

Effect of a 0.5% Dilution of Propofol on Pain on Injection during Induction of Anesthesia in Children

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Background: Pain on injection of propofol in children has been reported to be as high as 30–80%. The reason for the pain is assumed to be the aqueous phase of the propofol emulsion. Therefore, for the first time, this study tested the hypothesis that dilution of propofol to a 0.5% emulsion might reduce the incidence of pain during propofol injection.

Methods: The study design was prospective, monocenter, double-blind, and randomized. Sixty-four children aged 2–6 yr were scheduled to receive 0.5% or 1.0% propofol in a medium-chain-triglyceride/long-chain-triglyceride emulsion. Incidence and intensity of pain were assessed by spontaneous expressions of pain and withdrawal of the arm. In a subgroup of 21 children, serum triglyceride levels were measured before and 3 and 20 min after induction. Adverse events were recorded.

Results: Amounts of propofol required until loss of eyelash reflex were 4.40 ± 1.01 mg/kg for 0.5% propofol and 4.31 ± 0.86 mg/kg for 1.0% propofol. Percentages of children who showed at least one pain reaction were 23.3% in the 0.5% propofol group and 70.0% in the 1.0% propofol group ($P < 0.001$). Serum triglycerides were higher in the 0.5% propofol group 3 and 20 min after injection (251.7 vs. 148.8 mg/dl; $P = 0.001$ and 135.5 vs. 75.5 mg/dl; $P = 0.03$). Adverse events or complications did not occur.

Conclusions: Dilution of propofol to a 0.5% medium-chain-triglyceride/long-chain-triglyceride emulsion reduced pain effectively during injection in children aged 2–6 yr. Cumulative doses until 4–5 mg/kg propofol led to moderate increases of triglyceride levels and did not result in significant adverse events.

PAIN on injection of propofol in children has been reported to be as high as 30–80%.^{1,2} There have been many attempts to reduce the pain, such as addition of lidocaine³ or thiopental,⁴ use of medium-chain-triglyceride (MCT)/long-chain-triglyceride (LCT) emulsions⁵ or nitrous oxide,⁶ or injection of ketamine before propofol.⁷ However, none of these methods have achieved a complete elimination of pain so far. The reason for the pain on injection is assumed to be the concentration of propofol in the aqueous phase of the emulsion.^{8,9} Propofol usually is available in a concentration of 1.0% propofol in a lipid emulsion containing 10% triglycerides. Re-

ducing the concentration of the drug by further diluting it with a 10% lipid emulsion to a lower concentration of propofol might reduce incidence and severity of pain on injection by decreasing the concentration of free propofol in the aqueous phase of the emulsion. Dilution, however, requires administration of a considerably higher quantity of lipid emulsion to reach similar effect site concentrations. This might cause hyperlipemia. Therefore, the current study consisted of two parts: In the first part, we evaluated whether commercially available 1.0% propofol in a 10% MCT/LCT emulsion (Propofol-Lipuro®; B. Braun Melsungen AG, Melsungen, Germany) further diluted with the 10% MCT/LCT formulation to a final concentration of 0.5% propofol in a 10% MCT/LCT formulation reduces the incidence and severity of pain on injection compared with the 1% emulsion. In the second part, we measured the time course of serum triglycerides after injection of the different propofol MCT/LCT emulsions in two subgroups of children (*i.e.*, the first 21 patients) to detect differences between the two groups. In addition, differences between groups in propofol requirement, hemodynamics, oxygen saturation, local skin reaction, and adverse events were recorded. For the investigation, we chose an MCT/LCT emulsion, because previous studies showed a significant reduction of pain compared with LCT emulsions.⁵

Materials and Methods

Patients and Methods

The study design was prospective, monocenter, double-blind, randomized, and approved by the local ethics committee (Ethikkommission der Medizinischen Fakultät der Universität zu Köln, University Hospital of Cologne, Cologne, Germany). Sixty-four children aged 2–6 yr, scheduled to undergo elective outpatient urologic or general surgery (*e.g.*, inguinal hernia repair, circumcision), and eligible for the study were included after obtaining parents' informed written consent. On the day of surgery, the children were randomly assigned according to a computerized allocating schedule into two groups receiving either 0.5% propofol or 1% propofol for induction of anesthesia. Exclusion criteria were intolerance of the drugs tested, current drug medication with sedative effect, renal or hepatic disease, cardiac insufficiency, hypovolemia, parental application of lipid emulsions, American Society of Anesthesiologists physical status III or IV, participation in another clinical trial, chronic pain, or history of seizures. Propofol was provided by B. Braun Melsungen AG (Melsungen, Germany).

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In the 1.0% propofol group, commercially available 1% propofol (Propofol-Lipuro[®]; B. Braun Melsungen AG) in a 10% MCT/LCT emulsion was administered. In the 0.5% propofol group, propofol was diluted by the manufacturer exclusively for the study with the same 10% MCT/LCT emulsion to a final concentration of 0.5% propofol in a 10% MCT/LCT emulsion. All children received a eutectic mixture of local anesthetics (EMLA[®]; AstraZeneca GmbH, Wedel, Germany) on the dorsum of both hands 2 h before the scheduled operation time and were premedicated with midazolam (0.5 mg/kg) orally 15–45 min before induction of anesthesia. In all children, a vein on the back of the hand was punctured. During preoxygenation, remifentanyl was administered ($0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) for 1 min by infusion pump. Then, 3 mg/kg propofol was injected over a period of 30 s by an infusion pump (Alaris Medical Systems, Baesweiler, Germany) in both groups. Therefore, children in the 0.5% propofol group received the same dose of propofol (3 mg/kg) but twice the amount of the MCT/LCT emulsion compared with the children in the 1.0% propofol group. The infusion pump was prepared by an investigator not involved in the administration of anesthesia or evaluation of the outcome variables. During the study, the pump was covered to prevent those who were evaluating the outcome variables from becoming unblinded. One investigator assessed the pain in all children, and a second administered the anesthetic and evaluated the level of sedation. According to his assessment, additional doses of 1.0 mg/kg propofol (every 30 s, administered over a period of 10 s) were titrated until loss of the eyelash reflex. After reaching a satisfactory level of sedation, a laryngeal mask airway was inserted, and anesthesia was maintained using remifentanyl $0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and sevoflurane (minimal alveolar concentration 0.5–1) in oxygen.

Assessment of Pain on Injection

Two approaches of an investigator-based pain estimation were used simultaneously: (1) During induction, investigator 1 held both hands of the child and assessed the attempt to draw back the infusion arm in comparison with the movements of the contralateral arm. These attempts were classified as follows: 0 = none, 1 = gentle, 2 = moderate, 3 = strong. (2) The intensity of spontaneous expressions of pain was classified as follows: 0 = none, 1 = grimacing, 2 = crying, 3 = screaming.

Efficacy, Triglyceride Levels, and Adverse Events

In the first 21 children, blood samples were drawn immediately before induction of anesthesia from the intravenous cannula on the back of the hand. After induction of anesthesia, two additional blood samples were collected at 3 and 20 min after the last dose of propofol from a venous catheter that had been inserted

in the contralateral arm. Serum triglycerides were analyzed using the triglyceride GPO-PAP test (Roche, Basel, Switzerland).¹⁰ The total dose of propofol administered to each child was the sum of the initial bolus dose and all subsequent doses. Oxygen saturation, heart rate, and blood pressure were observed during the whole investigation period. Adverse events, such as affections of the puncture site, erythema, exanthema, hiccoughs, myoclonus, or vomiting were assessed using the following scales: 0 = minor, 1 = moderate, 2 = severe. The decision to treat an adverse event was left to the discretion of the attending anesthesiologist, who was blinded to the study medication.

Statistical Analysis

Statistical analysis was performed by the Institut für Angewandte Statistik GmbH, Bielefeld, Germany. Data were compared in and between the two groups by means of the *t* test (baseline hemodynamic parameters, age, body weight, body height, baseline triglyceride values), Mann-Whitney U test (propofol dosage, signs reflecting the intensity of pain), Fisher exact test (binary data), chi-square test (sex), and analysis of covariance for the repeated measurement design (triglyceride values). All tests were performed two-tailed with a significance level of $\alpha = 0.05$ and $1 - \beta = 0.80$. The sample size was determined prospectively according to the following criteria: The incidence of pain was estimated to be 66% after 1.0% propofol²; the target was to reduce the incidence of pain by half to 33%. Therefore, the sample size was calculated as $n = 29$ for each group ($n = 32$ with a dropout rate of approximately 10%).

Results

Patient Characteristics and Dropouts

Sixty-four children were enrolled in this study (32 in each group). In the 0.5% propofol group, the mean age was 4.6 (± 1.3) years, the mean body weight was 18.3 (± 4.1) kg, and the mean height was 107 (± 9) cm. All children were male. In the 1.0% propofol group, the mean age was 4.2 (± 1.4) years, the mean body weight was 17.6 (± 4.0) kg, and the mean height was 104 (± 10) cm. Two children were female. The demographic and baseline characteristics of the children did not differ between groups. In 4 children (2 in each group), the trial had to be terminated prematurely after randomization because the venous access at the back of the hand was not possible. The remaining patients completed the study as scheduled. Therefore, the study population consisted of 60 children.

Assessment of Pain

The overall incidence as well as the intensity to draw back the arm were significantly decreased in the 0.5%

Table 1. Pain on Injection

	0.5% Propofol (n = 30)	1% Propofol (n = 30)	P Value (Test)
Attempt to draw back the arm			
Intensity			< 0.001 (U test)
No	23 (76.7)	9 (30.0)	
Gentle	4 (13.3)	5 (16.7)	
Moderate	2 (6.7)	13 (43.3)	
Strong	1 (3.3)	3 (10.0)	
Overall incidence	7 (23.3)	21 (70.0)	< 0.001 (Fisher)
Spontaneous expressions of pain			
Intensity			0.04 (U test)
No signs	29 (96.7)	24 (80.0)	
Grimacing	1 (3.3)	2 (6.7)	
Crying	—	4 (13.3)	
Screaming	—	—	
Overall incidence	1 (3.3)	6 (20.0)	0.10 (Fisher)

Values are n (%).

propofol group compared with the 1.0% propofol group. Assessing the intensity of pain by using a graduated scale of nonverbal expressions, severity of pain on injection was significantly attenuated in the 0.5% propofol group compared with the 1.0% propofol group ($P = 0.04$). However, the overall incidence of spontaneous expressions of pain did not differ between groups ($P = 0.10$). Details are summarized in table 1.

Efficacy, Triglyceride Levels, and Adverse Events

Similar amounts of propofol were required in both groups to obtain loss of the eyelash reflex (0.5% propofol: 4.40 ± 1.01 mg/kg; 1.0% propofol: 4.31 ± 0.86 mg/kg). Although baseline triglyceride values did not differ between groups, they significantly increased in the 0.5% propofol group compared with the 1.0% propofol group 3 and 20 min after administration of propofol. Results are presented in figure 1. No erythema, whealing, or other skin reactions were seen after surgery at the venous puncture site. Two children in the 1.0% propofol group had to be treated postoperatively because of vomiting. After induction, blood pressure and heart rate

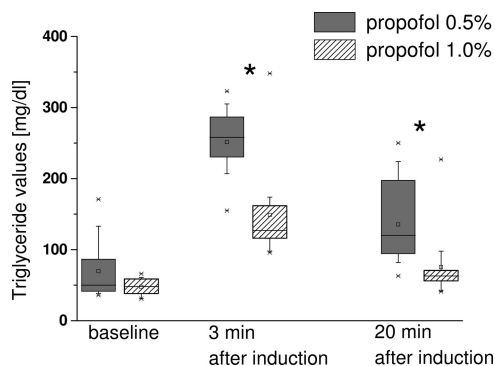


Fig. 1. Triglyceride values (mg/dl). * $P < 0.05$ for 0.5% propofol versus 1.0% propofol. Bottom symbol = 1st percentile; bottom of vertical line = 5th percentile; bottom of box = 25th percentile; median line = 50th percentile; top of box = 75th percentile; top of vertical line = 95th percentile; symbol above vertical line = 99th percentile; square symbol in box = mean.

decreased in both groups without necessity of a therapeutic intervention. Absolute values of mean arterial pressure did not differ between groups. However, because the baseline value of the mean arterial pressure in the 0.5% propofol group was slightly higher, the differences T1 (immediately after initial bolus) – T0 (baseline) and T2 (absence of eyelash reflex) – T0 were significantly higher in the 0.5% propofol group compared with the 1.0% propofol group ($P < 0.05$; fig. 2).

Discussion

This prospective and double-blind investigation showed a significant reduction of pain intensity in children aged 2–6 yr after intravenous injection of propofol diluted with a 10% MCT/LCT emulsion to a final concentration of 0.5% compared with the standard formulation of 1.0% propofol in a similar 10% MCT/LCT emulsion. These findings might be of importance for all physicians sedating or anesthetizing children for various clinical procedures. According to the manufacturer, the emulsion of 0.5% propofol used in this study is stable at room temperature, is not currently approved for clinical use,

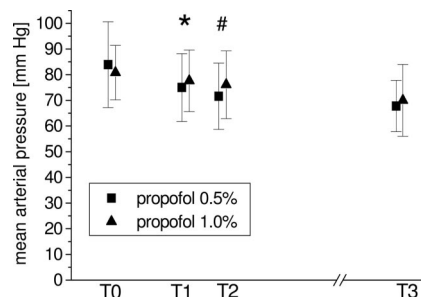


Fig. 2. Mean arterial pressure (mmHg \pm SD). T0 = baseline; T1 = immediately after initial bolus; T2 = loss of eyelash reflex; T3 = end of anesthesia; T1 – T0 = difference of mean arterial pressure between T1 and T0; T2 – T0 = difference of mean arterial pressure between T2 and T0. * $P < 0.05$ for T1 – T0 between both groups. # $P < 0.05$ for T2 – T0 between both groups.

and is not currently available for clinical use (personal communication with the company representative, Tamara Dehnhardt, August 2006).

The incidence of pain on injection of propofol has been reported to range from 30% to 90%.^{1,2,5} To improve this situation, many different strategies have been performed, including the use of MCT/LCT emulsions instead of LCT emulsions,⁵ diluting the drug with glucose,¹¹ administering intravenous anesthetics^{1,2,4} before or simultaneously with propofol, previous injection of lidocaine, or mixing lidocaine with propofol.^{1,2} These measures are able to reduce the incidence of pain on injection of propofol to approximately 40%.¹ In this study, the use of 0.5% propofol resulted in an incidence of only 23%.

Dilution of propofol with aqueous liquids does not seem to alleviate pain on injection of propofol.¹¹ Therefore, the higher content of lipids might be the main reason for reducing the incidence of pain in our investigation. Our results are supported by Doenicke *et al.*⁸ and Klement *et al.*,⁹ reporting a reduced intensity of pain after injection of propofol diluted with a lipid emulsion in adult patients or volunteers. These data in summary strongly support the hypothesis that the amount of propofol in the aqueous phase of the emulsion might be the main trigger for pain on injection.

The incidence and severity of pain during injection of 1% MCT/LCT propofol in our study are comparable with the results of other investigators using MCT/LCT emulsions and criteria for assessing pain during injection such as withdrawing the arm and spontaneous expression of pain. In detail, Schaub *et al.*¹² reported expression of pain in 47% and withdrawal of the arm in 24% of 92 adult women treated with 1% MCT/LCT propofol. Röhm *et al.*³ found an incidence of pain of 53% during injection of 1.0% MCT/LCT propofol and no difference between LCT propofol and 1.0% MCT/LCT propofol in a study including 202 adult patients.

In contrast to a study of Larsen *et al.*,⁵ the use of an MCT/LCT emulsion did not lead to a low overall incidence of pain in our investigation, although remifentanyl had been administered before injection of propofol. In the study of Larsen *et al.*,⁵ only 10% of a subgroup of 20 children treated with 1.0% MCT/LCT propofol reported pain. Nevertheless, in the group treated with 1.0% LCT propofol, the incidence of pain after propofol injection was also low (25%).

Because of the difficulty of assessing pain and various methods and study designs, records about the incidence and intensity of pain during propofol injection are difficult to compare with each other. Furthermore, studies and data about children are rare in this context. Certainly, children finding themselves in a strange and menacing situation like an operating room are not able to adequately express their degree of pain. As a result, most of the studies are performed using an investigator-based

pain evaluation assessing arm withdrawal, crying, screaming, or grimacing.^{5,13,14} Therefore, we decided to use several approaches of an investigator-based pain evaluation simultaneously.

A limitation of our study might be the lack of a further group pretreated with lidocaine and a tourniquet for 120 s or inhalation of nitrous oxide before propofol injection. As a consequence, we are not able to compare the efficacy of our regimen directly to the most effective techniques currently available.^{1,2} In addition, because of the administration of remifentanyl before injection of propofol, the reactions to the painful stimulus might be attenuated in both groups, therefore affecting the results of our study. However, in many institutions, it is common clinical practice to inject a potent opioid such as remifentanyl or fentanyl before induction of anesthesia to reduce patients' reaction to tracheal intubation or insertion of the laryngeal mask. Therefore, to reflect a routine clinical situation, we decided to administer a moderate dose of remifentanyl ($0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) over a short period of 1 min before induction of anesthesia with the study emulsions. Furthermore, because we could demonstrate a higher incidence of pain on injection after 1.0% propofol MCT/LCT emulsion when compared with the study of Larsen *et al.*,⁵ the amount of remifentanyl infused before injection of the study drugs seems to be of only marginal significance.

With regard to the efficacy of the 0.5% propofol preparation, we did not find any differences in drug doses compared with 1% propofol, and the amounts required were in a normal range for children of this age, suggesting that efficacy is not altered by the dilution. This concept is supported by the fact that the use of other propofol formulations with higher propofol concentrations did not lead to changes in dosage requirements.^{14,15} However, because the study was not designed for dosage finding, studies with that endpoint should follow to answer this question.

Regarding hemodynamic changes, no therapeutic interventions had to be performed by the attending anesthesiologist blinded to the study medication. In both groups, all vital parameters were always in an acceptable range for children aged 2–6 yr. Hemodynamic parameters did not differ between groups in absolute values. Nevertheless, the decrease of mean arterial pressure in the 0.5% propofol group was more pronounced compared with the 1.0% propofol group. Whether this decrease is caused by a lower sympathetic tone due to an attenuated pain stimulus in the 0.5% propofol group cannot be answered by our data.

The incidence of pain on injection of propofol decreased threefold with the 0.5% formulation, from 70% with a 1% MCT/LCT emulsion of propofol to 23% with a 0.5% concentration. In the small population of our study, cumulative doses up to 4–5 mg/kg propofol led to mod-

erate increases of triglyceride levels and did not result in significant adverse events.

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