Prevention of propofol-induced pain in children: combination of alfentanil and lidocaine vs alfentanil or lidocaine alone

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Background. Pain from a propofol injection is a common side-effect in paediatric patients. This prospective, randomized, double-blind study evaluated the efficacy of a combined pretreatment of alfentanil with lidocaine on the incidence and severity of propofol injection pain in children.

Methods. After obtaining parental consent, 120 paediatric patients were allocated randomly into one of the three groups (n=40, in each). The patients in the alfentanil group received alfentanil 15 μg kg⁻¹ 90 s before the propofol injection. The patients in the lidocaine group received propofol 3 mg kg⁻¹ premixed with lidocaine 0.1% over a 15 s period. The patients in the combination group received both alfentanil and lidocaine.

Results. The incidence of propofol injection pain (severity 2 or more) in the combination group (2.6%) was significantly lower than that in the alfentanil and lidocaine groups (30% and 38.5%, respectively) (P=0.001 and <0.001, respectively). No patient in the combination group complained of moderate or severe pain from propofol injection.

Conclusions. Our study demonstrated that the combination treatment of two different analgesic modalities, alfentanil and lidocaine, could prevent the moderate and severe pain on propofol injection, and reduce the incidence of mild pain compared with each drug alone.

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One disadvantage of propofol is pain on injection, which is quite distressing to the patients. Macario and colleagues¹ reported that expert anaesthetists ranked propofol injection pain during anaesthesia induction as seventh out of 33 clinical problems, when both the clinical importance and the frequency were considered.

The pain on a propofol injection in paediatric patients has been reported to be as high as 30–80%.²³ There have been many attempts to reduce the pain, such as the addition of lidocaine,⁴ nitrous oxide,⁵ ketamine,⁶ remifentanil, or alfentanil injection before the propofol injection in children.⁷ However, none has achieved the complete elimination of pain. Recent studies showed that a combination of two different analgesic modalities, opioids and lidocaine, can reduce the incidence and severity of propofol injection pain compared with each drug alone in adults.⁸–¹⁰ However, there are no reports on the use of these combination methods to reduce propofol injection pain in children.

Therefore, this prospective, randomized, double-blind study evaluated the efficacy of a combination of a pretreatment with alfentanil and premixing of lidocaine on the incidence and severity of propofol injection pain in children.

Methods

Our study was approved by the institutional review board, and informed parental consent was obtained. The study
was carried out prospectively on 120 patients aged 3–10
yr, ASA physical status I or II, undergoing general anaes-
thesia for elective surgery. Patients with known allergies
to opioids, local anaesthetics, asthma, neurological defi-
cits, those who had received analgesics or sedatives within
the previous 24 h, and crying children upon arrival in the
operating theatre were excluded.

No premedication was administered before surgery.
Before arriving at the operating theatre, a 24 gauge
cannula was inserted in the dorsum of the hand, and its
position was confirmed by the free flow of a dextrose/saline
infusion by gravity. Upon arrival at the operating
theatre, all patients were monitored with ECG, pulse oximeter, non-invasive arterial pressure, and capnography.

Patients were randomly allocated to one of the three
groups using computer-generated randomization list gener-
ated by a statistician in a sealed envelope, and an independ-
dent researcher prepared study syringe for each patient
according to his/her treatment group. Patients in the alfentanil
group received alfentanil 15 µg kg \(^{-1}\) (diluted with
normal saline to make 0.1 mg ml \(^{-1}\) of alfentanil) over
15 s followed 90 s later by propofol premixed with normal
saline over 20 s. The patients in the lidocaine group
received normal saline (0.15 ml kg \(^{-1}\) saline over 20 s. The patients in the lidocaine
15 s followed 90 s later by propofol premixed with normal
saline/infusion by gravity. Upon arrival at the operating
theatre, all patients were monitored with ECG, pulse oximeter, non-invasive arterial pressure, and capnography.

The patients, anaesthesia providers, and investigators
who scored the movements were blinded to the treatment
group. All study drugs were prepared before injection at
room temperature. For propofol premixed with lidocaine (or
normal saline), 9 ml of 1% standard (long-chain triglycer-
ide) propofol (Fresofol\textsuperscript{16}, Fresinus Kabi, Hamburg,
Germany) was mixed with 1 ml of lidocaine 1% (or normal
saline 1 ml). All the drugs were administered through the
rubber port connected to the i.v. cannula with the free flow
of the i.v. fluid. After preoxygenation, general anaesthesia
was induced with propofol 3 mg kg \(^{-1}\). Mask ventilation
was initiated with oxygen 100% once the patient became
unconscious and apnoeic. The patient response after the
propofol injection was graded by the investigator according
to the following four-point scale:\textsuperscript{4} 1, no pain (no reaction to
the injection); 2, slight pain (a minor verbal/facial response
or motor reaction to the injection); 3, moderate pain (a clear
verbal/facial response or motor reaction to the injection);
and 4, severe pain (the patient both complained of pain and
withdrew the arm). The assessment was made from the start
of the propofol injection to the point when the patient lost
consciousness. The investigator also recorded the incidence
of coughing and breath holding. Anaesthesia was then
carried on at the anaesthetist’s convenience.

From previous studies,\textsuperscript{4,7} the incidence of injection pain
in the alfentanil or lidocaine group was expected to be
\(~40\%\). Therefore, 38 subjects per group would be needed
to decrease this incidence to 5% (power 80% and
\(\alpha=0.05\)). The sample size was increased to 40 patients per
group assuming the occurrence of dropouts. Statistical ana-
alyses were performed using SPSS software (version 12.0,
SPSS Inc., IL, USA). The differences in the incidence of
propofol injection pain between the groups were analysed
using the \(\chi^2\) test with the Bonferroni correction for mul-
tiple comparisons and a corrected \(P\)-value <0.05/3 was
considered significant. All values are expressed as mean
\(\pm\) standard deviation, median (IQR), or absolute numbers (%).

### Results

Initially, 120 patients were enrolled in the study. Two
patients were excluded from the analysis due to technical
problems, such as a disconnection or blocking of venous
cannulation. Hence, the data for 118 patients are presented.
There was no significant difference in the patient’s charac-
teristics between the three groups (Table 1).

The incidence of a painful propofol injection (severity 2
or more) in the combination group (2.6%) was signifi-
cantly lower than that in the alfentanil and lidocaine
groups (30% and 38.5%, respectively) (\(P=0.001\) and
<0.001, respectively) (Table 2). In the combination group,
no patient experienced moderate or severe pain.

Mean heart rate (HR) and mean arterial pressure (MAP)
were maintained within normal limit in all three groups
and there was no hypotension or bradycardia during the
study period. None of the patients suffered from hypoxae-
mia, desaturation, apnoea, chest wall rigidity, or other
adverse effects during the induction of anaesthesia.

### Discussion

Our study demonstrated that the combination treatment
with an alfentanil 15 µg kg \(^{-1}\) pretreatment and premixing
propofol with lidocaine 0.1% can significantly reduce the incidence of propofol injection pain in paediatric patients compared with each treatment used alone.

The pain on propofol injection is considered to be a common and difficult to eliminate problem in children.\textsuperscript{11} The most popular technique for reducing injection pain is to mix lidocaine with propofol.\textsuperscript{3–5} Lidocaine may act by stabilizing the kinin cascade,\textsuperscript{12} which was activated by contact with free propofol.\textsuperscript{13} The analgesic effect of lidocaine on a propofol injection is not only based on its local anaesthetic effects, but also on the decrease in pH of the propofol–lidocaine mixture. A recent study demonstrated that mixing lidocaine 1% with standard (long-chain triglyceride) propofol 1% at a 1:10 volume ratio reduced the incidence of a painful injection from 59% to 22.5% in preschool children.\textsuperscript{14} In addition, the incidence of a painful injection of propofol mixed with lidocaine in our study was even higher, which was \textasciitilde 40%. As a result, this incidence is unacceptable, which lead us to search for a new method.

Pretreatment with opioids has been reported to reduce the incidence and severity of pain during a propofol injection with varying results. A previous study demonstrated the efficacy of remifentanil 0.5 \(\mu\)g kg\(^{-1}\) and alfentanil 15 \(\mu\)g kg\(^{-1}\) pretreatment, which were equally effective in reducing the pain associated with a propofol injection in children.\textsuperscript{7} In their study, the incidence of injection pain was 85% in the placebo group but could be reduced significantly to 40% using i.v. alfentanil, which was comparable with our results of the alfentanil group.

Among other opioids, alfentanil has a peak onset of 1 min, which does not delay the induction time, and a duration of 20–30 min, which can be ideal for short surgeries. Although remifentanil also has a short onset and an even shorter duration of action, alfentanil was used in our study because it can be used as a bolus dose instead of infusion and is less expensive. Similar to other opioids, the action site of alfentanil may either be central or be peripheral. Our assumption was that the pain-reducing action of alfentanil was mainly central because a tourniquet technique was not used and adequate time was allowed for the onset of alfentanil (90 s).

In our study, the injection pain of propofol was reduced to \textasciitilde 3% of patients in the combination group. In contrast, 30–40% of patients in the alfentanil and lidocaine groups suffered from painful injection. These results suggest that alfentanil enhances the analgesic efficacy of lidocaine premixture. Further study elucidating the mechanism of this effect is warranted.

Although the decrease in MAP and HR before intubation was statistically significant in the alfentanil and combination groups, the MAP and HR before intubation were well above 55 mm Hg and 70 beats min\(^{-1}\), respectively, which were within the normal limits.

In conclusion, the combination treatment of two different analgesic modalities, alfentanil and lidocaine, prevents the moderate and severe pain on propofol injection, and reduces the incidence of mild pain compared with each drug alone.

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**References**


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