Propofol injection pain in children: a prospective randomized double-blind trial of a new propofol formulation versus propofol with added lidocaine

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Background. The incidence of pain on injection of propofol remains unacceptably high in children, despite various strategies to reduce it. A new drug formulation of propofol has, in adult studies, been reported to cause less injection pain compared with other propofol solutions. The aim of the present prospective randomized double-blind clinical trial was to compare the incidence of pain-free injection following the use of this new formulation with that following the use of propofol with added lidocaine in children undergoing day case surgery.

Methods. Eighty-three children (age range 2–18 yr) were randomized to receive 3 mg kg\(^{-1}\) of either Propofol-Lipuro\(^\text{®}\) (propofol dissolved in a mixture of medium- and long-chain triglycerides [MCT–LCT]; group pL, \(n=42\)) or Diprivan\(^\text{®}\) (propofol dissolved in long-chain triglycerides [LCT]) with added lidocaine (0.3 mg kg\(^{-1}\)) (group pD, \(n=41\)). A specially trained nurse anaesthetist assessed the occurrence of injection pain using a four-graded pain scale.

Results. Significantly fewer patients had an entirely pain-free propofol injection in group pL (33.3%) than in group pD (61.0%) (\(P=0.016\)).

Conclusions. A new MCT–LCT propofol formulation as a plain solution was associated with a higher incidence of injection pain than LCT propofol with added lidocaine when used for induction of anaesthesia in children.

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Although propofol should not be used for long-term paediatric intensive care sedation,\(^{1,4}\) it has become a popular choice for anaesthesia induction and short-term sedation for various procedures in children. However, despite using various strategies to reduce propofol injection pain, this still represents a clinical problem in both adults and children, with reported incidences of injection pain of 30–90%.\(^{5,7}\) One of the most common practices adopted to reduce the incidence of injection pain is to add lidocaine to the propofol solution.\(^{6,8}\) Although the addition of \(\geq 0.2\) mg kg\(^{-1}\) of lidocaine is able to reduce the incidence of injection pain by \(\sim 70–80\%\),\(^{5,7,9}\) this practice involves extra work and also introduces the risks associated with drug mixing (e.g. bacterial contamination, drug mixing errors).

Recently a new propofol formulation, using a different lipid solvent, has been registered. In this formulation propofol is dissolved in a lipid mixture of medium- and long-chain triglycerides (MCT–LCT) that differs from other propofol emulsions where only long-chain triglycerides (LCT) are used. This new formulation has been shown to reduce injection pain in adults,\(^{10–12}\) but paediatric data are limited.\(^{13}\)

The aim of the current prospective randomized double-blind study was to compare the incidence of injection pain...
between this new propofol formulation and our current standard (LCT propofol+lidocaine) in a mixed paediatric outpatient population.

Methods
Following ethical committee approval and parental informed consent, paediatric outpatients (age range 2–18 yr) were prospectively randomized to receive either the new MCT–LCT propofol formulation (Propofol-Lipuro® 10 mg ml⁻¹, B. Braun, Melsungen, Germany) or LCT propofol (Diprivan® 10 mg ml⁻¹, AstraZeneca, Södertälje, Sweden) with added lidocaine (Xylocain®, AstraZeneca, Södertälje, Sweden) for induction of anaesthesia. Exclusion criteria were ASA ≥3 or known contraindications to propofol or lipid emulsions.

Following the application of EMLA cream, all patients had an intravenous cannula (Optiva 0.9 mm, Johnson & Johnson, New Brunswick, NJ, USA) inserted on the dorsum of the hand. This procedure was performed in the day-care unit before arrival in the operating room. All patients were given intravenous midazolam 0.05 mg kg⁻¹ and rectal acetaminophen 40 mg kg⁻¹ as premedication before transfer to the operating room where standard monitoring was applied. Propofol was then injected according to the previous randomization. Coded propofol syringes were prepared by the hospital pharmacy in order to ensure blinding. Lidocaine (1 ml of a 10 mg ml⁻¹ solution) was added to each 10 ml of LCT propofol whereas MCT–LCT propofol was used as a plain solution. However, all syringes were delivered filled to a total amount of 11 ml and no differences between syringes could be detected visually. The speed of the propofol injection was similar for both study drugs (approximately 0.4 ml s⁻¹) and patients were given a total dose of 3 mg kg⁻¹. All patients had a parent present during the induction process.

A specially trained nurse anaesthetist (KvH) assessed injection pain according to a four-point scale: 1=no pain (no reaction to injection), 2=slight pain (minor verbal/facial response or motor reaction to injection), 3=moderate pain (clear verbal/facial response or motor reaction to injection) and 4=severe pain (the patient both complained of pain and withdrew the arm). The assessment was made from the start of the injection to the point when the patient lost consciousness. Following the induction of anaesthesia the study was terminated, and the anaesthetic was continued as necessary in relation to the planned surgical intervention.

Before the patient was discharged from the outpatient clinic the injection site was inspected for signs of residual irritation, and the parents and patient were asked if there were any problems with pain from the injection site. All patients received a follow-up telephone call the day after surgery and were asked if there had been any problems from the injection site following discharge from the hospital.

A prospective randomized double-blind controlled study design was used. The randomization process was performed using a computer-generated random list (GraphPAD StateMate, version1.01) and was carried out by the hospital pharmacy. The primary endpoint of the study was the number of patients in each group without injection pain. Based on our initial clinical experience and the opportunity to detect a 25% difference in the primary endpoint between groups with an α value <0.05 and a β value of 80%, a sample size of 40 patients was generated for each group. The difference in primary outcome between the treatment groups and the distribution of gender in the treatment groups as well as in groups of patients with/without pain was evaluated by the Fisher exact test.

Results
A total of 83 patients were included in the study; 42 patients were assigned to the MCT–LCT propofol group (group pL) and 41 patients were assigned to the LCT propofol plus lidocaine group (group pD). All patients completed the study. The median age was 10.2 (2.2–14.0) yr in group pL and 9.0 (3.0–18.0) yr in group pD. The gender distribution was 11 girls and 31 boys in group pL, and 22 girls and 19 boys in group pD (P=0.013).

A significantly higher number of patients in group pD were pain free (pain score=0) during the injection compared with group pL (61.0% vs 33.3%) (P=0.016) (Fig. 1). No correlation between the occurrence of injection pain and patient characteristics (e.g. age, weight) could be identified. None of the patients reported any pain or discomfort from the injection site either at the control before discharge or at the telephone follow-up the day after surgery.

There were no differences in treatment outcome between females and males (P-values of 0.46 and 0.76 for groups pL and pD, respectively; P=0.18 all patients taken together).

As a result of this study, a further randomized double-blind pilot study was performed in 20 patients comparing the incidence of injection pain, in the same manner as described...
above, between MCT–LCT propofol with lidocaine and LCT propofol with lidocaine. The results of this pilot study are given in the Appendix.

Discussion
The main finding of the present study was that the use of the new MCT–LCT propofol formulation as a plain solution was associated with a higher incidence of injection pain than experienced with LCT propofol with added lidocaine. Thus, the addition of lidocaine appears to be necessary in order to minimize the risk for propofol injection pain in children regardless of the propofol solution used.

The incidence of pain on injection of propofol in children has been reported to range from 30% to 90%.9,13–15 In order to improve this situation a number of different strategies, including addition of local anaesthetics and cooling of the propofol solution, have been attempted in paediatric patients, but the incidence still remains at ~10–30%.9,14–16

In adult studies, the use of propofol dissolved in a new lipid emulsion (MCT–LCT) has been found to result in significantly less injection pain compared with propofol solutions dissolved in LCT lipid emulsion.11,12 A recent paediatric study reported a reduced incidence of injection pain when using this new propofol drug formulation compared with plain propofol (10% vs 25%).13 Since the addition of ≥0.2 mg kg⁻¹ of lidocaine to propofol solutions has been shown to reduce the risk of injection pain in children,9,15 we decided that a more clinically relevant comparison would be to compare this new formulation with propofol with added lidocaine.

In contrast with the adult data,10–12 the new propofol formulation was associated with fewer patients having a pain-free injection when compared with propofol with added lidocaine. However, this discrepancy can be explained by the fact that previous comparisons of MCT–LCT propofol with LCT propofol have been performed in a context where either both were in a plain solution or both were mixed with lidocaine.

More recent adult data, which were published after the design of the present study, comparing MCT–LCT propofol with propofol and lidocaine are in agreement with our present paediatric study.17,18 Thus the reduced incidence of injection pain associated with the new lipid emulsion appears to be less than that obtained with the addition of lidocaine. For further studies and also to assess whether addition of lidocaine does affect injection pain associated with the new propofol formulation in children we conducted a second pilot study, using the same study design (see Appendix). No firm conclusions can be drawn from a pilot study, but the addition of lidocaine does appear to be effective with the new propofol preparation and thus is advocated regardless of which propofol preparation is used.

Unfortunately, the randomization process resulted in a significant difference in gender distribution between the two study groups. However, when the primary outcome parameter was correlated with gender, no gender-associated effect could be identified. In addition, we believe that it is unlikely that boys and girls would have a significantly different pain reaction in response to propofol injection. However, this unusual outcome of gender distribution caused by the computer-generated randomization must be kept in mind when interpreting the results of the study.

In conclusion, the use of a new MCT–LCT propofol formulation as a plain solution was associated with a higher incidence of injection pain compared with LCT propofol with added lidocaine when used for induction of anaesthesia in children.

Appendix
To assess whether addition of lidocaine is useful with the new MCT–LCT propofol preparation, we performed a second prospective randomized double-blind pilot study. Twenty patients were randomly assigned to be induced with either MCT–LCT propofol with lidocaine (group pLl, n=10) or LCT propofol with lidocaine (group pDl, n=10) using the same methodology as in the main study. Nine patients in group pLl and seven patients in group pDl had entirely pain-free injections.

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