

# Effect Of Mixed Versus Unmixed Lidocaine With Propofol

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## Abstract

Propofol is a commonly used agent for induction of general anesthesia. Propofol bolus is often associated with pain. Lidocaine is commonly used to decrease the pain on injection with propofol. The method of administering lidocaine often varies among individual anesthesia providers. A double-blind study was performed on 52 ASA1-3 ambulatory surgery patients, comparing the effectiveness in reducing pain of propofol bolus by administering lidocaine 40 mg as pretreatment versus a mixture of 40mg lidocaine and propofol. An induction dose of propofol at 2.5mg/kg was divided equally and administered simultaneously and into each upper extremity. One aliquot contained solely propofol following a 40mg lidocaine bolus, the other contained propofol mixed with 40mg of lidocaine. Each patient served as his own control. Our data indicates that lidocaine, when mixed with propofol, was more effective in reducing the pain of injection ( $p < 0.001$ ) than when given as a pretreatment.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Departments of the Army, Air Force or Defense. There are no commercial associations in conjunction with these investigators.

## INTRODUCTION

Propofol is a commonly used agent for the induction of general anesthesia, especially for outpatient surgical procedures. It affords a rapid recovery with minimal side effects. However, bolus injection of propofol is often associated with pain. Although the exact mechanism by which propofol injection causes pain is unknown, numerous studies have been performed in attempts to alleviate this pain, including warming<sup>(1)</sup> or cooling the injectate<sup>(2,3,4)</sup>, aspirating blood prior to injection<sup>(5)</sup> and using larger antecubital and forearm veins<sup>(6)</sup>. Furthermore, multiple agents have been administered as either pretreatment or given concurrently including: tiopentone<sup>(7)</sup>, pethadine<sup>(8)</sup> fentanyl/alfentanil<sup>(9)</sup>, metoclopramide<sup>(10)</sup> nitroglycerin<sup>(11)</sup>, procaine<sup>(12)</sup>, prilocaine<sup>(13)</sup> and ketorolac<sup>(14)</sup>. These concomitant medications have had variable results. Two of the most commonly accepted techniques are the administration of lidocaine immediately prior to the injection of propofol or mixing lidocaine with the propofol itself. An early study by Brooker et al.<sup>(15)</sup>, found that mixing lidocaine with propofol was more efficacious than administering it immediately prior to injection. However, this study was confounded by the preinduction administration of opioid

analgesics. Further studies showed that temporary venous occlusion following premedication with 100 mg of lidocaine did indeed diminish the intensity of pain but did not alter the incidence of pain<sup>(16,17)</sup>.

Other investigators have attempted to quantify the optimal lidocaine dose/concentration in lidocaine /propofol mixtures<sup>(18)</sup>. Perhaps the greatest limitation of all these prior studies is that there may be inter patient variability in pain perception and lack of a true control group. We describe an alternative method for comparing the efficacy of two techniques of administering lidocaine to diminish pain associated with the injection of propofol. In this study, we allowed each individual patient to serve as his or her own control, by placing two IV catheters, one in the dorsum of each hand. We then administered the propofol on one side mixed with lidocaine and propofol on the other side unmixed following pretreatment of lidocaine. The patient was then able to directly compare each technique.

## METHODS

After obtaining institutional review board approval and written informed consent, 52 ASA Classification I to III patients were enrolled. Patients scheduled for same-day ambulatory surgeries, requiring a general anesthetic, were enrolled. Exclusion criteria included patients who were not ideal candidates to receive propofol for induction secondary to cardiovascular co-morbidities. Further exclusion criteria included patients with a history of adverse reactions to

anesthetics or propofol, major vascular or cardiac surgery and age less than 18. An 18ga IV catheter was placed in the dorsum of each hand. Patients were then premedicated with 2 mg of midazolam Intravenously (IV). No opioids were administered prior to induction of anesthesia.

For induction of general anesthesia, a total of 2.5mg/kg of propofol, (Diprivan, Zeneca) divided into two equal doses, was administered into each intravenous catheter simultaneously. Each dose was prepared by members of the research team in the operating room immediately prior to induction, but was given by the attending anesthesia providers, who were blinded to the content of each syringe. In one hand a solution containing 40 mg of 2% lidocaine mixed with one-half of the induction dose of propofol was given preceded by 2ml of normal saline. The 2ml of saline served as a placebo so the anesthesia providers administering the propofol would still remain blinded to which hand received the mixed or unmixed propofol. Simultaneously, in the other hand 40mg of lidocaine (2%) in 2ml volume was given approximately 60 seconds prior to injecting an equal volume of propofol. Therefore, all medications and placebo were given simultaneously by 2 different individuals, who were blinded to the contents of the syringes.

The total dose and volume of medications were equal on each side. Immediately following these injections, the patients were asked to indicate in which extremity they experienced greater pain or discomfort. Patients were to indicate which arm experienced greater pain or discomfort by simply raising that arm as they were instructed to do during the preoperative interview. Patients were allowed to verbalize “neither” if no pain was experienced or “same” if both sides were equivalent. Both the patients and attending anesthesia providers were blinded to the medications in each syringe. We propose that mixing an induction dose of propofol with lidocaine will significantly decrease the pain and discomfort associated with the bolus injection of propofol, as compared to giving lidocaine unmixed prior to injection.

**Figure 1**

Table I: Patient Population Summary

<u>Group</u>	<u>N</u>	<u>%</u>
All	52	
Male	23	44.23
Female	29	55.77
Age >50	20	38.46
Age < 50	32	61.54
ASA 3	6	11.54
ASA 1-2	46	88.46

**RESULTS**

Selected patient demographics are summarized in Table I. With a mean age of

48.9, they constitute a representative sample of the ambulatory surgery patients at our hospital. No selection bias other than an absence of cardiac dysrhythmias and history of adverse reactions to anesthetics or propofol was evident. We were able to enroll an

equal proportion of patient populations including different sexes and ages. Our results were as follows:

**Figure 2**

Table II: Patient Response Summary

<u>Group</u>	<u>With Greater Pain:</u>	<u>Unmixed</u>	<u>%</u>	<u>Mixed</u>	<u>%</u>
All		37	71.1	12	23.1
Male		15	65.2	6	26.1
Female		22	75.9	6	20.7
Age >55		12	60.0	7	35.0
Age <=55		25	78.1	5	15.6
ASA 3		5	83.3	1	16.7
ASA 1-2		32	69.6	11	23.9

Patient responses are summarized in Table II. Considering overall responses, this data indicates that 71.1% of patients felt that the propofol, when mixed with lidocaine as a solution, was less painful than the unmixed propofol pretreated with lidocaine. Differences in the subgroups presented in Table II were explored using both the Chi-squared and Mann-Whitney Rank Sum Tests. Our study demonstrated that there is a greater proportion of patients who experienced greater discomfort with propofol when given unmixed with lidocaine. This proportion was overwhelming and when applied with the McNemars Test

and a Wilcoxon Signed Ranks Test, the results were able to achieve a p value of < 0.001.

### DISCUSSION

Our results clearly indicate that propofol when mixed with lidocaine causes less pain on injection than when given after a lidocaine pretreatment. In comparing these results with previous work, one finds several studies which deal with similar lidocaine pretreatment techniques [7, 8, 12, 17,18], and several using propofol mixed with lidocaine solutions [4, 10, 13, 16, 15, 21]. Only three of these [15, 16, 21], made an attempt to compare these two techniques. While our findings are consistent with the results of Brooker et al [15], it is important to realize that their results were from an uncontrolled pilot study “with some variation in technique,” according to the authors. Specifically, use of a variable premedication, variable pre-induction opioid and lack of controls complicate their findings. This study did not allow the use of opioids as a premedication in order to eliminate the influence of opioids on the patients' perception of pain on injection. However, we did allow the use of benzodiazepine as a premedication since it was felt that it was not our purpose during this study to deprive our patients of an anxiolytic for the surgery. The benzodiazepine should not confuse our patients' perception of pain whereas an opioid might. Also, we felt that at the dosage of the benzodiazepine used, our patients should still be more than capable of sensing pain. The work of Johnson et al [16] employed 20 and 40 mg lidocaine doses both as pretreatment and mixed with propofol. While they consistently found the higher lidocaine dose to be more effective, no significant difference was found between the mixed and unmixed techniques. Scott et al [21] investigated a number of modes of administration of propofol and lidocaine, and they also found mixture to be most effective technique for preventing pain on injection.

The mechanism by which propofol causes pain on injection remains unclear, but is believed to involve interaction between the active component of the emulsion and the vascular endothelium. It has been proposed [21] that there is considerable interspecies variability of the sensitivity of pain on injection of propofol in animal studies, with rats being more severely affected than dogs, cats, pigs, and rabbits. This variability has been used to suggest that the kinin cascade, which is not attributable to every animal, is involved. More importantly, this also may explain the significant inter-patient variability observed, since some individuals do not have the same threshold for triggering this

cascade. This factor in particular was the major impetus for the present study. By placing an intravenous catheter on each arm, we allowed each patient to serve as his/her own control. Therefore, the inter-patient variability was removed, allowing the determination of an unambiguous result with considerably fewer patients than was originally anticipated. We placed only 18g intravenous catheters in our patients and we required that all of the catheters be placed on the dorsum of the hand. Because of this, we were able to prevent the size of the intravenous catheter from influencing the incidence of discomfort or pain the patient may have experienced.

Three of the 52 patients in this study (5.57%) were unable to identify which technique caused more pain. We considered the response from these patients as a tie from a statistical standpoint. Nevertheless, the number of patients in this group was miniscule and did not affect the results of the rest of the study. It was not a surprise that we did encounter patients who could not make the distinction between which arm was more uncomfortable or painful. This is because the overall incidence of pain with injection of propofol according to previous studies is in the range of 40-86% [9,16].

However, this study is limited in several respects. We did not attempt to determine the incidence or severity of the pain with either technique. The fact that we were unable to determine the severity of pain experienced by the patient could explain for the small group of patients who could not distinguish which technique induced greater pain. The patients in this group may have felt either no pain or equal pain bilaterally. In the design of the study, we chose not to have the patients assign a numeric value to the pain in each extremity. We felt that given inter-patient variability in onset of induction, this may have been too difficult a task for patients to follow at induction. Admittedly, assigning a numeric score would have been valuable. While we may state unequivocally that the mixed technique caused less pain on injection, the magnitude of this reduction remains undetermined.

### CONCLUSION

Lidocaine more effectively reduces pain on injection of propofol when it is administered as a mixture than when given as pretreatment before the propofol injection.

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