# Duration of venous occlusion with lidocaine for preventing propofol induced pain

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## ABSTRACT

**الأهداف:** دراسة تأثير فترة الحبس الوريدي مع استخدام الليدوكايين على نسبة وشدة الألم المحدث بالبروبوفول.

**الطريقة:** أجريت دراسة افتراضية عشوائية، في مستشفى الجامعة الأردنية – عمان – الأردن، في الفترة مابين أكتوبر 2007م وحتى نوفمبر 2007م. شملت الدراسة 150 مريضاً تراوحت أعمارهم بين (14–70سنة) وذوي حالة سريرية (ASAI) و(ASAII) حسب تصنيف جمعية أطباء التخدير الأمريكية. قُسم المرضى إلى ثلاثة مجموعات، خضعوا جميعاً لعمليات جراحية تحت التخدير العام. طُبق على المجموعات الثلاثة الحبس الوريدي مع الليدوكايين والتسريب الوريدي ثابت التركيز (1%) من البروبوفول. طُبّق الحبس الوريدي لمدة 15 ثانية للمجموعة الاولى:50 مريض، 30 ثانية للمجموعة الثانية: 50 مريض، 60 ثانية للمجموعة الثالثة: 50 مريض. تم تقييم الألم خلال فترة حقن البروبوفول وذلك تبعاً لمقياس الم من أربعة نقاط.

**النتائج:** من المجموعة الأولى تألم 14 مريض (28%) مقارنةً بـ16 مريض (32%) من المجموعة الثانية و 9 مرضى (18%) من المجموعة 3. هذا الاختلاف غير دال إحصائياً ($p>0.05$) لنسبة حدوث الألم وشدته.

**خاتمة:** رغم إن الحبس الوريدي مع الليدوكايين هو طريقة فعالة لإزالة ألم البروبوفول، فقد وجدنا أنه لا يوجد اختلاف عندما كانت فترة الحبس الوريد 15 ، 30 أو 60 ثانية.

**Objective:** To study the effect of the venous occlusion duration using lidocaine on the incidence and severity of propofol induced pain.

**Methods:** A prospective double-blind randomized study was designed at Jordan University Hospital, Amman, Jordan between October 2007 and November 2007. One hundred and fifty patients aged 14-70 years, American Society of Anesthesiologists (ASA) clinical status I and II who underwent elective surgeries under general anesthesia, were divided into 3 groups. All 3 groups had propofol 1% infusion at a constant rate after applying venous occlusion with lidocaine. The occlusion was applied for 15 seconds (group I, n=50), 30 seconds (group II, n=50) and 60 seconds (group III, n=50). Pain was assessed during injection according to a verbal pain score.

**Results:** Fourteen patients (28%) had pain in group I, compared to 16 patients (32%) in group II, and 9 patients (18%) in group III. This difference did not reach statistical significance ($p>0.05$) for the incidence and severity of pain.

**Conclusion:** While venous occlusion with lidocaine is an effective method in relieving propofol induced pain, we found no difference when the duration of venous occlusion was 15, 30, or 60 seconds.

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The use of propofol has increased rapidly in daily anesthesia practice due to its excellent anesthetic profile. Pain on injection is the major drawback of propofol use, this pain has been reported to occur in 28-90% of patients receiving the drug.[1] Different methods and drugs to relieve injection pain have been

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proposed, with varying degrees of success, of which lidocaine is the most commonly used.[2] We previously found that the optimal method to decrease the incidence and severity of propofol induced pain was to inject lidocaine while applying a venous occlusion (Bier´s block) for 60 seconds.[3] This was followed by the release of the tourniquet and the administration of propofol. The duration of 60 seconds, was used in several studies,[4,5] and was believed to allow enough time for the drug to exhibit its local actions. Since lidocaine is an immediate acting drug, and since the pressure that may result from the tourniquet itself, or the injected drug while applying a venous occlusion may be annoying for the patients, the decrease of the time of venous occlusion in spite of having adequate pain relief may be more justified. The aim of this study is to compare different duration times of venous occlusion with lidocaine (15, 30, or 60 seconds) on the incidence and severity of propofol induced pain.

**Methods.** After obtaining scientific and IRB (Institutional Review Board) committee approval, 150 (males=71, females=79) who were scheduled for elective surgeries under general anesthesia were enrolled. All patients were American Society of Anesthesiologists (ASA) clinical status I and II, and aged 14-70 years. The study was carried out at the Department of Anesthesia and Intensive Care, University of Jordan, Amman, Jordan, between October 2007 and November 2007. Informed written consent was obtained from all patients recruited in the study protocol. The sample size (n) was calculated based on our previous study,[3] where the prevalence rate of propofol induced pain was reduced significantly (<0.05) to 14% compared to 70% in the control group. By using the following formula:

$$N=Z^2Pq/\delta^2$$

(where Z=1.96, P=14, q=1-P, $\delta^2$ =the precision),[6]

the sample size (n) was found to be 128, therefore, we increased it to 150, (50 in each group) to magnify the power of the study. 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 operating room including EMLA cream (Emulsion of Local Anesthesia) at the site of the intravenous cannula insertion, positive history of hypersensitivity reaction to anesthetic agents, decompensated heart failure, or had more than one trial of venous cannulation. On arriving to the operating room and after institution of routine monitoring, a 20-gauge intravenous cannula was inserted in the largest vein of the dorsum of the non dominant hand, a free flowing Ringer Lactate solution was started after which a venous occlusion with a rubber tourniquet was applied to the forearm approximately 10 cm distal to the elbow joint, tight enough to prevent the free flow of the infused solution. Lidocaine 2% 40 mg (2 ml) was injected in stat and the tourniquet was released after 15 seconds in group I, 30 seconds in group II, and after 60 seconds in group III. Patients were randomly assigned into one of 3 groups, using a table of random numbers, each group containing 50 patients. The study drug was administered by an infusion pump (Alaris IVAC® P6000 TIVA, Alaris Medical System, UK) at an infusion rate of 2.5 mg/second, and the anesthesia resident who was blinded to the group assignment immediately entered the operation room and started to evaluate the propofol induced pain according to a pain scale consisting of 4 points: 0=no pain, 1=mild pain (facial grimacing), 2=moderate pain (verbal complaint), 3=severe pain (verbal complaint associated with behavioral signs [tears, arm withdrawal or strong vocal response]).[5] All propofol used was propofol 1% Fresenius,® Bad Homburg, Germany in a total dose of 1.5-2.5 mg/kg body weight, which was kept at room temperature and used within 30 minutes of preparation, and all lidocaine used was lidocaine 2%®, Rotexmedica, Trittau, Germany.

Statistical analysis was carried out using the statistical analysis software STATGRAPHICS Centurion XV professional edition version 15.1.02 (StatPoint Inc., VA, USA). A one-way analysis of variance (ANOVA) was carried out for pain score to compare between the means of the 3 groups. After performing ANOVA, multiple range tests were also studied to tell which means are significantly different from which others. For the values expressed as medians, Kruskal-Wallis Test was used. A $p$ value of 0.05 or less was considered statistically significant. Results were expressed as means ± SD or medians. Other results were ratios with percentages.

**Results.** The 3 groups were comparable for age, gender, ASA clinical risk and the body mass index (BMI) (**Table 1**). Although only 9 patients (18%) in group III had pain when the tourniquet was left for 60 seconds, compared to 14 patients (28%) in group I, and 16 patients (32%) in group II, when the tourniquet was left for 15 or 30 seconds, no significant difference in pain score incidence among the 3 groups was found ($p$>0.05). The results also showed similar incidence in the pain severity among the 3 groups, although one patient in group II had severe pain that resulted in a strong verbal response, most of the patient who suffered had mild pain (pain score 1) that resulted in facial grimacing. The overall incidence of pain in the 3 pretreated groups was (26%) 39 patients.

**Table 1 .** Demographic Data for each of the 3 groups.

| Parameter | Group 1 | Group 2 | Group 3 | *P*-value |
|---|---|---|---|---|
| Age (mean ± SD ) | 38.7 ± 14.8 | 37.6 ± 12.6 | 41.0 ± 16.6 | NS |
| ASA (median) | 1 | 1 | 1 | NS |
| BMI (mean ± SD ) | 26.9 ± 5.9 | 26.9 ± 8 | 29.0 ± 18.1 | NS |
| Gender (m/f) | 22/28 | 24/26 | 25/25 | NS |

All values are expressed as either mean ± standard deviation (SD) or median. For the means, ANOVA method was used to compare between the means of the 3 groups. Numbers were also used when appropriate. m/f -males/females, ASA- American Society of Anesthesiologist clinical risk, BMI- Body Mass Index

**Table 2 .** Four-point pain scale for propofol induced pain.

| Group | No. of patients with Pain / no pain | No. of patients according to Pain scale (0,1,2,3) | | | |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 |
| I | 14/36 | 36 | 10 | 4 | 0 |
| II | 16/34 | 34 | 10 | 5 | 1 |
| III | 9/41 | 41 | 7 | 2 | 0 |

(Pain scale): 0- no pain, 1- mild pain (facial grimacing), 2- moderate pain (verbal complaint), 3- sever pain (verbal complaint associated with behavioral signs (tears, arm withdrawal or strong vocal response)

**Discussion.** Although several methods for preventing propofol induced pain were studied, the most effective and popular method was found to be venous retention of lidocaine with a tourniquet before the propofol injection.[2] In a previous study our data proved that 60 seconds of venous occlusion with 40 mg (2 ml) lidocaine was superior to other methods like premixing the propofol with lidocaine or administering the lidocaine 60 seconds prior to the propofol administration without venous occlusion.[3] In the literature, the venous occlusion duration to relieve propofol pain, using lidocaine and other drugs were variable and ranged from 10-120 seconds.[4,7-11] The aim of applying the venous occlusion with drugs that have a local anesthetic effect is mainly allowing enough time for blocking the Aδ fibers, which are responsible for pain transmission in the inner wall of the blood vessel.

Lidocaine is an amide local anesthetic agent with an immediate onset of action. This fact makes the application of a relatively long duration of venous occlusion unjustified, since it may result in a longer period of patient discomfort due to the tourniquet. On the other hand, the application of 60-120 seconds of venous occlusion with lidocaine for preventing propofol induced pain seems to have a negative effect on the pain incidence and seems to be a habit rather than a calculated needed duration. It seems that it was applied for reassuring the applicant himself. Ewart and Whitwam,[12] in their study found that the incidence of pain was increased with increasing the time interval between the injection time of lidocaine and propofol, and that the pain was significantly reduced in the groups given lidocaine 10-30 seconds before propofol. They suggested that lidocaine was most effective in reducing pain when given immediately before propofol, and there was no significance in the frequency of pain after injection of propofol between 60 and 90 seconds of venous occlusion and the control group. However, the results in our study indicate that lidocaine was equally effective when retained inside the vein for 15, 30, or 60 seconds before the propofol injection, and no significant difference among the 3 groups was found.

In their study, Alyafi and Rangasami[7] found that 20 seconds of venous retention with lidocaine was enough to significantly decrease the incidence of propofol induced pain, but were not associated with a significant change when fentanyl 100 micrograms was used and they concluded that lidocaine, acting locally, reduce propofol injection pain while fentanyl does not. On the other hand, Pang et al[8] found that 60 seconds of intravenous retention of fentanyl 150 micrograms, although less effective than that of lidocaine, is still showing local analgesic effect in reducing the pain on propofol injection. The controversial result in these studies is properly explained by the different doses used or the different duration of venous occlusion, a factor, which is very important and difficult to determine. Most of the studies that evaluated the local analgesic effect of drugs such as meperidine,[4] metaclopramide,[5] remifentanil,[9] tramadol,[10] and others, used mostly a venous occlusion duration of 60-120 seconds, a duration which seems to be enough for the local analgesic effect of these drugs to act, and to make these drugs comparable to immediate acting local anesthetic drugs like lidocaine. While venous retention with another immediate acting local anesthetic prilocaine was very effective in reducing the pain in 3 generic propofol formulation after 10 seconds of venous occlusion,[11] the incidence of pain following propofol injection was reduced by other drugs such as ketorolac when given in 10 mg dose with venous occlusion for 120 seconds, but not 10 mg of the same pretreatment drug after 60 seconds.[13]

In this study, we used 2 ml of 2% (40 mg) lidocaine, a volume that we believe is enough for the drug distribution when the tourniquet is placed in the forearm 10 cm from the wrist. Augmenting this volume, although may result in a better distribution can result in increasing the venous pressure, which can lead to patient discomfort. Authors in their studies applied the tourniquet at variable distances from the wrist joint, but used also variable volumes, they increased

the volume of the treating drugs when they wanted to increase the distribution in case of high tourniquet localization. Huang et al[13] inserted the tourniquet 25 cm from the wrist in the upper arm, and used 2 ml of the pain treating drugs, and he had successful results with the higher doses of ketorolac when associated with longer venous occlusion, but not with the small doses. On the other hand, Fujii and Nakayama,[14] who applied the tourniquet for 2 minutes and used 20 mg of 2% lidocaine, or 50 mg of flurbiprofen added to normal saline to have a total volume of 6 ml, applied the tourniquet high in the forearm, and could reduce the pain incidence during the injection of propofol significantly by both treating drugs.

In our study, one limitation represents the comparison of only 3 different durations of venous occlusion. In future studies, comparing more times (>60 seconds or even <15 seconds) might help us fine tune the optimal duration for venous occlusion in propofol induced pain. Another point that needs to be considered is that a drug like lidocaine has an immediate onset of local anesthetic action, and this needs to be compared with other drugs with slower onset of local action.

In conclusion, our study shows that propofol induced pain is reduced by venous occlusion with lidocaine, yet there was no difference when the duration of venous occlusion was 15, 30, or 60 seconds.

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## Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.