



# Lidocaine added to propofol decreases the severity but not the frequency of pain on injection compared to injecting lidocaine before propofol in patients undergoing colonoscopy

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## ABSTRACT

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**Background and Aims:** Pain on injection is common in non-premedicated patients receiving propofol for colonoscopy. Multiple studies have examined strategies to prevent propofol injection pain in surgical patients. However, many of these studies were not blinded or randomized and many of the studied patients received premedication prior to propofol injection. This study was designed to test the hypothesis that injecting a premixed solution of propofol/lidocaine will be associated with less pain than when lidocaine is injected separately before propofol. The study's propofol induction protocols closely mirrored those used routinely at our institution.

**Methodology:** This was a randomized, double-blinded, comparative study performed with IRB approval and patients' informed consent. One 150 patients scheduled for screening colonoscopy were randomly assigned into two groups of 75 patients in each group. In Group-LB, patients received 40 mg lidocaine IV followed by propofol from a syringe containing 19 ml propofol and 1 ml saline. In Group-ML, patients received 2 ml saline IV followed by propofol from a syringe containing 19 ml propofol and 1 ml 2% (20 mg) lidocaine. Following the initial IV injection of the 2 ml clear solution the patients were asked about symptoms of systemic lidocaine (light headedness, ringing in the ears, or metallic taste in the mouth). Disregarding the minor dilution of the 19 ml propofol with the added 1 ml clear solution, propofol 0.75 mg/kg was then injected at a constant rate over 15 seconds. The patients were asked to grade any associated pain or discomfort at the injection site on a 4 point scale: (0) no pain, (1) mild pain, (2) moderate pain, (3) severe pain and/or grimacing or withdrawal of limb. Thirty second later a second dose of 0.75 mg/kg propofol was injected. The patients continued to be questioned about pain on injection until they lost consciousness. Fisher's exact test was used to compare the proportion of patients who experienced pain and the incidence of experiencing systemic lidocaine symptoms between the 2 groups. Wilcoxon rank sum test was used to compare the severity of pain for patients who experienced pain in the two groups.

**Results:** There was no difference in pain rates between the two groups ( $p=1$ ). If they did experience pain, patients in Group-ML experienced less pain compared to patients in the Group-LB ( $p < 0.001$ ). The incidence of experiencing lidocaine symptoms was significantly higher in the Group-LB ( $p < 0.001$ ).

**Conclusion:** This study suggests that it is better to mix lidocaine with propofol than to give lidocaine bolus before propofol injection in non-premedicated patients since the mixture is associated with less severe injection pain. An additional benefit of mixing

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lidocaine with propofol is that it spares patients from experiencing the potentially unpleasant symptoms of systemic lidocaine.

**Key words:** Propofol pain; lidocaine; lidocaine/propofol mixture; systemic effects of lidocaine.

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## INTRODUCTION

Propofol is widely used for sedation during colonoscopy.<sup>1</sup> Its use leads to faster recovery and discharge times, and increased patient satisfaction.<sup>1</sup>

Pain on injection with propofol is a common problem and can be very distressing to the patient.<sup>2,3</sup> Pain on injection is particularly a problem in patients receiving propofol for colonoscopy since, unlike surgical patients, colonoscopy patients receive only propofol and lidocaine without sedative or opioid premedication. Therefore, we sought to find a more effective method to minimize propofol pain in this group of patients. Based upon existing literature we changed our practice to mixing lidocaine with propofol from giving lidocaine bolus. Our impression was that mixing lidocaine with propofol decreased propofol pain. This study was designed to prospectively test the validity of that clinical impression by testing the hypothesis that injecting a premixed solution of propofol/lidocaine will be associated with less pain on injection than when lidocaine is injected separately before propofol in patients receiving propofol and lidocaine for colonoscopy without any sedative or opioid premedication.

In our experience, when non-premedicated patients received lidocaine 40 mg IV some of them experienced symptoms of systemic lidocaine which some found unpleasant. Therefore, this study also sought to quantify the frequency of such an experience.

## METHODOLOGY

This was a randomized, double-blind, comparative study performed with IRB approval and patients' informed consent. Using an internet-based randomization program, one hundred and fifty patients scheduled for screening colonoscopy were randomly assigned into two groups of 75 patients in each group. Based on data from a comparable study<sup>3</sup>, the two-sided Fisher's exact test estimated that a sample size of 77 in each group was required to achieve 81% power considering a 20% loss to follow

up.

Exclusion criteria included patients ASA physical status 3-5, allergy to propofol, soya, or lidocaine, communications difficulty, receiving opioids or sedatives, and emergency procedures. All patients were instructed to recognize the symptoms of systemic lidocaine and were taught how to quantify the severity of pain on propofol injection if it occurred.

All patients had a 22 gauge IV catheter inserted in the dorsum of the right hand without local anesthesia. After intravenous access was established, the patients received an infusion of lactated Ringer's solution. Supplemental oxygen (3 L/min) was delivered by nasal cannula. Vital signs (noninvasive blood pressure, heart rate, respiratory rate, pulse oximetry, and capnography) were monitored before and every 3 min throughout the procedure.

The operating room research pharmacy prepared for the first group (lidocaine bolus or Group-LB) a syringe containing 2 ml of 2% lidocaine (40 mg) and a syringe containing 1 ml of normal saline. For the second group (mixed lidocaine group or Group-ML) the pharmacy prepared a syringe containing 2 ml of normal saline and a syringe containing 1 ml of 2% lidocaine (20 mg). The anesthesiologist and the patients were blinded to the contents of the syringes. Immediately before the start of the study the 1 ml clear solution was added to a syringe containing 19 ml propofol (1%). The 2 ml clear solution was then injected intravenously. Accordingly, patients in the Group-LB received 40 mg lidocaine IV followed by propofol and patients in the Group-ML received saline IV followed by propofol from a syringe containing 19 ml propofol and 20 mg lidocaine.

Following the initial IV injection of the 2 ml clear solution the patients were asked about symptoms of systemic lidocaine (light headedness, ringing in the ears, or metallic taste in the mouth). Disregarding the minor dilution of the 19 ml propofol with the added 1 ml clear solution, propofol 0.75 mg/kg was then injected at a constant rate over 15 seconds. The

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patients were asked to grade any associated pain or discomfort at the injection site on a 4 point scale: (0) no pain, (1) mild pain, (2) moderate pain, (3) severe pain and/or grimacing or hand withdrawal. Thirty seconds later a second dose of 0.75 mg/kg propofol was injected. The patients continued to be questioned about pain on injection until they lost consciousness.

Fisher's exact test was used to compare the proportion of patients who experienced pain and the incidence of experiencing systemic lidocaine symptoms between the 2 groups. Wilcoxon rank sum test was used to compare the severity of pain for patients who experienced pain in the two groups.

## RESULTS

Data were collected over approximately six months period. Patients' demographics are summarized in Table 1.

The frequency of pain on propofol injection in all patients exceeded 50% and was not different between the two groups (Table 1). However, when they experienced pain on propofol injection, patients in the Group-ML experienced less severe pain compared to patients in the Group-LB ( $p < 0.001$ ) (Table 2).

Sixty percent of patients who received 40 mg lidocaine IV experienced some symptoms of systemic lidocaine when asked about them before the propofol injection, a significantly higher incidence than in the group who received saline injection ( $p < 0.001$ ) (Table 3).

## DISCUSSION

Propofol is successfully used for sedation during colonoscopy. Severe sharp, stinging or burning pain on injection is a common problem in this non-premedicated patient population.<sup>2,3</sup> Multiple studies have examined strategies to prevent propofol injection pain in surgical patients.<sup>3-10</sup> Many of these studies, however, were not blinded or randomized and involved surgical patients who received premedication prior to propofol injection.

The mechanism of pain caused by injection of propofol is unclear. The pain can be immediate or delayed between 10 and 20 seconds. Immediate pain probably results from a direct irritant effect whereas delayed pain probably results from an indirect effect via the kinin cascade.<sup>3</sup> Pain on injection is reduced by reducing the propofol concentration in the aqueous phase with intralipid.<sup>8</sup>

If the pain is caused by direct irritation of afferent nerve endings within the vein, pre-treatment with lidocaine may give substantial relief. The use of lidocaine to prevent propofol injection pain is the most extensively studied technique and is the most common method used in clinical practice. Many studies have shown that the use of lidocaine is effective.<sup>3</sup> However, the protocols of these studies and the patient population studied varied significantly which resulted in varied conclusions.<sup>3-10</sup> This study compared two common methods used to administer lidocaine and propofol: Pretreatment with lidocaine and mixing lidocaine with the propofol, in non-premedicated patients undergoing colonoscopy. The study showed that the latter approach decreased the severity of propofol pain but not its incidence.

**Table 1: Demographics and study data. Data are presented as N (%)**

Parameter	Group LB (N = 75)	Group-ML (N = 75)	Statistical Significance
Gender (M/F)	41/34	44/31	NS
Age (Years) (Mean $\pm$ SD)	51.9 $\pm$ 10.9	53.2 $\pm$ 11.7	
Weight (Kg) (Mean $\pm$ SD)	77.5 $\pm$ 17.1	79.8 $\pm$ 15.7	

**Table 2: Symptoms of systemic lidocaine**

Symptoms	Group LB (N = 75)	Group-ML (N = 75)	Statistical Significance
Any symptom	45 (60%)	11 (15%)	$p < 0.001$
Light headedness	26 (35%)	4 (5%)	
ringing in ears	31 (41%)	3 (4%)	
Metallic taste	26 (37%)	8 (11%)	

**Table 3: Pain on injection**

Pain	Group LB (N = 75)	Group-ML (N = 75)	Statistical Significance
Any Pain	43 (57%)	42 (56%)	NS
Mild	8 (11%)	28 (37%)	$p < 0.001$
Moderate	26 (35%)	10 (13%)	
Severe	9 (12%)	4 (5%)	

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Other methods were shown to be effective in decreasing propofol pain including using a large antecubital veins, rapid bolus injection of propofol, and briefly occluding the vein with a tourniquet before injecting the lidocaine in order to maximize the contact time between the vein wall and the local anesthetic.<sup>4/10</sup>

The fact that we used 22 gauge IV catheter inserted in the dorsum of the hand for propofol injection must have contributed to the relatively high incidence of pain. It is recommended that propofol be given in a large antecubital vein to prevent pain on injection.<sup>10</sup>

Brosh-Nissimov<sup>11</sup> demonstrated that the therapeutic concentrations of lidocaine can be up to 5.5 mg/L, whereas a plasma level of 8-12 mg/L and above is associated with CNS and cardiotoxicity. The percentage of systemic side effects of lidocaine in this study was significant considering the relatively small dose of lidocaine used. The fact that the patients were not premedicated must have been a factor. Accordingly, it would be prudent to warn patients about the possibility of experiencing systemic lidocaine symptoms before injecting it intravenously into non-premedicated patients.

The addition of lidocaine to propofol can compromise the physicochemical stability of the propofol

emulsion and result in time- and dose-dependent increases in oil droplet diameters in the emulsion.<sup>10/11</sup> Therefore, mixing large doses of lidocaine with propofol may, over time, be associated with the risk of pulmonary embolism. That risk, however, is unlikely to be clinically important following the addition of 20 mg of lidocaine to 200 mg of propofol emulsion immediately prior to propofol injection.<sup>12/13</sup>

## CONCLUSIONS

This study suggests that mixing lidocaine with propofol is associated with less severe injection pain than giving lidocaine as a bolus before propofol injection in non-premedicated patients undergoing colonoscopy. Mixing lidocaine with propofol also spares patients from experiencing the potentially unpleasant symptoms of systemic lidocaine.

Since lidocaine has a destabilizing potential on propofol emulsion, the mixing should take place shortly before injecting propofol.

**Conflict of interest:** Nil

**Authors' contribution:**

MH: Concept, conduction of the study, manuscript editing.

JL, TC: Conduction of the study.

ET, LC: Statistical analysis.

## REFERENCES

1. Singh H, Poluha W, Cheang M, Baron K, Taback S. Propofol for sedation during colonoscopy. *Cochrane Database Syst Rev.* 2008 Oct 8;(4) [PubMed]
2. Stark R, Binks S, Dutka V, O'Connor K, Arnstein M, Glen J. A review of safety and tolerance of propofol ("Diprivan"). *Postgrad Med J* 1985;61(3):152-6
3. Tan C, Onsiang M. Pain on injection of propofol. *Anaesthesia.* 1998 May;53(5):468-76 [PubMed] [Free Full Text]
4. Scott RPF, Saunders DA, Norman J. Propofol: clinical strategies for preventing pain on injection. *Anaesthesia* 1988;43(6):492-4 [PubMed] [Free Full Text]
5. Mangar D, Holak EJ. Tourniquet at 50 mmHg followed by intravenous lidocaine diminishes hand pain associated with propofol injection. *Anesth Analg* 1992;74(2):250-2 [PubMed]
6. Walker B, Neal J, Mulroy M, Humsi J, Bittner R, McDonald S. Lidocaine pretreatment with tourniquet versus lidocaine-propofol admixture for attenuating propofol injection pain. A randomized controlled trial. *Reg Anesth Pain Med.* 2011 Jan-Feb;36(1):41-5 [PubMed]
7. Lee P, Russell W. Preventing pain on injection of propofol: A comparison between lignocaine pre-treatment and lignocaine added to propofol. *Anaesth Intensive Care* 2004;32(4):482-4 [PubMed] [Free Full Text]
8. Doenicke A, Roizen M, Rau J, Kellermann W, Babl J. Reducing pain during propofol injection: the role of the solvent. *Anesth Analg* 1996;82(3):472-4 [PubMed]
9. Euasobhon P, Dej-arkom S, Siriussawakul A, Muangman S, Sriraj W, Pattanittum P, Lumbiganon P. Lidocaine for reducing propofol-induced pain on induction of anaesthesia in adults. *Cochrane Database Syst Rev.* 2016 Feb 18;2:CD007874 [PubMed]
10. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, et al. Prevention of pain on injection of propofol: Systematic review and meta analysis. *BMJ.* 2011;342:d1110 [PubMed] [Free Full Text]
11. Brosh-Nissimov T, Ingbir M, Weintal I, Fried M, Porat R. Central nervous system toxicity following topical skin application of lidocaine. *Eur J Clin Pharmacol.* 2004;60(9):683-4 [PubMed]
12. Masaki Y1, Tanaka M, Nishikawa T. Physicochemical compatibility of propofol-lidocaine mixture. *Anesth Analg* 2003;97(6):1646-51 [PubMed]
13. Lilley E, Isert P, Carassoandr A, Kennedy A. The effect of the addition of lignocaine on propofol emulsion stability. *Anaesthesia.* 1996;51(9):815-8 [PubMed] [Free Full Text]

