Avoiding propofol injection pain in children: a prospective, randomized, double-blinded, placebo-controlled study

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Background. Pain on injection limits the use of propofol in children. The combination of lidocaine and propofol is widely used to reduce pain. A new solvent [medium-chain triglyceride (mct)/long-chain triglyceride (lct)] has been advocated to be less painful than standard (lct) propofol in adults, but no information is available of its usefulness in pre-school children. We designed a prospective, randomized, double-blinded, placebo-controlled study to assess injection pain with two different propofol emulsions, each given with or without lidocaine in children <7 yr.

Methods. A total of 160 ASA I–III children were randomly assigned to receive lct–propofol or mct/lct–propofol, 5 mg kg⁻¹, with lidocaine 10 mg ml⁻¹ or saline. The site and size of venous cannulation and restlessness before injection were recorded in each patient. A pain score graded 0–6 was established based on spontaneous verbal and motor reaction during injection, each graded 0–3. Kruskall–Wallis and Mann–Whitney tests were used for statistical analysis.

Results. Median pain scores decreased in all groups compared with lct–propofol–saline (P<0.001) and were least in the lct/mct–propofol–lidocaine group (P<0.001). Painless injection (score, 0–2) occurred in 92.5% of patients in the mct/lct–propofol–lidocaine group compared with 41–77% in the others (P<0.001).

Conclusions. Mct/lct–propofol caused significantly less pain than lct–propofol in preschool children. Mixing of lidocaine with mct/lct–propofol resulted in a further significant decrease, virtually eliminating the pain on injection.

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Well-known advantages of propofol¹ should make it a gold standard in paediatric anaesthesia. However, pain on injection, experienced by 70% of adults² and in up to 85% of children,¹ prevents its use in young children. The most popular method to prevent painful injection in children is mixing lidocaine with propofol immediately before injection. Significant but heterogeneous results have been obtained in adults, but, to our knowledge, no information is available in preschool children. This knowledge is important because painful injection is particularly undesirable in paediatric population, and it is most likely to occur in these patients as a result of the size of accessible veins. Recently, a medium-chain triglyceride/long-chain triglyceride (mct/lct) emulsion has been introduced as a solvent for propofol injection. It has been advocated to reduce injection pain compared with standard (lct) propofol in both adults and teenagers.³ ⁴ However, neither mixing with lidocaine nor the solvent alone could eliminate pain.

We conducted a prospective, randomized, double-blinded, placebo-controlled study to assess injection pain with two different propofol emulsions, with or without lidocaine, in preschool children.
Methods

After obtaining the approval from Institutional Review Board, all children up to 7 yr old, ASA-PS I–III, undergoing elective general anaesthesia without any contraindication to propofol anaesthesia were approached and an informed consent was obtained from their parents.

The patients fasted for 6 h, and clear liquids were allowed up to 2 h before anaesthesia. They received midazolam 0.4 mg kg⁻¹ as rectal premedication 30 min before anaesthesia. EMLA® cream was applied on the dorsum of one hand for 1 h and removed 15 min before anaesthesia. Once in the operating theatre, an i.v. cannula was inserted, an infusion line attached, and routine monitoring applied. If i.v. catheter insertion was unsuccessful or appeared difficult in the EMLA® treated zone, the patient was given N₂O 70% in O₂ as analgesia until another venous line was secured. The child was then allowed to breathe O₂ 100% for at least 5 min, and total clearance of N₂O was ensured from expired gas monitoring.

We hypothesized that children would be at least as sensitive to injection pain as adults. From the information available in adults, it was calculated that, given α=0.05 and β=0.8, 280 patients were required to recognize a 50% decrease in injection pain. As no paediatric information was available, an intermediate analysis was performed after recruiting 100 patients to adjust the number of patients to be studied if necessary. Therefore, the α significance level was adjusted to 0.029 in the final analysis to avoid increasing type I error, as recommended by the European Medicines Agency.

For the induction of anaesthesia, patients received either lct–propofol (propofol 1%, Fresenius Kabi France) or mct/lct–propofol (Propofol-lipuro 1%, B. Braun medical), 5 mg kg⁻¹, with lidocaine or an equal volume of saline, and lct–propofol–saline was considered the control group. The patients were assigned to one of the four groups according to a computer-generated table of randomization equilibrated by series of four patients. In an adjacent room, an attendant anaesthetist nurse opened the sealed envelope and prepared either lct– or mct/lct–propofol together with lidocaine or saline (1 ml of lidocaine 1% mixed with 10 ml of propofol) to be injected within a few minutes. The attendant anaesthetist was blinded to the patient’s group, and the appearance of the drug to be injected was similar in all groups. Propofol was injected over 30 s, spontaneous behaviour of the patient during injection was graded according to a specifically designed scale, and anaesthesia was then carried on as decided by the anaesthetist.

Using the specifically designed composite pain scale, the pain was graded 0–6. The score was based on the assessments of patients’ motor and verbal reactions during propofol injection until loss of consciousness (Table 1). This scale had been previously used by our group and proved satisfactory for inter-observer correlation (unpublished data). Pain score ≥2 was considered unacceptable.

Age, weight, ASA-PS, type of analgesia for i.v. cannula insertion, site and size of cannula, and restlessness of the patient immediately before injection were also recorded. Mean arterial pressure (MAP), heart rate (HR), S₂O₃ value, and unexpected side-effects were recorded before, during, and up to 3 min after injection.

Statistical analysis was carried out using SAS enterprise guide, version 2. The main outcome measurement was occurrence of pain score ≥2 and the secondary outcome measurement was pain intensity, other data were considered side-effects. Continuous data distribution was described by median and interquartile range, and categorical data were described by frequency count and percentage. Continuous data were compared by Student’s t-test, Mann–Whitney–Wilcoxon, or Kruskal–Wallis test as appropriate. Categorical data were compared by χ² or Fischer’s exact test as appropriate. Whenever significant discrepancies appeared, each group was compared separately with others in order to analyse the differences with Bonferroni correction when appropriate. \( P<0.029 \) was considered significant.

Results

In the intermediate analysis after recruiting 100 patients, 25 in each group, incidence of pain was found to be 70% in Group lct–propofol–saline and 8% in Group mct/lct–propofol–lidocaine. On the basis of these results, it was calculated that 21 patients had to be included in each group to meet our objectives. It was also found that there were a larger number of restless patients before propofol injection in mct/lct–propofol–saline group. Restlessness being a part of pain scale, validity of pain scoring could have been impaired. Therefore, it was decided to recruit 42 patients in each group in order to increase the scope of the study and to eliminate this potential confounding factor. Of the 168 patients, eight were excluded from analysis after randomization because of lack of essential data: four in the lct–propofol–saline group, one in the

<table>
<thead>
<tr>
<th>Motor events</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
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<tbody>
<tr>
<td>No movement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight hand withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked withdrawal, rubbing, trying to tear off the line</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>General restlessness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbalization scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No vocalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purposeless moaning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explicit protest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screams, cries</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Total</th>
<th>0–6</th>
</tr>
</thead>
</table>

Table 1 Composite injection pain score applicable upon anaesthesia induction in preschool children
lct–propofol–lidocaine group, and three in the mct/lct–propofol–saline group.

A total of 160 children, 34% females, 68% males, participated in the study. The median (range) age was 38.5 (0–95) months and the weight was 15.5 (2–38) kg. Seventy-two per cent of the children were scored ASA-PS I and 20% ASA-PS II. Eighty per cent was calm at the time of injection. MAP, HR, and \( {\text{Sp}}_2 \) were similar in all groups (Table 2). Thirty-five per cent had their infusion line inserted with EMLA\(^{\circ}\) alone, 35% with \( {\text{N}}_2\text{O} \) alone, 8% with both, 20% had an infusion line already attached, and 3% did not receive any analgesic for cannula insertion. I.V. cannula, Ga 22 in 84% of patients and Ga 24 in others, was inserted into a vein of the dorsum of the hand in 82% of patients. No differences were found between groups for all these factors (Table 3).

All patients lost consciousness by the end of injection. During injection and within 3 min, MAP and HR remained essentially stable and similar in all groups [mean (sd) decrease in MAP 10.2 (16.5) mm Hg, \( P=0.18 \); decrease in HR 10.2 (14) beats min\(^{-1}\), \( P=0.19 \)]. No significant side-effects were recorded in any group: three benign cutaneous rashes occurred (two in the lct–propofol–saline group and one in the mct/lct–propofol–saline group).

Occurrence of pain score \( \geq 2 \) was significantly different in all arms (\( P<0.004 \)) except between Groups lct–propofol–lidocaine and mct/lct–propofol–saline (Fig. 1). Median pain score was reduced in all groups compared with lct–propofol–saline (\( P<0.001 \)). Median pain score value was zero in the mct/lct–propofol–lidocaine group (Fig. 2). Here again, arms lct–propofol–lidocaine and mct/lct–propofol–saline were comparable. To evaluate the possible confounding factors, the results were plotted against analgesia required to insert cannula, site of infusion, and gauge of cannula: no correlation was found with pain on injection. Special attention was paid to restlessness of patients before injection as a possible confounding factor. Although restless patients were found in similar numbers in all arms, comparisons were done again after eliminating restless patients: the results corroborated with those with the entire groups.

**Discussion**

Avoiding pain on propofol injection in preschool children is highly desirable, insofar as pain appears to be a limiting factor to an otherwise useful anaesthesia. We present the first study addressing the decrease of pain associated with propofol injection, conducted in a large group of preschool children, meeting suitable methodological requirements. We found that the combination of a new propofol carrier, 10% mct/lct emulsion, in addition to lidocaine, 10 mg ml\(^{-1}\), mixed with propofol immediately before injection, significantly reduced the incidence and the intensity of pain.

It had already been suggested in a paediatric study that mct/lct–propofol injection was less painful than lct–propofol.\(^4\) However, only two arms of 20 children, aged 7–14 yr, were included. Comparing mct/lct–propofol and lct–propofol with lidocaine in 83 children aged 2–18 yr, Nyman and colleagues\(^7\) reported that 33.3% were pain free in the former, and 61% in the latter group. Therefore, he concluded that lidocaine was more effective than mct/lct in preventing pain. These results conflict with adult studies, which reported that both formulations are equivalent and painful in 24–38% of patients and that mct/lct–propofol–lidocaine reduces pain occurrence to 4%.\(^8\) One large adult study showed that both formulations reduced the incidence of pain from 64 to 31–53% and a

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**Table 2** Characteristics of the patients before injection. Continuous data are presented as median (IQR). Categorical data are presented as numbers. No statistical differences were found between the groups.

<table>
<thead>
<tr>
<th></th>
<th>( n )</th>
<th>Age (months)</th>
<th>Weight (kg)</th>
<th>ASA-PS (n)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats min(^{-1}))</th>
<th>( {\text{Sp}}_2 ) (%)</th>
<th>Quiet (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Lct–propofol–saline</td>
<td>38</td>
<td>54 (25–68)</td>
<td>15.5 (12–19.5)</td>
<td>23</td>
<td>11</td>
<td>2</td>
<td>69 (57–88)</td>
<td>103 (83–121)</td>
</tr>
<tr>
<td>Lct–propofol–lidocaine</td>
<td>41</td>
<td>37 (19–66)</td>
<td>16 (10.5–21)</td>
<td>25</td>
<td>10</td>
<td>2</td>
<td>70 (64–86)</td>
<td>105 (90–120)</td>
</tr>
<tr>
<td>Mct/lct–propofol–saline</td>
<td>39</td>
<td>28 (18–67)</td>
<td>15 (11–18)</td>
<td>28</td>
<td>7</td>
<td>3</td>
<td>71 (64–87)</td>
<td>118 (100–140)</td>
</tr>
<tr>
<td>Mct/lct–propofol–lidocaine</td>
<td>42</td>
<td>34 (24–67)</td>
<td>15 (12–20.5)</td>
<td>33</td>
<td>6</td>
<td>1</td>
<td>75 (66–81)</td>
<td>106 (84–123)</td>
</tr>
</tbody>
</table>

**Table 3** Characteristics of venous cannulation. Data are presented as number of patients. No statistical differences were found.

<table>
<thead>
<tr>
<th>Analgesia for cannulation</th>
<th>Line in place</th>
<th>EMLA(^{\circ})</th>
<th>( {\text{N}}_2\text{O} )</th>
<th>Both</th>
<th>None</th>
<th>20</th>
<th>22</th>
<th>24</th>
<th>Site of cannulation</th>
<th>Hand</th>
<th>Wrist</th>
<th>Radial</th>
<th>Elbow</th>
<th>Saphen</th>
<th>Other</th>
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<tbody>
<tr>
<td>Lct–propofol–saline</td>
<td>7</td>
<td>15</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>32</td>
<td>4</td>
<td>30</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lct–propofol–lidocaine</td>
<td>10</td>
<td>13</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>32</td>
<td>6</td>
<td>33</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mct/lct–propofol–saline</td>
<td>8</td>
<td>10</td>
<td>16</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>30</td>
<td>7</td>
<td>31</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mct/lct–propofol–lidocaine</td>
<td>7</td>
<td>17</td>
<td>14</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>34</td>
<td>6</td>
<td>34</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>
Propofol injection pain in children

Fig 1 Percentage of patients with painful injection. Statistical differences appear between patients who experienced pain (score >2) during injection: $P<0.004$, according to $\chi^2$ test. Group mct/lct–propofol–lidocaine experienced significantly less pain than all others ($P<0.001$). Groups lct–propofol–lidocaine and mct/lct–propofol–saline were similar (ns), and Group lct–propofol–saline had significantly more pain than the other three ($P<0.001$).

Fig 2 Pain intensity expressed as box plots: median (dotted line), 25–75 interquartile (box), 10–90 percentile (bar), and range values (solid circle) of pain score in each group. Pain on injection is significantly lower in Group mct/lct–propofol–lidocaine and significantly higher in Group lct–propofol–saline than in all other groups ($P<0.001$). Groups lct–propofol–lidocaine and mct/lct–propofol–saline are not statistically different.

Combination of mct/lct–propofol–lidocaine further reduced the pain occurrence to 16%. Intensity of pain was simultaneously reduced. Our results strongly agree with this paper in our homogenous population. The occurrence of painful injection decreased from 59 down to 22.5–24% in lct–propofol–lidocaine and mct/lct–propofol–saline arms, respectively, and to 7.5% with the mct/lct–propofol–lidocaine combination. Simultaneously, pain intensity was significantly reduced, with the median pain score decreasing from 3 down to 1 and 0, respectively. Incidentally, we found that propofol injection pain occurs as often in young children as in older children or in adults, and is more likely to be reduced than in adults.

Pain on propofol injection has been classified by a panel of expert anaesthetists as the third most important clinical outcome to avoid in adult anaesthesia. Incidence of pain is considered to be much more common and more difficult to eliminate in children and still represents a challenge. Topical skin analgesia by EMLA does not prevent injection pain in adults. Among numerous strategies advocated to reduce pain, the most documented in adults and older children is the use of lidocaine, either given before propofol injection with a tourniquet or mixed with propofol. It is difficult to keep a tourniquet on the forearm of a young child for 1–2 min, which is the reason why we did not choose this strategy. Though effective only in 60% of adults, mixing lidocaine with propofol remains the only method applicable to young children. Mixing lidocaine with propofol immediately before injection may be important for the result.

Concentration of free propofol in the aqueous phase is thought to be responsible for pain. A means to decrease the concentration of free propofol in the aqueous phase is to dilute propofol to 0.5%; this practice resulted in pain reduction in preschool children, in the same range as in our intermediate groups (23% of pain occurrence), but it also increased serum triglyceride. As the concentration of free propofol is lower in both mct/lct–propofol and lct–propofol–lidocaine than in lct–propofol, pain reduction with the two preparations has been attributed to this finding. Met/lct–propofol has been found to be relatively less painful in descriptive, non-comparative adult studies.

Pain on injection of mct/lct–propofol is reported similar to lct–propofol mixed with lidocaine in adults. In adults, studies comparing pain on injection of mct/lct–propofol and lct–propofol, with or without lidocaine, are controversial. In a small series of teenagers, mct/lct–propofol has been favourably compared with lct–propofol. Until recently, no report was available on propofol injection pain in preschool children and, up to date, only one comparison between mct/lct–propofol and lct–propofol with added lidocaine has been published in children, including some preschool children. Our randomized, prospective, double-blinded comparison focused on clinical practice in young children closely. In this respect, it may be argued that our control group received a formulation that would never have been used in practice (i.e. lct–propofol–saline). This was necessary to manage a blinded study (same volume to inject, same propofol concentration, and same appearance of the product). Furthermore, as far as dilution has been claimed to decrease pain, it is unlikely that this limitation impaired our results.

Most available studies include verbal description of pain by the patient when a test dose of propofol is given, and recollection of injection pain after anaesthesia. These data are not accurate in preschool children, and no paediatric study has used this approach. Moreover, no specific test has been designed to assess pain during induction of anaesthesia. To evaluate pain as objectively as possible, a composite pain score was created based on our experience of child behaviour upon anaesthesia induction. Outcome measures in our study were very similar to those used in available paediatric studies. Simultaneous evaluation of pain by several staff members resulted in close
corroboration between evaluations (85% of similar score, unpublished results); hence, the scale was considered valid for the study. We believe that limited variability in the results strengthens the relevance of our criteria.

Pre-existing restlessness at the time of injection remains a hindrance to pain scoring. Precaution was taken to pacify children before anaesthesia. If unsuccessful, changes in child’s behaviour were considered: attendant nurse and anaesthetist scored patient’s behaviour separately and pooled their evaluations. In addition to these precautions, post hoc analysis excluding restless patients confirmed that this difficulty did not alter the results. The results were crossed with other possible confounding factors: site of injection, cannula gauge, and analgesia used for line insertion. Site and size of cannulation, size of injection, and site of cannulation are unlikely to affect our results: EMLA cream has been proved ineffective in preventing propofol injection pain11 and N2O was carefully washed out before propofol injection. Analysis confirmed that these factors could have played a role in different circumstances. Similarly, analgesia used to ensure venous cannulation is unlikely to affect our results: EMLA cream has been proved ineffective in preventing propofol injection pain11 and N2O was carefully washed out before propofol injection. Analysis confirmed that these factors did not alter our results.

In conclusion, we have shown that the combination of mct/lct–propofol and lidocaine allows for nearly full suppression of injection pain in preschool children. In our opinion, these results provide new reasons to consider i.v. anaesthesia in young children more favourably, in addition to otherwise advocated arguments.17

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