Author's response to reviews

Title: A randomized controlled trial of sucrose and/or pacifier as analgesia for infants receiving venipuncture in a pediatric emergency department

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Author's response to reviews: see over
To: BMC Pediatrics Editorial Board

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RE: Revision of manuscript: A randomized controlled trial of sucrose and/or pacifier as analgesia for infants receiving venipuncture in a pediatric emergency department

We respectfully respond to the reviewers’ comments below:

Reviewer 1: Sharyn Gibbins

Re: Use of control group (no analgesia) for painful procedure

This is an interesting point for discussion and several factors were involved in choice of this control arm.

There is convincing evidence for the use of sucrose and pacifiers in the neonatal population but the majority of these studies have looked at the procedure of heel lance and usually in the NICU population. Our research group wondered if the Pediatric Emergency Department (PED) neonatal population might be different from a physiological and disease perspective. Also, few studies have looked specifically at the procedure of venipuncture and none in the PED population that we were aware of when this study began. When looking past the neonatal age a paucity of research with respect to sucrose and pacifier exists and those studies are largely for the procedure of immunization in otherwise healthy infants. Thus, because the existing evidence was derived from a different population and largely for a different procedure, we were unsure as to the efficacy of this mode of analgesia in our PED population for the procedure of venipuncture.

The patients in the control arm were not denied the usual comfort measures that a parent might choose to use such as cuddling, swaddling, soothing voice… Administration of sucrose and pacifier were not standard of care for venipuncture in our department at the time of the study. Choice of the control group as a standard of care arm to be compared to an intervention that would hopefully show decreased pain was therefore considered to be reasonable.

Based on discussion at conferences, with a wide variety of practitioners (including NICU) I have discovered that under use of sucrose and pacifiers is not uncommon despite the large body of evidence that exists for this mode of analgesia most particularly in, but not exclusively to, the neonatal population. Perhaps this speaks to the challenge of knowledge translation of research. In terms of evidence for this, recently, Stephen MacLean et al published a retrospective review of procedural pain management treatments in a US PED. He found that “few to no patients undergoing venipuncture, intravenous catheter placement, fingersticks, intramuscular or subcutaneous injections, urethral catheterization, or nasogastric tube placement received pain management”. He
also mentioned that sucrose was not available for use in that PED [1]. Reference added on page 17.

Carrying out this study in our department has resulted in an increased awareness of pain management for this and other procedures and we are currently developing a standing order for sucrose and pacifier use for venipuncture in infants 0-3 months in our division.

a) The intention of this study was to recruit infants between the ages of 0 and 6 months. The PIPP scale would not have been valid for this single age group. (Clarified on page 17.) Very few infants at the upper end of this range were recruited, reflecting the visit and illness spectrum of this group and also chance. The median age was 48 days and the mean age was 30 days. Thus younger infants were represented strongly and older infants were underrepresented in this study. Therefore we could not draw valid conclusions about the effectiveness of our interventions on infants older than 3 months of age. I believe this is still an age group to be studied.

b) The reviewer makes a valid point. Heart rate is taught to be and has widely been used as a surrogate measure for pain. However I am not certain that the correct way of collecting or interpreting this data has been established. On reviewing studies in this field the data collection methodology is highly variable and there often does seem to be a dissociation between pain scale findings and physiological responses such as heart rate [2,3]. In fact it may be questionable as to whether this is indeed a valid surrogate measure of pain at all and if so, for which age groups and for which types of pain? [4,5] The majority of pediatric research looking at this matter seems to be neonatal and physiological response likely varies with age and pain experience amongst other variables [6]. Pereira et al evaluated the validity of heart rate measurements for neonatal pain assessment in an RCT and concluded that heart rate variations are an inconsistent and insensitive way to evaluate pain in that population [7]. However, we decided on this method of assessing heart rate from a review of previous studies in this area, as it is commonly used as an outcome measure in such studies and chose this method over others as it seemed reasonable and similar in concept to those previous studies [2]. Heart rate data was recorded at each minute over the five minute period post procedure and once prior to the procedure. To clarify, our reported heart rate data is the difference between the highest value recorded over that 5-minute period and the baseline measure recorded prior to the procedure. Looking back, the most ideal way to collect this data would have been to collect a rhythm strip throughout the procedure, noting the initiation of venipuncture on the strip and then to have looked at the data at several points. However, at that time in our busy department, access to monitors with rhythm strip production could not be guaranteed for research purposes. Clarification is added into pages 10 and 18.

c) The procedure was not videotaped due to budgetary constraints. Timing of the procedure was standardized - a timer was used to ensure that venipuncture took
place at 2 minutes post-solution administration. The procedure itself was as per standard nursing practice. The research nurse assigned a baseline FLACC score prior to administration of the sucrose solution and again between 30 seconds and one minute after the procedure. Several different research nurses were trained by our research nurse coordinator in performing FLACC scores and other details related to outcome assessment prior to each of the study periods. One refresher session was offered throughout each study period also to ensure skills remained consistent. Clarifications are added to pages 9 - 11.

d) The reason that we chose to describe increases in the FLACC score in this sentence is that we used change from baseline as our outcome as opposed to simply the final scores. This has been clarified in the methods section (page 9) and the results section (pages 14 - 16).

Reviewer 2: Mats Eriksson

Re: Opioid-mediated mechanisms of sweet solutions.
This is another interesting area for discussion. Even though the analgesic effect of sucrose has been thought to be mediated by endogenous opioid mechanisms, several papers raise questions as to whether other mechanisms may be at play instead. Gradin et al have demonstrated that administration of an opioid antagonist did not reduce the pain relieving effect in newborns of oral glucose, which contradicts findings in previous animal studies [8]. Also, tolerance did not develop in neonates who were given repeated doses of glucose nor in infants receiving immunizations up to 12 months of age [9,10]. Other theories for this analgesic action of sucrose are through non-opioid endogenous pain inhibiting systems, activation of the pleasure center with dopamine release and initiation of the sucking response. Clarifications have been added to the introduction on page 4.

Re: Inclusion and randomization process:
This is a typographical error that was carried throughout. To clarify 84 syringes were prepared consistent with sample size calculations. However, at the study conclusion 87 individuals had been approached; two refused consent and one was deemed too ill, at the discretion of the attending physician. This resulted in 84 patients randomized to the study arms. Corrections have been made throughout the text.

The observation is, again, correct and clarification has been made on page 10. To clarify, all patients aged 0-6 months who arrived during study hours were identified and eligible patients were approached for recruitment. Unfortunately we did not collect data on those patients who were not approached for recruitment due to lack of study nurse availability. The clinicians involved with this study feel that these patients are unlikely to significantly differ from those captured for study but we cannot substantiate this with data.

There were not any significant differences between patients from the two study periods. To maximize efficiencies with respect to study nurses and budget, this study was run alongside another RCT that depended on the presentation of a seasonal infection. The
populations of both periods were similar in baseline characteristics and disease presentations. Clarified on page 13.

Yes, block randomization was used via a computer-generated block randomization scheme generated through our pharmacy. There were 21 blocks of 4 subjects. Clarification added on page 8.

Regarding ‘unlucky’ dissimilarities of one group in baseline characteristics:
Randomization should ensure that baseline characteristics are equally distributed but there is a small chance that this will not occur. This is a rare occurrence but unfortunately happened in our study. Standard deviations have been added to Table 1 to give some indications of the variations in baseline rates. We have also addressed the imbalance in our discussion (page 20).

Re: High Sucrose concentration:
Doses up to 0.5g have been studied and determined to be safe for use in the neonatal period. Although it is true from numerous studies that there does not seem to be much benefit to using higher doses for newborns, Haouari et al found a dose response for 0.25g, 0.5g and 1g administered to full term infants and did not report any adverse effects [11]. We did not have a lot of similar information for those older than neonatal age and the available information has come from immunization studies. Reis et al used up to 10 ml of a 25% (2.5 g) solution for infants receiving their two-month immunizations [12]. Lewindon et al used 2 ml of a 75% (1.50g) for infants receiving their 2, 4 or 6 month immunizations [13]. We chose a 44% solution as this was easily prepared by our pharmacy, which uses an 88% sucrose solution to mix oral pediatric medications, and diluted this solution for the purposes of our study. Therefore based on convenience, no evidence of harm and some evidence that an older infant may benefit from a stronger solution we decided to use 44%. The question of the best concentration for older infants needs to be clarified in future research. Clarified on page 19.

Re: Interrater reliability:
One research nurse coordinated the study in the department. She ensured that the study ran smoothly and trained other research nurses in recruitment practices and outcome assessments. Thus several nurses were outcome assessors. Clarification on page 9. Because this scale was new to some of our nurses, we had originally planned to do interrater reliability measurements to ensure that differences in the outcome assessors would not be a confounding variable in interpretation of our results. Due to oversights however this did not happen. Even though the nurses had several training sessions regarding this pain score some uncertainty remains about whether this had some impact in our not finding significant results in our primary outcome. However, we do know that the FLACC scale has been shown to have good interrater reliability coefficients therefore we feel that this is unlikely to be a major factor.
We hope that our responses suitably address your concerns and queries. Please do not hesitate to contact us for any further clarification.

Yours sincerely,

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On behalf of Drs. Jou, Ali, Klassen and Ben Vandermeer

References


