

PAIN

Efficacy of intravenous acetaminophen and lidocaine on propofol injection pain

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Background. Different methods and propofol formulations have been used to decrease propofol injection pain, but it remains an unresolved problem. We aimed to investigate the effect of i.v. acetaminophen pretreatment on the propofol injection pain.

Methods. One hundred and fifty ASA I–II patients undergoing general anaesthesia were randomly allocated into three groups. A 20-gauge catheter was inserted into a superficial radial vein of the left hand, and after the occlusion of venous drainage, Groups I, II, and III were pretreated with 40 mg of lidocaine in saline, 50 mg of i.v. acetaminophen, and 5 ml of saline, respectively. The occlusion was released after 2 min and one-fourth of the total propofol dose was injected into the vein over a period of 5 s. During the injection of both pretreatment solution and propofol, patients' pain was assessed and recorded as 0–3, corresponding to no, mild, moderate or severe pain, respectively. χ^2 and Kruskal–Wallis tests were used for the statistical analysis. For all analyses, differences were considered to be significant at $P < 0.05$.

Results. Patient characteristics were similar among the groups. Incidence of pain on injection of propofol in control, i.v. acetaminophen, and lidocaine groups was 64%, 22% and 8%, respectively ($P < 0.05$).

Conclusions. Pretreatment with i.v. acetaminophen seems to be effective in attenuating pain during i.v. injection of propofol.

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Propofol remains the most common drug for induction of general anaesthesia, although it causes considerable pain or discomfort on injection. During induction of anaesthesia, the incidence of injection pain has been shown to vary between 28% and 90% in adults.¹ Several methods have been proposed over the years in the literature to reduce the pain associated with i.v. injection of propofol. These include the addition of lidocaine to propofol;² cooling or warming the drug;³ and pretreatment with ephedrine, ondansetron, metoclopramide, opioids, thiopental, ketamine,³ ketorolac,⁴ or nafamostat.⁵

Of the techniques used to decrease the incidence and intensity of pain resulting from propofol injection, the most effective method is to inject lidocaine at 0.5 mg kg⁻¹

i.v. while applying venous occlusion before administering propofol. Although the cause of propofol injection pain is unknown, the activation of pain mediators such as the release of a kininogen from the vein wall triggering a local kinin cascade system during i.v. injection has been suggested. Moreover, non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to diminish prostaglandin (PG) synthesis and inhibit kinin cascade, thereby reducing pain on injection of propofol.⁶

As an alternative to NSAIDs and selective COX-2 inhibitors, acetaminophen, whose action at a molecular level is still not known, is widely used for pain management. Although acetaminophen does not inhibit COX enzymes at therapeutic concentrations *in vitro*, it is shown

to inhibit a variant of COX enzymes *in vivo*. Simmons and colleagues⁷ demonstrated a COX-2 variant, which is sensitive to acetaminophen.

These proposed mechanisms prompted us to investigate the effect of i.v. acetaminophen on propofol injection pain. In this randomized, double-blind, placebo-controlled study, we aimed to compare the effect of i.v. acetaminophen with that of lidocaine for the prevention of propofol-induced pain during induction of anaesthesia.

Methods

After ethics committee approval of the hospital and having obtained informed consent, 150 patients aged 20–60 yr, ASA I or II, and undergoing general anaesthesia were included in this study. Patients were randomly allocated to one of the three groups of 50 each using a table of random numbers. Patients with vascular diseases, habituation to analgesics, sedatives or anti-anxiety drugs; allergic diseases or sensitivity to lidocaine, propofol or acetaminophen, and infection on the dorsum of their left hands were excluded from the study.

None of the patients was premedicated before entering the operation room. After routine monitoring (ECG, non-invasive arterial pressure, and pulse oximeter), a 20-gauge catheter was inserted into a superficial radial vein of the left hand and lactated Ringer's solution was infused at 100 ml h⁻¹. After 5 min, lactated Ringer's infusion was stopped and the arm with the i.v. line was elevated for 15 s for gravity drainage of venous blood. After occluding the venous drainage using a pneumatic tourniquet (pressure inflated to 70 mm Hg) on the upper arm, the patients were pretreated over a period of 10 s with one of the pretreatment solutions; 40 mg of lidocaine diluted to 5 ml (Group I), 50 mg (5 ml) of acetaminophen (Perfalgan[®]) (Group II), or 5 ml of normal saline (Group III). We asked the patients if they felt any pain during the administration of the pretreatment solution. The pain that occurred during propofol injection was assessed on a four-point scale (none=0, mild=1, moderate=2, and severe=3).

An independent anaesthetist prepared the solutions and the investigator was blind to the contents of the solutions. After 2 min, the occlusion was released and one-fourth of the total calculated dose of propofol [Diprivan 1% (Zeneca Ltd, Macclesfield, Cheshire, UK)] was delivered through the i.v. line over a period of 5 s. No other analgesics or sedatives were administered before propofol injection. During the injection, the patients were asked standard questions regarding comfort of the injection. A clinician blinded to the group assignment evaluated propofol-induced pain using a verbal rating scale: none=0 (negative response to questioning), mild pain=1 (pain reported only in response to questioning with no behavioural signs), moderate pain=2 (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously

without questioning), severe pain=3 (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears). Thereafter, induction of anaesthesia continued with i.v. fentanyl 2–3 µg kg⁻¹ followed by the remainder of the calculated dose of propofol, and vecuronium 0.1 mg kg⁻¹ to facilitate endotracheal intubation.

Heart rate, systolic, diastolic, and mean arterial pressures were recorded before the administration of pretreatment solution (considered as baseline), laryngoscopy, and 1 and 5 min after the intubation. Within 24 h after the operation, the injection site was checked for pain, oedema, or allergic reaction by an anaesthesiologist who was blinded to group assignment.

On the basis of previous studies, the expected incidence of pain was 30% in lidocaine group and 60% in saline group.⁸ A power analysis indicated that a sample size of 50 was sufficient to detect a large statistical difference with an $\alpha=0.05$ and power $1-\beta=0.8$. The data obtained were analysed statistically using the χ^2 test, analysis of variance for demographic data, and the Kruskal–Wallis test for the incidence of propofol injection pain scores among the groups. $P<0.05$ was considered significant.

Results

The patient characteristics were similar among all the groups (Table 1). The data on the severity and incidence of pain during injection of pretreatment solution in the three groups are given in Table 2. The overall incidence of pain during i.v. injection of pretreatment with acetaminophen was 2%, compared with 20% and 16% in each of the lidocaine and control groups, respectively ($P<0.05$). Pretreatment with i.v. acetaminophen produced mild pain in 2% of patients. Pretreatment with lidocaine produced mild pain in 18% and moderate pain in 2% of the patients.

Table 1 Patient characteristics. Data are given as mean (range), mean (sd) or numbers of patients

Groups	Age (yr)	Sex (M/F)	ASA class (I/II)	Weight (kg)
Group I lidocaine (n=50)	35.02 (22–60)	20/30	46/4	68.9 (12.3)
Group II i.v. acetaminophen (n=50)	30.7 (20–54)	30/20	48/2	63.7 (11.4)
Group III control (n=50)	39.3 (20–60)	26/24	47/3	70.5 (12.7)

Table 2 Number of patients with pain during i.v. injection of pretreatment solution. * $P<0.05$ i.v. acetaminophen vs lidocaine and control

Severity of pain	Group I lidocaine (n=50)	Group II i.v. acetaminophen (n=50)	Group III control (n=50)
No pain	40	49	42
Mild pain (A)	9	1	3
Moderate pain (B)	1	0	5
Severe pain (C)	0	0	0
Pain (A+B+C)	10	1*	8

Table 3 Number of patients with pain during i.v. injection of propofol. * $P < 0.05$ drugs vs control

Severity of pain	Group I lidocaine ($n=50$)	Group II i.v. acetaminophen ($n=50$)	Group III control ($n=50$)
No pain	46*	39*	18
Mild pain (A)	3	5	8
Moderate pain (B)	1	5	14
Severe pain (C)	0	1	10
Pain (A+B+C)	4*	11*	32

When we evaluated the pretreatment pain in saline group, there was mild pain in 6% and moderate pain in 10% of the patients.

The overall incidence of pain during i.v. injection of propofol in the three groups is shown in Table 3. In the control group, 64% of the patients had pain during i.v. propofol injection whereas 22% and 8% of the patients had pain in i.v. acetaminophen and lidocaine groups, respectively ($P < 0.05$). During the first 24 h after the operation, there were no complications such as pain, oedema, or allergic reaction at the injection site. In addition, haemodynamic variables such as heart rate, systolic, diastolic, and mean arterial pressures that were recorded at different time intervals were similar between the groups.

Discussion

In this study, we found that i.v. acetaminophen was effective, although not as much as lidocaine, in decreasing the incidence of pain during i.v. injection of propofol. Previous studies have shown that the incidence of pain on injection of propofol is around 30% with lidocaine pretreatment and 60% in saline group.^{9 10} The overall incidence of pain during i.v. injection of propofol in the control group was 64% compared with 22% in i.v. acetaminophen and with 8% in lidocaine group, suggesting that i.v. acetaminophen injection is effective in reducing propofol injection pain compared with control. Moreover, the overall incidence of pain during i.v. injection of pretreatment with peralgan was 2% when it was compared with 20% and 16% that were observed in each of the lidocaine and control groups, respectively. That is to mean, i.v. acetaminophen causes less pretreatment pain with respect to lidocaine and control groups ($P < 0.05$ for both comparisons). It was different from the previous studies that the incidence of pretreatment pain of lidocaine and control groups was unexpectedly high in our study.¹¹

In our study, the overall incidence of pain during i.v. injection of propofol in the lidocaine group was 8% and it was similar to the results of Pang and colleagues¹² who reported it to be 11%. But, in some other studies higher incidences, such as 18%¹³ or 42%,¹¹ have been reported. In these studies, the vein on the dorsum of the hand and

the pneumatic tourniquet technique was used, as in the present study. However, the investigators did not mention about the gravity drainage of venous blood which could be the reason of lower incidence for propofol injection pain in lidocaine group in our study.

We evaluated the pain using a score of 0–3 scale system. This verbal rating scale has been used in several previous reports that investigate the intensity of pain on injection of propofol.^{14 15}

Pain on injection of propofol can be immediate or delayed. The immediate pain could be the result of a direct irritant effect, but the kinin cascade is probably the cause of delayed pain.¹⁶ The lipid solvent for propofol activates the plasma kallikrein–kinin system which results in bradykinin production that increases local vein permeability and dilation. The aqueous-phase propofol diffuses into more free nerve endings outside the endothelial layer of the vessel which is more permeable and dilated because of bradykinin effect, thereby intensifying pain on injection. Inhibition of bradykinin generation by nafamostat mesylate is shown to reduce propofol-induced pain.¹⁶ Moreover, cold appears to lessen propofol injection pain through suppressing the activation of plasma kallikrein–kinin system that in turn initiates enzymatic cascade.^{3 17} In addition to cold, non-steroidal anti-inflammatory drugs such as ketorolac are also demonstrated to reduce the propofol injection pain aggravated by the release of local kininogens.¹⁸

In a recent study, Lee and colleagues¹⁹ showed that acetaminophen selectively suppresses peripheral PG E2 release and increases COX-2 gene expression in a clinical model of acute inflammation. Similarly, in another recent study, bradykinin, a bradykinin B2-receptor agonist, has been shown to enhance both basal and lipopolysaccharide-induced PG E2 synthesis in rat neonatal glial cells in culture.²⁰ Also in a recent study of Ando and colleagues,²¹ they have shown that propofol characteristically causes vascular pain that occurs in response to prostanoids, particularly PG E2. The findings of these studies indicate that there is a relationship between PG E2, which is selectively suppressed by acetaminophen, and bradykinin, which determines the intensity of propofol injection pain.

The present results suggest that i.v. acetaminophen (50 mg) pretreatment appears to be effective in reducing the pain experienced during i.v. injection of propofol. Further studies are required to determine the optimal doses of i.v. acetaminophen to control propofol-induced pain.

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