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Breastfeeding for procedural pain in infants beyond the neonatal period (Protocol)

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[Intervention Protocol]

Breastfeeding for procedural pain in infants beyond the neonatal period

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the effect of breastfeeding on procedural pain in infants beyond the neonatal period (first 28 days of life) up to one year of age, undergoing painful procedures, compared to no intervention, placebo, parental holding, breast or formula milk, oral sucrose or glucose, distraction, or other interventions.

BACKGROUND

Infants and children require needle-related painful procedures for scheduled childhood immunisations (PHA Canada 2014) as well as medical procedures performed for diagnostic and treatment purposes during the course of childhood illnesses (Johnston 2011). Such procedures are known to be painful, causing distress at the time of the procedure and for many children, anxiety and fear during subsequent needle-related procedures (Schechter 2007; Taddio 2007; Taddio 2009; Wright 2009) and altered pain responses later in life (Taddio 2005). Fear of the pain associated with immunisations, with subsequent fear of needles, has been shown to be one of the reasons why parents do not complete their infants' recommended immunisation schedule (Mills 2005; Schechter 2007; Taddio 2007; Taddio 2009; Wright 2009). It is therefore imperative that effective pain management strategies be consistently used for infants and children in diverse settings where needle-related painful procedures are performed.

Recently conducted systematic reviews of pain management strategies in the newborn period demonstrated that breastfeeding (Shah 2012) and sweet solutions of sucrose (Stevens 2013) and glucose (Bueno 2013) reduced behavioural responses and composite pain scores during painful procedures. In addition, systematic reviews of sweet tasting solutions beyond the neonatal period up to one year of age, demonstrated analgesic effects during needle-re-

lated painful procedures when compared to water or no treatment (Harrison 2010a; Kassab 2012). Three published trials have also demonstrated analgesic effects of breastfeeding infants beyond the neonatal period, during scheduled childhood immunisation (Dilli 2009; Efe 2007; Razek 2009). There is a need for this evidence relating to analgesic effects of breastfeeding beyond the newborn period to be systematically reviewed on an ongoing basis to critically evaluate the effectiveness of this intervention in infants up to one year of age.

Description of the condition

As outlined above, healthy infants may experience multiple painful procedures during scheduled early childhood immunisations and during other medical procedures occurring over the course of childhood illnesses, and hospitalised infants undergo many more painful needle-related procedures over the course of their hospitalisation (Johnston 2011). Studies of pain management strategies used during commonly performed needle-related procedures consistently show inconsistent use of recommended interventions (Harrison 2013; Johnston 2011; Taddio 2007), yet it is known that untreated or poorly treated procedural pain has negative effects, including infant and parental distress at the time of the procedure, with the risk of longer term fear of needles (Schechter 2007; Taddio 1995; Taddio 2007; Taddio 2009; Wright 2009).

Description of the intervention

High quality evidence from randomised controlled trials (RCTs) and systematic reviews supports the role of breastfeeding in reducing procedural pain during the neonatal period (first 28 days of life). Shah et al. conducted a systematic review of 20 RCTs or quasi-RCTs evaluating breastfeeding (ten studies) or supplemental breast milk (ten studies) during heel lance or venipuncture in newborn infants (Shah 2012). The authors concluded that breastfeeding effectively reduced behavioural responses, including crying duration and total crying time, facial expressions and pain scores, as well the physiological response of heart rate, compared to positioning (swaddled and nursed in a crib), holding by the mother, placebo or no intervention. Effects of small amounts of supplemental breast milk however, were variable; breast milk given in small quantities failed to consistently reduce physiological or behavioural pain indicators or composite pain scores. This discrepancy may be due to the contribution of multiple factors influencing analgesia during breastfeeding other than taste alone, including maternal contact, skin-to-skin contact, familiar smell, sucking, and intake of naturally occurring endorphins present in the breast milk (Harrison 2010b; Zanardo 2001). As the sugar in breast milk is primarily lactose, the least sweet of the sugars (sucrose > fructose > glucose > lactose) (Blass 1992), the mildly sweet taste most likely contributes little to analgesia in isolation (eg delivered by oral syringe or via pacifier).

Studies have also evaluated breastfeeding for pain management in infants beyond the neonatal period during scheduled childhood immunisation (Dilli 2009; Efe 2007; Razek 2009). Results were comparable to the neonatal studies, showing a reduction in cry duration for infants in the breastfeeding group compared to being held by mothers, or simply swaddled and nursed in a crib. In 2009, Shah and colleagues, in a systematic review of strategies to reduce immunisation pain, included breastfeeding as one of the interventions (Shah 2009). They pooled results for cry duration from three studies (Dilli 2009; Efe 2007; Razek 2009), including 344 infants. Results showed a significant reduction in cry duration (weighted mean difference (WMD) -38 seconds (95% Confidence Interval (CI)) -42 to - 34 seconds). Thus, breastfeeding infants during immunisation and other painful procedures, when feasible, shows promise as an effective pain management strategy for infants up to one year of age.

How the intervention might work

There are several elements which are postulated to contribute to the analgesic effects of breastfeeding. These include: skin-to-skin contact; sight; sound and smell of the mother; sucking; distraction; pleasant, slightly sweet taste; and intake of naturally occurring endorphins that are present in breast milk (Blass 1995; Blass 1997; Shah 2012). As detailed in Shah 2012, breast milk also contains higher concentrations of tryptophan (Heine 1999), a precursor to melatonin, which in animal studies, has been shown to increase concentrations of beta-endorphin (Barrett 2000), a naturally occurring endorphin which is assumed to be one of the mechanisms responsible for the analgesic effects of breast milk.

Why it is important to do this review

Although a systematic review of breastfeeding newborn infants during painful procedures was shown to effectively reduce pain (Shah 2012), and a systematic review of multiple strategies to reduce immunisation pain, which included breastfeeding, also demonstrated analgesic effects of breastfeeding (Shah 2009), there is no current, ongoing systematic review of breastfeeding for pain management during all painful procedures beyond the neonatal period. This review is therefore important to further establish the effectiveness of this intervention in this population of infants. As infants usually become highly distressed during needle-related painful procedures, identifying and consistently using effective pain management strategies is important to the well-being of infants. If breastfeeding, when feasible, during painful procedures, consistently demonstrates analgesic effects in infants up to one year of age, it can be recommended as a simple, cost-effective and easily integrated strategy in diverse inpatient and outpatient set-

tings (Razek 2009). If effective, this strategy has universal applicability, as it requires no additional cost, no special equipment and no special preparation or storage.

OBJECTIVES

To determine the effect of breastfeeding on procedural pain in infants beyond the neonatal period (first 28 days of life) up to one year of age, undergoing painful procedures, compared to no intervention, placebo, parental holding, breast or formula milk, oral sucrose or glucose, distraction, or other interventions.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs and quasi-RCTs.

Types of participants

Infants undergoing a painful procedure who are ≥ 28 days postnatal age (corrected for prematurity, 37 weeks plus 28 days) up to infants aged 12 months or receiving their 12-month immunisations. The procedures will include, but are not limited to: subcutaneous or intramuscular injection, venipuncture, intravenous line insertion, heel lance and finger lance.

Types of interventions

Breastfeeding during painful procedure, with or without additional interventions such as topical anaesthetic agents. We will not class as breastfeeding, expressed breast milk delivered by methods such as a dropper, syringe, spoon or bottle, but will include such delivery methods as comparators in control or other treatment arms.

Comparators include oral administration of: water, sweet solutions (such as sucrose), formula milk or breast milk or no intervention, use of pacifiers, positioning, cuddling, distraction, topical anaesthetics and skin-to-skin care, also referred to as kangaroo care.

We will include all settings where breastfeeding is evaluated for pain reduction during painful procedures. These may include inpatient hospital units, emergency departments, outpatient, or community settings.

Types of outcome measures

Primary outcomes

The primary outcome is pain, as assessed by at least one of the following.

1. Behavioural indicators such as: i) cry variables (duration of crying, expressed in total seconds of crying or proportion of duration of painful procedure and following completion of painful procedure (recovery period)); ii) facial expressions (grimace); or iii) body posture and movements.
2. Physiological responses such as heart rate, heart rate variability, respiratory rate, transcutaneous oxygen ($TcPO_2$), transcutaneous carbon dioxide ($TcPCO_2$), oxygen saturation (SpO_2) or other measures such as skin conductance or biomedical markers (such as serum, salivary or urinary cortisol).
3. Composite pain measures: uni-dimensional or multidimensional (including a combination of behavioural, physiological and contextual indicators).

Secondary outcomes

- Other clinically important outcomes reported by authors of included studies (not prespecified).
- Any adverse effects reported by any authors (eg choking, gagging, spitting).

Timing of measurements and aggregation of data will vary from study to study but common times of measurement include:

- baseline prior to delivery of intervention/control;
- upon commencement of procedure;
- 15, 30 and 60 seconds following commencement of procedure;
- throughout entire duration of procedure; and
- up to 10 minutes following completion of procedure.

Search methods for identification of studies

Electronic searches

We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* (latest issue).
- MEDLINE including In-Process & Other Non-Indexed Citations (OVID) (1946 to present day).
- EMBASE (OVID) (1947 to present day).
- PsycINFO (OVID) (1806 to present day).
- CINAHL (EBSCO) (1982 to present).

The MEDLINE search strategy was developed by a librarian experienced in systematic review searching, and peer reviewed by another librarian, using the Peer Review of Electronic Search Strate-

gies (PRESS) standard (McGowan 2010). We will adapt the MEDLINE search strategy for the other databases. It is presented in Appendix 1. We will limit study design to controlled trials only in MEDLINE and EMBASE. We will apply no language limits. We will include studies irrespective of their publication status, unless explicitly justified.

In addition, we will contact investigators of included studies to identify additional studies, and we will review eligible studies for cited references.

Searching other resources

As per Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group recommendations, we will also search the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing trials. In addition, we will check reference lists of reviews and retrieved articles, relevant recent neonatal, paediatric and pain journals, and paediatric and paediatric pain conference proceedings.

Data collection and analysis

Selection of studies

Two review authors (JR and MB or CL) will independently screen abstracts to identify potentially eligible studies identified via electronic searching; conflicts will be resolved through a consensus process, with a third review author (DH) if required. The reviewers will also search other resources (handsearching reference lists, experts) for relevant abstracts and articles. Full text articles of all potentially relevant abstracts will be retrieved and independently assessed for inclusion by two review authors. We will resolve all full text discrepancies through a consensus process. We plan to include a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram in the full review (Liberati 2009) to document the screening process, as recommended in Part 2, Section 11.2.1 of the Cochrane Handbook (Higgins 2011a).

Data extraction and management

We will extract the following data from each study: study design, setting, age of infants, overall sample size, sample size per group, number of groups, painful procedure, outcomes, and adverse events. Two review authors ((JR and MB or CL)) will independently extract data from the studies using a standardised data extraction form. Differences will be resolved through a consensus process or by a third review (DH) author when necessary.

Assessment of risk of bias in included studies

We will use the Oxford Quality Score (Jadad 1996) as the basis for inclusion, limiting inclusion to studies that are randomised and double-blind as a minimum.

We will use standard methods of The Cochrane Collaboration to assess the potential risk of bias using the Cochrane 'Risk of bias' classification tool (Higgins 2011b).

Two authors (JR and MB) will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion or a third review author (DH), if necessary. The review authors will not be blinded to authors or institutions. We will assess the following for each study.

Random sequence generation (checking for possible selection bias). We will assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, eg random number table; computer random number generator); or unclear risk of bias (method used to generate sequence not clearly stated). We will exclude studies using a non-random process (eg odd or even date of birth; hospital or clinic record number).

Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as: low risk of bias (eg telephone or central randomisation; consecutively numbered sealed opaque envelopes); or unclear risk of bias (method not clearly stated). We will exclude studies that do not conceal allocation (eg open list).

Blinding of outcome assessment (checking for possible detection bias). We will assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We will assess the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, eg identical tablets; matched in appearance and smell); or unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). We will exclude studies that were not double-blind.

Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We will assess the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study, or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); or high risk of bias (used 'completer' analysis).

Size of study (checking for possible biases confounded by small size). We will assess studies as being at low risk of bias ($\geq$ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (< 50 participants per treatment arm).

We will integrate risk of bias results into the analyses and results of this review.

Measures of treatment effect

We will use Review Manager (RevMan) 5.3, as provided by The Cochrane Collaboration (RevMan 2012). For continuous outcomes, we will extract mean scores and their standard deviations in the treatment and control groups. For dichotomous outcomes, we will collect the number of events per comparison group.

Unit of analysis issues

The unit of analysis will be the infants receiving breastfeeding or control. If multiple intervention groups are included, the primary comparison will be breastfeeding compared to the control group, or group receiving placebo. For cross-over trials, we will use the data from the first condition the infants undergo and we will treat the study as a RCT. Studies may have repeated measures - we will report these. For pooled analyses, we will include the most comparable data in terms of times of data collection during and following the painful procedures.

Dealing with missing data

If the data are not presented in a format that allows for their use in the statistical package, RevMan 5.3 (too sparse, low quality, or provided in graphic form only), then we will report the data in narrative form only. We will make efforts to obtain data from authors in a format that can be used in RevMan 5.3 (RevMan 2012). We will attempt to contact the authors in case of missing information/data, or for data clarification, for the purposes of both data extraction and assessment of risk of bias.

Assessment of heterogeneity

We will report between-study heterogeneity using the I^2 statistic (Higgins 2011a) and visually inspect forest plots for heterogenous estimates of effect. We will attempt to explain sources of methodological, clinical and statistical heterogeneity within the analyses.

Assessment of reporting biases

We will report and assess RevMan funnel plots for assymetry (Higgins 2011a; Sterne 2011).

Data synthesis

For continuous outcomes measured on differing scales, we will report standardised mean differences (SMDs) and associated 95% CIs. For dichotomous outcomes, we will pool events between groups across studies using risk ratios (RRs) and 95% CIs. For ease of interpretation, we will also calculate risk differences (RDs) for dichotomous outcomes, in addition to the number needed to treat (NNT) to benefit (NNTB) or the number needed to treat to harm (NNTH). Using the I^2 statistic for between-study heterogeneity, we will assess the appropriateness of pooling data from studies for meta-analyses. We will pool meta-analyses for all outcomes in RevMan 5.3 using random-effects models. Using GRADEpro (GRADEpro 2008), we we will present a 'Summary of findings' table in the full review.

Subgroup analysis and investigation of heterogeneity

As it is expected that the majority of eligible trials will be during the procedure of immunisation, we will perform subgroup analyses according to the early childhood immunisation schedules of two months, four months, six months, and 12 months age groups. If trials using breastfeeding plus another intervention are included, we will subgroup these into breastfeeding alone and breastfeeding plus another intervention. We will perform subgroup analyses on different comparisons (ie no treatment, water, sucrose) and different settings, if numbers permit.

Sensitivity analysis

We will determine sensitivity analysis post hoc by exclusion of studies with excessive heterogeneity. We will include all studies regardless of their risk of bias, and will include a narrative discussion of the potential influence of the risk of bias if required.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. (procedur* adj3 pain*).tw.
2. Needles/
3. exp Immunization/
4. exp Injections/
5. exp Punctures/
6. exp Biopsy/
7. exp Vascular Access Devices/
8. exp Catheterization/
9. exp Paracentesis/
10. thoracocent*.mp.
11. exp Blood Specimen Collection/
12. exp Administration, Intravenous/

13. exp Infusions, parenteral/
14. needle*.tw.
15. (blood sampl* or immuni* or inoculat* or vaccin* or inject*).tw.
16. (finger prick* or heel prick* or heel lanc* or heel punctur* or heel stick* or sutur* or (laceration* adj3 repair*)).tw.
17. (lumbar punctur* or spinal tap*).tw.
18. (bone marrow adj4 (aspiration* or biops*)).tw.
19. (intravenous or intra venous or venepuncture* or venipuncture* or venous cannulation* or (arterial blood gas* adj4 cannul*)).tw.
20. (catheter* or port-a-cath* or portacath*).tw.
21. (central line adj6 (insert* or remov*)).tw.
22. (central venous catheter* adj6 insert*).tw.
23. (local analges* or local anaesthe* or local anesthe*).tw.
24. (arter* adj6 punctur*).tw.
25. arterial line*.tw.
26. (thoracocentesis or paracentesis).tw.
27. or/1-26
28. Breast Feeding/
29. (breastfeed* or breastfed or (breast adj2 feed*) or (breast adj2 fed)).mp.
30. 28 or 29
31. (Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or prematur* or preterm*).mp.
32. 27 and 30
33. limit 32 to "all infant (birth to 23 months)"
34. 32 and (Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or prematur* or preterm*).mp.
35. 33 or 34
36. (35 and ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. or quasi*.it,ab.)) not (exp animals/ not humans.sh.)
37. remove duplicates from 36

CONTRIBUTIONS OF AUTHORS

Denise Harrison (DH) will oversee the entire process of conducting the systematic review. In addition, DH will arbitrate if required when there are disagreements relating to data collection, data extraction and risk of bias ratings. All authors will assist in the conduct of the systematic review. Jessica Reszel (JR) and Mariana Bueno (MB) will primarily be responsible for reviewing and rating articles. Lucy Turner (LT) will serve as the methodological expert.

DECLARATIONS OF INTEREST

All authors (Denise Harrison, Jessica Reszel, Mariana Bueno, Margaret Sampson, Vibhuti S Shah, Anna Taddio, Catherine Larocque, Lucy Turner) have no declarations of interest to declare.

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