

Title

An unnecessary pain: a commentary on Gao et al. (2018)

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Dear Editors,

We read with great interest the article by Gao et al. (2018) on the management of repeated procedural pain in preterm infants. This is an important issue since preterm infants hospitalized in neonatal intensive care units undergo many painful procedures which can adversely impact their neurological development (Ranger et al., 2015; Valeri et al., 2016). Gao et al. (2018) conducted a four-group randomized clinical trial (RCT) to evaluate how effective different interventions on repeated heel pricks would be to reduce pain. The four study groups were: sucrose, non-nutritive sucking, a combination of sucrose and non-nutritive sucking, and the control group. We believe some of the authors' methodological choices are questionable, namely the relevance of the four groups in the study and the intervention received by the control group.

Gao et al. (2018) chose to administer sucrose only to one group to evaluate its efficacy on pain. However, according to a Cochrane systematic review updated by Stevens et al. in 2016, sucrose is an effective intervention to reduce the repeated pain associated with heel lances in preterm infants. The recommendations from this systematic review are to conduct research on combining various interventions with sucrose to manage repeated pain in preterm infants (Stevens et al., 2016). The administration of sucrose alone is considered a "gold standard". How relevant is it then to conduct a study with four groups of which one is sucrose without it being considered a control group?

In the study conducted by Gao et al. (2018), the standard care given to the control group was "gentle touch". The authors do not provide a definition for "gentle touch" and quote two studies: one referring to therapeutic touch (Bahman Bijari et al., 2012), and the other to touch-contact (Herrington and Chiodo, 2014). Therapeutic touch pertains to a practice in alternative medicine whereby practitioners place their hands above the newborn without touching him/her. A Cochrane systematic review by Pillai Riddell et al. (2015) suggests that this intervention is not effective in relieving pain in preterm infants. On the other hand, touch-contact involves holding the preterm infant into foetal position during heel lancing as well as during the following recovery period. However, there is no sufficient evidence to support touch-contact as being an effective intervention to reduce pain in preterm infants (Pillai Riddell et al., 2015). Moreover, the application of "gentle touch" by Gao et al. (2018) is questionable since it was performed only

when preterm infants cried during the painful procedure. It is important to note that preterm infants may experience pain without crying given that pain expression is primarily characterized by physiological and behavioural responses in this population (Gibbins et al., 2014).

In addition, pain scores in the control group exceeded 13 (score out of 21), indicating moderate to severe pain, assessed as such when the score is greater than 12 (Stevens et al., 1996). These scores collected by the authors reveal that pain management was overly inadequate for the preterm infants in the control group. Given the current knowledge about pain management interventions, we find these research practices ethically questionable (equipoise issue). It is now accepted that poorly managed repeated pain can have a major impact on the development of preterm infants, such as the recurrence of hypersensitivity up until the age of seven (Valeri et al., 2016), as well as alterations in brain development (Ranger et al., 2015). Shouldn't sucrose, considered a "gold standard", be administered to the control group? And this, more specifically in studies dealing with repeated pain? The context in China may differ from that in North America, but the authors cited systematic reviews by Stevens et al. (2016) and Pillai Riddell et al. (2015). In a context of research, the scientific community should question the publication of studies which fail to provide the control group with appropriate pain management in the light of current knowledge. More ethical research practices should be promoted for this vulnerable population in order to lessen the impact of untreated pain, no matter which group the preterm infant is assigned to. Thus, alternative types of specifications could be considered, including non-inferiority or equivalence RCTs rather than superiority RCTs (Friedman et al., 2015).

Therefore, while Gao et al. (2018) addressed an important issue regarding the lack of effective pain management intervention for the control group raises important ethical and methodological concerns. We trust these comments will serve to initiate discussions about research practices involving preterm infants and the subsequent publication of these studies.

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