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Sugaring the pill. Ethics and uncertainties in the use of sucrose for newborn infants

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Abstract

Sucrose is widely used for the management of procedural pain in newborn infants, including capillary blood sampling, venepuncture and vascular cannulation. Multiple randomised controlled trials have demonstrated that sweet-tasting solutions reduce behavioural responses to acute painful stimuli. It has been claimed that sucrose should be a standard of care in neonatal units, and that further placebo-controlled trials of sucrose are unnecessary and unethical.

However, recently published neuroscientific studies cast doubt on the analgesic properties of sucrose. We review this new evidence and analyse the philosophical and ethical questions that it raises, including the “problem of other minds”. Sugar may be better understood not as an analgesic, removing or relieving pain, but as a compensating pleasure.

There is a need for further research on the mechanism of sucrose’s effect on pain behaviour and on the long-term effects of sucrose treatment. Such trials will require comparison with placebo or with other interventions. Given uncertainty about the benefit of sucrose it may be wise to use alternative analgesics or non-pharmacological interventions where these are available and appropriate. Sucrose may not be the answer to procedural pain in newborns.

Keywords

infant, newborn; pain; analgesia; sucrose; medical ethics

INTRODUCTION: THE CHANGING FACE OF NEONATAL PAIN MANAGEMENT

Neonatal pain management has undergone a revolution in the last three decades. In the early 1980s major textbooks stated emphatically that newborn infants did not require and should not receive post-operative opiate analgesia.[1] It was common at that time for preterm infants undergoing thoracotomy for ligation of a patent ductus arteriosus to receive muscle relaxant without any analgesic or sedative.[2, 3] Practice differed dramatically from older children or

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adults, in part because of a pervasive belief that newborn infants did not feel pain, and in part because of a fear of the side effects of analgesics.[4, 5] However, several factors converged to change this mindset including accumulating evidence of improved short term outcome with better intraoperative analgesia[6, 7], the measurement of reproducible physiological and behavioural responses following painful events[8-10], evidence of long-term neurodevelopmental consequences of pain in the newborn period, (eg. altered sensory processing[11, 12]), as well as vocal complaints from infants' parents.[3] These days, intraoperative and post-operative pain management for newborn infants is routinely undertaken using similar analgesics to older children.[13] It is now felt to be unethical to do otherwise.[4, 13, 14]

In the last decade there has been particular interest in the development of strategies for managing procedural pain in neonatal intensive care.[15] Infants admitted to neonatal units have a large number of painful procedures performed, including capillary blood sampling, venepuncture, cannulation and insertion of gastric tubes.[16, 17] Currently, however, interventions to reduce pain are provided for only a minority of these procedures.[16, 18, 19] One intervention that has been widely promoted for procedural pain in newborn infants is oral sucrose.[2, 18] In this paper, we review recently-published neuroscientific evidence that casts some doubt on the analgesic properties of sucrose. This evidence raises ethical and philosophical questions about pain management in non-verbal patients and the role of neuroscience in assessing pain. Furthermore, the sucrose debate highlights the frequent trade-offs in neonatal medicine between short and long-term outcomes, between benefit and harm and the difficulty of choosing best clinical practice in the face of conflicting evidence. We make several recommendations for clinical care and further research.

SUCROSE

Sucrose was first suggested to have analgesic properties in studies in rodents, where intra-oral infusions of sucrose appeared to increase tolerance for a noxious heat stimulus,[20] Later, sucrose was shown to have a calming effect when given to crying human infants.[21] The mechanism of this effect was attributed to opioid pathways in animal models, though there is conflicting evidence in human studies.[22]

Subsequently, over 100 randomised controlled trials in human infants have been performed, using sucrose or other sweet-tasting solutions to provide "analgesia" for a range of procedures.[23] Almost all of these studies found sucrose to have a beneficial effect on behavioural response or composite pain assessment tools.[23] Although heterogeneity between studies limits meta-analysis, a recent Cochrane review found sucrose effective in reducing crying, grimacing, heart rate or vagal response, and uni or multi-dimensional pain scores in infants having heel lances.[24] The evidence of effectiveness of sucrose for other procedures was less consistent,[24] but it appears very clear that oral sucrose reduces external manifestations of distress when given to newborn infants prior to acute painful procedures. On the basis of these and other results it has been claimed that sucrose is a safe and effective analgesic for procedural pain management in infants,[24] and that its provision should be a standard of care in neonatal units.[23, 25, 26] Moreover, it has been claimed that it would be unethical to perform further placebo-controlled trials of sucrose.[18, 23, 27, 28]

RECENT EVIDENCE

Recent evidence, however, casts doubt on the analgesic properties of sucrose. Near-infrared spectroscopy (NIRS) studies have demonstrated that infants as young as 25 weeks gestation, mount specific and reproducible cortical activity in response to acute noxious stimuli.[29-31] Although this activity correlates with clinical pain scores and change in facial expression, some infants manifest cortical responses without a change in facial expression.[32] This raises

the possibility that the reduction or obliteration of behavioural activity may not indicate effective analgesia.

Further evidence comes from electroencephalography (EEG) studies.[33-35] Noxious stimulation evokes a specific pattern of brain activity in the infant brain[35] that is sensitive to clinical characteristics, such as the age of the infant at birth.[34] In a randomised controlled trial, sucrose administered prior to a noxious heel lance procedure, resulted in dissociation between infant behaviour, nociceptive reflex withdrawal activity and nociceptive-specific brain activity.[33] Although infants who received sucrose had reduced pain scores compared to infants who received placebo, and were less likely to have a facial response to the heel lance, there was no reduction in the nociceptive-specific brain activity nor in the spinal reflex withdrawal following the procedure.[33]

One final piece of evidence relates to a lack of long-term benefit from sucrose. One of the adverse effects of painful procedures in newborn infants is the development of hyperalgesia with increased sensitivity to subsequent painful events. It has been hoped or assumed that procedural pain management would diminish this effect, however, sucrose-treated infants appear to be just as prone to subsequent hyperalgesia as infants receiving placebo.[36]

PHILOSOPHICAL QUESTIONS

One challenging epistemological question raised by these studies is this: how do we know if an infant is experiencing pain? This question is related to the broader and long-standing philosophical “problem of other minds”.[37] Does another being have conscious experience like our own? The problem of other minds is most acute for those who are unable to communicate, including human newborn infants[5, 13, 38] and fetuses,[39] severely brain-injured adults [37] and non-human animals.[40, 41] It has particular ethical significance when we are trying to understand whether or not a being is suffering or in pain.[37] In the absence of direct report, we usually infer that pain is being experienced when a stimulus (that would normally cause pain in us) results in pain behaviour that we associate with experiencing pain.[37] We make a corresponding negative inference (that pain is not being experienced) when pain behaviour is absent.

However, the problem of other minds might lead to two different forms of scepticism about pain behaviour. The first sort of scepticism applies when behavioural evidence of response to a painful stimulus is present, but the inference about pain experience is questioned. For example, some philosophers continue to question whether non-human animals have sufficient higher-level thought processes to be conscious.[42] Similarly, while premature infants with significant parenchymal brain injury manifest similar behavioural responses to noxious stimulation as uninjured infants,[43] it has been suggested that these behavioural responses may be mediated at the level of the brainstem and do not reflect the conscious experience of pain.[44] An opposite form of scepticism arises when external reaction to pain is *not* observed, but the negative inference is cast into doubt.[45] Neuroimaging, for example, has demonstrated that although some adult patients in a minimally conscious state lack purposeful behavioural reactions to a painful stimulus, they have similar patterns of brain activation to controls, suggesting that they retain the capacity to perceive pain.[46]

How should we interpret new evidence about sucrose? Do we trust the evidence of our eyes, or the evidence given by recent electrophysiological studies? Should we infer from the EEG study[33] that painful stimuli are still experienced, even if pain behaviour is reduced? No test is able, or is likely to be able to tell us the actual conscious experience of newborn infants, hence the importance of piecing together different pieces of indirect evidence. When evidence is discordant we must decide which we are going to trust.

Although the EEG studies are thought provoking, one first cautionary note is that there is considerably more behavioural evidence of sucrose's benefit, than there is neuroscientific evidence of a lack of benefit. Replication of the study results will help confirm that the observed phenomenon is real. There are also a number of different ways of interpreting the dissociated cortical-behavioural response to heel lance with sucrose.

One possibility is that activity in primary sensory areas reflects the *sensory* aspects of pain, including its location, form and intensity.[41] However, negative psychological or *affective* aspects of pain are believed to be mediated by other neural pathways, including more medial areas of the brain such as the anterior cingulate cortex.[41, 47, 48] It is possible that infants treated with sucrose retain perception of pain from a heel prick, but are less distressed by it. As an analogy, morphine has been thought to cause this sort of dissociation between sensory and affective elements of painful experience.[37, 41, 49] (In fact, more recent neuroscientific evidence suggests that morphine attenuates the neural correlates of both sensory and affective elements of pain.[50, 51]) A second possibility is that sucrose might reduce response to procedural pain by acting as a sedative rather than an analgesic (similar to the use of benzodiazepines for procedural sedation [52]). But a third possibility is that sucrose acts in newborn infants as a distraction or as a pleasurable compensation for perceived painful stimuli, perhaps akin to offering an injured child a lollipop. Simple and complex pleasures, from drugs, to food, to sex, activate common reward pathways involving dopaminergic and opioid receptors.[53] The analgesic property of sucrose appears to be related to sweet preferences in children – in one study, those children who preferred more sugary solutions tolerated higher levels of a painful stimulus when given sucrose, supporting the pleasure hypothesis.[54] Distraction or compensation might lead to reduced behavioural responses without affecting cortical nociceptive or spinal reflex activity.

ETHICAL QUESTIONS

The philosophical questions raised by this new evidence have significant ethical implications. Determining how sucrose reduces pain behaviour in infants is important to whether we should use it in the care of newborn infants. If sucrose is an effective analgesic it should continue to be used for procedural pain management in neonatal units. But if sucrose does *not* actually relieve pain, is it misleading caregivers into thinking that they are aiding the infant while the infant's suffering is undiminished? If sucrose acts as a sedative, is it appropriate to treat pain by inhibiting behavioural responses? If sucrose acts as a compensatory pleasure, how much pleasure does it takes to overcome the unpleasantness of pain?

The other question relevant to a decision whether or not to use sucrose, is whether sucrose improves or harms long-term outcome when used for procedural pain. The use of any analgesic must balance the desire to reduce pain, with the potential for side effects. For newborn infants in particular, there may be a trade-off between short term benefit and long term cost (for example as seen with the use of post-natal steroids for infants with chronic lung disease[55]). There is accumulating evidence in neonatal animal models that commonly used anaesthetics and sedatives harm the developing brain.[38, 56] Randomised controlled trials of opioid sedation for ventilated pre-term newborn infants have not demonstrated any benefit on long-term outcome.[57] In the only large trial of morphine analgesia, open-label morphine was associated with higher rates of brain injury.[58] There have been few studies that have looked at longer-term outcome with sucrose use.[59, 60] (Neither of the two published studies assessed outcome beyond infancy). There is some concern about sucrose's potential effect on attention and motor development.[22] Reinforcing this, one study found worse surrogate neurodevelopment scores at term in very premature infants who received multiple doses of sucrose (>10 per day) in the first week of life.[60] It is also possible that

sucrose may adversely affect long term health given the influence of early post-natal on developmental programming.[61] If the benefit of sucrose is not as significant as has been assumed, the potential risks of treatment become much more significant.

RECOMMENDATIONS FOR PRACTICE

One obvious upshot of the above analysis is that there is a need for further research into sucrose. The mechanism of sucrose's effect on pain behaviour in newborn infants needs to be re-examined. Further neuroimaging studies may provide insight into the effect of sucrose on the various pathways and brain areas involved in the pain response. Such studies may also help to identify the best behavioural markers of pain perception. Ultimately, it may be that composite behavioural and electrophysiological measures provide the best tools for assessing infant pain. Secondly, there is a need for better data on the effect of sucrose on long-term neurodevelopment. Both of these types of study will require comparison arms, either with other types of pain relief, or with placebo. Such studies, contrary to recent claims, *would* be ethical because of legitimate questions about the efficacy and safety of sucrose. What should we do in the meantime, and how should we treat infants not enrolled in trials? Generally it is much worse to ignore real pain, than it is to unnecessarily treat pain.[41, 62]

Given uncertainty about whether or not sucrose is actually relieving pain – we should perhaps assume that sucrose is not effective in reducing pain experience, and use alternative or additional methods of analgesia or anaesthesia where these are available.

What alternatives are there to sucrose? It is probably safe to assume that non-pharmacological methods of managing procedural pain[63] such as swaddling, or breast-feeding[64] are without risk of long-term harm (though there are no studies that have measured this). Studies of breastfeeding for heel-lance procedures suggest that it is as effective[65] or more effective [66] than sucrose in reducing pain scores in newborn infants. However, breastfeeding is not an option for infants who are too premature or too sick to feed. Alternatives include skin-to-skin contact,[67] dummies[68], facilitated tucking[69] or expressed breast milk[64]. Importantly, although all of these interventions have been shown to reduce pain behaviour, following the new evidence about sucrose it is unclear whether any of these alternative interventions provide analgesia rather than merely pacifying infants,[70] or providing compensatory pleasure. Local anaesthetic creams may have a role in term infants,[71] but have not been shown to result in any reduction in pain behaviour in preterm infants having heel pricks[72] or venepuncture.[73] Opiate infusions do not appear to have any benefit on pain scores following a heel-prick in ventilated newborn infants,[74] though bolus doses of morphine reduced facial grimacing in preterm infants having a central venous line placed.[75]

This mixed evidence highlights the difficulty in assessing pain and in developing a robust suite of methods of addressing it in newborn infants, and the need to develop and robustly test pharmacological and non-pharmacological means of reducing procedural pain in newborn infants. Neuroscientific tools, including EEG, NIRS and imaging have the potential to play an increasingly important role in validating behavioural correlates of pain, and in independently assessing the effectiveness of interventions. However, these techniques are also likely to continue to raise challenging philosophical and ethical questions about the assessment and management of pain in non-verbal patients.

The jury remains out on sucrose. It may be reasonable to administer sucrose to provide a calming effect during noxious procedures, particularly where no other means of reducing pain is available or suitable. Yet recent evidence highlights multiple unanswered questions

both in the assessment and in the management of newborn pain. Sucrose may not be the hoped-for answer to procedural pain in newborn infants.

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Abbreviations

EEG	Electroencephalography
NIRS	Near Infra-red spectroscopy

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