An admixture of 3 mg·kg⁻¹ of propofol and 3 mg·kg⁻¹ of thiopentone reduces pain on injection in pediatric anesthesia

[Un mélange de 3 mg·kg⁻¹ de propofol et de 3 mg·kg⁻¹ de thiopental réduit la douleur à l'injection d'anesthésique chez les enfants]

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Purpose: To evaluate the incidence of pain on injection in children during anesthetic induction with a 3:1.2 volume admixture of 1% propofol and 2.5% thiopentone (P/T) compared to a 10:1 volume admixture of 1% propofol and 2% lidocaine (P/L).

Methods: After Ethics Committee approval and informed written parental consent, 127 children, aged one to ten years were studied and randomized into two groups; Group P/L received an induction with 5 mg·kg⁻¹ of 1% propofol and 1 mg·kg⁻¹ of lidocaine, Group P/T with 3 mg·kg⁻¹ of 1% propofol and 3 mg·kg⁻¹ of 2.5% thiopentone in a standardized fashion. A single, blinded observer scored pain behaviour defined as a motor response of the arm, a verbal complaint of pain, cry and/or one of three standardized facial expressions of pain.

Results: The incidence of pain was 14% in the P/T group, compared to 35% in the P/L group ($\chi^2_1 = 7.5$, $P = 0.006$). Motor response was the most frequent pain response in the P/L group (68%).

Conclusion: The P/T admixture is a practical and efficacious alternative to P/L for reducing pain on induction in children. Further work to evaluate the optimum proportions and possible adverse effects of this admixture should be done.

Objectif : Évaluer l'incidence de douleur pendant l'injection d'anesthésique d'induction chez les enfants avec un mélange de volume de 3:1,2 de propofol à 1 % et de thiopental à 2,5 % (P/T) comparé à un volume de 10:1 de propofol à 1 % et de lidocaïne à 2 % (P/L).

Méthode : L'approbation du Comité d'éthique et le consentement écrit des parents ont permis l'étude de 127 enfants, de un à dix ans,

répartis en deux groupes. Ceux du groupe P/L ont reçu une induction avec 5 mg·kg⁻¹ de propofol à 1 % et 1 mg·kg⁻¹ de lidocaïne et ceux du groupe P/T, 3 mg·kg⁻¹ de propofol à 1 % et 3 mg·kg⁻¹ de thiopental à 2,5 % de façon normalisée. Un observateur objectif a noté le comportement face à la douleur, défini par une réponse motrice du bras, une plainte verbale, un cri et/ou une des trois expressions faciales de douleur reconnues.

Résultats : L'incidence de la douleur a été de 14 % dans le groupe P/T et de 35 % dans le groupe P/L group ($\chi^2_1 = 7,5$, $P = 0,006$). La réponse motrice a été la réaction la plus fréquente dans le groupe P/L group (68 %).

Conclusion : Le mélange de P/T constitue une solution de rechange pratique et efficace au mélange P/L pour la réduction de la douleur lors de l'induction de l'anesthésie chez les enfants. Il reste à évaluer les dosages optimaux et les effets indésirables possibles de ce mélange.

PROPOFOL causes pain on injection in both adult and pediatric patients.¹⁻³ The etiology of this pain is uncertain but two causes have been suggested. Firstly, the phenol may cause immediate pain from a local irritant effect on the vein. This decreases when propofol in the aqueous phase is diluted by adding it to fat emulsion.¹ Secondly, delayed pain (after 10–20 sec) from an indirect action on the endothelium releasing kininogens, may trigger painful stimuli in the nerve endings between the intima and the media of the vessel wall.²

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The incidence of pain on injection of propofol has been extensively studied and ranges from 50–100%.³ A mainly adult meta-analysis of this clinical problem concludes that the optimum treatment is to give *iv* lidocaine 0.5 mg·kg⁻¹ while a tourniquet is applied to the arm for at least 30–120 sec prior to the injection of the propofol.⁴ This recommendation is, in our view, impractical in the pediatric population.

Pediatric studies describe a high incidence of pain on injection (50%) when propofol alone is injected into a vein on the dorsum of the hand.⁵ A routinely used technique to reduce the pain on injection in children is to admix preservative-free lidocaine in a dose of 1 mg·kg⁻¹ with an induction dose of propofol 5 mg·kg⁻¹. The efficacy of this technique in a study of 50 children was 100%.⁶ In an unblinded, observational pilot study of 50 children using this technique at our institution, the incidence of pain was 20%.

The admixture of thiopentone and propofol may also reduce injection pain. Adult studies using thiopentone demonstrated that *pretreating* a vein with 50 mg of thiopentone prior to propofol injection was not as efficacious in reducing injection pain as 40 mg of lidocaine.⁷ In contrast, *pretreating* with 100 mg thiopentone was more effective than 20 mg of lidocaine.⁸ In children, *pretreatment* with 3 mg·kg⁻¹ of thiopentone prior to injecting propofol 1.5 mg·kg⁻¹ with lidocaine 0.075 mg·kg⁻¹ reduced the injection pain from 81% to 27%.⁹ A 1:1 and 3:1 admixture of 1% propofol and 2.5% thiopentone (23% and 37% pain respectively) were superior to propofol and lidocaine in a 5:1 ratio (40% pain) in relieving pain on injection in adults.¹⁰

We hypothesized that the incidence of pain on injection during anesthetic induction with an admixture of 1% propofol, 3 mg·kg⁻¹ and 2.5% thiopentone, 3 mg·kg⁻¹ (P/T) would be less than that with an admixture 1% propofol, 5 mg·kg⁻¹ and 2% lidocaine, 1 mg·kg⁻¹ of (P/L).

Methods

After University and Institutional Ethical Board approval and informed written parental consent, 127 children were randomized into two groups. All ASA I and II patients undergoing *iv* induction requiring access in the dorsum of the hand, who were more than one year and less than ten years of age and weighed ≤ 40 kg, were invited to participate in the study.

Subjects who had a body mass index > 30, or an allergy to any of the local anesthetics, analgesics or induction agents, or who did not receive acetaminophen preoperatively were excluded. Any child who had cognitive-behavioural disturbances or a par-

ent or caregiver who could not be present at induction was also excluded from the study.

Randomization was achieved using a computer generated random numbers table and randomizing in blocks of ten. The induction sequence of events was standardized (see Appendix 1). Any subject who was not calm and cooperative immediately prior to induction or responded “No” to the question “Does your hand feel OK?” after establishment of *iv* access and prior to induction was excluded from further study.

Demographic data including the age, weight and gender of the subjects were recorded. The time from administration of a preoperative oral dose of acetaminophen 20 mg·kg⁻¹ to induction was recorded.

Group P/L received 1% propofol, 5 mg·kg⁻¹ mixed with 2% lidocaine, 1 mg·kg⁻¹. Group P/T received 1% propofol, 3 mg·kg⁻¹ mixed with 2.5% thiopentone, 3 mg·kg⁻¹.

The study drugs were prepared immediately prior to induction by the staff anesthesiologist not involved in the observations. The syringes were visually indistinguishable. Pain was recorded as a dichotomous variable, yes or no. Intensity was not evaluated. A yes was scored when any one of the following pain outcomes occurred: verbal, motor, facial action and cry (see Appendix 2).

Sample size was calculated for the primary outcome, pain. Based on a pilot study of 50 patients, it was estimated that the incidence of pain on injection of P/L was 20%. In order to detect an 18% decrease in pain in the P/T group with 0.8 power and type one error of 0.5, 62 subjects were randomized to each group. This number of subjects was sufficient to achieve an estimate of the difference in pain incidence with confidence intervals (CI) of width 20%.

The statistical package, SPSS (version 10.0), was used to analyze the data. Demographic data are presented as either percent, mean ± SD, or median and range. The two blinded observers (JMcF/RP) independently scored the first 11 patients to test for agreement between observers. An assessment to ensure agreement between observers was carried out using the Kappa statistic. A single observer scored the rest of the subjects (RP).

The primary outcome of pain in each group was analyzed using the Pearson's Chi squared test statistic. Logistic regression was used to explore the influences of appropriateness of acetaminophen to induction time and group (P/L *vs* P/T) on pain.

Results

A total of 176 families were approached for enrollment in the study and 46 (26%) did not consent. One

TABLE I Patient characteristics

	Group P/L (n = 63)	Group P/T (n = 64)
Age* (yr)	5.0 (1.25–10)	4.0 (1.25–6)
Weight* (kg)	18.0 (10–36)	17.0 (10–38)
Gender† (M/F)	42/21 (66%/33%)	42/22 (65%/34%)
Acetaminophen-induction* (min)	25 (5–90)	30 (5–180)

* = median (range); † = number of patients (%). P/L = 1% propofol and 2% lidocaine; P/T = 1% propofol and 2.5% thiopentone.

TABLE II Age and ability to respond to pain questions

Pain question	Responders		Non-responders	
	Number of patients	Age*	Number of patients	Age*
Does your hand feel ok?	94 (74%)	5.0 (2–10)	33 (26%)	2.0 (1.25–6)
Does your arm feel ok?	86 (68%)	5.0 (2–10)	41 (32%)	3.0 (1.25–7)

* = median (range).

hundred and thirty-nine subjects were recruited. Of these, nine subjects (median age = 3, range 2–7 yr) were withdrawn from the study due to inability to cooperate as demonstrated by persistent distress after the insertion of the *iv* cannula. Three subjects were eliminated from the study because they did not receive preoperative acetaminophen.

The age, weight and gender of the 127 subjects (P/L = 63, P/T = 64) in the two treatment groups were similar (Table I). The acetaminophen administration-to-induction times were also similar in the two groups (Table I). There was a wide range in these times due to scheduling issues. In 115 (90%) subjects, venous cannulation was achieved on the first attempt. In 12 (9%) subjects multiple attempts were required. Despite multiple attempts at cannulation, these few subjects were calm, did not report hand pain prior to induction and were thus eligible to continue with the study. One subject in each group proceeded to give a positive pain response during the *iv* injection.

In response to the first question, “Does your hand feel OK?” after *iv* access was established, 33 (25%) children gave no response. There were no subjects who responded

ed “No” to the question. The subjects who responded to the question were older than the non-responders (Table II). After the test dose of 0.1 mL·kg⁻¹ of induction agent, the number of subjects who did not respond to the second question, “Does your arm feel OK?” increased to 41 (32%) presumably because of the initial sedative effect of the induction agents. Again, subjects who responded to the question were older than the non-responders. The age of responders to the pain questions before and after the injection was similar (Table II). There was good agreement, 91% (10/11), of pain observations between the two observers [Kappa = 0.74, 95% CI = (0.28, 1.0)].

The primary outcome of interest in this study was pain. Thirty-one (24%) subjects demonstrated at least one of the outcome measures of pain. The incidence of pain on injection was higher in the P/L group, 22 (34%) subjects experienced pain compared with nine (14%) in the P/T group ($\chi^2_1 = 7.5$, $P = 0.006$). Motor response occurred more frequently in the P/L group (68%). No subject demonstrated facial action alone. Cry occurred in seven (25%) subjects who concurrently demonstrated other positive pain variables, and in one subject as a sole pain score. The distribution of pain responses for each subject is shown in the Figure.

Acetaminophen administration to induction time was subdivided into inadequate (≤ 30 min, ≥ 90 min) and adequate (30–90 min) and the relationship between these two groups and the primary outcome, pain, was investigated by logistic regression. Controlling for acetaminophen administration time did not affect the relationship between pain and group. The P/L group was still more likely to experience pain [odds ratio = 3.37, 95% CI = (1.40, 8.15)].

Discussion

In pediatric patients with a mean age of 4.5 yr, *iv* induction with a P/T 3:1.2 admixture is more efficacious in reducing pain on injection than a P/L 10:1 admixture.

The efficacy of lidocaine in doses of 0.1–1.0 mg·kg⁻¹ in reducing pain on injection in children ranges from 21–100% in various studies (Table III). Previous investigators using composite pain outcome measures (cry, self report, arm withdrawal and grimace) have concluded that the efficacy of lidocaine appears to be best in a dose of 1 mg·kg⁻¹.⁶ With our outcome measure, the efficacy of this technique was 66%. Although accurate pain measurement is very challenging in children, our composite dichotomous score based on any one of verbal self-report, motor responses, three robust facial expressions and cry measured a clinically relevant difference. While this tool is

TABLE III Efficacy of lidocaine and propofol in reducing pain on injection in children

Reference	Patients (n)	Age (yr)	Injectate	Incidence of pain
Morton ⁵	40	1–10	P 2 mg·kg ⁻¹ + L 0.1 mg·kg ⁻¹ , T 5 mg·kg ⁻¹	P 55% T 0%.
Valtonen ¹³	40	3–10	P 2–2.5 mg·kg ⁻¹ + L 0.5 mg·kg ⁻¹ , P 2–2.5 mg·kg ⁻¹ + 5% glucose 1 mL	P/L 20% pain Glucose 80% pain
Morton ⁶	50	3–10	P 3 mg·kg ⁻¹ , + L 1 mg·kg ⁻¹	0%
Hannallah ¹¹	90	3–12	P 1–3 mg·kg ⁻¹ into ACF vein	7%
Cameron ¹²	100	1–10	P 3 mg·kg ⁻¹ + L 0.1–1.0 mg·kg ⁻¹	P/L 0.2–1.0 mg·kg ⁻¹ 0% P/L 0.1 mg·kg ⁻¹ 23%
Cheng ⁹	127	3–6	P 3 mg·kg ⁻¹ + L 1 0.15 mg·kg ⁻¹ L, L 2 0.3 mg·kg ⁻¹ , L 3 0.6 mg·kg ⁻¹ , T 3 mg·kg ⁻¹ , P 1.5 mg·kg ⁻¹ + L 0.075 mg·kg ⁻¹	L1 = 81%, L2 = 79%, L3 = 62%, T = 27%

P = propofol 1%; T = thiopentone 2.5%; L = lidocaine 2%; ACF = antecubital fossa.

FIGURE Number and distribution of categories of pain responses.

not a recognized one, it was devised by our group based on our pre-clinical trial and had good inter-observer agreement over the initial 11 patients in this study. The apparently most robust elements of this tool were motor response of arm or hand withdrawal, reaching for the arm and self-report of pain in a previously calm and distracted child. These were the outcome variables that we observed in 93% of subjects having pain. Age and the ability to self-report was a

factor in this study. Older children were able to respond to the phrases more often.

After the initial test dose the number of responders decreased by 10%, but the age distribution of non-responders was not changed. The test dose was administered to allow the subject time to respond to any nociceptive input prior to the onset of hypnosis. While sedation after this initial dose was not formally evaluated, this is the most likely cause of the decreased response rate. The pain caused by the P/L injection is clinically important despite any initial negative effects of the induction test dose on the ability to experience and self-report pain.

While facial action has been studied previously in children in recovery room situations, it has not been validated for this particular pain model.¹⁴ We elected to choose what might be considered the more robust facial actions of brow lower, eye squeeze, and cheek raiser. It was beyond the resources of our group to provide multiple observers, videotaping and fully trained facial action raters for each subject. Interestingly, none of these facial actions occurred without concurrent positive behaviours. Cry was also considered valid in this setting as no subjects were crying after venous cannulation and prior to start of the injection. Cry may be a non-specific behaviour and only occurred in isolation in one subject. No effort was made to assign an intensity rating to any of these pain behaviours. A valid pain outcome measure for use in this setting is required.

The speed of injection has been implicated as a factor in the incidence of injection pain.^{2,15} A meta-analysis by Picard found no correlation between speed of injection and the incidence of pain.³ We standardized the duration of administration. After an initial dose of 0.1 mL·kg⁻¹, five seconds elapsed to allow the subject time to experience and report any possible pain. This technique also presumably standardized the degree of sedation.

The P/T admixture may be less painful to inject simply because propofol is diluted. Propofol diluted 1:1 with 5% dextrose caused significantly less injection pain.¹⁶ Diluting propofol with a 2:1 lipid emulsion reduced injection pain more successfully than a 2:1 admixture with saline¹ suggesting that it is the amount of propofol in the aqueous phase that causes the pain. Both these studies diluted the propofol significantly more than our 3:1 thiopentone admixture. The method by which pain is reduced may be due to the high pH of the admixture driving the propofol from aqueous phase into lipid phase. The effect of thiopentone on the surface tension properties of the propofol oil/water interface also needs further evaluation.¹⁰ The optimum ratio of dilution of propofol with thiopentone may not be 3:1 and requires a dose-finding study evaluating in detail the efficacy and side-effects of other ratio's of admixtures.

The P/T admixture has the advantages of stability,^{17,18} less support of bacterial growth,¹⁹⁻²¹ no change in recovery profile,²² and decreased expense. In our institution, July 2001, in Canadian currency, for a 20 kg patient, propofol 3 mg·kg⁻¹ and thiopentone 3 mg·kg⁻¹ costs \$1.60, whereas propofol 5 mg·kg⁻¹ and lidocaine 1 mg·kg⁻¹ costs \$2.80; approximately 60% less. The elimination of the local anesthetic, lidocaine during induction, may add a margin of safety when other local anesthetics are used at a maximum dose for regional anesthesia. It was beyond the scope of this study to examine in detail any disadvantages to the use of this admixture.

Despite the use of the oral analgesic, acetaminophen as a premedicant, the incidence of pain was significant in the P/L group, 35%. As acetaminophen was used in both groups the incidence of pain may be even higher when this premedicant is not given.

Limitations: the hemodynamic effects, immediate in-hospital or late recovery profile and incidence of postoperative nausea and vomiting of these admixtures were not evaluated in this study. In summary, the use of an admixture of 1% propofol, 3 mg·kg⁻¹ and 2.5% thiopentone, 3 mg·kg⁻¹ (P/T) compared to an admixture of 1% propofol, 3 mg·kg⁻¹ and 2% lidocaine, 1 mg·kg⁻¹ (P/L) reduced the pain on injection

at induction of anesthesia in pediatric patients from 34% to 14%. The propofol and thiopentone admixture is a practical and efficacious alternative to propofol and lidocaine for reducing pain on injection.

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APPENDIX 1 Standardized induction sequence

1. All subjects received analgesic premedication of acetaminophen 20 mg·kg⁻¹ orally prior to induction.
2. EMLA cream was applied to the cannulation site for at least 45 min prior to cannulation.
3. The *iv* cannula site was on the dorsum of the hand.
4. A standard 24 gauge *iv* cannula was used.
5. The cannula was flushed with normal saline 1.5 mL.
6. All inductions were conducted with parent or caregiver presence.
7. The subject was not distressed and was able to keep his/her arm still voluntarily prior to the start of the injection. Any subject who did not meet these criteria was then excluded from the study.
8. The subject was distracted using an age-appropriate cognitive-behavioural relaxation-distraction technique such as bubble blowing.
9. Immediately prior to injection, the anesthesiologist asked the child: "*Does your hand feel OK?*"
10. The anesthesiologist injected 0.1 mL·kg⁻¹ of injectate and waited five seconds.
11. The anesthesiologist asked: "*Does your arm feel OK?*"
12. The remainder of induction agent was given over the next 10 to 15 sec.

APPENDIX 2 Pain outcomes

The presence of any of the following behaviours was scored as YES by the dedicated observer.

1. Verbal:
 - a. An unsolicited voluntary verbal complaint (self-report) of pain in the hand during injection.
 - b. Self-report of pain in injectate hand after the question: "*Does your arm feel OK?*"

2. Motor:
 - a. Withdrawal of the hand and/or arm during the injection.
 - b. Reaching for the injectate hand with the non-injectate hand.
3. Facial action:
 - a. Brow lower
 - b. Eye squeeze
 - c. Cheek raiser
4. Crying on injection

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