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Review

Efficacy and safety of repeated oral sucrose for repeated procedural pain in neonates: A systematic review

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ABSTRACT

Background: Although sucrose is most extensively examined for its analgesia effect on a single procedural pain, neonates in neonatal intensive care units can be exposed to numerous painful procedures every day requiring multiple doses of sucrose. Some experiments have been performed to examine the efficacy and safety of repeated sucrose administration for repeated procedural pain; however, a systematic review of this topic has not yet been carried out.

Objective: To identify and assess the evidence demonstrating the efficacy and safety of repeated sucrose for repeated procedural pain in neonates.

Method: A systematic review was conducted using the Cochrane methodology. Pubmed, Cochrane Library, Web of Science, CINAHL (Cumulative Index to Nursing and Allied Health Literature), CBMdisc, CNKI, VIP, and Wanfang databases were searched through December 2015. All related abstracts were reviewed and the full texts of relevant articles were studied. Randomized controlled trials (RCTs) were included. Risk of bias was assessed for RCTs using quality critical appraisal criteria recommended by Cochrane Handbook. A standardised data form was used to extract information.

Results: Eight RCTs met our inclusion criteria. Different study designs were used in the included RCTs, which did not allow us to carry out a meta-analysis. The findings from this review indicated that repeated sucrose was effective in reducing both behavioral pain response and composite pain scores during repeated procedural pain. However, as for physiological pain response, one trial found less variability in physiological pain response for term neonates in the sucrose group than the sterile water group, while two trials demonstrated repeated sucrose was inefficacious for preterm neonates. Regarding the clinical outcomes, no study reported adverse effects related to the repeated sucrose administration. Regarding the neurobehavioral development, two trials reported repeated sucrose for repeated procedural pain would not lead to poor neurologic development, while one trial reported that preterm infants <31 weeks' gestational age who received >10 doses of sucrose per 24 h in the first week of life had poorer neurologic development compared with infants who received fewer sucrose doses. What's more, no study reported the long-term neurobehavioral development outcome of neonates who repeatedly received sucrose across repeated procedural pain.

Conclusion: Evidence regarding the efficacy and safety of repeated sucrose across repeated procedural pain for neonates is limited. More prospective, multi-centered, large randomized controlled clinical trials with a standardised study design are required before sucrose can be recommended widely as an analgesia for repeated procedural pain in neonates.

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Contents

1. Introduction

Painful procedures are routinely performed during neonatal intensive care on a daily basis (Anand, 2000; Carbajal et al., 2008; Chen et al., 2012b; Cignacco et al., 2009; Grunau, 2013; Jeong et al., 2014). There are substantial studies presenting short-term and long-term adverse neurodevelopmental consequences of painful procedures (Hohmeister et al., 2009; Slater et al., 2010; Hohmeister et al., 2010), which increased analgesic usage prior to painful procedures (Johnston et al., 2011). Sucrose is the most frequently studied nonpharmacological intervention for relief of procedural pain in neonates, and has been recommended by many national and international clinical guidelines to prevent or treat procedural pain. However, studies have demonstrated infrequent utilization of oral sucrose during minor, painful procedures (Gray et al., 2006; Harrison et al., 2006). One possible explanation for it may be the concern regarding the efficacy and safety profile of repeated administration of sucrose for frequently performed painful procedures.

Goubet et al. demonstrated that preterm neonates at a post-conceptional age of 30–35 weeks could learn stimulus association and anticipate responses to painful procedures in neonatal intensive care unit (Goubet et al., 2001). It is questionable whether the repeated doses of sucrose for pain relief could provoke conditioning responses in preterm infants through association between the pleasant sweet taste and aversive painful stimuli. Furthermore, studies have shown that the early and repeated exposure to painful experiences may reduce the pain threshold and provoke hyperalgesia (Gibbins and Stevens, 2003; Grunau, 2002). Thus, it is necessary to determine if the analgesic effect decreased with sucrose repeatedly used in repeated painful events. In addition, given the interplay between the underlying mechanism for sucrose analgesia—promoting the release of dopamine and acetylcholine (Hajnal et al., 2004; Rada et al., 2005) and the tolerance to the sucrose-mediated release of dopamine developing with repetitive stimulation (Avena et al., 2008), it would be reasonable to hypothesize that downregulation of the dopaminergic system secondary to early repetitive receptor stimulation may potentially have adverse consequences on neurologic function in later life. Therefore, randomized controlled trials (RCTs) should be performed to examine the efficacy and safety of repeated sucrose for repeated procedural pain in neonates.

To date, a few studies have evaluated the efficacy and safety of repeated use of sucrose during painful procedures in neonates (Banga et al., 2015; Boyer et al., 2004; Chen et al., 2012a; Cignacco et al., 2012; Gaspardo et al., 2008; Harrison et al., 2009; Johnston et al., 2002; Linhares et al., 2014; Stevens et al., 2005; Taddio et al., 2008). This systematic review aimed to identify and assess the evidence demonstrating the efficacy and safety of repeated sucrose for repeated procedural pain in neonates, in order to provide health-care professionals with the necessary information for neonatal pain management.

2. Methods

2.1. Data sources and searches

This review was conducted as per the Cochrane guidelines for systematic reviews of interventions and reported as per the PRISMA guidelines (Higgins and Green, 2011; Moher et al., 2009). With no time limit, literature searches were performed in the following 4 English databases and 4 major Chinese databases from their inception up to December, 2015: Pubmed, Cochrane Library, Web of Science and CINAHL (Cumulative Index to Nursing and Allied Health Literature), CBMdisc, CNKI, VIP, and Wanfang databases. In the 4 English databases, the following search strategy for searching relevant studies was used: ("Sucrose" [MeSH Terms] OR "sucrose" [All fields]) AND ("infant, newborn" [MeSH Terms] OR ("infant" [All Fields] AND "newborn" [All Fields]) OR "newborn infant" [All Fields] OR "neonate" [All Fields]) AND ("pain" [MeSH Terms] OR "pain" [All Fields]). For the 4 major Chinese databases, subject heading terms and text words included: ("蔗糖" (Sucrose)) AND ("新生儿" (newborn infant/neonate) OR "婴儿" (infant)) AND ("疼痛" (pain)). The searches were performed by the first and second authors. The first author completed a title and abstract review of the search results to select articles eligible for a full text review. All authors were involved in reading, discussing, and identifying the final articles. In addition, extensive hand searching of the listed references in reviews and original articles was also performed.