		**26**			**28.4 %**	**-0.57 [-1.13, -0.01]**
Heterogeneity: Chi^2 = 0.12, df = 1 (P = 0.73); I^2 =0.0%							
Test for overall effect: Z = 1.98 (P = 0.047)							
3 percent increase in time crying							
Taddio 1997	29	21 (27)	30	46 (25)		30.7 %	-0.95 [-1.49, -0.41]
Subtotal (95% CI)	**29**		**30**			**30.7 %**	**-0.95 [-1.49, -0.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.44 (P = 0.00058)							
Total (95% CI)	**96**		**93**			**100.0 %**	**-0.78 [-1.08, -0.48]**
Heterogeneity: Chi^2 = 4.19, df = 5 (P = 0.52); I^2 =0.0%							
Test for overall effect: Z = 5.10 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.92, df = 2 (P = 0.63), I^2 =0.0%							

Analysis 3.3. Comparison 3 EMLA versus placebo or no treatment, Outcome 3 Heart rate (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 3 EMLA versus placebo or no treatment

Outcome: 3 Heart rate (by unit)

Study or subgroup	EMLA N	EMLA Mean(SD)	Placebo or no tx N	Placebo or no tx Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 in bpm							
Benini 1993	14	148.45 (11.41)	13	162.87 (9.1)		37.5 %	-14.42 [-22.18, -6.66]
Joyce 2001	5	144.02 (16.03)	5	149.63 (35.78)		1.9 %	-5.61 [-39.98, 28.76]
Woodman 1999	20	137.36 (14.12)	21	155.53 (14.16)		30.1 %	-18.17 [-26.83, -9.51]
Subtotal (95% CI)	**39**		**39**			**69.5 %**	**-15.80 [-21.50, -10.10]**
Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² =0.0%							
Test for overall effect: Z = 5.44 (P < 0.00001)							
2 in bpm change-from-baseline							
Lander 1997	15	20.6 (23.61)	11	46.7 (38.17)		3.5 %	-26.10 [-51.63, -0.57]
Taddio 1997	19	7 (13)	20	17 (16)		27.1 %	-10.00 [-19.13, -0.87]
Subtotal (95% CI)	**34**		**31**			**30.5 %**	**-11.83 [-20.42, -3.23]**
Heterogeneity: Chi² = 1.35, df = 1 (P = 0.24); I² =26%							
Test for overall effect: Z = 2.70 (P = 0.0070)							
Total (95% CI)	**73**		**70**			**100.0 %**	**-14.59 [-19.34, -9.84]**
Heterogeneity: Chi² = 2.67, df = 4 (P = 0.61); I² =0.0%							
Test for overall effect: Z = 6.02 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² =0.0%							

Analysis 3.4. Comparison 3 EMLA versus placebo or no treatment, Outcome 4 Oxygen saturation (%).

Review: Pain relief for neonatal circumcision

Comparison: 3 EMLA versus placebo or no treatment

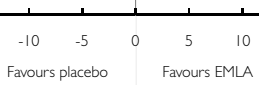
Outcome: 4 Oxygen saturation (%)

Study or subgroup	EMLA N	Mean(SD)	Placebo or no tx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Benini 1993	14	92.05 (2.59)	13	86.15 (5.05)		12.8 %	5.90 [2.84, 8.96]
Joyce 2001	5	94.4 (3.22)	5	91.7 (2.18)		10.3 %	2.70 [-0.71, 6.11]
Woodman 1999	20	97.33 (1.91)	21	97.5 (2.17)		76.9 %	-0.17 [-1.42, 1.08]
Total (95% CI)	**39**		**39**			**100.0 %**	**0.90 [-0.19, 2.00]**

Heterogeneity: Chi^2 = 14.13, df = 2 (P = 0.00085); I^2 =86%

Test for overall effect: Z = 1.62 (P = 0.11)

Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3 EMLA versus placebo or no treatment, Outcome 5 Respiratory rate (rpm).

Review: Pain relief for neonatal circumcision

Comparison: 3 EMLA versus placebo or no treatment

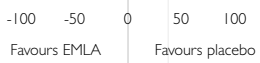
Outcome: 5 Respiratory rate (rpm)

Study or subgroup	EMLA N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Joyce 2001	5	48.13 (12.95)	5	52.44 (13.63)		100.0 %	-4.31 [-20.79, 12.17]
Total (95% CI)	**5**		**5**			**100.0 %**	**-4.31 [-20.79, 12.17]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable

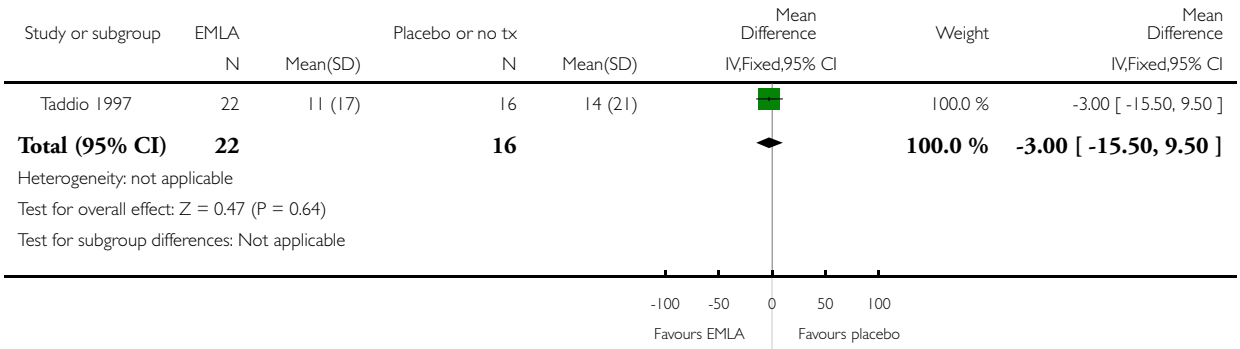


Analysis 3.6. Comparison 3 EMLA versus placebo or no treatment, Outcome 6 Systolic blood pressure (mmHg) change-from-baseline.

Review: Pain relief for neonatal circumcision

Comparison: 3 EMLA versus placebo or no treatment

Outcome: 6 Systolic blood pressure (mmHg) change-from-baseline

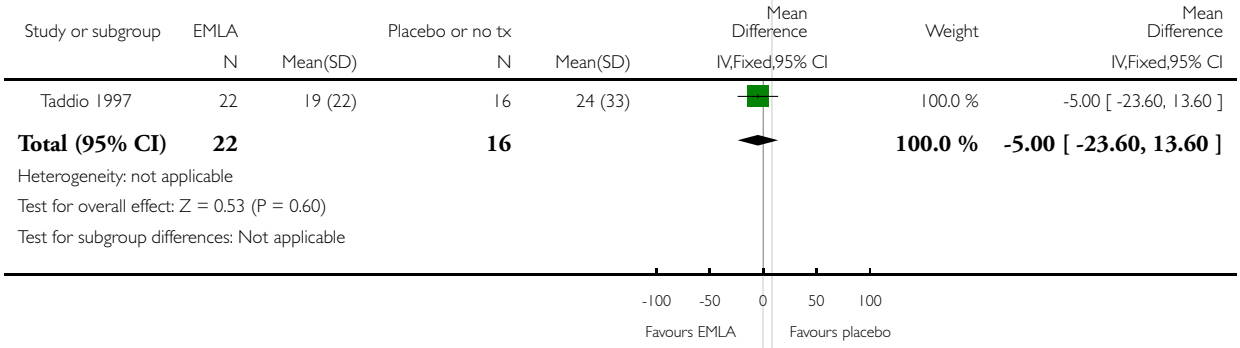


Analysis 3.7. Comparison 3 EMLA versus placebo or no treatment, Outcome 7 Diastolic blood pressure (mmHg) change-from-baseline.

Review: Pain relief for neonatal circumcision

Comparison: 3 EMLA versus placebo or no treatment

Outcome: 7 Diastolic blood pressure (mmHg) change-from-baseline



Analysis 4.1. Comparison 4 Topical lidocaine versus placebo, Outcome 1 Pain score.

Review: Pain relief for neonatal circumcision

Comparison: 4 Topical lidocaine versus placebo

Outcome: 1 Pain score

Study or subgroup	Lidocaine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 % change- from-baseline in time spent in Brazelton state 6 (full cry)							
Weatherstone 1993	12	7 (18)	13	15 (20)		100.0 %	-8.00 [-22.90, 6.90]
Subtotal (95% CI)	**12**		**13**			**100.0 %**	**-8.00 [-22.90, 6.90]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.05 (P = 0.29)

Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 Topical lidocaine versus placebo, Outcome 2 Cry time (s).

Review: Pain relief for neonatal circumcision

Comparison: 4 Topical lidocaine versus placebo

Outcome: 2 Cry time (s)

Study or subgroup	Lidocaine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Mudge 1989	20	195 (90.19)	24	263 (90.19)		54.2 %	-68.00 [-121.52, -14.48]
Woodman 1999	20	172 (80.67)	21	222 (108.07)		45.8 %	-50.00 [-108.19, 8.19]
Total (95% CI)	**40**		**45**			**100.0 %**	**-59.75 [-99.14, -20.36]**

Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.66); I^2 =0.0%

Test for overall effect: Z = 2.97 (P = 0.0029)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Topical lidocaine versus placebo, Outcome 3 Heart rate (bpm).

Review: Pain relief for neonatal circumcision

Comparison: 4 Topical lidocaine versus placebo

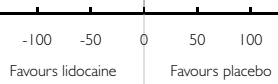
Outcome: 3 Heart rate (bpm)

Study or subgroup	Lidocaine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Mudge 1989	20	148.4 (9.75)	24	160.27 (14.16)		52.2 %	-11.87 [-18.97, -4.77]
Woodman 1999	20	149.25 (9.75)	21	155.53 (14.16)		47.8 %	-6.28 [-13.69, 1.13]
Total (95% CI)	**40**		**45**			**100.0 %**	**-9.20 [-14.32, -4.07]**

Heterogeneity: Chi^2 = 1.14, df = 1 (P = 0.29); I^2 =12%

Test for overall effect: Z = 3.52 (P = 0.00044)

Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4 Topical lidocaine versus placebo, Outcome 4 Oxygen saturation (%).

Review: Pain relief for neonatal circumcision

Comparison: 4 Topical lidocaine versus placebo

Outcome: 4 Oxygen saturation (%)

Study or subgroup	Lidocaine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Mudge 1989	20	91.43 (0)	24	87.55 (0)		0.0 [0.0, 0.0]
Woodman 1999	20	97 (1.91)	21	97.5 (2.17)		-0.50 [-1.75, 0.75]
Total (95% CI)	**40**		**45**			**-0.50 [-1.75, 0.75]**

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.78 (P = 0.43)

Test for subgroup differences: Not applicable

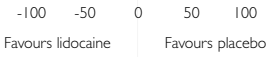
Analysis 4.5. Comparison 4 Topical lidocaine versus placebo, Outcome 5 Respiratory rate (rpm).

Review: Pain relief for neonatal circumcision

Comparison: 4 Topical lidocaine versus placebo

Outcome: 5 Respiratory rate (rpm)

Study or subgroup	Lidocaine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Mudge 1989	20	41.53 (0)	24	44.65 (0)		0.0 [0.0, 0.0]



Analysis 4.6. Comparison 4 Topical lidocaine versus placebo, Outcome 6 B-endorphin (pg/mL).

Review: Pain relief for neonatal circumcision

Comparison: 4 Topical lidocaine versus placebo

Outcome: 6 B-endorphin (pg/mL)

Study or subgroup	lidocaine N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Weatherstone 1993	15	65 (57)	15	114 (54)		100.0 %	-49.00 [-88.73, -9.27]
Total (95% CI)	**15**		**15**			**100.0 %**	**-49.00 [-88.73, -9.27]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.42 (P = 0.016)

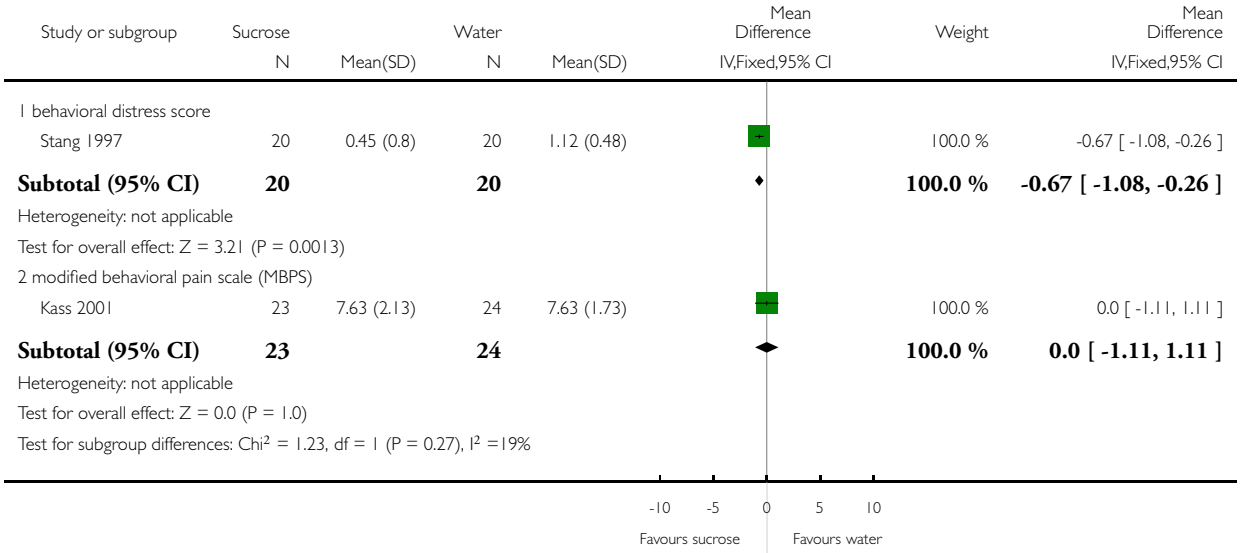
Test for subgroup differences: Not applicable

Analysis 5.1. Comparison 5 Sucrose versus water or no treatment, Outcome 1 Pain score.

Review: Pain relief for neonatal circumcision

Comparison: 5 Sucrose versus water or no treatment

Outcome: 1 Pain score



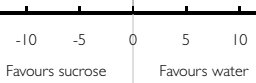
Analysis 5.2. Comparison 5 Sucrose versus water or no treatment, Outcome 2 Cry time (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 5 Sucrose versus water or no treatment

Outcome: 2 Cry time (by unit)

Study or subgroup	Sucrose N	Mean(SD)	Water N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 in %							
Blass 1991 A	5	29.2 (18.66)	10	48 (18.97)		10.8 %	-0.94 [-2.08, 0.20]
Blass 1991 B	5	29.2 (18.66)	10	66.5 (11.07)		6.2 %	-2.53 [-4.04, -1.03]
Zahorodny 1998	13	76 (18.66)	13	76 (18.97)		23.9 %	0.0 [-0.77, 0.77]
Subtotal (95% CI)	**23**		**33**			**41.0 %**	**-0.63 [-1.22, -0.05]**
Heterogeneity: Chi^2 = 9.00, df = 2 (P = 0.01); I^2 =78%							
Test for overall effect: Z = 2.11 (P = 0.035)							
2 in seconds							
Kass 2001	23	256 (68)	24	225 (39)		41.5 %	0.55 [-0.03, 1.14]
Zolnoski 1993	10	279.8 (84.07)	10	242 (35.31)		17.5 %	0.56 [-0.34, 1.46]
Subtotal (95% CI)	**33**		**34**			**59.0 %**	**0.56 [0.07, 1.04]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%							
Test for overall effect: Z = 2.22 (P = 0.026)							
Total (95% CI)	**56**		**67**			**100.0 %**	**0.07 [-0.31, 0.44]**
Heterogeneity: Chi^2 = 18.29, df = 4 (P = 0.001); I^2 =78%							
Test for overall effect: Z = 0.36 (P = 0.72)							
Test for subgroup differences: Chi^2 = 9.29, df = 1 (P = 0.00), I^2 =89%							

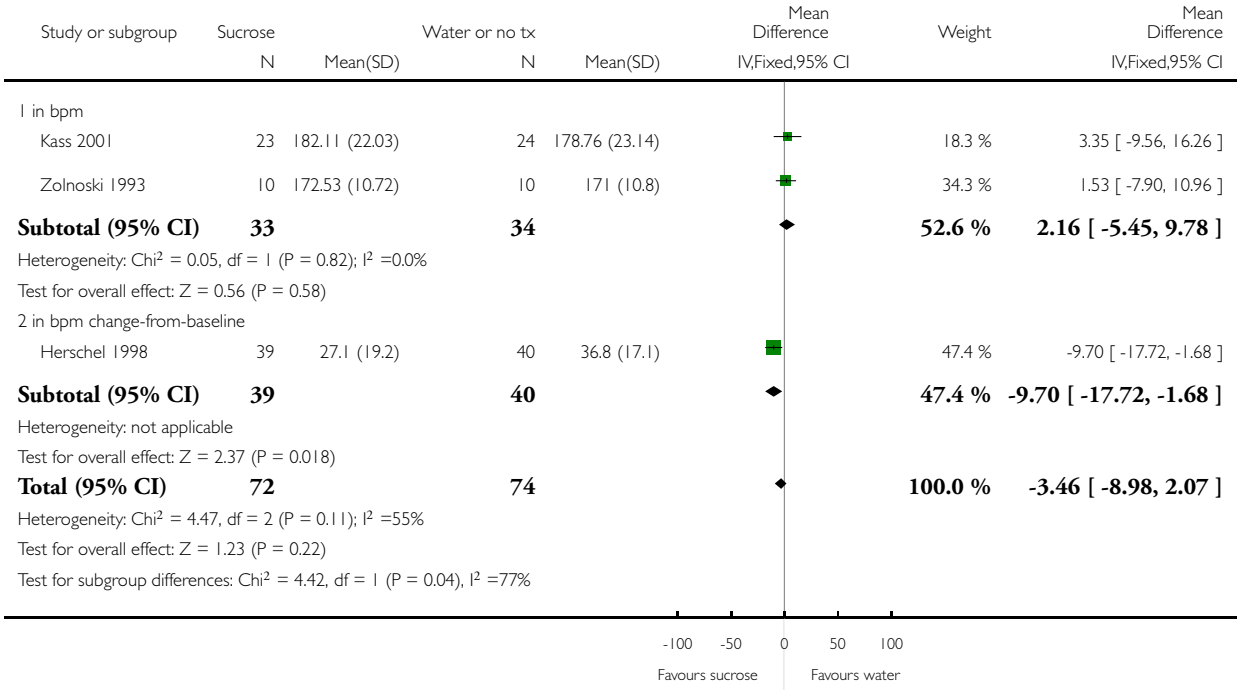


Analysis 5.3. Comparison 5 Sucrose versus water or no treatment, Outcome 3 Heart rate (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 5 Sucrose versus water or no treatment

Outcome: 3 Heart rate (by unit)

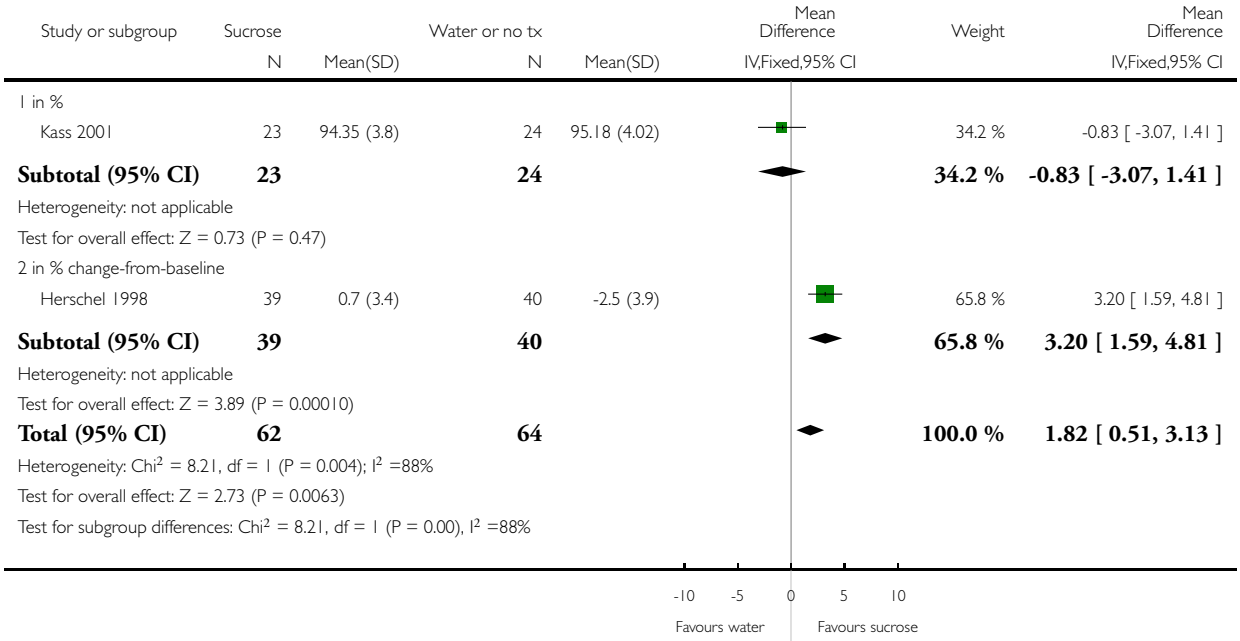


Analysis 5.4. Comparison 5 Sucrose versus water or no treatment, Outcome 4 Oxygen saturation (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 5 Sucrose versus water or no treatment

Outcome: 4 Oxygen saturation (by unit)

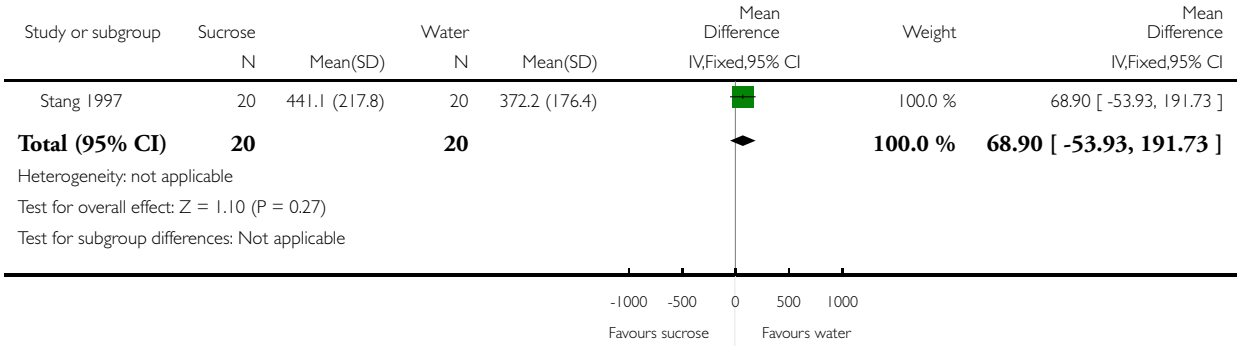


Analysis 5.5. Comparison 5 Sucrose versus water or no treatment, Outcome 5 Serum cortisol (nmol/dL) 30 min post.

Review: Pain relief for neonatal circumcision

Comparison: 5 Sucrose versus water or no treatment

Outcome: 5 Serum cortisol (nmol/dL) 30 min post

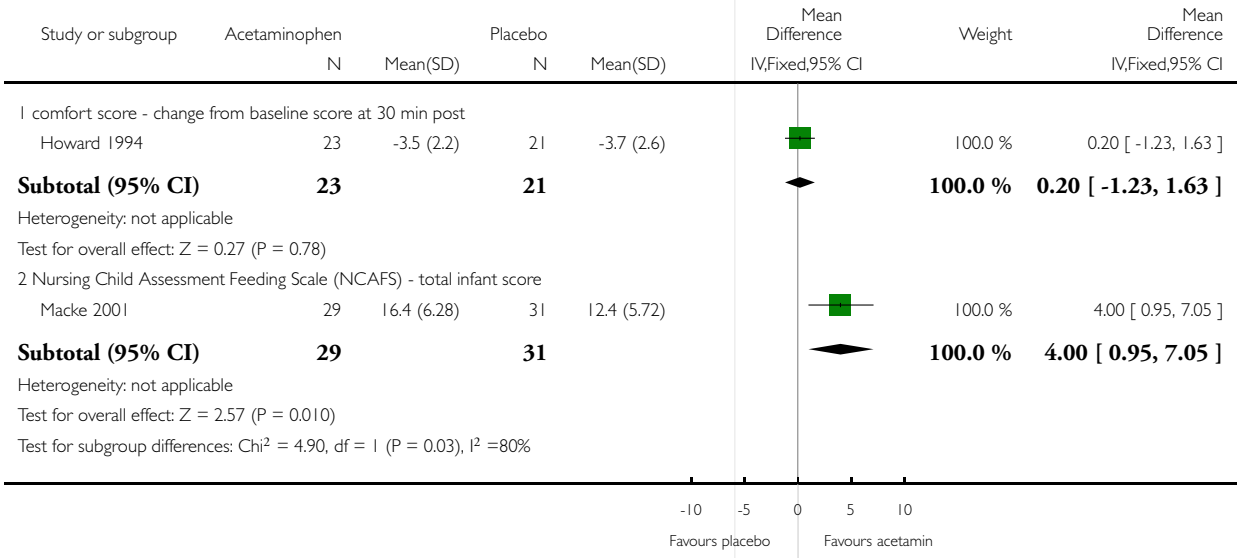


Analysis 6.1. Comparison 6 Acetaminophen versus placebo, Outcome 1 Pain / behavior score.

Review: Pain relief for neonatal circumcision

Comparison: 6 Acetaminophen versus placebo

Outcome: 1 Pain / behavior score

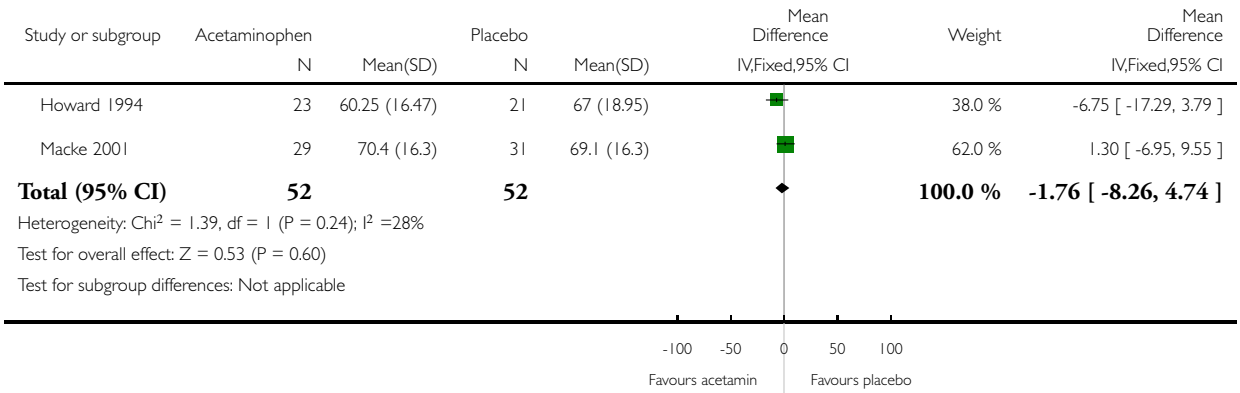


Analysis 6.2. Comparison 6 Acetaminophen versus placebo, Outcome 2 Cry time (%).

Review: Pain relief for neonatal circumcision

Comparison: 6 Acetaminophen versus placebo

Outcome: 2 Cry time (%)

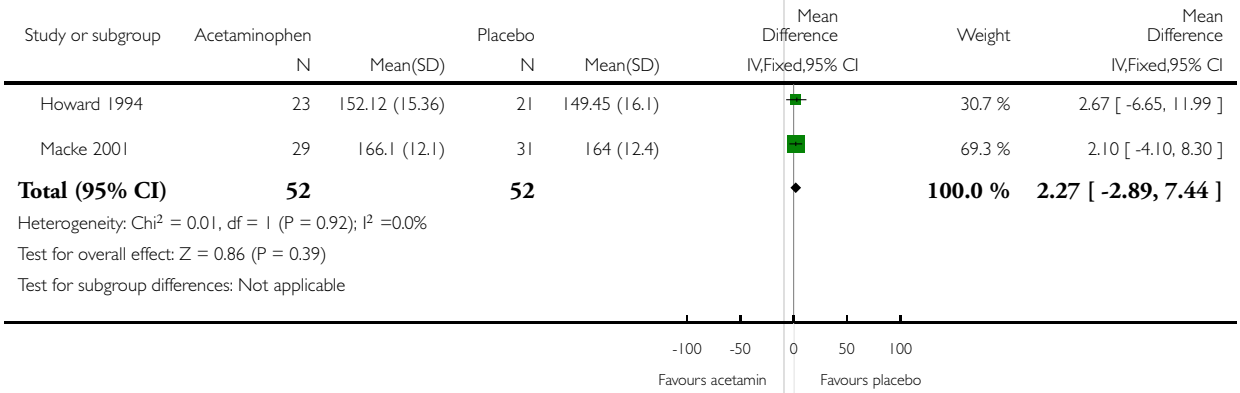


Analysis 6.3. Comparison 6 Acetaminophen versus placebo, Outcome 3 Heart rate (bpm).

Review: Pain relief for neonatal circumcision

Comparison: 6 Acetaminophen versus placebo

Outcome: 3 Heart rate (bpm)

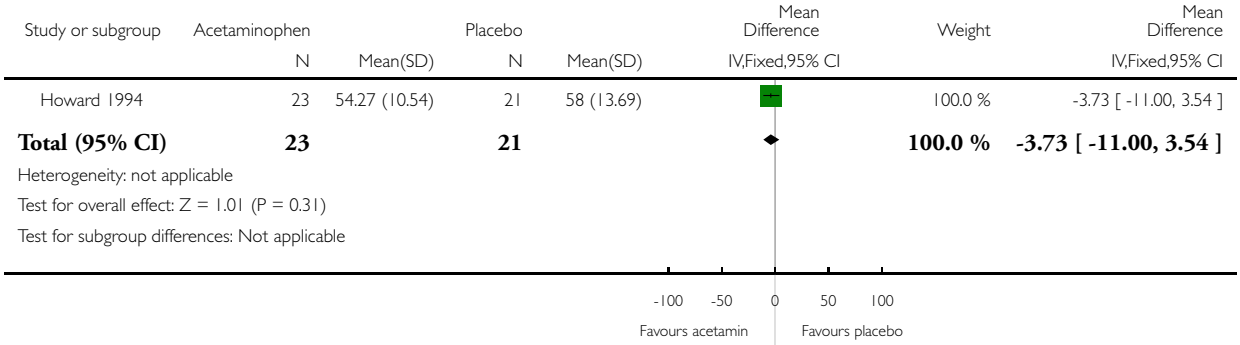


Analysis 6.4. Comparison 6 Acetaminophen versus placebo, Outcome 4 Respiratory rate (rpm).

Review: Pain relief for neonatal circumcision

Comparison: 6 Acetaminophen versus placebo

Outcome: 4 Respiratory rate (rpm)

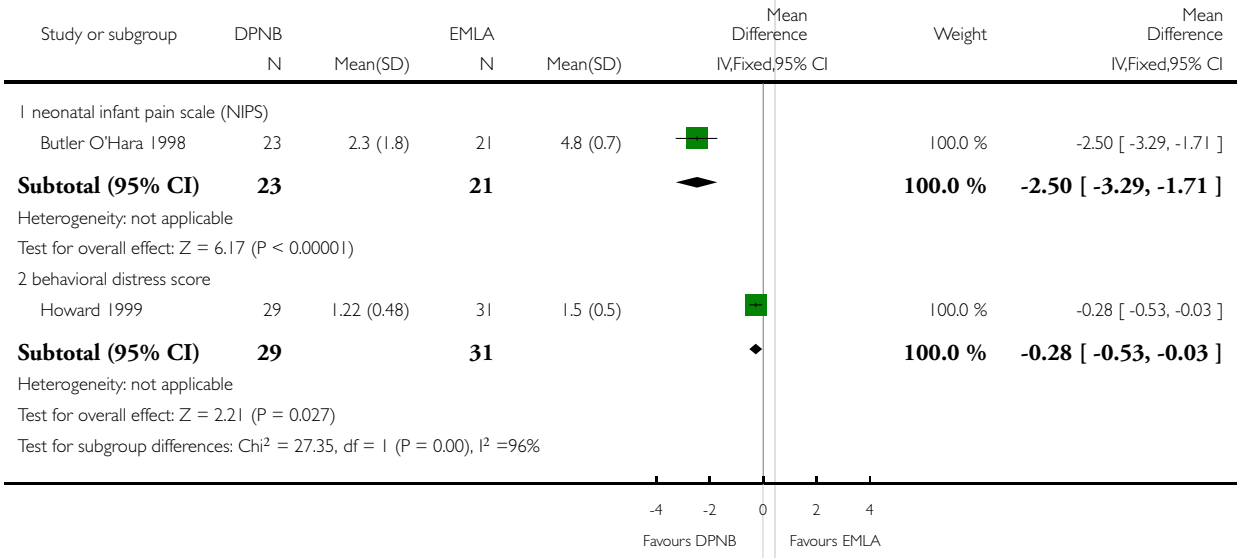


Analysis 7.1. Comparison 7 DPNB versus EMLA, Outcome 1 Pain score.

Review: Pain relief for neonatal circumcision

Comparison: 7 DPNB versus EMLA

Outcome: 1 Pain score

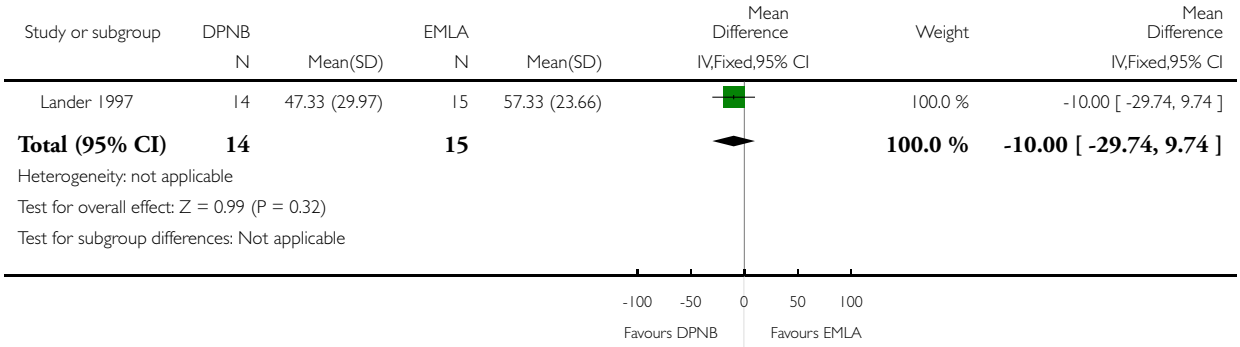


Analysis 7.2. Comparison 7 DPNB versus EMLA, Outcome 2 Cry time (%).

Review: Pain relief for neonatal circumcision

Comparison: 7 DPNB versus EMLA

Outcome: 2 Cry time (%)

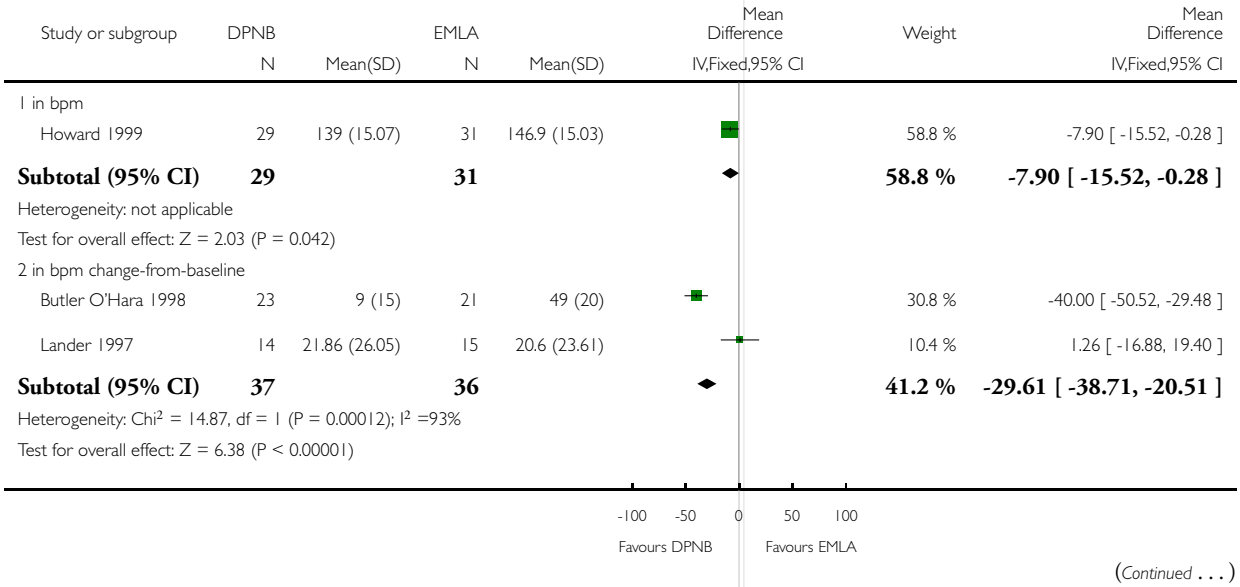


Analysis 7.3. Comparison 7 DPNB versus EMLA, Outcome 3 Heart rate (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 7 DPNB versus EMLA

Outcome: 3 Heart rate (by unit)



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Study or subgroup	DPNB N	DPNB Mean(SD)	EMLA N	EMLA Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Total (95% CI)	**66**		**67**		◆	**100.0 %**	**-16.85 [-22.69, -11.00]**
Heterogeneity: Chi² = 27.72, df = 2 (P<0.00001); I² =93%							
Test for overall effect: Z = 5.65 (P < 0.00001)							
Test for subgroup differences: Chi² = 12.84, df = 1 (P = 0.00), I² =92%							

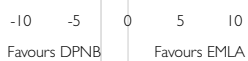
Analysis 7.4. Comparison 7 DPNB versus EMLA, Outcome 4 Heart rate by wait time.

Review: Pain relief for neonatal circumcision

Comparison: 7 DPNB versus EMLA

Outcome: 4 Heart rate by wait time

Study or subgroup	DPNB N	DPNB Mean(SD)	EMLA N	EMLA Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 wait time after anesthetic administration </= 5 min							
Butler O'Hara 1998	23	9 (15)	21	49 (20)	■	31.0 %	-2.24 [-3.01, -1.47]
Howard 1999	29	139 (15.07)	31	146.9 (15.03)	■	69.0 %	-0.52 [-1.03, 0.00]
Subtotal (95% CI)	**52**		**52**		◆	**100.0 %**	**-1.05 [-1.48, -0.62]**
Heterogeneity: Chi² = 13.27, df = 1 (P = 0.00027); I² =92%							
Test for overall effect: Z = 4.82 (P < 0.00001)							
2 wait time after anesthetic administration > 5 min							
Lander 1997	14	21.86 (26.05)	15	20.6 (23.61)	■	100.0 %	0.05 [-0.68, 0.78]
Subtotal (95% CI)	**14**		**15**		◆	**100.0 %**	**0.05 [-0.68, 0.78]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.13 (P = 0.89)							
Test for subgroup differences: Chi² = 6.53, df = 1 (P = 0.01), I² =85%							



Analysis 7.5. Comparison 7 DPNB versus EMLA, Outcome 5 Respiratory rate (rpm).

Review: Pain relief for neonatal circumcision

Comparison: 7 DPNB versus EMLA

Outcome: 5 Respiratory rate (rpm)

Study or subgroup	DPNB N	Mean(SD)	EMLA N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Howard 1999	29	53.4 (9.15)	31	56.3 (8.9)		100.0 %	-2.90 [-7.47, 1.67]
Total (95% CI)	**29**		**31**			**100.0 %**	**-2.90 [-7.47, 1.67]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.24 (P = 0.21)

Test for subgroup differences: Not applicable

Analysis 8.1. Comparison 8 DPNB versus sucrose, Outcome 1 Pain score.

Review: Pain relief for neonatal circumcision

Comparison: 8 DPNB versus sucrose

Outcome: 1 Pain score

Study or subgroup	DPNB N	Mean(SD)	Sucrose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 modified behavioral pain scale							
Kass 2001	24	4.4 (2.8)	23	7.63 (2.13)		100.0 %	-3.23 [-4.65, -1.81]
Total (95% CI)	**24**		**23**			**100.0 %**	**-3.23 [-4.65, -1.81]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.46 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 8.2. Comparison 8 DPNB versus sucrose, Outcome 2 Cry time (s).

Review: Pain relief for neonatal circumcision

Comparison: 8 DPNB versus sucrose

Outcome: 2 Cry time (s)

Study or subgroup	DPNB N	Mean(SD)	Sucrose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kass 2001	24	90 (87)	23	256 (68)		100.0 %	-166.00 [-210.54, -121.46]
Total (95% CI)	**24**		**23**			**100.0 %**	**-166.00 [-210.54, -121.46]**

Heterogeneity: not applicable

Test for overall effect: Z = 7.30 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 8.3. Comparison 8 DPNB versus sucrose, Outcome 3 Heart rate (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 8 DPNB versus sucrose

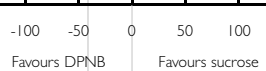
Outcome: 3 Heart rate (by unit)

Study or subgroup	DPNB N	Mean(SD)	Sucrose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 in bpm							
Kass 2001	24	133.03 (22.19)	23	182.11 (22.03)		28.9 %	-49.08 [-61.72, -36.44]
Subtotal (95% CI)	**24**		**23**			**28.9 %**	**-49.08 [-61.72, -36.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.61 (P < 0.00001)							
2 in bpm change-from-baseline							
Herschel 1998	40	9.7 (17.3)	39	27.1 (19.2)		71.1 %	-17.40 [-25.47, -9.33]
Subtotal (95% CI)	**40**		**39**			**71.1 %**	**-17.40 [-25.47, -9.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.23 (P = 0.000024)							
Total (95% CI)	**64**		**62**			**100.0 %**	**-26.56 [-33.36, -19.76]**

Heterogeneity: Chi^2 = 17.14, df = 1 (P = 0.00003); I^2 =94%

Test for overall effect: Z = 7.66 (P < 0.00001)

Test for subgroup differences: Chi^2 = 17.14, df = 1 (P = 0.00), I^2 =94%

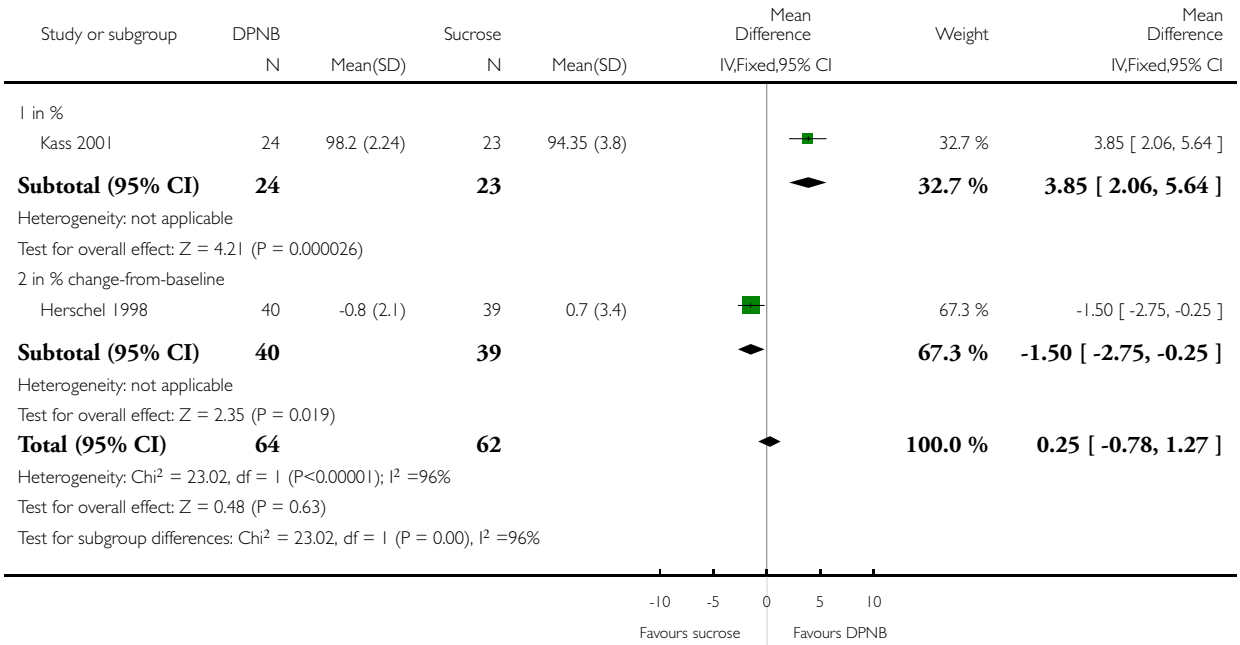


Analysis 8.4. Comparison 8 DPNB versus sucrose, Outcome 4 Oxygen saturation (by unit).

Review: Pain relief for neonatal circumcision

Comparison: 8 DPNB versus sucrose

Outcome: 4 Oxygen saturation (by unit)



Analysis 9.1. Comparison 9 DPNB versus ring block, Outcome 1 Cry time (%).

Review: Pain relief for neonatal circumcision

Comparison: 9 DPNB versus ring block

Outcome: 1 Cry time (%)

Study or subgroup	DPNB N	Mean(SD)	RB N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Lander 1997	14	47.33 (29.97)	12	41 (27.91)		100.0 %	6.33 [-15.94, 28.60]
Total (95% CI)	**14**		**12**			**100.0 %**	**6.33 [-15.94, 28.60]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.56 (P = 0.58)

Test for subgroup differences: Not applicable

Analysis 9.2. Comparison 9 DPNB versus ring block, Outcome 2 Heart rate (bpm) change-from-baseline.

Review: Pain relief for neonatal circumcision

Comparison: 9 DPNB versus ring block

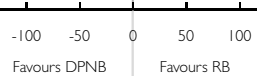
Outcome: 2 Heart rate (bpm) change-from-baseline

Study or subgroup	DPNB N	Mean(SD)	RB N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Lander 1997	14	21.86 (26.05)	12	17.43 (22.99)		100.0 %	4.43 [-14.42, 23.28]
Total (95% CI)	**14**		**12**			**100.0 %**	**4.43 [-14.42, 23.28]**

Heterogeneity: not applicable

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

Test for subgroup differences: Not applicable

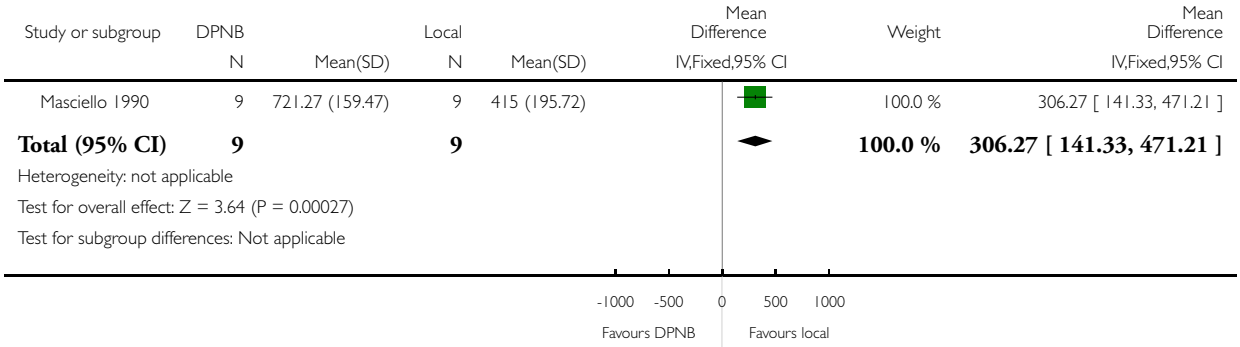


Analysis 10.1. Comparison 10 DPNB versus local block, Outcome 1 Serum cortisol (nmol/dL) 30 min post.

Review: Pain relief for neonatal circumcision

Comparison: 10 DPNB versus local block

Outcome: 1 Serum cortisol (nmol/dL) 30 min post

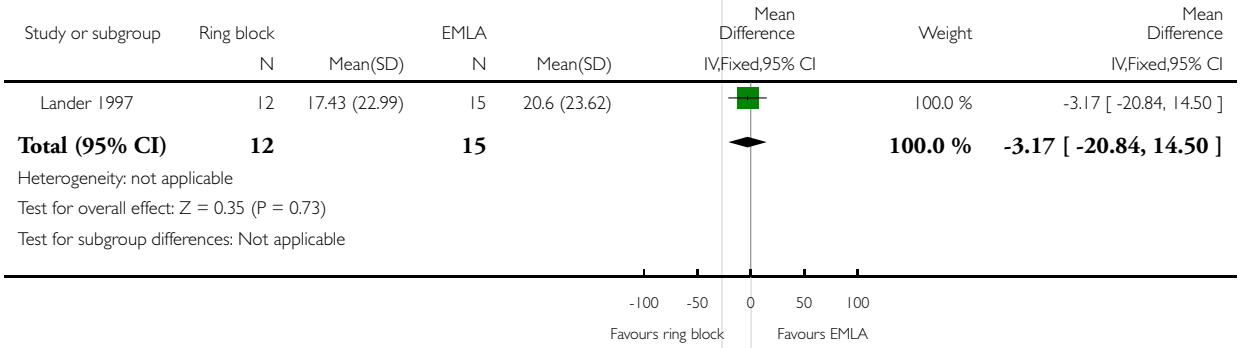


Analysis 11.1. Comparison 11 Ring block versus EMLA, Outcome 1 Heart rate (bpm) change-from-baseline.

Review: Pain relief for neonatal circumcision

Comparison: 11 Ring block versus EMLA

Outcome: 1 Heart rate (bpm) change-from-baseline

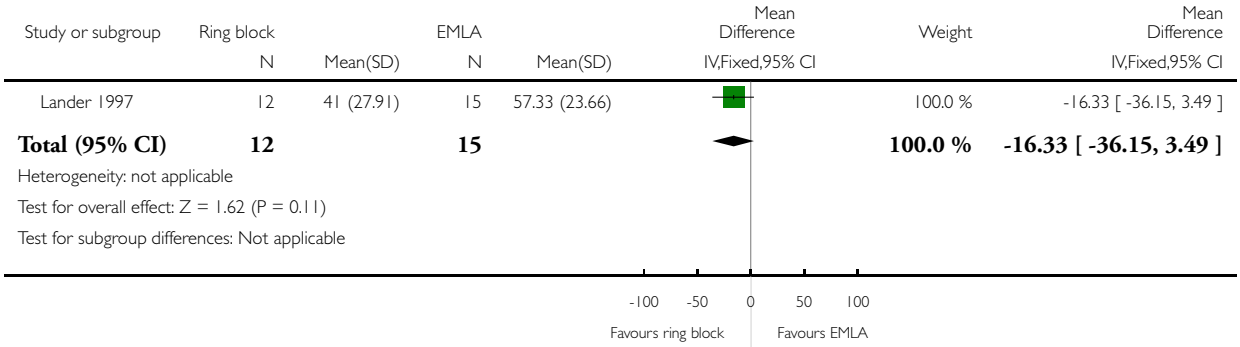


Analysis 11.2. Comparison 11 Ring block versus EMLA, Outcome 2 Cry time (%).

Review: Pain relief for neonatal circumcision

Comparison: 11 Ring block versus EMLA

Outcome: 2 Cry time (%)

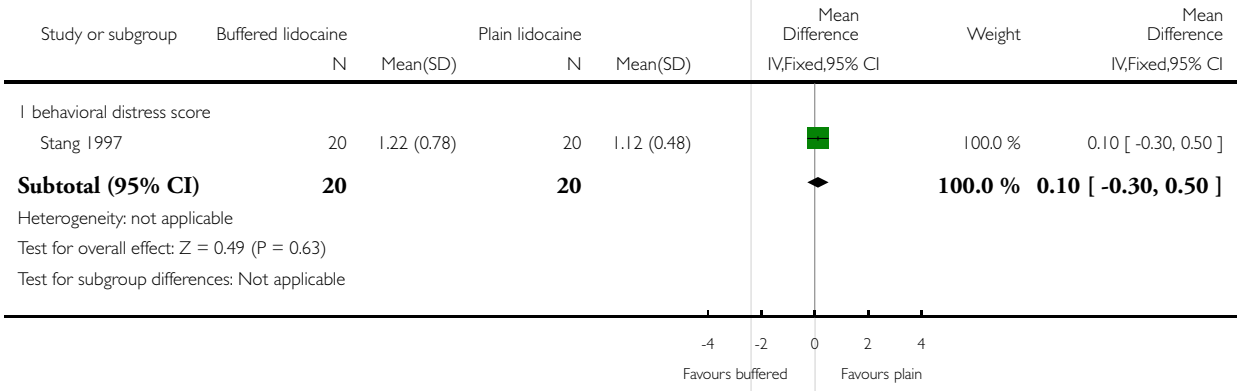


Analysis 12.1. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB, Outcome 1 Pain score.

Review: Pain relief for neonatal circumcision

Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

Outcome: 1 Pain score



Analysis 12.2. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB, Outcome 2 Cry time (%).

Review: Pain relief for neonatal circumcision

Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

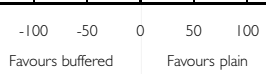
Outcome: 2 Cry time (%)

Study or subgroup	Buffered lidocaine N	Mean(SD)	Plain lidocaine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Newton 1999	102	65 (74)	92	56 (73)		100.0 %	9.00 [-11.71, 29.71]
Total (95% CI)	**102**		**92**			**100.0 %**	**9.00 [-11.71, 29.71]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.85 (P = 0.39)

Test for subgroup differences: Not applicable



Analysis 12.3. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB, Outcome 3 Heart rate (bpm).

Review: Pain relief for neonatal circumcision

Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

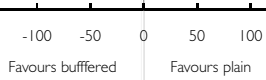
Outcome: 3 Heart rate (bpm)

Study or subgroup	Buffered lidocaine N	Mean(SD)	Plain lidocaine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Newton 1999	102	121.8 (21.1)	92	126 (23.5)		100.0 %	-4.20 [-10.51, 2.11]
Total (95% CI)	**102**		**92**			**100.0 %**	**-4.20 [-10.51, 2.11]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable

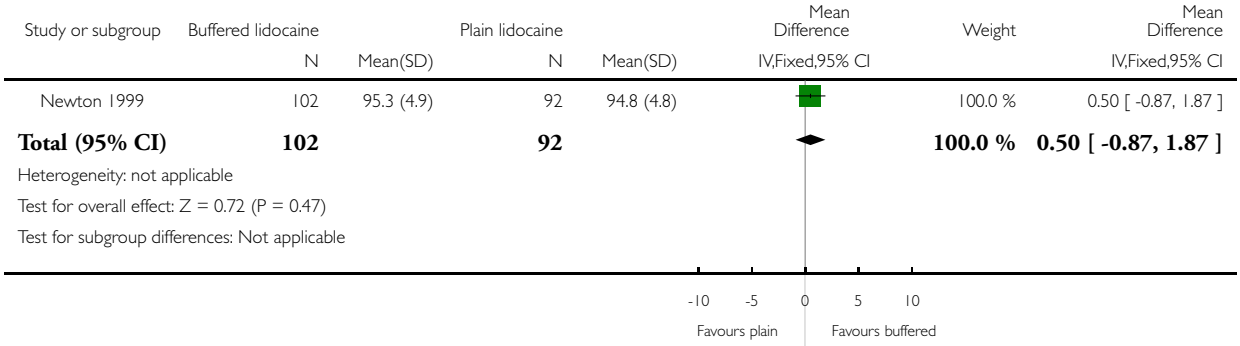


Analysis 12.4. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB, Outcome 4 Oxygen saturation (%).

Review: Pain relief for neonatal circumcision

Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

Outcome: 4 Oxygen saturation (%)

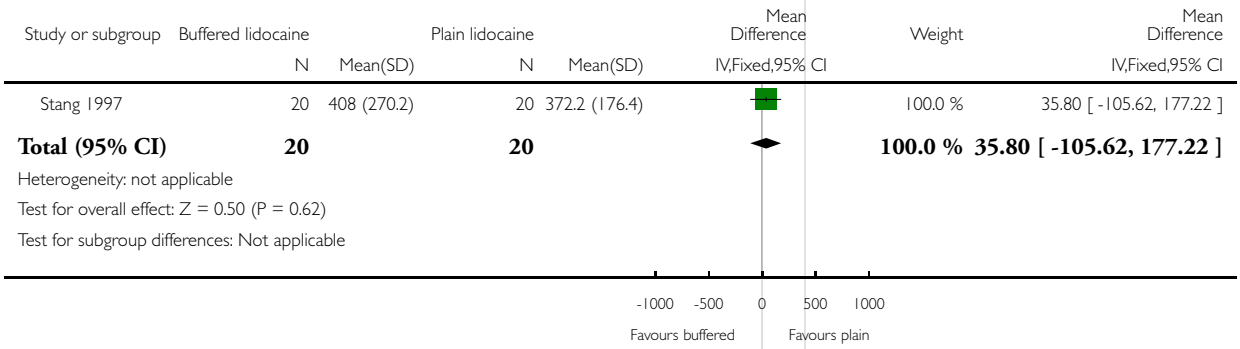


Analysis 12.5. Comparison 12 Buffered lidocaine DPNB versus plain lidocaine DPNB, Outcome 5 Serum cortisol (nmol/dL) 30 min post.

Review: Pain relief for neonatal circumcision

Comparison: 12 Buffered lidocaine DPNB versus plain lidocaine DPNB

Outcome: 5 Serum cortisol (nmol/dL) 30 min post



Analysis 13.1. Comparison 13 EMLA versus 30% topical lidocaine, Outcome 1 Cry time (s).

Review: Pain relief for neonatal circumcision

Comparison: 13 EMLA versus 30% topical lidocaine

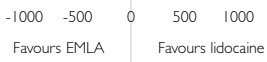
Outcome: 1 Cry time (s)

Study or subgroup	EMLA N	Mean(SD)	Lidocaine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Woodman 1999	20	155 (104.91)	20	172 (80.68)		100.0 %	-17.00 [-75.00, 41.00]
Total (95% CI)	**20**		**20**			**100.0 %**	**-17.00 [-75.00, 41.00]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.57 (P = 0.57)

Test for subgroup differences: Not applicable



Analysis 13.2. Comparison 13 EMLA versus 30% topical lidocaine, Outcome 2 Heart rate (bpm).

Review: Pain relief for neonatal circumcision

Comparison: 13 EMLA versus 30% topical lidocaine

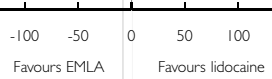
Outcome: 2 Heart rate (bpm)

Study or subgroup	EMLA N	Mean(SD)	Lidocaine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Woodman 1999	20	137.37 (14.12)	20	149.25 (9.75)		100.0 %	-11.88 [-19.40, -4.36]
Total (95% CI)	**20**		**20**			**100.0 %**	**-11.88 [-19.40, -4.36]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.10 (P = 0.0020)

Test for subgroup differences: Not applicable



Analysis 13.3. Comparison 13 EMLA versus 30% topical lidocaine, Outcome 3 Oxygen saturation (%).

Review: Pain relief for neonatal circumcision

Comparison: 13 EMLA versus 30% topical lidocaine

Outcome: 3 Oxygen saturation (%)

Study or subgroup	EMLA N	Mean(SD)	Lidocaine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Woodman 1999	20	97.33 (1.91)	20	97.5 (2.17)		100.0 %	-0.17 [-1.44, 1.10]
Total (95% CI)	**20**		**20**			**100.0 %**	**-0.17 [-1.44, 1.10]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.26 (P = 0.79)

Test for subgroup differences: Not applicable

Analysis 14.1. Comparison 14 EMLA versus sucrose, Outcome 1 Cry time (%).

Review: Pain relief for neonatal circumcision

Comparison: 14 EMLA versus sucrose

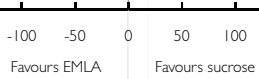
Outcome: 1 Cry time (%)

Study or subgroup	EMLA N	Mean(SD)	Sucrose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Zahorodny 1998	13	66 (24.5)	13	76 (18.66)		100.0 %	-10.00 [-26.74, 6.74]
Total (95% CI)	**13**		**13**			**100.0 %**	**-10.00 [-26.74, 6.74]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Not applicable



Analysis 14.2. Comparison 14 EMLA versus sucrose, Outcome 2 Heart rate (bpm).

Review: Pain relief for neonatal circumcision

Comparison: 14 EMLA versus sucrose

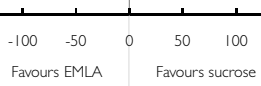
Outcome: 2 Heart rate (bpm)

Study or subgroup	EMLA N	Mean(SD)	Sucrose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Mohan 1998	20	147.88 (15.86)	21	157.23 (19.12)		100.0 %	-9.35 [-20.08, 1.38]
Total (95% CI)	**20**		**21**			**100.0 %**	**-9.35 [-20.08, 1.38]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.71 (P = 0.088)

Test for subgroup differences: Not applicable



Analysis 14.3. Comparison 14 EMLA versus sucrose, Outcome 3 Oxygen saturation (%).

Review: Pain relief for neonatal circumcision

Comparison: 14 EMLA versus sucrose

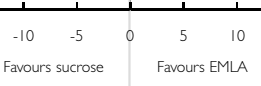
Outcome: 3 Oxygen saturation (%)

Study or subgroup	EMLA N	Mean(SD)	Sucrose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Mohan 1998	20	95.38 (2.28)	21	96.2 (3.52)		100.0 %	-0.82 [-2.63, 0.99]
Total (95% CI)	**20**		**21**			**100.0 %**	**-0.82 [-2.63, 0.99]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable



Analysis 14.4. Comparison 14 EMLA versus sucrose, Outcome 4 Systolic blood pressure (mmHg).

Review: Pain relief for neonatal circumcision

Comparison: 14 EMLA versus sucrose

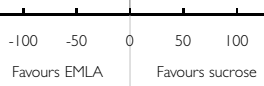
Outcome: 4 Systolic blood pressure (mmHg)

Study or subgroup	EMLA N	Mean(SD)	Sucrose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Mohan 1998	20	71.78 (17)	21	83.5 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**20**		**21**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 14.5. Comparison 14 EMLA versus sucrose, Outcome 5 Diastolic blood pressure (mmHg).

Review: Pain relief for neonatal circumcision

Comparison: 14 EMLA versus sucrose

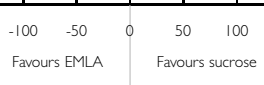
Outcome: 5 Diastolic blood pressure (mmHg)

Study or subgroup	EMLA N	Mean(SD)	Sucrose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Mohan 1998	20	43.05 (22)	21	51.95 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**20**		**21**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

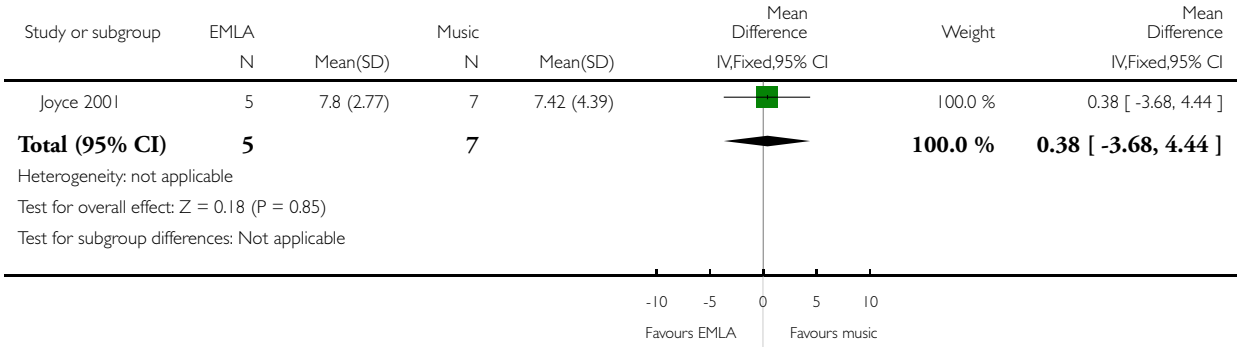


Analysis 15.1. Comparison 15 EMLA versus music, Outcome 1 Cry time (min).

Review: Pain relief for neonatal circumcision

Comparison: 15 EMLA versus music

Outcome: 1 Cry time (min)

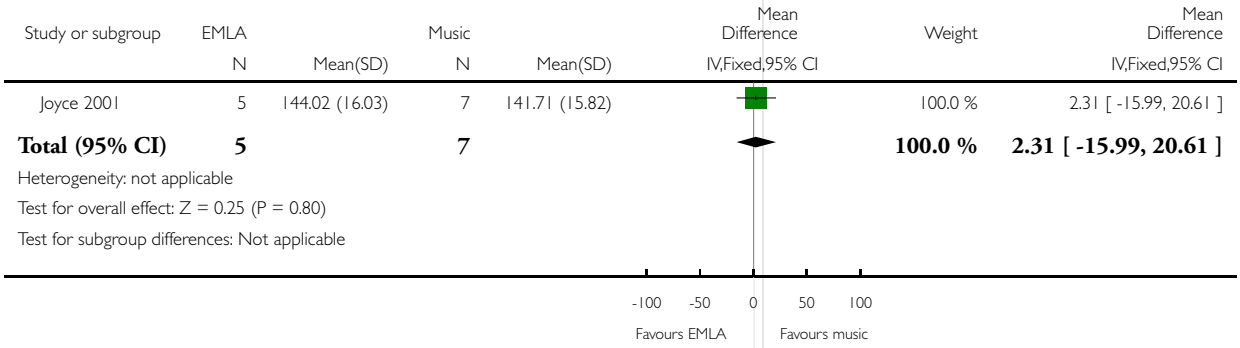


Analysis 15.2. Comparison 15 EMLA versus music, Outcome 2 Heart rate (bpm).

Review: Pain relief for neonatal circumcision

Comparison: 15 EMLA versus music

Outcome: 2 Heart rate (bpm)



Analysis 15.3. Comparison 15 EMLA versus music, Outcome 3 Oxygen saturation (%).

Review: Pain relief for neonatal circumcision

Comparison: 15 EMLA versus music

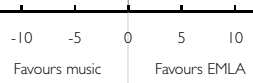
Outcome: 3 Oxygen saturation (%)

Study or subgroup	EMLA N	Mean(SD)	Music N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Joyce 2001	5	94.4 (3.22)	7	94.21 (3.33)		100.0 %	0.19 [-3.56, 3.94]
Total (95% CI)	**5**		**7**			**100.0 %**	**0.19 [-3.56, 3.94]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Not applicable



Analysis 15.4. Comparison 15 EMLA versus music, Outcome 4 Respiratory rate (rpm).

Review: Pain relief for neonatal circumcision

Comparison: 15 EMLA versus music

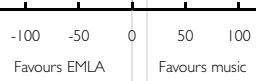
Outcome: 4 Respiratory rate (rpm)

Study or subgroup	EMLA N	Mean(SD)	Music N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Joyce 2001	5	48.13 (12.95)	7	46.61 (13.49)		100.0 %	1.52 [-13.60, 16.64]
Total (95% CI)	**5**		**7**			**100.0 %**	**1.52 [-13.60, 16.64]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable

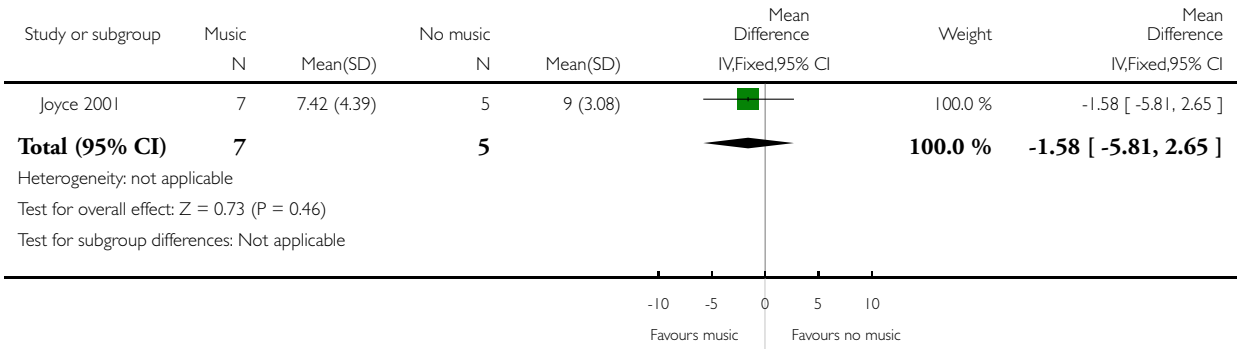


Analysis 16.1. Comparison 16 Music versus no treatment, Outcome 1 Cry time (min).

Review: Pain relief for neonatal circumcision

Comparison: 16 Music versus no treatment

Outcome: 1 Cry time (min)

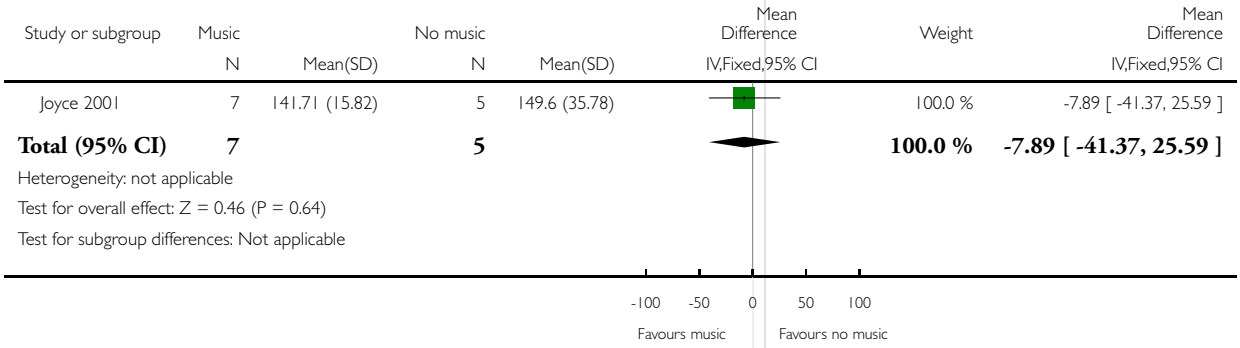


Analysis 16.2. Comparison 16 Music versus no treatment, Outcome 2 Heart rate (bpm).

Review: Pain relief for neonatal circumcision

Comparison: 16 Music versus no treatment

Outcome: 2 Heart rate (bpm)



Analysis 16.3. Comparison 16 Music versus no treatment, Outcome 3 Oxygen saturation (%).

Review: Pain relief for neonatal circumcision

Comparison: 16 Music versus no treatment

Outcome: 3 Oxygen saturation (%)

Study or subgroup	Music N	Mean(SD)	No music N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Joyce 2001	7	94.21 (3.33)	5	91.7 (2.19)		100.0 %	2.51 [-0.62, 5.64]
Total (95% CI)	**7**		**5**			**100.0 %**	**2.51 [-0.62, 5.64]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.57 (P = 0.12)

Test for subgroup differences: Not applicable

Analysis 16.4. Comparison 16 Music versus no treatment, Outcome 4 Respiratory rate (rpm).

Review: Pain relief for neonatal circumcision

Comparison: 16 Music versus no treatment

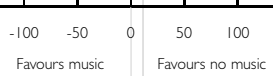
Outcome: 4 Respiratory rate (rpm)

Study or subgroup	Music N	Mean(SD)	No music N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Joyce 2001	7	46.61 (13.49)	5	52.44 (13.63)		100.0 %	-5.83 [-21.41, 9.75]
Total (95% CI)	**7**		**5**			**100.0 %**	**-5.83 [-21.41, 9.75]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.73 (P = 0.46)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Trials assessing pain/behavior scores

Study ID	scale	measurement method	data reported	data preparation
Arnett 1990	infant irritability irritabilify graded subjectively on a scale of 1 to 6 with 1 representing the least crying/agitation and 6 the most	nurse and physician rating of infant irritability graded before, during and 1 hour after circumsion	mean/SD of assessment during procedure	data entered into meta-analysis as reported
Benini 1993	Neonatal Facial Action Coding System (Grunau , 1990b) 10 facial actions scored, 7 (brow bulge, eye squeeze, nasolabial furrow, open mouth, vertical stretching of mouth, horizontal stretching of mouth, taut tongue) entered into analysis	facial actions videotaped continuously, second by analysis of facial actions 10 facial actions scored, 7 facial actions entered into analysis total score computed by summing 7 categories	outcome data (means/SDs) obtained from authors	cal- culate arithmetic mean of scores across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var (x) + Var(Y) + 2Cov(X, Y)) "procedure" = [application of dorsal clamp, incision, adhesion lysis, Gomco clamp on, foreskin excision, Gomco clamp off, restraints removed]
Butler-O'Hara 1998	Neonatal Infant Pain Scale (NIPS) consists fo 6 behavioral components with a composite score of 0 to 6 5 components used - facial expression, cry, breathing pattern, arm movements, state of arousal (Lawrence, 1993)	procedure videotaped NIPS scores assigned for each of 6 events (clamping of foreskin, adhesion lysis, dorsal cut, adhesion lysis, tying of Plastibell, foreskin excision) mean NIPS score calculated for each infant	mean(SD) NIPS score/group	data entered into meta-analysis as reported
Dixon 1984 (Holve 1983 is primary study report)	Brazelton Neonatal Assessment Scale (BNAS) consists of 27 behavioral items, each scored on scale of 1 to 9, and 20 reflexes scored on 3 point scale scale examines organi-	examinations conducted prior to (exam 1), following the circumcision (exam 2), and 1 day after circumcision (exam 3)	mean scores/item for 3 exam times	states "variation in item scores precluded determination of statistically significant differences between groups' not included in meta-analysis

Table 1. Trials assessing pain/behavior scores (*Continued*)

	zation and integration of behavior in response to positive and adversive situations			
Hardwick-Smith 1998	behavioral state (Stang et al 1988) score 1 - 6 in order of increasing arousal	scored at baseline, 10 intervals during procedure, and 2 hr post-circumcision	p values	not included in meta-analysis
Holliday 1999	behavioral scale - includes 8 behavior state variables (sleep state, cry, facial expression, torso movement, soothability, response to distress, need for tactile stimulation, environmental noise) each variable scored 1 to 6, scores totaled for each infant	assessed 20 min before, during and after circumcision	means scores/group reported in graph format	graph extractions to obtain mean/SD
Howard 1994	Postoperative Comfort Score (Attia 1987) 10 behaviors, each scored 0, 1, or 2, possible scores 0 to 20, lower score = less comfortable	assessed baseline, and postcircumcision at 30, 60, 90, 120, 360 min	mean/SD scores/group/interval mean/ SD change from baseline scores/group/interval	data entered into meta-analysis as reported for 30 min post-circumcision scores
Howard 1999	behavioral distress scale (from Stang et al 1997) score 0 - 3 based on Brazelton statte assessment score 0 = neutral to 3 = sustained cry	videotape of procedure assessed and scores assigned every 30 s of the procedure	mean/SE scores / group for stages 2 to 6 of procedure	data entered into meta-analysis as reported "procedure" = [block administration to recovery; includes 4 min WT and Gomco clamp left on for 5 min]
Joyce 2001	Riley Infant Pain Scale 6 categories of behavior (vocal, facial expression, body movement, sleep, consolability, response to touch) rates on scale of 0 (no pain) to 3 (severe pain)	videotape of procedure assessed at baseline, undressing, restraints, cleanse, clamping, cutting, end of procedure, 15 min post and 30 min post	RIPS score / group / phase presented in graphic format p values	not included in meta-analysis

Table 1. Trials assessing pain/behavior scores (*Continued*)

Kass 2001	MBPS - modified behavioral pain scale (Taddio et al, 1995) rates facial expression, crying, and body movements to obtain a score of 0 to 10	scored at 30 s intervals	mean/SD for baseline and procedure MBPS / group obtained from authors	mean/SD procedure scores entered into meta-analysis
Macke 2001	Nursing Child Assessment Feeding Scale (NCAFS) 76 behavioral binary items (yes,no) grouped into 6 subscales based on concepts of adaptation and synchronism	scored during feeding interaction before and after circumcision	mean/SD score pre/post circumcision	data included as reported
Newton 1999	Brazelton Neonatal Assessment Scale - scale categorized to 6 level\s - (deep sleep (1) , light sleep (2) drowsy (3), quiet alert (4) active alert (5) crying (6) (Brazelton, 1984)	3 evaluations - baseline, injection, clamp application	modal state/group	data not included
Stang 1988	behavioral state 6 levels = quiet sleep (1), active sleep (2), drowsy (3), alert (4), active awake (5), crying (6) (Brazelton, 1973)	assessed at baseline, during injection, during circumcision, and 30 min from the start of the circumcision	modal response / group / time period	data not included
Stang 1997	behavioral state scale and behavioral distress scale 4 levels - neutral (0), minimal fuss (1), moderate fuss (2), sustained cry (3) (Brazelton, 1973)	behavioral state and distress scored every 30 s beginning 2 min before circumcision scores averaged for 5 periods - preinjection, injection, 2 min post-injection, 4 min post-injection, circumcision	mean/SD /group / study period	mean/SD for circumcision period included
Taddio 1997	Neonatal Facial Coding System (Grunau et al, 1987; 1990) codes presence or absence of	facial actions continuously recorded on videotape facial actions scored from videotape in	mean/95% confidence intervals for facial activity score / group / 13 phases reported in graph format	data extraction to obtain mean/SD facial score for circumcision phases circumcision (7 phases) = [application of forceps

Table 1. Trials assessing pain/behavior scores (*Continued*)

	10 discrete facial actions (brow bulge, eye squeeze, nasolabial furrow, open mouth, vertical stretching of mouth, horizontal stretching of mouth, lip pursing, taut tongue, chin quiver, tongue protrusion) higher score = more pain	2 s intervals for first 20 s of each phase raw scores of each facial action expressed as proportion of time observed/phase; poorly correlated facial actions deleted leaving 6 facial actions; the six scores were weighted and totaled to arrive at overal score for facial action	data extracted from graphs	to foreskin excision] calculate arithmetic mean/group across phases of circumcision calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var (x) + Var(Y) + 2Cov(X, Y)) SE = ((high CI - low CI) /2)/1.96 SD = SE (sqrt(n))
Weatherstone 1993	newborn pain behavior scale adapted from 3 other scales (Brazelton 1973; Yarrow 1975; Ross 1988) score includes assessment of behavioral state, leg and arm movement, facial expression, torso movement, respiratory pattern, soothability, response to distress by caregivers, tactile stimulation	videotape of procedure scored in 30 s intervals	increase in mean/SD % of time behavior observed post-cirucmcision compared to pre- circumcision/group	data not included

Table 2. Trials assessing heart rate outcome variables

Study ID	measurement method	data reported	preparation of data
Arnett 1990	HR measured by pulse oximetry at baseline, every min for 4 min, and 5 min post-circumcision	mean HR/group/phase reported in graph format	graph extraction for means graph extraction for SDs (averaged over 4 phases of the circumcision procedure) "procedure" = [min 1 to min 4]; steps not described or standardized
Benini 1993	HR measured continuously by pulse oximeter	outcome data (mean/SDs) obtained from authors	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y)

Table 2. Trials assessing heart rate outcome variables (*Continued*)

			+ 2Cov(X,Y)) "procedure" = [application of dorsal clamp, incision, adhesion lysis, Gomco clamp on, foreskin excision, Gomco clamp off, restraints removed]
Butler-O'Hara 1998	HR monitored continuously using cardiac monitor	mean/SD heart rate (bpm) at completion of circumcision by group mean/SD heart rate (bpm) change from baseline at completion of circumcision by group	data entered into meta-analysis as reported
Joyce 2001	HR monitored continuously using cardiac monitor	data (bpm) obtained from authors	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [cut, end of procedure]
Hardwick-Smith 1998	HR monitored continuously using cardiac monitor highest HR recorded at start of each interval	increase in HR from baseline per group for operative interval reported in graph format	graphs did not depict SDs (whiskers); researchers reported control infants had significantly greater increase over baseline during 7 out 10 operative intervals; they did not comment on differences between the groups/interval
Herschel 1998	HR monitored continuously using cardiac monitor	mean/SD HR (bpm) change from baseline during procedure by group	data entered into meta-analysis as reported "procedure" = lateral clamp of foreskin to foreskin excision
Holliday 1999	HR monitored continuously using cardiac monitor HR recorded every 5 min before, during, 5 and 20 min after circumcision	mean/SD HR (bpm)/group reported in graph format for 4 time points (before, during, 5 min after, 20 min after)	graph extraction to obtain mean/SD during procedure
Holve 1983	HR continuously recorded using monitor	mean change in HR from baseline (bpm) weighted averages/group for 6 phases reported in graphic format	no SDs, SEs depicted on graphs

Table 2. Trials assessing heart rate outcome variables (*Continued*)

Howard 1994	HR counted via auscultation every 30 s	mean/SD HR (bpm) / group / phase mean/SD HR (bpm) change from baseline by group/phase	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [dissection, clamp on, excision, clamp off]
Howard 1999	HR recorded every 60 s using cardiac monitor	- mean/SE HR (bpm) during procedure by group	means included as reported convert SE to SD using formula: SD = SE (sqrt (n)) "procedure" = [block administration to recovery; includes 4 min WT and Gomco clamp left on for 5 min]
Kass 2001	HR monitored at 1 min intervals during procedure	mean/SD HR (bpm) during procedure by group obtained from authors	mean/SD entered into meta-analysis
Kurtis 1999	HR monitored continuously using cardiac monitor	mean/SD % HR change from baseline during procedure by clamp used (Mogen, Gomco) and by penile block status (block, no block)	data entered into meta-analysis as reported "procedure" = [lysing adhesions to 60 sec after closing clamp]
Lander 1997	HR monitored continuously using cardiac monitor	mean/SD HR (bpm) change from baseline by phase by group	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [separation, clamp on, clamp off]
Macke 2001	HR recorded every 15 s using cardiac monitor	mean/SD HR (bpm) during circumcision by group	data included as reported
Marchette 1989	HR monitored	mean HR /phase / group no SDs reported	not included
Marchette 1991	HR monitored and data collected during 14 cirumcision steps	RMANOVA over 14 steps	not included

Table 2. Trials assessing heart rate outcome variables (*Continued*)

Masciello 1990	HR monitored continuously using cardiac monitor peak HR during each step recorded	mean HR as a percent of baseline HR reported in graphic format	not included
Maxwell 1987	HR monitored continuously by pulse oximeter peak HR during each period recorded	mean/SD HR change / group / period as a % of control (baseline) reported in graph format	graph extraction to obtain mean/SD during circumcision procedure
Mohan 1998	HR monitored continuously by pulse oximeter HR recorded at each of 9 steps	mean HR / group / procedure step reported in graph format	graph extraction to obtain mean HR / group / procedure step substituted weighted average treatment-specific SDs from 5 studies: Benini 1993, Joyce 2001, Lander 1997, Taddio 1997, Woodman 1999 for EMLA and from 3 studies: Herschel 1998, Kass 2001, Zolnoski 1993 for sucrose
Mudge 1989	HR measured by monitor at 5 time points during circumcision	mean HR / group / event reported in graph format RMANOVA for 4 events (adhesion breakdown to clamp off)	graph extraction to obtain mean HR/group for events 2 - 5 calculate arithmetic mean HR / group across 4 phases of the procedure (adhesion breakdown, clamp on, tighten clamp, clamp off) substitute SDs from Woodman 1999 who applies same outcome to same comparison
Newton 1999	HR monitored continuouslly by pulse oximeter HR recorded at 10 s intervals	mean/SD HR / group at baseline, injection, clamp application	included as reported
Spencer 1992	HR monitored by pulse oximeter recorded highest HR for each of 6 events	mean change in HR (bpm) from baseline / group / event	no SDs, not included
Taddio 1997	HR continuously monitored by cardiac monitor	mean/SD HR (bpm) change from baseline during procedure	data included as reported "procedure" = [forcep application, lysis of adhesions, dorsal incision, clamp application, pull foreskin through clamp, tighten clamp, cut foreskin] procedure does not include clamp removal at 5 min after cut foreskin

Table 2. Trials assessing heart rate outcome variables (*Continued*)

Weatherstone 1993	HR monitored at 5 min intervals for 20 min	none	not included
Williamson 1983	HR monitored continuously	mean/SD HR (bpm) change from baseline for 3 min "dissection" period	mean/SD data included as reported dissection does not include clamp application
Woodman 1999	HR monitored continuously using pulse oximeter recorded peak heart rate during or immediately following 7 stages of circumcision procedure	mean/SD peak HR (bpm) / group	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [clamp, adhesionlysis, dorsal clamp, bell on, clamp tightening, bell off]
Zolnoski 1993	HR monitored continuously using cardiac monitor HR (bpm) recorded at beginning of 7 procedure steps	- mean/SD HR (bpm) /group for 4 procedure steps	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y))

Table 3. Trials assessing cry outcome variables

Study ID	**measurement method**	**data reported**	**data preparation**
Benini 1993	cry tape recorded	% time crying/phase (duration of time crying) reported in graph format	means, SEs (assumed) extracted from graph; calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var (Y) + 2Cov(X,Y)) "procedure" = [dorsal clamp, incision, lysis, clamp on, foreskin cut, clamp off, unrestrained]
Blass 1991	cry tape recorded	mean % time crying (duration of time crying) during entire procedure reported in graph format	- graph extraction of group mean/SE; - SD calulated using formula:

Table 3. Trials assessing cry outcome variables (*Continued*)

			SD = SE (sqrt (n))
Holve 1983	cry tape recorded	mean % time crying /interval reported in graphic format	no SDs, not included
Hardwick-Smith 1998	cry tape recorded	mean/SD minutes crying/group during operative interval (lateral clamping to clamp removal)	convert reported time to seconds data included in meta-analysis
Howard 1994	used stopwatch to time crying during each phase	mean/SD % time crying by group/phase mean/SD % time crying change from baseline/group/phase	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var (Y) + 2Cov(X,Y)) "procedure" = [dissection, clamp on, excision, clamp off]
Joyce 2001	behavior videotaped calculated total time crying from start of foreskin cut until crying ceased or 30 min elapsed	cry time (min) for each subject obtained from authors	calculate mean/SD time crying in min and sec/group
Kass 2001	primary outcome variable behavior videotaped	mean/SD time crying (s) /group during procedure obtained from authors	mean/SD included in meta-analysis
Kurtis 1999	behavior videotaped calculated time crying using stopwatch	mean/SD % time crying during procedure reported by clamp used (Mogen, Gomco) and by penile block status (block, no block)	mean/SD included as reported
Lander 1997	behavior videotaped proportion of time crying calculated/subject	mean/SD % time crying/interval	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var (Y) + 2Cov(X,Y))- "procedure" = [separation, clamp on, clamp off)
Macke 2001	continuous vocalizations of 15 s or more classified as crying and tape recorded total s used to calculate % time crying	mean/SD % time crying during circumcision period by group	data included as reported

Table 3. Trials assessing cry outcome variables (*Continued*)

Mohan 1998	stopwatch used to measure duration of crying	mean % time crying / group during entire procedure	not included
Mudge 1989	crying time tape recorded during procedure measured by stop watch	mean total crying time (s)/group for entire procedure t-statistic, p value	mean crying time included as reported SD imputed from t statistic procedure includes 5 events (baseline, adhesion breakdown, clamp on, tighten clamp, clamp off)
Spencer 1992	cry duration measured by modified Brazelton Neonatal behavioral Scale (Stang et al, 1988) 6 behavioral states recorded for each of 6 events	mean % change from baseline / group	no SDs, not included
Stang 1988	not described	mean/SEM % time crying during circumcision period/group	means included as reported SEM converted to SD using formula: SD = SEM (sqrt (n))
Taddio 1997	behavior videotaped calculated % of time crying during each phase	mean/SD % increase from baseline in time crying during procedure	data included as reported "procedure" = [forcep application, lysis of adhesions, dorsal incision, clamp application, pull foreskin through clamp, tighten clamp, cut foreskin] does not include clamp removal at 5 min after foreskin cut
Williamson 1983	time crying recorded using event marker	mean/SD % time crying change from baseline during 3 min dissection period	mean/SD data included as reported
Woodman 1999	behavior videotaped recorded time crying based on facial actions with or without audible cry	mean/SD time crying (s) for 6 phases by group	add time crying for 6 of 8 stages (clamp, adhesionlysis, dorsal clamp, clamp on, clamp tightening, clamp off) to obtain total time crying during procedure add SD to obtain total SD for group
Zahorodny 1998	not reported	mean % time crying/group	substituted weighted average treatment-specific SDs from three other studies: Benini 1993, Lander 1997, Taddio 1997 for EMLA vs placebo/ no treatment substituted treatment-specific

Table 3. Trials assessing cry outcome variables (*Continued*)

			SDs from Blass 1991 A (also versus water) for sucrose vs placebo/ no treatment substituted with the SDs used in the two above comparisons for EMLA vs sucrose
Zolnoski 1993	cry tape recorded, measured using stopwatch	time cry (s)/infant	mean/SD cry time (s)/group calculated

Table 4. Trials assessing oxygen saturation outcome variables

Study ID	measurement method	data reported	data preparation
Arnett 1990	measured by pulse oximetry at baseline, every min for 4 min during procedure, and 5 min postcircumcision	mean oxygen saturation (%) / group / phase and SDs presented graphically	graph extraction of means, graph extraction of SDs, averaged over 4 phases
Benini 1997	O2sat continuously monitored using pulse oximeter	outcome data (mean/SD) obtained from authors	calculate arithmetic mean/group across phases of the procedure calculate variance for arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) procedure = [application of dorsal clamp, incision, adhesion lysis, Gomco clamp on, foreskin excision, Gomco clamp off, restraints removed]
Hardwick-Smith 1998	O2sat monitored continuously by pulse oximeter, lowest O2sat recorded at the start of each interval during some intervals of procedure, O2sat not recorded in up to 50% of infants	mean/SD of O2sat (%)/group for operative intervals	data included in meta-analysis as reported "operative interval" = [llateral clamp, blunt dissection, dorsal clamp, adhesion takedown, Gomco bell on, Gomco clamp applied, Gomco clamp removed]
Herschel 1998	O2sat continuously monitored via pulse oximetry substantial proportion of data lost due to excessive motion (31% control, 10% DPNB, 8% sucrose)	mean/SD O2sat (%) change from baseline during operative procedure by group	data included in meta-analysis as reported "operative procedure" = [lateral clamp of foreskin, adhesion lysis, dorsal clamp, dorsal cut, foreskin retraction, Gomco application, Gomco tightened, foreskin excision]

Table 4. Trials assessing oxygen saturation outcome variables (*Continued*)

Holliday 1999	O2sat continuously monitored, recorded every 5 min before, during, 5min and 20 min after circumcision	mean/SD O2sat (%)/group reported in graph format for 4 time points (before, during, 5 min after, 20 min after)	graph extraction for mean/SD during procedure
Joyce 2001	O2sat monitored continuously using pulse oximeter recorded O2sat (%) at each of 6 data collection points	raw data per subject per 6 phases obtained from authors	calculate mean/SD by group/phase calculate arithmetic mean/group across phases of the procedure calculate variance for arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) procedure = [cut, end]
Kass 2001	monitored O2sat at 1 min intervals during procedure	mean/SD O2sat during procedure by group data obtained from authors	mean/SD included in meta-analysis
Kurtis 1999	O2sat (%) monitored continuously and transferred to computer	- mean/SD % change from baseline during procedure reported by clamp used (Mogen, Gomco) and by penile block status (block, no block)	data included in meta-analysis as reported procedure = [lysing adhesions to 60 sec after closing clamp]
Marchette 1991	tcpO2 monitored and recorded during 14 circumcision steps	RMANOVA over 14 steps	not included
Masciello 1990	O2sat monitored continuously by pulse oximeter lowest level during each interval recorded	mean O2sat / group / interval reported in graphic format	not included
Maxwell 1987	O2sat monitored continuously using pulse oximeter peak value during period recorded	mean/SD O2sat /group / period reported in graph format	graph extraction to obtain mean/SD during circumcision period
Mohan 1998	O2sat monitored continuously using pulse oximeter recorded at each of 9 procedure steps	mean O2sat / group / procedure step reported in graph format	graph extraction to obtain mean O2sat / group / step substituted weighted average treatment-specific SDs from 3 trials: Benini 1993, Joyce 2001, Woodman 1999 for EMLA and from 2 trials: Herschel 1998, Kass 2001 for sucrose

Table 4. Trials assessing oxygen saturation outcome variables (*Continued*)

Mudge 1989	O2sat measured by pulse oximeter and recorded at five time points during circumcision	mean O2sat (%) /group/event reported in graph format	graph extraction to obtain mean O2sat/group for events 2 - 5 calculate arithmetic mean O2sat / group across 4 phases of the procedure (adhesion breakdown, clamp on, tighten clamp, clamp off)
Spencer 1992	O2sat monitored by pulse oximeter recorded lowest level for each of 6 events	mean O2sat % change from baseline / group / event	no SDs, not included
Weatherstone 1993	O2sat monitored at 5 min intervals for 20 min	none	not included
Williamson 1983	O2sat measured using transcutaneous electrode (tcpO2)	mean/SD O2sat (torr) change from baseline for 3 min dissection period	data included in meta-analysis as reported dissection does not include clamp application
Woodman 1999	O2sat monitored continuously using pulse oximeter recorded peak/nadir during or immediately following 7 stages of circumcision procedure	- mean/SD peak/nadir O2sat / stage / group	calculate arithmetic mean/group across phases of the procedure calculate variance for arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) procedure = [clamp, adhesiolysis, dorsal clamp, clamp on, clamp tightening, clamp off)

Table 5. Trials assessing respiratory rate outcome variables

Study ID	measurement method	data reported	preparation of data
Butler-OHara 1998	RR monitored continuously starting after anesthetic administration, and 1 and 4 hr after procedure	RR variable and difficult to evaluate not reported	not included in meta-analysis
Hardwick-Smith 1998	highest RR recorded at start of each interval (anesthesia/restraint, 3 min post restraint/anesthesia, lateral clamp, blunt dissection, dorsal clamp, adhesion breakdown, Gomco bell on, Gomco clamp on, Gomco clamp re-	mean/SD increase from baseline RR/group for operative intervals (lateral clamping to Gomco clamp removal)	data included in meta-analysis as reported

Table 5. Trials assessing respiratory rate outcome variables (*Continued*)

	moved)		
Holliday 1999	RR monitored continuously using cardiac monitor HR recorded every 5 min before, during, 5 and 20 min after circumcision	mean/SD RR (bpm)/group reported in graph format for 4 time points (before, during, 5 min after, 20 min after)	graph extraction for mean/SD during procedure
Howard 1994	RR assessed by visual observation every 30 s	mean/SD RR (rpm) / group / phase mean/SD RR (rpm) change from baseline by group/phase	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [dissection, clamp on, excision, clamp off]
Howard 1999	RR counted and recorded every 60 s	mean/SE RR (rpm) by group for procedure	means included as reported convert SE to SD using formula: SD = SE (sqrt (n)) "procedure" = [block administration to recovery; includes 4 min WT and Gomco clamp left on for 5 min]
Joyce 2001	RR monitored continuously, recorded at 6 data collection points	raw data obtained from authors	calculate arithmetic mean/group across phases of the procedure calculate variance for the arithmetic mean using general formula for linear combinations of variance (i.e. Var (X+Y) = Var(x) + Var(Y) + 2Cov(X,Y)) "procedure" = [cut, end of procedure]
Kurtis 1999	RR monitored continuously using physiologic monitor	mean/SD % change from baseline during procedure reported by clamp used (Mogen, Gomco) and by penile block status (block, no block)	data entered into meta-analysis as reported "procedure" = [lysing adhesions to 60 sec after closing clamp]
Mudge 1989	RR measured by pneumography monitor at 5 time points	mean RR / group / event reported in graph format RMANOVA for 4 events (adhesion breakdown to clamp off)	graph extraction to obtain mean RR/group for events 2 - 5 calculate arithmetic mean RR / group across 4 phases of the procedure (adhesion breakdown, clamp on, tighten clamp, clamp off)

Table 5. Trials assessing respiratory rate outcome variables (*Continued*)

Weatherstone 1993	RR monitored at 5 min intervals for 20 min	none	not included

Table 6. Trials assessing biochemical outcome variables

Study ID	measurement method	data reported	data preparation
Masciello 1990	blood drawn via heel stick 30 minutes post-circumcision	mean/SD plasma cortisol levels in mg/dL	mg/dL multiplied by 27.59 = nmol/L nmol/L included in meta-analysis
Stang 1988	blood drawn via heel stick for 1/2 subjects at 30 min post-circumcision, and 90 min for remaining 1/2 subjects	mean/SEM plasma cortisol levels in nmol/L and ug/dL	means (nmol/L) included in meta-analysis SEM converted to SD using formula: SD = SEM (sqrt(n))
Williamson 1986	blood drawn by heel stick at baseline and 30 min post-circumcision	mean/SEM plasma cortisol levels in ug/dL	SEM converted to SD using formula: SD = SEM (sqrt(n)) ug/dL
Holliday 1999	serum B-endorphin levels - blood sample taken before and 20 min post-circumcision	mean/SD / group in pmol/L	data included as reported
Joyce 2001	salivary cortisol samples collected at baseline abd 30 min after procedure	mean/SD before/after no units of measurement results not broken down by group	not included
Kurtis 1999	salivary cortisol	collected sample at baseline and 30 min post-circumcision	mean/SD included as reported
Stang 1997	plasma cortisol 30 min after beginning of circumcision	mean/SD / group nmol/dL and ug/dL	mean /SD (nmol/dL) included as reported
Weatherstone 1993	serum B-endorphin level taken preoperatively and 15 min after circumcision	mean/SD B-endorphin level (pg/mL) for pre and post circumcision period/group	mean/SD level for post-circumcision period included as reported
Williamson 1986	plasma cortisol obtained at baseline and 30 min after Gomco clamp applied	mean/SEM plasma cortisol levels (ug/dL)/group	ug/dL multiplied by 27.59 = nmol/L SEM converted to SD using formula: SD = SEM (sqrt(n))

Table 7. Trials assessing blood pressure outcome variables

Study ID	measurement method	data reported	data preparation
Holliday 1999	systolic BP monitored continuously using cardiac monitor HR recorded every 5 min before, during, 5 and 20 min after circumcision	mean/SD BP (mmHg)/group reported in graph format for 4 time points (before, during, 5 min after, 20 min after)	graph extraction for mean/SD during procedure
Marchette 1991	systolic and diastolic BP monitored and recorded during 14 steps of the cirumcision procedure	RMANOVA over 14 steps	not included
Maxwell 1987	BP measured by Doppler every 5 min	mean/SD systolic BP change as a % of control / group / period reported in graph format	graph extraction to obtain mean/SD during circumcision period
Mohan 1998	systolic and diastolic BP measured over upper arm at each of 9 procedural steps	mean systolic and diastolic BP (mm Hg) reported in graph format	graph extraction to obtain mean / group / step substituted treatment-specific SDs from Taddio 1997 for EMLA; no SDs available for sucrose
Taddio 1997	systolic and diastolic BP measured at baseline and during lysis of adhesions	mean/SD increase mm Hg in systolic and diastolic BP	data included as reported
Weatherstone 1993	BP monitored at 5 min intervals for 20 min	none	not included

Table 8. Trials reporting adverse effects

Study ID	intervention(s)	adverse effects
Arnett 1990	0.4 ml lidocaine DPNB (n=23) 0.4 ml saline DPNB (n=22) control (n=7)	lidocaine group - 1 emesis treated with suction saline group - 2 bleeding post-procedure, 1 required suture control - 1 bleeding post-procedure controlled with pressure
Butler-O'Hara 1998	0.5 ml LP cream (n=21) 0.7 ml - 1.0 ml lidocaine DPNB + placebo cream (n=23)	DPNB group - 10 hematoma; 1 penile edema on day 5 LP cream group - 3 erythema
Holve 1983 & (primary study) Dixon 1984	0.8 ml lidocaine DPNB (n=15) 0.8 ml saline DPNB (n=8)	lidocaine group - 1 small unilateral hematoma

Table 8. Trials reporting adverse effects (*Continued*)

	control (n=8)	
Holliday 1999	0.8 ml lidocaine DPNB + placebo cream (n=19) placebo cream (n=19) original protocol included LP cream group (n=12)	LP cream group - 2 redness and blistering of foreskin, LP cream group discontinued
Lander 1997	2 g LP cream (n=15) placebo cream (n=12) 0.8 ml lidocaine DPNB (n=14) 0.8 ml lidocaine RB (n=13)	placebo group - 1 apnea and emesis, 1 choking and apnea
Newton 1999	0.8 ml lidocaine DPNB (n=92) 0.8 ml buffered lidocaine DPNB (n=102)	lidocaine group - 4 had minor bleeding buffered lidocaine group - 6 had minor bleeding
Stang 1988	0.8 ml lidocaine DPNB (n=20) 0.8 ml saline DPNB (n=20) control (n=20)	occasional insignificant bleeding - groups and numbers not specified
Taddio 1997	1 g LP cream (n=29) 1 g placebo cream (n=30)	LP cream group - 12 minor foreskin pallor, 1 mild edema placebo group - 4 minor foreskin pallor
Williamson 1997	lidocaine DPNB (n=20) control (n=10)	DPNB group - 9 bleeding, 12 swelling, 1 erythema control group - 5 bleeding, 5 swelling, 1 hematoma, 3 erythema
Zolnoski 1993	2.4 ml 24% sucrose (n=10) 2.4 ml water (n=10)	sucrose group - 1 gagging water group - 2 regurgitation after circumcision

WHAT'S NEW

Last assessed as up-to-date: 2 August 2005.

Date	Event	Description
28 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 3, 2004

Date	Event	Description
3 August 2005	New search has been performed	This review updates the existing review "Pain relief for neonatal circumcision" which was published in The Cochrane Library Issue 3, 2004 (Brady-Fryer 2004). The review has been updated to correct the numbers reported for total patients randomized for the included trials. Results of meta-analyses were not effected except in one case, comparison 03.02 where the effect size changed from [WMD = 15.8%, 95% CI -20.8 to -6.8] to [WMD = 15. 22%; 95% CI 21.08 to 9.36]. Abstract was changed to note that data from three (not four) trials of DPNB versus EMLA including 133 patients were subjected to meta-analysis. No new trials were identified as a result of the most recent search
1 May 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Brady-Fryer - protocol development; study selection; data extraction; contact authors; data preparation & analysis; write report

Wiebe - data extraction; data preparation & analysis; write report

Lander - protocol development and review; review draft and final report

Brankston - study selection; data extraction

DECLARATIONS OF INTEREST

Two of the reviewers, Brady-Fryer and Lander, were authors of a trial, Lander 1997, included in this review.

SOURCES OF SUPPORT

Internal sources

- Capital Health, Canada.
- Faculty of Nursing, University of Alberta, Canada.

External sources

- Alberta Association of Registered Nurses, Canada.
- Canadian Nurses Association, Canada.
- Canadian Health Services Research Foundation, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics; Anesthetics, Local; Circumcision, Male [*adverse effects]; Infant, Newborn; Lidocaine; Nerve Block [methods]; Pain [*prevention & control]; Pain, Postoperative [prevention & control]; Prilocaine; Randomized Controlled Trials as Topic

MeSH check words

Humans; Male