ARTICLE

Cost-effectiveness Analysis of Anesthetic Agents During Peripheral Intravenous Cannulation in the Pediatric Emergency Department

Jay Pershad, MD; Stephanie C. Steinberg, MBA, MHA; Teresa M. Waters, PhD

Objective: To conduct a cost-effectiveness analysis of anesthetic agents to reduce the pain of peripheral intravenous cannulation in an emergency department (ED) setting.

Design: Cost-effectiveness analysis in which costs were measured as the cost of the agent plus costs associated with time in the ED using data from our hospital cost accounting system. Outcomes were measured as improvements in the self-reported visual analog scale (VAS) pain scores. Variables considered unique to the various agents were cost of the agent, time to peak onset, success rates of cannulation, and mean reduction in VAS scores.

Setting: Decision model.

Patients: A cohort of patients aged 3 through 18 years enrolled in randomized controlled trials that compared analgesic modalities to facilitate peripheral intravenous cannulation was identified through medical databases searched from their inception (earliest year, 1966) through June 2007.

Main Outcome Measures: The main outcome measure was the incremental cost-effectiveness ratio, which represented the additional cost that must be incurred by the hospital to obtain a reduction of 1 additional unit (10 mm or 1 cm) in the VAS score compared with a baseline option of no anesthetic.

Results: Our results suggest that the needle-free jet injection of lidocaine device had the lowest incremental cost-effectiveness ratio, followed by intradermal injection of buffered lidocaine; lidocaine iontophoresis; nitrous oxide inhalation analgesia; a heated lidocaine and tetracaine patch; sonophoresis with lidocaine cream, 4%; lidocaine cream alone, 4%; and use of a eutectic mixture of lidocaine and prilocaine cream.

Conclusion: Currently, the needle-free jet injection of lidocaine device and injection of buffered lidocaine appear to provide the most cost-effective alternatives to pediatric ED physicians.

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Author Affiliations: Division of Emergency Medicine, Department of Pediatrics, University of Tennessee Health Science Center and Le Bonheur Children's Medical Center (Dr Pershad), and Department of Preventive Medicine, University of Tennessee Health Science Center (Ms Steinberg and Dr Waters), Memphis.

IT IS WELL KNOWN THAT EVEN MINOR and frequently performed procedures, such as peripheral intravenous (PIV) cannulation, invoke significant pain in children and increase fear and anxiety in children and their caregivers.[1-3] During the last decade, several anesthetics have been investigated in clinical trials to explore the best options for amelioration of low to moderate pain associated with needlesticks in children.[4-6] Consequently, pediatric emergency care physicians have several modalities to select from, each with varying time to onset, acquisition cost, and success rates. We are not aware of any prior comparative pharmacoeconomic analysis of pain management practices during PIV cannulation in the pediatric emergency department (ED) setting.

Our primary objective was to conduct a cost-effectiveness analysis that compared costs and outcomes associated with anesthetic agents during pediatric PIV cannulation. Costs were measured as the cost of the agent plus costs associated with time in the ED. Outcomes were measured as improvements (decreases) in self-reported visual analog scale (VAS) pain scores. A decision analytic model was constructed using relevant probabilities of success and outcomes from published studies of pediatric patients who underwent PIV cannulation aided by analgesia.

METHODS

TYPES OF STUDIES

For this decision analysis, we included randomized controlled trials that involved use of analgesics for relief of needlestick pain. Unpublished data and results from phase 3 trials that were not subject to peer review were excluded.

TYPES OF PARTICIPANTS

We included trials that involved children and youth between the ages of 3 and 18 years, of all ethnic origins, of both sexes, and regardless of the reason for the needlestick procedure (ie, chronic vs acute condition).

TYPES OF INTERVENTION

We included trials that compared the efficacy of topical and/or inhalation (nitrous oxide) analgesic modalities. These trials may have included a placebo comparison, a no treatment control, or a comparison of other topical anesthetics. We restricted trials to those that involved peripheral intravenous cannulation only because, based on clinical experience, pain associated with venipuncture is not equivalent to that experienced during intravenous cannulation in children. For studies that fulfilled the initial review criteria, full-text articles were obtained and assessed for possible inclusion. To be included, studies were required to be randomized controlled trials.

TYPES OF OUTCOME MEASURES

Self-reported measure of pain and ease of cannulation (success rate with first attempt) were the primary outcomes for this decision analysis. The studies we reviewed also contained other outcomes measures, such as skin changes or other adverse reactions, including anxiety that precluded child participation, time from onset of application to effective anesthesia and duration of anesthetic effect, and cost and acceptability of the analgesic agent to the child, parent, or physician measured by self-report.

SEARCH METHODS OF IDENTIFICATION OF STUDIES

A combination of medical subject heading (MeSH) and free-text search terms was used to search the literature databases for possible articles. The following MeSH terms (uppercased) and free-text terms (lowercased) were used: (1) *ANESTHETICS, LOCAL*; (2) *PHLEBOTOMY*; (3) *ANESTHETICS, LOCAL* and *PHLEBOTOMY*; (4) *CATHETERIZATION, PERIPHERAL*; (5) *intravenous* and *peripheral*; (6) *ANESTHETICS, LOCAL* and *CATHETERIZATION, PERIPHERAL*; and (7) *nitrous oxide* and *venous cannulation*.

In addition to computer-assisted literature searches, we identified other eligible literature through the manual review of identified reports and reference lists, focusing especially on review articles to identify additional relevant references. We also used articles and other items on the topic that we had been collecting since 2003 through regular review of the literature on pediatric pain management, professional interactions (eg, conferences), and ad hoc literature searches. Our search was restricted to English-language articles. Based on our experience and the preoperative literature, nitrous oxide inhalation analgesia is a useful adjunct to facilitate PIV cannula placement with or without topical anesthetic. It is ideally suited for the older anxious child (aged >5-6 years) who is mature enough to breathe through the nasal hood.

DATABASES

The following databases were searched: Cochrane Database of Systematic Reviews (1993 to June 2007), MEDLINE (1966 to June 2007), PubMed (1966 to June 2005), EMBASE (1988 to June 2007), Clinicaltrials.gov (2002 to June 2007), and EBM Reviews (1991 to June 2006).

DATA ANALYSIS

Using the search strategy, we identified 113 unique references. Fifty-eight studies fulfilled the review criteria. Forty-two were excluded for 1 or more reasons. Nineteen trials included adult participants. In 3 studies[7-9] that investigated vapocoolant sprays, the intervention was not superior to placebo (ie, lacked efficacy). Nine studies[10-18] involved a topical anesthetic (amethocaine gel or tetracaine) that was not available in the United States. In 4 studies,[18-21] the intervention was venipuncture without venous cannulation. Four studies[22-25] used a measurement tool other than the self-reported VAS. Two studies[26,27] included patients who were younger than 3 years. One study[28] was published as an abstract only. Seventeen trials[29-45] that enrolled 1287 children were included in the decision analysis model.

PAIN ASSESSMENT

The primary clinical outcome for this decision analysis was pain during intravenous cannulation. Because pain is a subjective experience, self-report is considered the criterion standard for measuring levels and changes in pain.[46] We chose to use the self-reported VAS measurement of pain because this scale has had extensive use in the measurement of pain in adult and pediatric patients and has been reported as a reliable and valid measure of pain intensity, with accuracy in assessing changes in pain perception over time.[46-51]

The minimum clinically important change for a VAS score is considered to range from 9 to 18 mm.[52-56] We included trials with the child's self-report of pain because parent's or health care professional's assessment of pain in the child has been shown to be inaccurate.[57,58]

We also considered the pain of actual drug provision in our model. Lidocaine iontophoresis is associated with significant discomfort and pain during application. The cumulative failure rate from the literature, due to inability to tolerate iontophoresis, was 6.9%.[33,36,44,45] This intolerability rate was included in our model. Lander et al[39] reported the mean (SD) pain score of dressing removal after application of a eutectic mixture of lidocaine and prilocaine cream (EMLA) in children to be 14.3 (20.7) mm on the VAS. Remaining consistent with our overall assumption that payoffs are additive, the pain of bandage removal was added to the overall pain score associated with EMLA. Data are conflicting on pain reported during application of the needle-free jet injection of lidocaine (NJILD) device from studies that involved adult participants.[59,60] However, a randomized, controlled, comparative trial[35] suggests that the jet injection device was not painful and was well tolerated by pediatric patients, with 84% of patients reporting no pain at application compared with 61% in the EMLA group at the time of dressing removal. Based on recent data on the use of laser preparation of the skin, the median pain of laser application was reported to be 0.[28] Therefore, with respect to the pain associated with activation of NJILD or use of laser or sonophoresis, because the child does not have an opportunity to reject these methods, we assumed that the global self-reported VAS score would incorporate the discomfort associated with these methods.

RESULTS

Eight methods for decreasing pain and distress associated with needlesticks were included in the decision analysis. **Table 1** summarizes the probabilities used in the analysis. When multiple studies reported VAS scores using the same agent, weighted means (based on the number

Table 1. Summary of Analgesic Modalities Included in Model

Pain Management Modality	Weighted Mean of VAS Scores	Success Rate of PIV Cannulation, %	Time to Onset, min	Age Range of Patients, y	Study Setting
Buffered lidocaine	28.9	72.3	2	NA	NA
Luhmann et al,[29] 2004	34	77	NA	4-17	ED
Klein et al,[30] 1995	23	67	NA	8-15	ED
Lidocaine and prilocaine	20.5	79.3	60	NA	NA
Kleiber et al,[37] 2002	20.5	70.5	NA	7-13	Health volunteers
Hee et al,[34] 2003	26.13	57	NA	8-15	Preoperative
Andrew et al,[31] 2002	20	95	NA	5-15	Preoperative
Jimenez et al,[35] 2006	28.9	92 (with nitroglycerine)	NA	7-19	Preoperative
Cordoni and Cordoni,[32] 2001	12.5	100	NA	4-12	Ward
Vetter,[43] 1995	28	100	NA	6-12	Preoperative
Koh et al,[38] 2007	17	NR	NA	8-17	Preoperative
Galinkin et al,[33] 2002	17	64	NA	7-16	Outpatient
Manner et al,[40] 1987	NR (range, 0-4)	NR	NA	4-10	Preoperative
Lander et al,[39] 1996	21.7	NR	NA	5-18	Preoperative, wards, outpatient
Lidocaine, 4%	25.3	72	30	NA	NA
Kleiber et al,[37] 2002	24	67	NA	7-13	Health volunteers
Luhmann et al,[29] 2004	26	77	NA	4-17	ED
Koh et al,[38] 2007	25.7	NR	NA	8-17	Preoperative
Iontophoresis	1.24	84.9	13	NA	NA
Zempsky et al,[44] 1998	15	94.6	NA	5-17	Outpatient and inpatient
Zempsky et al,[45] 2004	14.5	86	NA	7-18	ED
Galinkin et al,[33] 2002	9	77	NA	7-16	Outpatient
Kim et al,[36] 1999	0.5	77	NA	7-18	ED
Nitrous oxide inhalation	12.5	100	5	NA	NA
Hee et al,[34] 2003	18.35	NR	NA	8-15	Preoperative
Vetter,[43] 1995	3.2	100	NA	6-12	Preoperative
Placebo	35.1	80.1	Immediate	NA	NA
Zempsky et al,[44] 1998	25.8	NR	NA	NA	NA
Klein et al,[30] 1995	44	72	NA	NA	NA
Sethna et al,[41] 2005	42	100	NA	NA	NA
Cordoni and Cordoni,[32] 2001	83.9	100	NA	NA	NA
Kim et al,[36] 1999	4	84	NA	NA	NA
Zempsky et al,[45] 2004	58.5	75	NA	NA	NA
Manner et al,[40] 1987	Mean NR (range, 0-10)	NR	NA	NA	NA
Lander et al,[39] 1996	42.7	NR	NA	NA	NA
Needle-free jet injection device					
Jimenez et al,[35] 2006	14.5	84	1.8	3-17	Preoperative
Lidocaine-tetracaine patch					
Sethna et al,[41] 2005	18	100	20	3-18	Preoperative
Sonophoresis with lidocaine					
Skarbek-Borowska et al,[42] 2006	22.9	92.1	6.5	8-18	ED

Abbreviations: ED, emergency department; NA, not available; NR, not reported; PIV, peripheral intravenous; VAS, visual analog score.

of patients receiving the particular agent in the study) were calculated.

Costs were measured as the cost of the agent plus costs associated with patient time in the ED. Unit costs for each of the agents were obtained from Le Bonheur Children's Medical Center's cost accounting system or through price quotes from vendors (for agents not currently in use at Methodist Le Bonheur Health Care). These prices represent the hospital's actual acquisition costs. Because the equipment and nitrous oxide gas is piped into the walls for use in the ED at Le Bonheur Children's Medical Center, the unit cost for nitrous oxide was included in the fixed ED cost. Similarly, in accordance with our hospital's cost accounting system, the cost of needles and syringes associated with use of injectable buffered lidocaine was also included in the fixed cost of supplies required to maintain a full-service ED. Furthermore, it is usual practice at our institution that once the 5-g tube of EMLA or lidocaine, 4%, is dispensed, it is charged to the patient regardless of the volume used.

Because we could not obtain consistent information on mean PIV cannulation times for pediatric ED patients, we conducted a prospective cohort study of a convenience sample of 25 patients in our own ED to determine these mean times. Overhead cost data from our hospital were used to estimate cost of patient time in the ED. Specifically, the costs of maintaining a full-service ED open 24 hours 7 days per week were converted to cost per ED room per hour. These costs included direct fixed costs (plant operations, biomedical instrumentation costs, and environmental services) and variable ED costs (salaries, benefits, and supplies) attributable to the ED by the hospital's cost accounting system. **Table 2** summarizes the cost data used in our analyses.

Probabilities of cannulation success, pain outcomes, and cost data were combined to construct a decision analytic

model that compared the cost-effectiveness of the 8 anesthetic agents for facilitating PIV cannulation in children. Tree Age Data 3.5 software (Tree Age Software Inc, Williamstown, Massachusetts) was used for decision analysis. Sensitivity analyses were used to vary the probabilities and costs from the no anesthetic option to assess the stability of the preferred strategy. Probabilities and costs were varied across the range of values given in Table 2. The variables of interest were those with relative uncertainty: time to start a PIV cannulation on first (5-30 minutes) and second (5-13 minutes) attempts, success rate of PIV cannulation (72%-100%), and cost of the agents and fixed ED costs. The University of Tennessee Health Sciences Center institutional review board approved this study.

Figure 1 provides a summary of the decision tree, and **Table 3** provides a summary of the various anesthetic strategies, costs, and outcomes relative to no anesthetic and the resulting incremental cost-effectiveness ratios (ICERs). In our study, the ICER represents the additional cost that must be incurred by the hospital to obtain a reduction of 1 additional unit (10 mm or 1 cm) in the VAS score compared with a baseline option of no anesthetic. Our results suggest that based on currently available data on outcomes and costs, the NJILD has the best ICER.

We conducted a number of 1-way sensitivity analyses to examine the robustness of our results to changes in key variables. Specifically, we explored the impact of changing: ED room costs per hour (range, $15-$64), the success rates of cannulation (range, 72%-100%), and the average time to initiate a PIV cannulation (range, 5-20 minutes). These ranges were selected based on ranges published in the literature (if available) or plausible extreme values based on internal data (**Figures 2**, **3**, and **4**).

Graphic representation of sensitivity analysis involves the creation of multiple graphs, each corresponding to a single value in the range of possible values in the sensitivity analysis. In Figure 2, we see that 3 options (buffered lidocaine, NJILD, and iontophoresis) create the "cost-effective frontier"; these modalities represent the 3 best available options because they represent the highest reduction in pain scores possible for the money spent. Buffered lidocaine represents the least costly option (ie, for a minimal expense, ED physicians are able to reduce pain modestly). The NJILD represents the most cost-effective option (ie, for a modest increment in cost, pain can be substantially reduced). If the institution is willing to spend more, they may want to consider iontophoresis as the highest cost option along this cost-effective frontier. All of the other options on the graph are dominated (ie, there is always a better choice that offers more pain relief for the same money or the same pain relief for less money).

Similarly, we prepared a series of graphs to explore the impact of changing cannulation success rates in the range of 72% to 100% (and the average time to initiate a PIV cannulation in the range of 5 to 20 minutes). These analyses revealed that, in a range of plausible scenarios, the use of NJILD remained the preferred strategy.

To the extent that ED personnel can anticipate the need for analgesia, they can minimize wait time by application of EMLA, lidocaine, or the lidocaine-tetracaine patch in triage. A sensitivity analysis that provides the range of costs that might be expected in this scenario was conducted. The relative ICERs with the assumption that wait time after application of these 3 modalities is 0 are given in **Table 4**.

Table 2. Summary of Costs

Variable	Unit Cost, $	Range for Sensitivity and Monte Carlo Analyses, $
Fixed cost of ED (based on 35 rooms)	32 per ED room per hour	15-64
Administrative costs (indirect overhead)	9.6 per ED room per hour	5-15
RN and ED technician costs	30.25 per hour (RN) and 20.66 per hour (ED technician)	20-40 (RN) and 10-30 (ED technician)
Physician costs	90 per hour	80-120
EMLA	7.69 per 5-g tube (2.5%)	2-10
Lidocaine cream, 4%	6.00 per 5 g	2-10
Iontophoresis	6.00 (Cost of unit absorbed by volume purchase of disposable kits)[a]	2-12
Nitrous oxide equipment and unit price of gas	Included in ED fixed costs	NA
Buffered lidocaine (20 mL of solution, 1%)	0.55	0.25-1
NJILD, price per cartridge and 0.25 mL of buffered lidocaine	2.10	1-4
Lidocaine-tetracaine patch	12[a]	1-15
Sonophoresis with lidocaine cream	12 (5000 cost of unit absorbed by volume purchase of disposable cartridge)[a]	5-10

Abbreviations: ED, emergency department; EMLA, a eutectic mixture of lidocaine and prilocaine cream; NA, not applicable; RN, registered nurse.
[a] From vendor quotation.

One anesthetic agent that did not make it into our model was laser-assisted anesthesia because currently available data come from studies that include extremely young children (aged <3 years) or those not yet published in peer-reviewed journals (abstract).[27,28] To assess the effect on our model of including these data, we conducted a separate decision analysis, including the additional anesthetic option and VAS scores reported by these researchers. In this model, laser-assisted anesthesia yielded an ICER of 20.06 relative to the no anesthetic option and was dominated by the 3 preferred strategies: NJILD, buffered lidocaine, and lidocaine iontophoresis.

Because it is possible that a young child may not allow injection of buffered lidocaine, we conducted a sensitivity analysis for the intolerability of buffered lidocaine. Even if this rate were as high as 6.9%, as reported for lidocaine iontophoresis, buffered lidocaine injection would still dominate iontophoresis, albeit with a lower ICER of 2.53.

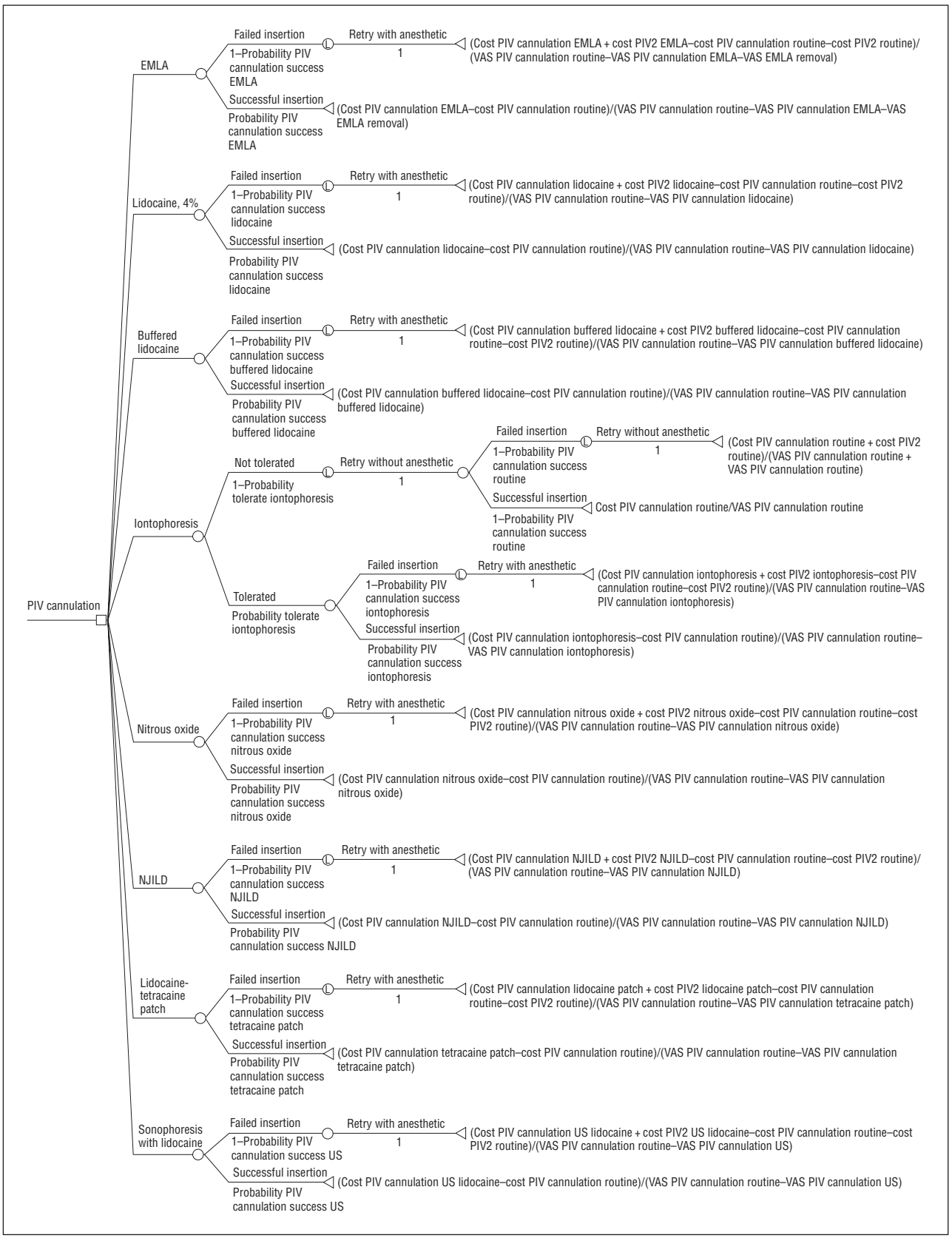

Figure 1. Decision analysis tree showing the 8 treatment options for analgesia during peripheral intravenous (PIV) cannulation. The patient may or may not have his or her intravenous cannula initiated at first attempt, which relates to the probability of successful intravenous cannula insertion with each modality. These probabilities and estimates of their costs are given in Table 1 and Table 2. The payoff node represents the additional cost associated with use of anesthetic compared with the routine practice of using no anesthetic and the improvement in visual analog scale (VAS) pain scores with use of analgesia. EMLA indicates a eutectic mixture of lidocaine and prilocaine cream; NJILD, needle-free jet injection of lidocaine; PIV2, second attempt at insertion of PIV cannula after failed initial attempt; and US, ultrasonography.

Table 3. Summary of Results

Strategy	Cost Increase, $	Effectiveness (Reduction in VAS Score), cm	Incremental Cost Effectiveness Ratio	Comment
No anesthetic			Comparison strategy	
Needle-free lidocaine injection device	3.9	2.05	1.89	Creates a disconcerting "pop" when activated; local hyperemia and minor bleeding
Buffered lidocaine, 1%	1.6	0.61	2.68	May not be accepted by some needle-phobic children; minor bleeding
Iontophoresis	11.8	4.07	2.89	May not tolerate the discomfort of the electrical current
Nitrous oxide	27.8	2.25	12.35	Some children may not tolerate the mask; transient nausea and emesis in some
Lidocaine-tetracaine patch	25.7	1.70	15.13	Minor erythema or blanching or edema at site
Sonophoresis with lidocaine cream	24.4	1.21	20.15	Minor erythema at site
Lidocaine, 4%	34.3	0.97	35.36	Transient local blanching, erythema, and itching
Eutectic mixture of lidocaine and prilocaine	59.6	0.02	2982.04	May cause vasoconstriction (blanching), temporary erythema, or edema

Abbreviation: See Table 1.

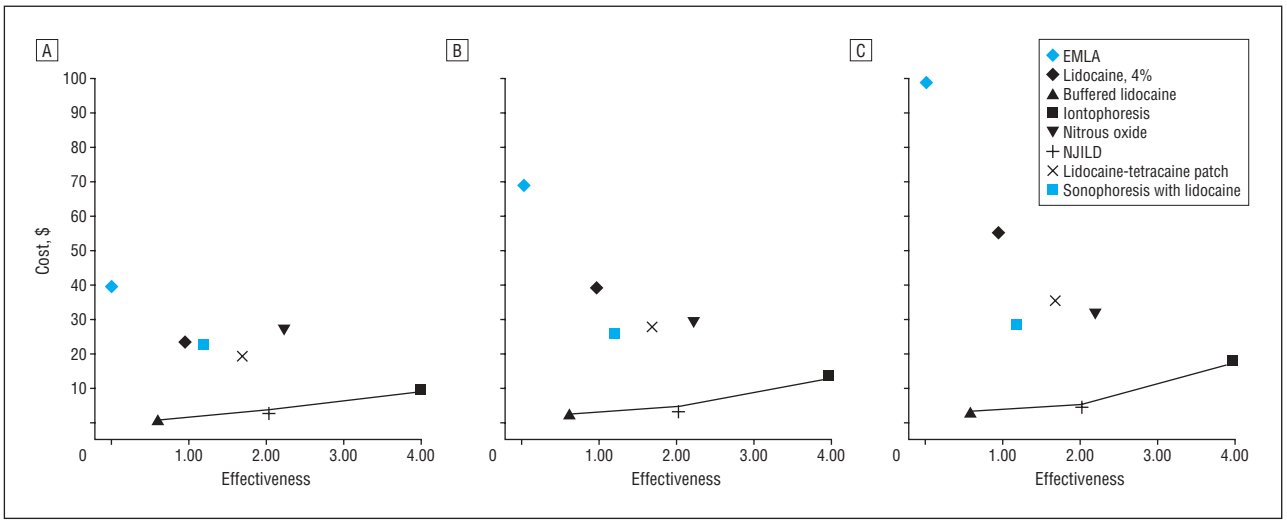

Figure 2. Report of results of sensitivity analysis to a change in the variable fixed cost per emergency department (ED) room per hour. A, Fixed cost of the ED room was $15; B, fixed cost of the ED room was $39.50; and C, fixed cost of the ED room was $64. EMLA indicates a eutectic mixture of lidocaine and prilocaine cream; NJILD, needle-free jet injection of lidocaine.

Given the paucity of pediatric literature on the use of NJILD, sonophoresis, and the lidocaine-tetracaine patch, the possibility of bias exists in favor of these relatively less investigated modalities. We, therefore, performed a final sensitivity analysis assuming uniform reduction in pain scores across all modalities, thereby concentrating strictly on acquisition cost and time alone. The ICERs assuming that a VAS pain score of 15 mm is achieved for all interventions are given in **Table 5**. The results highlight the fact that the absolute reduction in VAS pain scores does not seem to influence the rank order of preferred options. It is cost of the intervention that appears to primarily drive the model.

We also conducted a Monte Carlo simulation to determine whether, under multiple conditions of uncertainty, NJILD remained a dominant strategy. The results indicate that NJILD remains a dominant strategy that was robust across 1000 iterations of the Monte Carlo simulation. Using uniform distribution sampling across the same sensitivity ranges used in the 1-way sensitivity analyses, NJILD was favored in all 1000 iterations. These results support NJILD as the optimal strategy for analgesia during PIV cannulation.

COMMENT

Although a great deal of evidence has been published on the costs and effectiveness of various analgesic options for pediatric PIV cannulation, comprehensive compari-

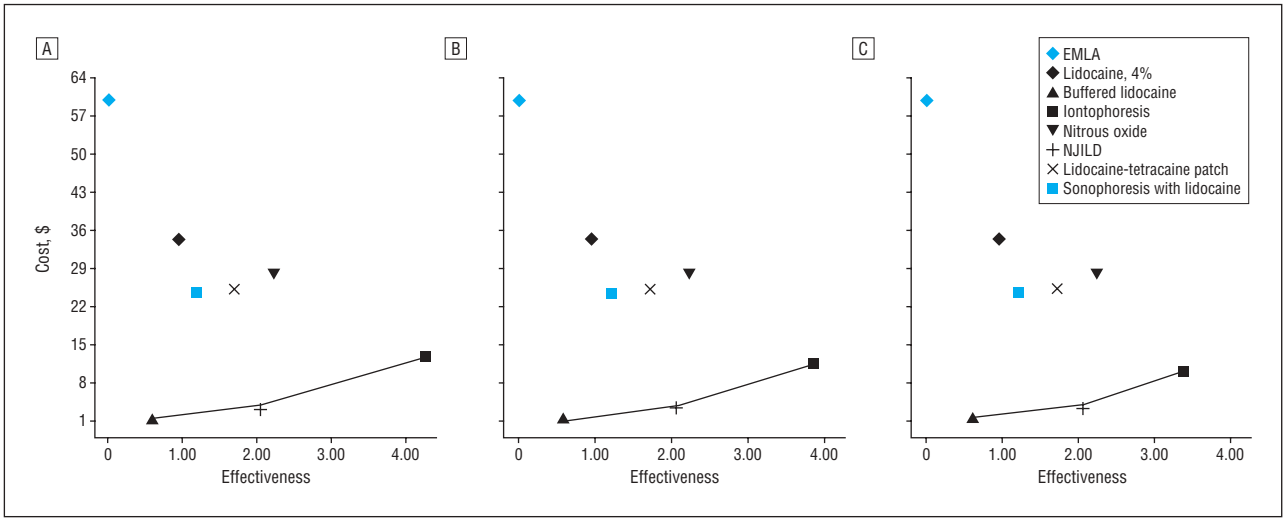

Figure 3. Report of results of sensitivity analysis to a change in the variable probability of peripheral intravenous cannulation success without anesthesia. A, Probability of peripheral intravenous cannulation success without anesthesia was 0.72; B, probability of peripheral intravenous cannulation success without anesthesia was 0.86; and C, probability of peripheral intravenous cannulation success without anesthesia was 1.00. EMLA indicates a eutectic mixture of lidocaine and prilocaine cream; NJILD, needle-free jet injection of lidocaine.

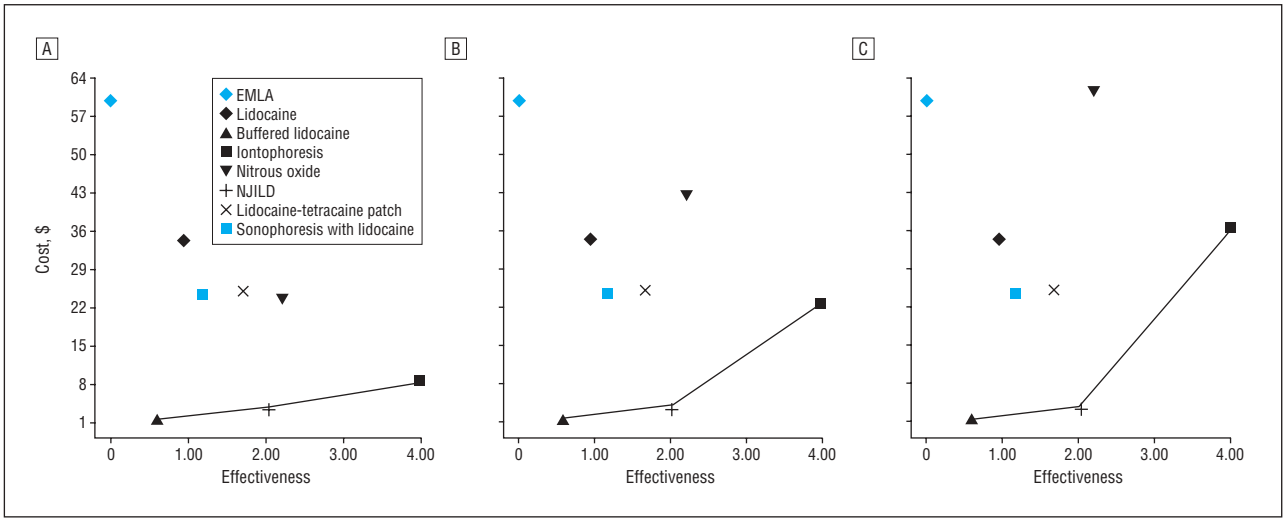

Figure 4. Report of results of sensitivity analysis to a change in the variable average time for a nurse to insert a peripheral intravenous (PIV) cannula, including set-up time. A, Average time to insert PIV cannula was 0.08 hour; B, average time to insert PIV cannula was 0.29 hour; and C, average time to insert PIV cannula was 0.50 hour. EMLA indicates a eutectic mixture of lidocaine and prilocaine cream; NJILD, needle-free jet injection of lidocaine.

son studies, allowing physicians and administrators to compare alternatives, have not been published. Decision analysis affords a method for simultaneously examining the costs and benefits of alternative clinical strategies and exploring the impact of varying key probabilities, costs, and outcomes. Our analysis suggests that the current best options include NJILD and buffered lidocaine. Their low unit cost combined with relative reduction in pain scores compared with placebo make them an attractive option for use in pediatrics.

To explore the sensitivity of our results to key variables, we conducted sensitivity and Monte Carlo analyses varying certain variables within reasonable ranges and found that our results were fundamentally unaltered. This process allowed us to determine the thresholds that could make our model applicable to other institutions with somewhat different costs, productivity, and PIV cannulation success rates.

Our analysis also provides important insight regarding costs and pain reduction that must be exhibited by new approaches to pediatric PIV cannulation pain management to be relatively cost-effective. Although other pain management approaches yielded better outcomes than the NJILD or buffered lidocaine injection (eg, iontophoresis, the lidocaine-tetracaine patch, and laser or ultrasonic preparation of the skin followed by topical lidocaine, 4%, had lower mean VAS pain scores), their unit costs made them less attractive. With the benchmark ICER of the NJILD at 1.89 (cost of $3.90; VAS pain score reduction of 2.05 cm), newer approaches will need to either have a cost less than $3.90 per patient coupled with similar pain score reductions or provide a greater than 2.05-cm reduction in VAS scores with similar unit costs.

Our analysis suggests that the most cost-effective alternative is the NJILD, yielding a 2.05-cm reduction in VAS pain score for $3.90. Alternatively, is the pain in-

Table 4. Sensitivity Analysis Assuming Emergency Department Wait Time of 0 for Lidocaine, EMLA, and Lidocaine-Tetracaine Patch

Strategy	Cost, $	Effectiveness	ICER
NJILD	3.9	2.05	1.89
Buffered lidocaine	1.6	0.61	2.68
Iontophoresis	11.8	4.07	2.89
Lidocaine-tetracaine patch	12.0	1.70	7.06
Lidocaine cream, 4%	7.7	0.97	7.92
Nitrous oxide	27.8	2.25	12.35
Sonophoresis	24.4	1.21	20.15
EMLA	9.3	0.02	465.24

Abbreviations: EMLA, a eutectic mixture of lidocaine and prilocaine cream; ICER, incremental cost-effectiveness ratio; NJILD, needle-free jet injection of lidocaine.

Table 5. Sensitivity Analysis Assuming Uniform Pain Reduction With All Analgesic Options

Strategy	Cost, $	Effectiveness	ICER
NJILD	3.9	2.00	1.89
Buffered lidocaine	1.6	2.00	2.68
Iontophoresis	11.8	4.05	2.89
Lidocaine-tetracaine patch	25.7	2.00	7.06
Lidocaine cream, 4%	34.3	2.00	7.92
Nitrous oxide	27.8	2.00	12.35
Sonophoresis	24.4	2.00	20.15
EMLA	59.6	2.00	465.24

Abbreviations: See Table 4.

voked with PIV cannulation worth spending $11.80? In that case, lidocaine iontophoresis might be considered, reducing the pain scores by 4.07 cm. Although our analysis provides information on which pain management modalities are on the cost-effective frontier and which alternatives are the most cost-effective, it cannot tell us how much we should be willing to spend. This is clearly an institutional and societal policy issue that must be considered in light of patient preferences, the ability to achieve clinically meaningful improvements in outcomes, and the relative cost-effectiveness of next-best alternatives.

Our study has a number of important limitations that should be considered when interpreting our results. Several studies included in this analysis were not ED based. However, we believe that pain associated with PIV cannulation in children will be similar across various hospital-based settings.

Our study also relies on self-reported VAS scores, PIV cannulation establishment times, and cannulation success rates across somewhat heterogeneous pediatric populations and physicians, with potentially varying levels of experience. Younger children, especially those aged 3 to 4 years, may rate the pain of procedures somewhat higher than their older counterparts. They also frequently show a different response when using continuous scales and select the extreme ends while neglecting the midportions of scales.[61] The study that cited relatively lower weighted mean VAS scores with NJILD included children between 7 and 19 years of age. This was in contrast to studies that used

Table 6. Summary of Studies That Enrolled Patients 3 to 17 Years of Age

Pain Management Modality	Age, y	
	Range	Mean (SD)
Buffered lidocaine		
Luhmann et al,[29] 2004	4-17	12.1 (4.5)
EMLA		
Andrew et al,[31] 2002	5-15	9.6 (with nitroglycerin) and 8.6 (with placebo)
Vetter,[43] 1995	6-12	8.8 (0.2) for placebo and 9.0 (0.4) nitrous oxide
Manner et al,[40] 1987	4-10	6.9 (1.8) and 6.4 (1.5) placebo
Lander et al,[39] 1996	5-18	12.3 (3.7) and 11.6 (3.7) placebo
Iontophoresis		
Zempsky et al,[44] 1998	5-17	10.2 (3.6) and 10.4 (3.4) placebo
Lidocaine-tetracaine patch		
Sethna et al,[41] 2005	3-17	8 (4.6) and 7.7 (4.4) placebo
Laser		
Singer et al,[58] 2002	1-18	11/30 patients <7 y

Abbreviation: See Table 4.

EMLA, lidocaine, or buffered lidocaine and included children as young as 4 to 5 years. This approach could potentially favor NJILD during calculation of the effectiveness of analgesia. Of the 18 trials in our model, 6 included patients who were 3 to 7 years in whom the self-reported VAS score had not been validated. However, the mean age of the patients in these studies was older than 7 years. To elucidate this, we have included a summary of the age range and means reported in these 8 studies (**Table 6**).

Our decision analysis required some simplifying assumptions. For example, we assumed that after 1 failed attempt, intravenous cannula insertion would be successful at the next attempt at another site using conventional protocols aided by local anesthesia. This assumption was based on 90% to 91% success rates reported with the second attempt using buffered lidocaine or placebo.[26] In addition, payoffs (pain scores and costs) after a failed initial attempt were considered additive across the 2 attempted intravenous cannula insertions. This is clearly a simplification that may not be true for all patients.

Furthermore, our study assumes that the local adverse effects of various modalities, other than an intolerability rate with lidocaine iontophoresis and bandage removal pain associated with EMLA, are minor and that there were no differences in the relative discomfort associated with the various modalities. Other topical agents have been known to cause minor erythema or transient cutaneous reactions. However, specific evidence to support nonparticipation or withdrawal of patients from clinical trials associated with their use was lacking. Therefore, our approach implicitly assumed that these minor reactions were included in the global self-reported pain score.

Several studies included in this analysis were not ED based. However, we believe that pain associated with PIV cannulation in children would be similar across various hospital-based settings.

We excluded analgesic agents that are not available in the United States, such as amethocaine, from our model. Given the obvious difficulties of acquiring costs of these agents, personnel costs, and hospital accounting data, combined with foreign currency fluctuations, we believe that making this more international is beyond the scope of the current study.

Finally, we relied on data from a pilot study in our ED to estimate average time to establish PIV cannulation. Although these data are not derived from multicenter trials, they are consistent with prior data.[30,62]

In summary, given the current data on costs and effectiveness profiles of available pain management modalities, the NJILD and injection of buffered lidocaine appear to be the preferred initial local anesthetic strategy for PIV cannulation in children. Low-dose lidocaine iontophoresis represents a third cost-effective option, although its total price of $11.80 (agent plus associated ED time) may be higher than some are willing to pay for a relatively modest incremental reduction in pain compared with the next best alternative (NJILD).

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Correspondence: Jay Pershad, MD, Division of Emergency Medicine, Department of Pediatrics, Le Bonheur Children's Medical Center, 50 N Dunlap St, Memphis, TN 38103 (pershadj@lebonheur.org).
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REFERENCES

1. Humphrey GB, Boon CM, van Linden van den Heuvell GF, van de Wiel HB. The occurrence of high levels of acute behavioral distress in children and adolescents undergoing routine venipunctures. *Pediatrics*. 1992;90(1, pt 1):87-91.
2. Menke EM. School-aged children's perception of stress in the hospital. *Child Health Care*. 1981;9(3):80-86.
3. Smith RW, Shah V, Goldman RD, Taddio A. Caregivers' responses to pain in their children in the emergency department. *Arch Pediatr Adolesc Med*. 2007;161(6):578-582.
4. Zempsky WT, Cravero JP. Relief of pain and anxiety in pediatric patients in emergency medical systems. *Pediatrics*. 2004;114(5):1348-1356.
5. Young KD. Pediatric procedural pain. *Ann Emerg Med*. 2005;45(2):160-171.
6. Houck CS, Sethna NF. Transdermal analgesia with local anesthetics in children: review, update and future directions. *Expert Rev Neurother*. 2005;5(5):625-634.
7. Costello M, Ramundo M, Christopher NC, Powell KR. Ethyl vinyl chloride vapocoolant spray fails to decrease pain associated with intravenous cannulation in children. *Clin Pediatr (Phila)*. 2006;45(7):628-632.
8. Ramsook C, Kozinetz CA, Moro-Sutherland D. Efficacy of ethyl chloride as a local anesthetic for venipuncture and intravenous cannula insertion in a pediatric emergency department. *Pediatr Emerg Care*. 2001;17(5):341-343.
9. Zappa SC, Nabors SB. Use of ethyl chloride topical anesthetic to reduce procedural pain in pediatric oncology patients. *Cancer Nurs*. 1992;15(2):130-136.
10. Arrowsmith J, Campbell C. A comparison of local anaesthetics for venepuncture. *Arch Dis Child*. 2000;82(4):309-310.
11. Choy L, Collier J, Watson AR. Comparison of lignocaine-prilocaine cream and amethocaine gel for local analgesia before venepuncture in children. *Acta Paediatr*. 1999;88(9):961-964.
12. Cárceles MD, Alonso JM, Garcia-Muñoz M, Nájera MD, Castaño I, Vila N. Amethocaine-lidocaine cream, a new topical formulation for preventing venopuncture-induced pain in children. *Reg Anesth Pain Med*. 2002;27(3):289-295.
13. Lawson RA, Smart NG, Gudgeon AC, Morton NS. Evaluation of an amethocaine gel preparation for percutaneous analgesia before venous cannulation in children. *Br J Anaesth*. 1995;75(3):282-285.
14. Rømsing J, Henneberg SW, Walther-Larsen S, Kjeldsen C. Tetracaine gel vs EMLA cream for percutaneous anaesthesia in children. *Br J Anaesth*. 1999;82(4):637-638.
15. Browne J, Awad I, Plant R, McAdoo J, Shorten G. Topical amethocaine (Ametop) is superior to EMLA for intravenous cannulation: eutectic mixture of local anesthetics. *Can J Anaesth*. 1999;46(11):1014-1018.
16. Molodecka J, Stenhouse C, Jones JM, Tomlinson A. Comparison of percutaneous anaesthesia for venous cannulation after topical application of either amethocaine or EMLA cream. *Br J Anaesth*. 1994;72(2):174-176.
17. van Kan HJ, Egberts AC, Rijnvos WP, ter Pelkwijk NJ, Lenderink AW. Tetracaine versus lidocaine-prilocaine for preventing venipuncture-induced pain in children. *Am J Health Syst Pharm*. 1997;54(4):388-392.
18. Soueid A, Richard B. Ethyl chloride as a cryoanalgesic in pediatrics for venipuncture. *Pediatr Emerg Care*. 2007;23(6):380-383.
19. Young SS, Schwartz R, Sheridan MJ. EMLA cream as a topical anesthetic before office phlebotomy in children. *South Med J*. 1996;89(12):1184-1187.
20. Eichenfield LF, Funk A, Fallon-Friedlander S, Cunningham BB. A clinical study to evaluate the efficacy of ELA-Max (4% liposomal lidocaine) as compared with eutectic mixture of local anesthetics cream for pain reduction of venipuncture in children. *Pediatrics*. 2002;109(6):1093-1099.
21. Brislin RP, Stayer SA, Schwartz RE, Pasquariello CA. Analgesia for venepuncture in a paediatric surgery centre. *J Paediatr Child Health*. 1995;31(6):542-544.
22. Squire SJ, Kirchhoff KT, Hissong K. Comparing two methods of topical anesthesia used before intravenous cannulation in pediatric patients. *J Pediatr Health Care*. 2000;14(2):68-72.
23. Gall O, Annequin D, Ravault N, Murat I. Relative effectiveness of lignocaine-prilocaine emulsion and nitrous oxide inhalation for routine preoperative laboratory testing. *Paediatr Anaesth*. 1999;9(4):305-310.
24. Taddio A, Soin HK, Schuh S, Koren G, Scolnik D. Liposomal lidocaine to improve procedural success rates and reduce procedural pain among children: a randomized controlled trial. *CMAJ*. 2005;172(13):1691-1695.
25. Paut O, Calméjane C, Delorme J, Lacroix F, Camboulives J. EMLA versus nitrous oxide for venous cannulation in children. *Anesth Analg*. 2001;93(3):590-593.
26. Sacchetti AD, Carraccio C. Subcutaneous lidocaine does not affect the success rate of intravenous access in children less than 24 months of age. *Acad Emerg Med*. 1996;3(11):1016-1019.
27. Singer AJ, Weeks R, Regev R. Laser-assisted anesthesia reduces the pain of venous cannulation in children and adults: a randomized controlled trial. *Acad Emerg Med*. 2006;13(6):623-628.
28. Berkowitz D. *Laser Assisted Anesthesia Prior to Intravenous Canulation: Acceptability and Effectiveness in Children*. Toronto, ON: Pediatric Academic Society; 2007.
29. Luhmann J, Hurt S, Shootman M, Kennedy R. A comparison of buffered lidocaine versus ELA-Max before peripheral intravenous catheter insertions in children. *Pediatrics*. 2004;113(3, pt 1):e217-e220 http://pediatrics.aappublications.org/cgi/content/full/113/3/e217. Accessed July 7, 2007.
30. Klein EJ, Shugerman RP, Leigh-Taylor K, Shneider C, Portscheller D, Koepsell T. Buffered lidocaine: analgesia for intravenous line placement in children. *Pediatrics*. 1995;95(5):709-712.
31. Andrew M, Barker D, Laing R. The use of glyceryl trinitrate ointment with EMLA cream for i.v. cannulation in children undergoing routine surgery. *Anaesth Intensive Care*. 2002;30(3):321-325.
32. Cordoni A, Cordoni LE. Eutectic mixture of local anesthetics reduces pain during intravenous catheter insertion in the pediatric patient. *Clin J Pain*. 2001;17(2):115-118.
33. Galinkin JL, Rose JB, Harris K, Watcha MF. Lidocaine iontophoresis versus eutectic mixture of local anesthetics (EMLA) for IV placement in children. *Anesth Analg*. 2002;94(6):1484-1488.
34. Hee HI, Goy RW, Ng AS. Effective reduction of anxiety and pain during venous cannulation in children: a comparison of analgesic efficacy conferred by nitrous oxide, EMLA and combination. *Paediatr Anaesth*. 2003;13(3):210-216.
35. Jimenez N, Bradford H, Seidel KD, Sousa M, Lynn AM. A comparison of a needle-free injection system for local anesthesia versus EMLA for intravenous catheter insertion in the pediatric patient. *Anesth Analg*. 2006;102(2):411-414.

36. Kim MK, Kini NM, Troshynski TJ, Hennes HM. A randomized clinical trial of dermal anesthesia by iontophoresis for peripheral intravenous catheter placement in children. *Ann Emerg Med*. 1999;33(4):395-399.
37. Kleiber C, Sorenson M, Whiteside K, Gronstal BA, Tannous R. Topical anesthetics for intravenous insertion in children: a randomized equivalency study. *Pediatrics*. 2002;110(4):758-761.
38. Koh JL, Harrison D, Swanson V, Norvell DC, Coomber DC. A comparison of laser-assisted drug delivery at two output energies for enhancing the delivery of topically applied LMX-4 cream prior to venipuncture. *Anesth Analg*. 2007;104(4): 847-849.
39. Lander J, Hodgins M, Nazarali S, McTavish J, Ouellette J, Friesen E. Determinants of success and failure of EMLA. *Pain*. 1996;64(1):89-97.
40. Manner T, Kanto J, Iisalo E, Lindberg R, Viinamäki O, Scheinin M. Reduction of pain at venous cannulation in children with a eutectic mixture of lidocaine and prilocaine (EMLA cream): comparison with placebo cream and no local premedication. *Acta Anaesthesiol Scand*. 1987;31(8):735-739.
41. Sethna NF, Verghese ST, Hannallah RS, Solodiuk JC, Zurakowski D, Berde CB. A randomized controlled trial to evaluate S-Caine patch for reducing pain associated with vascular access in children. *Anesthesiology*. 2005;102(2):403-408.
42. Skarbek-Borowska S, Becker BM, Lovgren K, Bates A, Minugh PA. Brief focal ultrasound with topical anesthetic decreases the pain of intravenous placement in children. *Pediatr Emerg Care*. 2006;22(5):339-345.
43. Vetter TR. A comparison of EMLA cream versus nitrous oxide for pediatric venous cannulation. *J Clin Anesth*. 1995;7(6):486-490.
44. Zempsky WT, Anand KJ, Sullivan KM, Fraser D, Cucina K. Lidocaine iontophoresis for topical anesthesia before intravenous line placement in children. *J Pediatr*. 1998;132(6):1061-1063.
45. Zempsky WT, Paulson DM, Hoath , SB . Evaluation of a low-dose lidocaine iontophoresis system for topical anesthesia in adults and children: a randomized, controlled trial. *Clin Ther*. 2004;26(7):1110-1119.
46. von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. *Pain*. 2007;127 (1-2):140-150.
47. Gift AG. Visual analogue scales: measurement of subjective phenomena. *Nurs Res*. 1989;38(5):286-288.
48. Abu-Saad H. Assessing children's responses to pain. *Pain*. 1984;19(2):163-171.
49. Maunuksela EL, Olkkola KT, Korpela R. Measurement of pain in children with self-reporting and behavioral assessment. *Clin Pharmacol Ther*. 1987;42(2): 137-141.
50. McGrath PA, Seifert CE, Speechley KN, Booth JC, Stitt L, Gibson MC. A new analogue scale for assessing children's pain: an initial validation study. *Pain*. 1996; 64(3):435-443.
51. van Dijk M, Koot HM, Saad HH, Tibboel D, Passchier J. Observational visual analog scale in pediatric pain assessment: useful tool or good riddance? *Clin J Pain*. 2002;18(5):310-316.
52. Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? *Acad Emerg Med*. 1998;5(11):1086-1090.
53. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emerg Med J*. 2001;18(3): 205-207.
54. Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analog pain score for children. *Ann Emerg Med*. 2001;37 (1):28-31.
55. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. *Ann Emerg Med*. 1996;27(4):485-489.
56. Todd KH, Funk JP. The minimum clinically important difference in physician-assigned visual analog pain scores. *Acad Emerg Med*. 1996;3(2):142-146.
57. Kelly AM, Powell CV, Williams A. Parent visual analogue scale ratings of children's pain do not reliably reflect pain reported by child. *Pediatr Emerg Care*. 2002;18(3):159-162.
58. Singer AJ, Gulla J, Thode HC Jr. Parents and practitioners are poor judges of young children's pain severity. *Acad Emerg Med*. 2002;9(6):609-612.
59. Lysakowski C, Dumont L, Tramèr MR, Tassonyi E. A needle-free jet-injection system with lidocaine for peripheral intravenous cannula insertion: a randomized controlled trial with cost-effectiveness analysis. *Anesth Analg*. 2003;96(1):215-219.
60. Cooper JA, Bromley LM, Baranowski AP, Barker SG. Evaluation of a needle-free injection system for local anaesthesia prior to venous cannulation. *Anaesthesia*. 2000;55(3):247-250.
61. Arts SE, Abu-Saad HH, Champion GD, et al. Age-related response to lidocaine-prilocaine (EMLA) emulsion and effect of music distraction on the pain of intravenous cannulation. *Pediatrics*. 1994;93(5):797-801.
62. Minville V, Pianezza A, Asehnoune K, Cabardis S, Smail N. Prehospital intravenous line placement assessment in the French emergency system: a prospective study. *Eur J Anaesthesiol*. 2006;23(7):594-597.