

# Venous occlusion with lidocaine for preventing propofol induced pain

## *A prospective double-blind randomized study*

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### ABSTRACT

**Objective:** Pain is a well-known complication of intravenous administration of propofol, and to find out the optimal method to decrease this pain, we studied 4 methods of delivering propofol.

**Methods:** The study took place at Jordan University Hospital, Amman, Jordan between November 2004 and March 2005 on 200 patients. The patients were divided into 4 groups, group I (n=50), the control group, propofol 1% was given alone. Group II (n=50), patients received propofol 1% premixed with 40 mg of lidocaine. Group III (n=50), patients received propofol 1% 60 seconds after giving 40 mg of lidocaine. Group IV (n=50), patients had venous occlusion for 60 seconds with the use of lidocaine 1% (40 mg), followed by release of the occlusion and administration of the propofol. Pain was assessed during injection and categorized into: no pain, pain, and pain with behavioral changes.

**Results:** In group I (control), 35 patient complained of pain, compared to 26 in group II, 23 in group III, and 7 patients in group IV, with a significant reduction in the incidence and intensity of pain in group II, III, and IV compared with the control ( $p<0.005$ ). The best reduction of intensity and incidence was achieved in group VI, when compared with groups I, II and III ( $p<0.005$ ), with no statistical difference between group II and III when compared with each other.

**Conclusion:** Of the 4 methods studied, the optimal method to decrease the incidence and intensity of pain resulting from propofol injection is to inject lidocaine while applying venous occlusion for 60 seconds prior to administering propofol.

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Pain resulting from propofol injection is distressing to patients and is one of the major draw backs of the drug. The pain, which occurs in 26-90% of patients,<sup>1</sup> may be severe enough to add to patients' stress from anesthesia and surgery, and most probably will be remembered in the recovery room.<sup>2</sup>

The pathophysiology of this pain is attributed till this moment to one and a combination of more than

one of 3 proposed mechanisms. The first mechanism relates the pain to the triggering of the local Kallikerin-Kinin cascade,<sup>3</sup> which explains the decrease in the incidence and the severity of non-immediate (delayed) pain resulting from propofol administration when the drug is premixed with lidocaine,<sup>4</sup> or other drugs like flurbiprofen axetil; a non steroidal anti-inflammatory agent, which inhibit the prostaglandins

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synthesis.<sup>5</sup> Another suggested mechanism was the stimulation of the nociceptive receptors at the free nerve endings located between the intima and the media layers of the venous wall, in which a direct and immediate response is transmitted through the A-delta fibers; making drugs like lidocaine,<sup>6</sup> fentanyl, meperidine, morphine<sup>7</sup> and procaine<sup>8</sup> effective when administered few seconds before propofol injection. The third proposed mechanism relates the pain to the pH and concentration of propofol; which when lowered by premixing it with lidocaine<sup>9</sup> or 10% intralipids<sup>10</sup> causes less pain. With the understanding of the 3 previous mechanisms of propofol induced pain, we can conclude that since premixing lidocaine with propofol before administration, which is the most common method used in practice, is explained by only one mechanism of the above 3 mechanism, and might not be sufficient alone to relief that pain. Venous occlusion technique (modified Bier's block) was studied before with the use of lidocaine<sup>4,11</sup> and other drugs<sup>5</sup> and was found to be effective in reducing pain incidence. However, it is still not that popular of a technique in practice.

In this study, our aim is to evaluate the efficacy of this technique (Venous occlusion technique (modified Bier's block) in reducing the incidence as well as the severity of the pain resulting from propofol, and to compare this method with 2 other more popular methods; which are premixing propofol with lidocaine, and with the pre administration of lidocaine without applying a tourniquet.

**Methods.** This prospective, randomized, double blinded study was conducted at the Department of Anesthesia and Intensive Care, University of Jordan, Amman, Jordan between November 2004 and March 2005. The study protocol was approved by the local institutional committee, and informed consent was obtained from all patients. We recruited 200 American Society of Anesthesiologists (ASA) I, II, and III adult patients (males=78, females=122) undergoing elective minor to moderate risk surgeries, and demanding laryngeal mask insertion. The sample size (N) was calculated using the following formula:  $N = Z^2 P q / \delta^2$  (Where  $Z=1.96$ ,  $P=30$ ,  $q=1-P$ ,  $\delta^2$ =the precision)<sup>19</sup> and it was found to be 158, therefore we increased the sample size to 200 to magnify the power of the study. The ages of the patients ranged from 15-90 years, while their weights fell in the range of 35-120 kg. Patients were excluded if they had any difficulty in communication, not cooperative, below 14 years old, received any type of analgesia before arriving to the operation room including emulsion

of local Anesthetic (Lidocaine 2.5% and Prilocaine 2.5%) cream at the site of intravenous cannula insertion, positive past history of hypersensitivity reaction to anesthetic agents or decompensated heart failure. After connecting the patients to routine monitoring devices, a 20 gauge cannula was inserted in the largest vein of the dorsum of the left hand, a free flowing Ringer lactate solution was then started, and the patients were randomly assigned into one of 4 groups, using a table of random number, each group containing 50 patients.

Group I (control) patients received propofol 1% without lidocaine. Group II patients received propofol 1% premixed with 40 mg of lidocaine. Group III received propofol 1% after 60 seconds of giving 40 mg of lidocaine in the same cannula. Group IV received propofol 1% following venous occlusion with a rubber tubing making sure, that occlusion pressure was high enough to prevent the free flow of the Ringers solution, after which 40 mg of lidocaine were injected, followed by waiting for 60 seconds before the release of the tourniquet and the administration of the propofol. All the propofol used was propofol 1% Fersenius® in a dose of 1.5-2.5 mg/kg body weight. The drug in all groups was given slowly over a period of 30-60 seconds until the clinical signs showed the onset of anesthesia.

Pain was assessed by the anesthesia resident doctor assigned to the operating room; who was unaware of the patients' group assignments. The resident doctor continuously assessed the presence of pain by asking the patient regarding the presence of pain, and noticing any behavioral signs associated. Behavioral signs were considered when the patient had tears, arm withdrawal, strong vocal response, or responses accompanied with facial grimacing.<sup>12,13</sup>

We performed multifactor analysis of variance for pain, and determined factors that have a statistically significant effect on pain. Variance was checked by multiple statistical analyses (Cochran's C test, Bartlett's test, and Levene's test). A *p*-value of 0.05 or less was judged significant. All the statistical analysis was performed using Statgraphics® software 5.1 (Manugistics, USA).

**Results.** We studied which factors (age, weight, gender, ASA, and therapy modality) had a statistically significant effect on pain, and then tested for significant interactions amongst the factors. The only factor found to be statistically significant was the therapy modality ( $p < 0.0005$ ), while none of the other factors was statistically significant (age  $p = 0.85$ , ASA  $p = 0.98$ , gender  $p = 0.72$ ) at confidence interval of 95%. All the 4 groups were comparable with respect

**Table 1** - Demographic distribution of patients in the 4 groups according to age, weight, ASA and gender.

Group	Age	Weight	ASA (I/II/III)	Gender (M/F)
1	38.2 ± 14.7	72.1 ± 14.3	39/8/3	25/25
2	40.3 ± 16.6	66.7 ± 11.6	39/7/4	16/35
3	43.6 ± 17.4	74.1 ± 14.7	35/11/4	18/32
4	43.0 ± 16.7	73.0 ± 13.3	37/9/4	20/30

ASA - American Society of Anesthesiologist, M - male, F - female

**Table 2** - Distribution of patients from all groups and their corresponding pain level.

Pain	Groups (N=50 in each group)			
	1	2	3	4
No pain	15	24	27	43
Pain	22	18	16	7
Pain with behavioral changes	13	8	7	0

**Table 3** - Comparisons between groups in regards to pain level.

Group - group	P-value
1 - 2	*0.28
1 - 3	*0.36
1 - 4	*0.82
2 - 3	0.08
2 - 4	*0.54
3 - 4	*0.46

\*Denotes a statistically significant difference  
Method: 95.% least significant difference (LSD)  
(Fisher's LSD procedure)

to age, weight, gender and ASA class (**Table 1**), the number of patients who experienced pain, and those who did not with the propofol injection is shown in **Table 2**.

The incidence of pain after drug administration was significantly higher in the control group (35 patients [70%]) compared with the 3 other groups (26 patients [52%]), (23 patients [46%]) and (7 patients [14%]), respectively with a significant  $p$ -value ( $p < 0.005$ ) when each group was compared with the control. There were no significant reduction in the pain incidence and intensity between group II and group III; when lidocaine was premixed with propofol or when it was pre-administered without applying the tourniquet. But the statistical analysis showed a

significant reduction of both incidence and severity in group IV (tourniquet group) compared to each group II and III, with a significant  $p$ -value  $< 0.005$  (**Table 3**).

**Discussion.** propofol is a very popular anesthetic agent, providing an excellent profile. Although recovery is very smooth, induction smoothness is affected sometimes by the pain on injection of the drug. Different methods were tried to alleviate or decrease the intensity and incidence of that pain, which included physical methods like using large veins, decreasing the rate of drug injection,<sup>4</sup> injecting the drug into a fast flowing fluid, diluting propofol with glucose water 5% or 10%,<sup>9</sup> cooling propofol to 4°C before administering, and others, but the more effective methods were the prior administration or the mixing of propofol with other drugs, these drugs are either local anesthetics, such as, lidocaine<sup>2,4,7-9</sup> or procaine,<sup>8</sup> narcotics like fentanyl,<sup>7</sup> alfentanil,<sup>14</sup> or Pethidine® (Meperidine)<sup>7</sup> or other drugs like metaclopramide,<sup>15</sup> ephedrine,<sup>16</sup> Pentothal® (sodium thiopental),<sup>13</sup> magnesium<sup>12</sup> and others.

Mixing propofol with lidocaine is the most popular method worldwide.<sup>17</sup> The usage of this technique is easy, fast, does not affect the physiochemical property of the drug and more importantly is associated with a clinically and statistically significant reduction in the incidence and severity of the pain.<sup>1-4</sup> Unfortunately, some patients do not respond well to this technique and still a good number of the patients continue to complain even with lidocaine administration. The mechanism of relieving the pain with this technique is mainly by the inhibition of the kinin cascade<sup>3,4</sup> or the dilutional effect on the propofol.<sup>9</sup> Nevertheless, although lidocaine is a known local anesthetic agent, its effect here as anesthetic agent is doubtful since the 2 drugs are co-administered. This finding correlated well with our findings, that although the incidence and severity of pain were significantly less with this method of application, still a good number of the patients complained of pain, which means that either the kinin cascade was not well inhibited, the drug was not enough diluted, the lidocaine did not work as anesthetic agent as we explained, or other mechanisms causing the pain are still not known.

The second method of alleviating pain in our study was to pre-administer the lidocaine 60 seconds before the propofol injection, this method is less popular than the pre mixing technique, although is still found to be effective.<sup>6-8</sup> This was proved in our study where we found that it is as effective as the premixing technique with no significant variation when the 2 groups were compared. This finding did not correlate

with a previous study carried out by Scott et al<sup>4</sup> where he found a significant decrease in the number of patients whom suffered pain when 1% lidocaine 1 ml were mixed with the propofol compared with the propofol induced pain when it was preceded by giving the lidocaine. This finding in our opinion may be explained by the small number of patients in the studied groups (15 patient each) and the smaller dose of lidocaine used (10 mg) compared to (40 mg) the dose in our study.

Although venous occlusion technique was studied long time ago and found to be effective. The method did not gain popularity in practice. In our study, the reduction in the pain incidence and severity were significant for this method when compared with the control, and with each group II and III. This finding correlates well with other studies<sup>7,17,18</sup> carried out before. Although Scott et al<sup>4</sup> (and may be due to the same reasons discussed before) found that lidocaine 1% (1 ml) with propofol had a better effect on reducing pain than when the venous occlusion technique was used. Venous occlusion technique is one of numerous strategies used in alleviating propofol injection pain; the mechanism of action most probably is due to blocking the nerve fibers responsible for pain transmission resulting from direct irritation effect of propofol on the inner wall of the blood vessels, this direct anesthetic effect of lidocaine is achieved when enough time for drug to work is allowed.

propofol induced Kallikerin-Kinin system and the release of bradykinins is also reduced by the prior administration of lidocaine, causing less hyperpermeability and less effect on the nerve endings. These 2 factors might have decreased the incidence and the severity of pain in our study when compared with the other 3 groups, but did not abolish it completely; because may be other mechanisms of alleviating propofol induced pain were not achieved example, the change of the pH and the osmolarity of propofol by premixing it with other drugs, or due to the time interval used to induce intravenous block before administration of propofol was not enough.

In conclusion, since lidocaine is widely used for reducing propofol injection induced pain, our finding showed that giving 40 mg lidocaine for 60 seconds with venous occlusion technique is better than the other traditional methods used, for example, the pre administration of lidocaine or the premixing of lidocaine with propofol, which are more widely used, on the other hand and based on our findings, it seems that there is no difference in the efficacy between the latter 2 techniques.

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