(Acta Anaesth. Belg., 2017, 68, 13-18)

Preventive methods using lidocaine for reduction of pain associated with propofol intravenous administration: a double blind randomized controlled trial

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Abstract : *Introduction***:** The aim of this randomized controlled trial (RCT) was to identify, among the commonly used ones, the most effective method of preventing pain upon the intravenous administration of propofol (PIP).
Methods : A total of 440, 18-80 year old, ASA 1 or 2 patients were randomized into four groups. All patients received an intravenous 2 mL pre-emptive intravenous injection and a 2 mL addition to the propofol solution (Propofol-Lipuro®). Patients in study group A received pre-treatment with normal saline (NS), and NS in the propofol solution. Group B received pre-emptive NS and 2% lidocaine as the propofol addition. Group C received pre-emptive 2% lidocaine and NS, while group D received 1% lidocaine twice. PIP was scored on a four point Ambesh scale (at induction) and on an eleven-point Numeric Rating Score (NRS) (for postoperative recall).
Results : Group B and D had significantly lower pain incidences and severity scores than the control group A.
Conclusions : Adding 2 mL of lidocaine to propofol 1% significantly reduces PIP in healthy patients undergoing general anesthesia.

Key words : Anesthesia ; Propofol-Lipuro ; Propofol MCT/LCT ; injection pain ; PIP.

Since its introduction in 1986, the intravenous anesthetic agent propofol (2.6-diisopropylphenol) has been very popular as an induction agent for general anesthesia. Despite its several advantages, including fast and smooth induction, it causes a painful burning sensation upon its intravenous injection, which is hypothesized to be a direct effect of propofol (1,2). This burning sensation is found to be the seventh most important clinical problem in anesthesia practice (3).

Originally, propofol was marketed as Diprivan® by Imperial Chemical Industries (now AstraZeneca, London, United Kingdom). Diprivan® is a sterile oil-in-water emulsion for intravenous injection, and mainly contains long-chain triglycerides (LCT) derived from soybean oil. This formulation contains propofol (10 mg/mL), soybean oil (100 mg/mL), glycerol (22.5 mg/mL), and egg phosphatide (12 mg/mL). In addition, it contains water for injection with sodium hydroxide for pH adjustment and disodium edentate (0.05 mg/mL) for prevention of microbial growth (4). The reported incidence of pain on injection of Diprivan® is as high as 70% (5).

In an attempt to lower pain upon the intravenous administrations of propofol (PIP), Propofol-Lipuro® (B. Braun, Melsungen, Germany) was developed. This oil-in-water emulsion, containing propofol 10 mg/mL, was changed to diminish the LCT concentration to its half (50 mg/mL). It further contains medium-chain triglycerides (50 mg/mL), glycerol (25 mg/mL), egg lecithin (12 mg/mL), sodium oleate (<10 mg/mL), and water for injection (6). Propofol-Lipuro® is associated with a PIP incidence of 40 to 50% (7-9). This lower incidence is hypothesized to be the result of a change in the equilibrium between the aqueous phase and the lipid phase of propofol in the medium-chain

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triglycerides/long-chain triglycerides (MCT/LCT) emulsion, as opposed to the LCT emulsion (2,10). The concentration of free propofol in the aqueous phase is thought to be lower in Propofol-Lipuro® than in Diprivan®, resulting in less propofol in direct contact with the endothelium of the vein upon injection.

In clinical practice, the most commonly used methods to prevent PIP are mixing propofol with lidocaine prior to injection, and the injection of lidocaine into the vein before the injection of propofol. However, as yet, due to lack of evidence, no method has been described as best clinical practice. The aim of this study was to compare three frequently used PIP-reducing methods, and identify the most effective one as compared to a placebo. We hypothesized that a combination of pretreatment of the vein with lidocaine, before injecting a mixture of propofol with lidocaine, would result in the lowest incidence of PIP.

Methods

Patients

Approval by the Medical Ethics Committee (Catharina Hospital, Eindhoven, The Netherlands, METC nr: M11-1118, Chairman: Dr. R.J.E. Grouls) was obtained, and written informed consent was received, before inclusion of patients. Included patients were aged 18 to 80 years, had an ASA physical status 1 or 2, and were scheduled for various elective surgeries under general anesthesia. Exclusion criteria included communication or psychological disorders, history of polyneuropathy, pre-existing underlying pathology associated with pain, emergency surgery, pregnancy, the use of anti-depressant medications, NSAIDs or opiates on a regular basis, and a known hypersensitivity to lidocaine, propofol, lipid emulsions, eggs or egg products.

Randomization

Patients were randomly assigned to one of four groups using a computer-generated list (Random Allocation Software, version 1.0.0, University if Medical Sciences, Ishafa, Iran). We used Propofol-Lipuro®, containing soya-bean oil, medium-chain triglycerides, glycerol, egg lecithin, sodium oleate, and water (6). Treatment in the study groups consisted of: pretreatment with 2 mL of normal saline (NS) and induction with a mixture of 2 mL NS added to 20 mL of 1% propofol (group A, control group); pretreatment with 2 mL NS and induction with a mixture of 2 mL of 2% lidocaine added to 20 mL of 1% propofol (group B); pretreatment with 2 mL of 2% lidocaine and induction with a mixture of 2 mL NS added to 20 mL of 1% propofol (group C); or pretreatment with 2 mL of 1% lidocaine and induction with a mixture of 2 mL of 1% lidocaine added to 20 mL of 1% propofol (group D). Drugs, as used in this trial, were produced by B. Braun™ (Melsungen, Germany).

Procedure

All patients received premedication [diazepam 10 mg, acetaminophen 1 g and a NSAID, naproxen 250 mg (Naprosyn®)] preoperatively, according to hospital standards. During this study, standard medication ampoules were used. Standard labels were removed and replaced by study labels: pretreatment ampoules were labeled with a 1, whereas the admixture ampoules received label 2. The study ampoules were relabeled prior to study commencement. Because all ampoules were numbered, the investigators could check in hindsight which medication was administered to an individual patient.

Demographic data were collected in the holding bay by the investigators, after which patients were randomly assigned to a study group. A copy of the study protocol and the assigned ampoules were attached to the patient's bed in a closed envelope, ensuring both anesthesiologist and nurse anesthetist were blinded for the assigned study medication.

In the holding bay, the vein size was measured before and after venal occlusion with a tourniquet, using a sling gauge (InaMed, now Allergan, Irvine, CA, USA). An 18 or 20 gauge intravenous (IV) cannula was inserted on the dorsum of the hand, and an infusion of Ringer's Lactate (RL) was initiated. Pain on IV cannulation was scored on an eleven-point Numeric Rating Scale (NRS). In the operating theatre, routine monitoring (ECG, pulse-oximetry and non-invasive blood pressure) was applied. The envelope was then opened by the nurse anesthetist. Contents from ampoule 1 were drawn in a 2 mL syringe. Contents from ampoule 2 were added to the propofol in a 20 mL syringe. Both syringes were then handed to the anesthesiologist.

Induction of anesthesia was standardized by a study protocol. Upon induction of anesthesia, infusion of RL was stopped and the pretreatment drug in the 2 mL syringe (with the content of ampoule 1) was injected over 5 seconds, followed by a 1-minute

pause. Subsequently, the propofol-mixture (propofol mixed with 2 mL of the content from ampoule 2) was injected, so as to reach a total dose of 2 $mg \cdot Kg^{-1}$ bodyweight over 20 seconds. Pain upon injection was scored according to the four-point Ambesh scale as observed by the anesthesiologist: score 0 = no pain (negative response on questioning); score 1 = mild pain (pain response upon questioning, no behavioral signs); score 2 = moderate pain (pain response upon questioning accompanied with behavioral signs or spontaneous report of pain); or score 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears) (11). Immediately after beginning, and 10 seconds after the injection of the propofol mixture, patients were asked to report any injection related pain on an eleven-point NRS. After induction, sufentanil was administered and general anesthesia was maintained according to usual care. After recovery of anesthesia, a blinded recovery nurse who was not involved in the study, asked patients whether they could recall the injection of propofol. If they were able to do so, they were asked to recollect the experience on the eleven-point NRS pain scale.

Statistical analysis

To detect a clinically relevant difference of 15% in PIP between the study groups, a sample size of 109 patients per group would result in a power of 80% at an alpha threshold of 0.05. A sample size of 110 patients per group was chosen. The primary outcome of the study was to establish the efficacy of the different methods used to reduce PIP. Secondary outcomes included evaluation for predictors of PIP. Continuous data were analyzed using a Kolmogorov-Smirnov test for normal distribution and presented as mean and standard deviation (SD), or median and range. Categorical data were presented as frequencies with proportions. Group differences were calculated using a Chi-squared test, two-way ANOVA-testing, Mann-Whitney U-test, the unpaired sample T-test or Fisher's exact test as appropriate. Pearson's correlation examined a potential confounding between variables on injection pain. A two-tailed p-value < 0.05 was considered as statistically significant. Patient analysis was based on intention-to-treat and patients with incomplete study registration forms or study violation were removed from the analysis. Data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 463 patients were enrolled in this study and randomly assigned to one of four study groups. Data of 23 patients were excluded due to incomplete data or study violation. Demographic data were comparable in all groups, as shown in Table 1.

As a result from the total study cohort, 136 (31%) patients experienced pain upon injection of propofol during induction of general anesthesia. Of the patients randomized to group A, 43 (39%) experienced PIP, whereas 17 (15%), 47 (43%), and

Table 1

Demographics of the study population

	Group A N = 110	Group B N = 110	Group C N = 110	Group D N = 110
Sex (male : female)	39 (35%) : 71 (65%)	46 (42%) : 64 (58%)	38 (35%) : 72 (65%)	53 (48%) : 57 (52%)
Age (yrs)	47 ± 16	44 ± 17	46 ± 16	46 ± 16
Height (cm)	172 ± 10	173 ± 9	172 ± 9	173 ± 9
Weight (Kg)	79 (48-144)	79 (44-159)	79 (38-132)	80 (43-160)
Vein diameter (mm) - no venous occlusion - venous occlusion	 2.5 ± 0.9 3.2 ± 1.0	 2.3 ± 0.8 3.1 ± 0.9	 2.3 ± 0.9 3.1 ± 1.0	 2.4 ± 0.9 3.2 ± 1.1
ASA physical status (1 : 2)	71 (65%) : 39 (35%)	67 (61%) : 43 (39%)	72 (65%) : 38 (35%)	61 (55%) : 48 (45%)
Dominant hand (right : left)	103 (94%) : 7 (6%)	94 (85%) :14 (15%)	101 (92%) : 9 (8%)	101 (92%) : 9 (8%)
IV site (right : left)	70 (64%) : 40 (36%)	71 (65%) : 39 (35%)	70 (64%) : 40 (36%)	76 (69%) : 34 (31%)
IV needle size (18 : 20 gauge)	26 (24%) : 84 (76%)	17 (15%) : 93 (85%)	21 (19%) : 89 (81%)	16 (15%) : 94 (85%)
Dose propofol (mg)	194 ± 14.5	197 ± 11.5	191 ± 20.7	193 ± 17.2

Values are mean ± SD, median (range) or numbers (proportion)

29 (26%) patients experienced PIP in the groups B, C and D respectively (Table 2). A statistically significant difference in PIP was detected between the study group A (control group) and B ($p < 0.001$, $X^2_{(1)} = 24.381$), and between study group A and D ($p < 0.001$, $X^2_{(1)} = 18.624$). Pretreatment with lidocaine (group C) showed no difference when compared to the control group (group A), resulting in no beneficial effect ($p = 0.79$, $X^2_{(1)} = 2.041$).

Treatment according to the study protocol of group B seemed to be most efficient, resulting in a 62% reduction in PIP-incidence, when compared to group A (NNT = 4.2). Pain severity – as a median pain score – was different between group A and B (0.59 and 0.19, $p < 0.001$, $X^2_{(1)} = 29.651$), group A and D (0.59 and 0.36, $p = 0.03$, $X^2_{(1)} = 7.182$), groups B and C (0.19 and 0.54, $p < 0.001$, $X^2_{(1)} = 28.491$), and groups B and D (0.19 and 0.36, $p = 0.04$, $X^2_{(1)} = 7.704$).

As secondary outcomes, patients' demographics (height, weight, gender, vein diameter, ASA classification, hand dominance, IV cannulation site and IV needle size), were analyzed to disclose predictors of PIP. However, no correlation could be detected ($R^2 = 0.031$, $P = 0.42$). We were not able to find a declining incidence of PIP with advancing age ($R^2 = 0.011$, $p = 0.18$), and no correlation was found between pain upon IV cannulation and PIP ($R^2 = 0.036$, $p = 0.45$).

In the recovery ward, 172 (39%) patients could recall the injection of propofol, of whom only 40 (23%) patients had a comparable Ambesh score. Of the 172 patients who could remember PIP postoperatively, 136 (79%) patients were scored positive by the anesthesiologist as having pain upon propofol administration.

Discussion

The main finding of this study was that adding 2 mL of 2% lidocaine 2% to 20 mL MCT/LCT of 1% propofol is the most effective method to reduce PIP, in comparison with the other study groups. This result is comparable to previously reported findings (7,9,12). The present study reports a 15% incidence of PIP in group B, where lidocaine was added to propofol, as did Sethi et al. (13). In general, our study confirms an incidence of PIP of 39%, which is in accordance with other publications (7-9,11,14).

Incidence of injection pain did not differ between group A and C, leading to the conclusion that pretreatment with a 2 mL injection of 2% lidocaine was not effective. In this study, we chose to use an easy, practical, and patient friendly approach, without using a tourniquet for venal occlusion when injecting the pretreatment drug. Our only intervention was to set the IV drip rate to nil before injecting the pretreatment drug over 5 seconds. Subsequently, after a one-minute pause, the IV drip rate was set to maximum and the propofol mixture was injected. Possibly, lidocaine might have been washed away before exerting any effect on the inner vessel wall, resulting in comparable pain scores between group A and C. Alternatively, propofol may alter the structure of the inner vessel wall, which means that pretreatment with lidocaine is not effective at lowering pain scores upon injection.

The mechanisms behind PIP have not been elucidated yet. A distinction is made between an immediate pain effect and a delayed effect (after seconds). The immediate pain is assumed to be a direct effect of propofol on the inner vessel wall, likely through stimulation of nociceptors and free

Table 2

Pain incidence and pain severity upon propofol intravenous administration

	Group A NS - NS	Group B NS – 2% lidocaine	Group C 2% lidocaine - NS	Group D 1% lidocaine- 1% lidocaine
None	67 (60.9%)	93 (84%)	65 (57.3%)	81 (73.6%)
Mild	26 (23.6%)	14 (12.7%)	38 (34.5%)	21 (19.1%)
Moderate	12 (10.9%)	2 (1.8%)	6 (5.5%)	5 (4.5%)
Severe	5 (4.5%)	1 (0.9%)	3 (2.7%)	3 (2.7%)
Incidence PIP	43 (39%)	17 (15%)*	47 (43%)†	29 (26%)* §

Values are numbers (proportion).

* = $p < 0.001$ when compared to control group A.

† = $p < 0.05$ when compared to group B.

§ = $p < 0.05$ when compared to group C.

Exact p-values for differences within the groups: A:B, $p < 0.001$ ($X^2_{(1)} = 24.381$); A:C, $p = 0.79$ ($X^2_{(1)} = 2.041$); A:D, $p < 0.001$ ($X^2_{(1)} = 18.624$); B:C, $p < 0.019$ ($X^2_{(1)} = 5.216$); B:D, $p = 0.71$ ($X^2_{(1)} = 3.092$); and C:D, $p = 0.031$ ($X^2_{(1)} = 7.324$).

nerve endings (1,15). The delayed pain effect is thought to be related to the involvement of the plasma kinin-kallikrein system, which is activated by the lipid solvent of the formulation (16,17). As a result, bradykinins would be formed, and would cause the wall to become more permeable and dilated, revealing intramural pain receptors. PIP seems to be directly related to the concentration of free propofol in the aqueous phase (2). The MCT/LCT propofol has a lower concentration of propofol in the aqueous phase as compared to LCT propofol, and therefore results in a lower incidence of PIP (10,18).

Lidocaine is used extensively as a method to prevent PIP, and is proven to be effective (5). It diminishes pain likely through a local anesthetic effect, although other additional mechanisms have been proposed. Nakane et al. suggest that lidocaine inhibits bradykinin generation by an unknown mechanism, whereas Sim et al. opposed to the involvement of this system (16,17). Another mechanism, suggested by Eriksson et al., concerns a shift in the equilibrium of propofol between the aqueous phase and the lipid phase, due to a change in the pH-ratio, which results in a lower concentration of free watery propofol. However, other groups have proposed alternative mechanisms (8, 19, 20).

A more recent trial by Singh et al. postulated that pretreatment with ramosetron, a serotonin $5HT_3$-receptor antagonist, has a similar effect as a pretreatment with 2% lidocaine (21). In their study, the reported incidence of PIP was 30% for ramosetron, and 35% for lidocaine.

In all intervention groups, we used 40 mg of lidocaine. We expected that a combination of pre-treatment with 1% lidocaine and a mixture of 1% lidocaine with 1% propofol (group D) would result in the lowest incidence of PIP, as this method combines common clinical practice of pre-treatment with the potential benefits of plasma kinin-kallikrein inhibition, and altered propofol free aqueous fraction achieved by mixing propofol and lidocaine. However, the lowest PIP incidence was found in group B (pretreatment with NS and a mixture of 2% lidocaine and 1% propofol), suggesting that adequate concentration of lidocaine mixed with propofol is the most important factor for reducing PIP. The lack of difference between group A (pretreatment with NS, mixture of NS and propofol) and C (pre-treatment with 2% lidocaine, mixture of NS and propofol), suggests that pre-treatment with lidocaine is not an effective way to reduce PIP. Although this method is widely used in clinical practice, our study does not support the use of lidocaine as a pre-treatment to mitigate PIP.

Given the greater efficacy of 2% lidocaine at reducing PIP, another interesting scheme could be the addition of 1 to 2 mL of 4% lidocaine to 1% propofol, insofar as lidocaine can be dosed up to 1 $mg \cdot Kg^{-1}$ bodyweight while not jeopardizing patient safety. Kim et al. showed that pretreatment with a higher dose of 2% lidocaine leads to a lower incidence of pain, and lower severity. Sixty mg seems to be the optimal dose as compared to 40 mg or 80 mg (22). Kim et al. also showed that the use of a tourniquet has a positive effect on PIP and, therefore, the use of a tourniquet may have yielded better results in this setting, by keeping lidocaine longer within the vein. For that reason we would anticipate a lower incidence of PIP in group C and D, by applying a tourniquet before giving the pretreatment drug (5, 23).

Locally injected acetaminophen (2 $mg \cdot Kg^{-1}$) has shown to be more effective than lidocaine, at a dose of 0.5 $mg \cdot Kg^{-1}$, suggesting that acetaminophen possibly has a local effect on the vessel wall (24). Perhaps, applying both strategies with acetaminophen as a pretreatment drug (administered with the use of a tourniquet) and the administration of a mixture of lidocaine with propofol upon induction of general anesthesia, the incidence of PIP could further be reduced.

Often, in clinical practice, opioids are administered prior to the hypnotic agent. In order to exclude the analgesic effects of the opioid and to assess the efficacy of our treatment, we chose to administer the opioids after propofol. However, we anticipate that well-timed opioid dosing prior to the propofol-lidocaine mixture will lower the incidence of PIP even further.

As a secondary outcome measure, we aimed at finding predictors for the presence of PIP. In contrast to the findings of Kang et al., who determined that younger patients and females experienced more pain upon propofol injection, our study did not demonstrate such (25). Furthermore, in the group of patients who remembered the injection of propofol in the recovery ward, only 23% of patients had a NRS score which was comparable to the pre-operative Ambesh scale. This finding could question the validity of this method and scale. However, we believe that this scale is superior to the NRS for judging pain when getting anesthetized, since it would be likely that patients would fall asleep before answering the question.

Limitations of this study include failure to standardize pre-medication in all patients, resulting in a possible non-comparable pain perception in patients undergoing general anesthesia. Moreover,

measurements of venous diameter were not performed by one single investigator, which could lead to bias.

Further research should focus on the use of different concentrations of lidocaine (4% or 5%) and propofol (2%) and their effect on diminishing PIP. The involvement of the kinin-kallikrein system in PIP and the possible inhibiting effects of medication, including propofol, lidocaine and a mixture of both, could be the focus of future research. Furthermore, it would also be beneficial to better understand the equilibrium of propofol in the aqueous phase at different time stages after mixing it with lidocaine.

Conclusion

This double blind randomized controlled trial aimed at identifying the most effective strategy to prevent pain upon the intravenous injection of propofol (PIP). This study supports that adding 2 mL of 2% lidocaine to MCT/LCT 1% propofol (Propofol-Lipuro®) is the most effective method at reducing this kind of pain. Applying pretreatment with 2 mL of 1% lidocaine combined with the administration of a mixture of 2 mL 1% lidocaine added to MCT/LCT 1% propofol is also effective at reducing PIP, but inferior to the previously cited strategy. An adequate concentration of lidocaine mixed with propofol may be the most important factor for reducing PIP.

Acknowledgements

The authors wish to acknowledge the contribution of Ms. Cienwen Town for editing the manuscript.

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