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Commentary

Age and efficacy of topical anesthetics

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Procedures involving a needle stick are commonly cited by children as among the most painful and stressful medical interventions even in comparison to disease-related and postoperative pain (Humphrey et al., 1992; Cummings et al., 1996). Topical anesthetics are analgesic drugs that cause temporary numbing of the superficial layers of the skin. Dozens of studies have been performed in children demonstrating their effectiveness for reducing pain from such procedures.

Despite these studies, clinicians have noted that topical anesthetics do not work for every child in every instance. Several investigators have attempted to determine factors that predict the effectiveness of topical anesthetics. In a randomized controlled trial including children 5 years of age and older undergoing venipuncture or venous cannulation, Lander et al. (1996) determined that longer duration of drug application, venipuncture procedure, and higher anxiety level of the child were significant predictors of effectiveness, but not child age. In another observational study of children aged 4-10 years treated with a topical anesthetic for venous cannulation, Kleiber and colleagues (2007) found that younger age, child anxiety level and the presence of a specific genetic polymorphism (endothelin receptor A gene-TT genotype) was predictive of analgesic effectiveness. In the latter study, the adjusted odds ratio revealed that for every year younger, children were 1.5 times more likely to be in the higher pain group indicating that despite higher reported anesthetic effectiveness in this group, younger children still report higher pain.

At present, it is not clear whether topical anesthetic effectiveness is a function of child age. In order to address this knowledge gap, we set out to estimate the effectiveness of topical anesthetics in different age groups using meta-analytic techniques.

We performed a literature search of Medline, Embase, International Pharmaceutical Abstracts, and the Cochrane Database, to identify all randomized controlled trials investigating topical anesthetics versus a placebo for common needle procedures, including: venipuncture, venous cannulation, and vaccine injections in children, for the time period up to 30 April 2009. The search identified 479 citations. These citations were scanned by 2 authors and 44 citations were identified for review. Of those, 28 citations met the inclusion criteria and were included in the review. We extracted pain scores (i.e. means and standard deviations for active treatment and placebo groups) for children of different age categories: 1-3 years, 4-6 years and 7-11 years. These groupings were based on trial composition and cognitive development of the child (Franck, 2000). Pain scores were obtained from the children themselves (i.e. self-report) for the 4-6 year and 7-11 year categories. Parent and observer ratings of children's pain were obtained for the 1-3 year and 4-6 year categories. Using the Revman statistical program (version 5.0), standardized mean differences (SMDs) and 95% confidence intervals (CI) were calculated in each predetermined age category. SMDs were computed to standardize study results to a uniform scale. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. SMDs were qualitatively compared among age categories; lower values were indicative of greater effectiveness.

Data needed for the analysis could be extracted from 7 of the 28 studies that met inclusion criteria for the review. These are identified by asterisks in the list of references following the manuscript. Pain scores were extracted from 6 of the studies and in 1 other study, the authors provided the required data.

Altogether, 2 to 4 trials were included in each meta-analysis and a summary of the results is shown in Table 1. SMDs were consistently lower for children aged 4-6 years (range: -0.58 to -0.67) compared to younger (range: -0.28 to -0.45) or older (-0.41) children regardless of the person that assessed the child's pain, suggesting greater effectiveness of the topical anesthetic for this age group.

It is important to note that we did not estimate SMDs for self-reported pain in young children (1-3 years) as these children are generally too young to self-report pain reliably and trials did not include these data. Similarly, we did not estimate SMDs for observer-rated pain in older children (7-11 years) because self-report is considered the primary source for pain assessment in this age group and trials did not include observer ratings of child pain.

Reasons why topical anesthetics appear more effective in children aged 4-6 years cannot be determined by this analysis, however, the following factors may play a role: underlying differences in pain mechanisms, identification and reporting of pain, or sensitivity of pain measures to detect change.

It has been suggested that nociceptors are more densely packed in small children resulting in a higher number being activated during procedures (Arts et al., 1994; Goodenough et al., 1997). It is unlikely that this factor alone accounts for the observed effects as it does not explain why observer ratings of child pain demonstrated less benefit for topical anesthetics in 1-3 year olds when compared to 4-6 year olds. In addition, it has been demonstrated that younger children self-report more pain than older children for the same stimulus (Fradet et al., 1990; Arts et al., 1994; Goodenough et al., 1997; Goodenough et al., 1999; Tak & van Bon, 2006). Younger children also favor the extreme ends of pain scales when self-reporting pain (Arts et al., 1994; Goodenough et al., 1997;

Table 1
Effectiveness of topical anesthetics vs. placebo by age of child

	Age of child		
Rater	1-3 years	4-6 years	7-11 years
Child self-reported pain		N=193	N=73
	-	-0.58	-0.41
		(-0.87, -0.28)	(-0.88, 0.06)
Parent-rated child pain	N=124	N=177	
	-0.28	-0.58	-
	(-0.63, 0.08)	(-0.88, -0.28)	
Observer-rated child pain	N=359	N=180	
	-0.45	-0.67	-
	(-0.66, -0.23)	(-0.97, -0.37)	

Note. Results are Standardized Mean Difference, SMD (95% Confidence Interval, CI); pain was measured using validated methods, including: Faces Pain Scale (FPS), Faces Pain Scale-Revised (FPS-R), Visual Analog Scale (VAS), Modified Behavioral Pain Scale (MBPS). Included studies are identified by asterisks in the reference list.

Chambers & Johnston, 2002). Taken together, these factors could lead to larger differences in scores between anesthetic and placebo-treated groups, resulting in larger effect sizes. It has also been suggested that older children may have a greater potential to experience a placebo effect from inert medicines (Goodenough et al., 1997). In the presence of low pain scores, a placebo effect may lead to lower scores, and small differences between groups. Parental and observer ratings similarly demonstrated increased effectiveness for topical anesthetics in children aged 4-6 years compared to younger children (1-3 years). It is not clear whether this is due to a more intense physical display and verbal response by the child, which in turn, directs observers to judge them as having more pain (Chambers et al., 1999). It is possible that observers overestimate pain in 4-6 year old children compared to younger children because of these issues.

The results are limited by the sample size and inclusion of different types of needle procedures, topical anesthetics and study populations. A relatively small number of children were included in some analyses. In addition, differences in the types of needle procedures (e.g. venipuncture versus immunization), population evaluated (e.g. hospitalized versus healthy children) and topical anesthetics used (e.g. lidocaine-prilocaine versus amethocaine) may have influenced the amount of pain experienced and effectiveness of the topical anesthetic. Of note, 5 of 7 included studies evaluated lidocaine-prilocaine cream. Despite these limitations, these preliminary results raise questions about current methods of evaluating analgesics in children. Additional investigation of the underlying mechanisms responsible for the observed results is needed.

In summary, topical anesthetics may be associated with higher magnitude of benefit for managing pain during common needle stick procedures in 4-6 year old children when compared to younger (1-3 year old) and older (7-11 year old) children. The observation of stronger SMDs for 4-6 year old children is consistent with anecdotal reports by clinicians that topical anesthetics are more effective in this age group and their increased utilization for needle stick pain management in 4-6 year old children relative to other age groups. The reasons for these observed differences are not known, but may involve issues related to pain perception and measurement.

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