British Journal of Anaesthesia **103 (3):** 410–12 (2009)
doi:10.1093/bja/aep163 Advance Access publication June 19, 2009

BJA

PAEDIATRICS

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

H. J. Kwak[1], S. K. Min[2], J. S. Kim[2] and J. Y. Kim[2]*

[1]Department of Anaesthesiology and Pain Medicine, Gachon University of Medicine and Science, Gil Medical Center, 1198, Guwol-dong, Namdong-gu, Incheon 405-760, Korea. [2]Department of Anaesthesiology and Pain Medicine, Ajou University School of Medicine, San 5, Wonchon-dong, Yeongtong-gu, Suwon 443-721, Korea

**Corresponding author. E-mail: kjyeop@ajou.ac.kr*

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.

Br J Anaesth 2009; **103**: 410–12

Keywords: anaesthesia, paediatric; anaesthetics i.v., propofol; anaesthetics local, lidocaine; analgesics opioid, alfentanil; pain, injection

Accepted for publication: May 11, 2009

One disadvantage of propofol is pain on injection, which is quite distressing to the patients. Macario and colleagues[1] 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%.[2 3] 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 anaesthesia for elective surgery. Patients with known allergies to opioids, local anaesthetics, asthma, neurological deficits, 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 generated by a statistician in a sealed envelope, and an independent researcher prepared study syringe for each patient according to his/her treatment group. Patients in the alfentanil group received alfentanil 15 $\mu g\ kg^{-1}$ (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}) over 15 s followed 90 s later by propofol premixed with lidocaine over 20 s. The patients in the combination group received alfentanil 15 $\mu g\ kg^{-1}$ (diluted with normal saline to make 0.1 mg ml^{-1} of alfentanil) over 15 s followed 90 s later by propofol premixed with lidocaine over 20 s.

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 triglyceride) propofol (Fresofol®, 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:[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,[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 α=0.05). The sample size was increased to 40 patients per group assuming the occurrence of dropouts. Statistical analyses 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 χ^2 test with the Bonferroni correction for multiple comparisons and a corrected P-value $<0.05/3$ was considered significant. All values are expressed as mean (SD), median (IQR), or absolute numbers (%).

Table 1 Patient characteristics. Values are mean (SD), median (IQR), or number of patients. There were no significant differences between the groups

	Alfentanil (n=40)	Lidocaine (n=39)	Combination (n=39)
Sex (M/F)	26/14	26/13	26/13
Age (yr)	7.9 (7.0–9.0)	7.0 (5.5–9.8)	8.0 (6.0–9.0)
Weight (kg)	27.9 (6.4)	27.3 (8.1)	30.5 (9.8)
ASA (I/II)	33/7	34/5	32/7

Table 2 Incidence and severity of pain on the propofol injection. Values are number of patients (%). *P<0.05 compared with the lidocaine group, †P<0.05 compared with the alfentanil group

Severity of pain	Alfentanil (n=40)	Lidocaine (n=39)	Combination (n=39)
1 (No pain)	28 (70.0)	24 (61.5)	38 (97.4)*,†
2 (Mild pain)	9 (22.5)	10 (25.6)	1 (2.6)*,†
3 (Moderate pain)	1 (2.5)	4 (10.3)	0 (0.0)
4 (Severe pain)	2 (5.0)	1 (2.6)	0 (0.0)

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 characteristics between the three groups (Table 1).

The incidence of a painful propofol injection (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) (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 hypoxaemia, 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 $\mu g\ kg^{-1}$ 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.[11] The most popular technique for reducing injection pain is to mix lidocaine with propofol.[3–5] Lidocaine may act by stabilizing the kinin cascade,[12] which was activated by contact with free propofol.[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.[14] In addition, the incidence of a painful injection of propofol mixed with lidocaine in our study was even higher, which was ~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.[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 ~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.

Funding

All funding was from departmental sources.

References

1 Macario A, Weinger M, Truong P, Lee M. Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. *Anesth Analg* 1999; **88**: 1085–91

2 Picard P, Tramer MR. Prevention of pain on injection with propofol: a quantitative systematic review. *Anesth Analg* 2000; **90**: 963–9

3 Cameron E, Johnston G, Crofts S, Morton NS. The minimum effective dose of lignocaine to prevent injection pain due to propofol in children. *Anaesthesia* 1992; **47**: 604–6

4 Nyman Y, von Hofsten K, Georgiadi A, Eksborg S, Lönnqvist PA. Propofol injection pain in children: a prospective randomized double-blind trial of a new propofol formulation versus propofol with added lidocaine. *Br J Anaesth* 2005; **95**: 222–5

5 Beh T, Splinter W, Kim J. In children, nitrous oxide decreases pain on injection of propofol mixed with lidocaine. *Can J Anaesth* 2002; **49**: 1061–3

6 Barbi E, Marchetti F, Gerarduzzi T, *et al.* Pretreatment with intravenous ketamine reduces propofol injection pain. *Paediatr Anaesth* 2003; **13**: 764–8

7 Rahman Al-Refai A, Al-Mujadi H, Petrova Ivanova M, Marzouk HM, Batra YK, Al-Qattan AR. Prevention of pain on injection of propofol: a comparison of remifentanil with alfentanil in children. *Minerva Anestesiol* 2007; **73**: 219–23

8 Kwak K, Chung H, Lim C, *et al.* A combination of lidocaine (lignocaine) and remifentanil reduces pain during propofol injection. *Clin Drug Investig* 2007; **27**: 493–7

9 Aouad MT, Siddik-Sayyid SM, Al-Alami AA, Baraka AS. Multimodal analgesia to prevent propofol-induced pain: pretreatment with remifentanil and lidocaine versus remifentanil or lidocaine alone. *Anesth Analg* 2007; **104**: 1540–4

10 Kwak K, Kim J, Park S, *et al.* Reduction of pain on injection of propofol: combination of pretreatment of remifentanil and premixture of lidocaine with propofol. *Eur J Anaesthesiol* 2007; **24**: 746–50

11 Morton NS, Johnston G, White M, March BJ. Propofol in paediatric anaesthesia. *Paediatr Anaesth* 1992; **2**: 89–97

12 Scott RP, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; **43**: 492–4

13 Dubey PK, Kumar A. Pain on injection of lipid-free propofol and propofol emulsion containing medium-chain triglyceride: a comparative study. *Anesth Analg* 2005; **101**: 1060–2

14 Rochette A, Hocquet AF, Dadure C, *et al.* Avoiding propofol injection pain in children: a prospective, randomized, double-blinded, placebo-controlled study. *Br J Anaesth* 2008; **101**: 390–4