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Original article

Comparison between Using Lidocaine Vs Hyoscine Vs Granisetron in Decreasing Pain During Injection of Propofol, Comparative Randomized Double Blind Study

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Abstract

Background: It's common knowledge that getting propofol via an IV may be a painful experience. The most effective remedy for reducing propofol-induced pain is unclear, despite the widespread use of a number of physical and pharmaceutical techniques. We set out to evaluate how well lidocaine, granisetron, and hyoscine work as pretreatments for painful propofol injections. **Methods:** This double-blind, randomized controlled trial was conducted after receiving the approval of our institutional research ethics board. A total of 150 patients were included after providing informed consent, and participants were placed into three equal groups: group A received lidocaine pretreatment prior to the injection of propofol, group B received granisetron pretreatment prior to propofol injection and group C received hyoscine pretreatment prior to the injection of propofol. After propofol injection, all participants were asked to evaluate pain at 0, 5, 10, 15 and 20 seconds of injection.

Results: There was no significant differences regarding the age, sex and ASA status. The most effective drug in reducing pain induced by propofol was lidocaine followed by hyoscine then granisetron. At 0 sec with induction of anesthesia 94% of patients had no pain Vs 86% in each hyoscine and granisetron group. After 20 sec of induction still lidocaine is the best drug in which 88% of patients had no pain Vs 70% for hyoscine and 60% for granisetron.
Conclusions: Lidocaine was better than hyoscine and that hyoscine is better than gransteron in reducing the incidence of propofol injection pain with no effect on the hemodynamics of the patients and no major post-operative complications or adverse effects.

1. Introduction:

Because of its rapid onset of action and rapid recovery, propofol has supplanted other intravenous anesthetics as the medication of choice for inducing and maintaining general anesthesia. Pain at the injection site and low blood pressure are frequent adverse effects of propofol, a phenol-structured medication (1).

Propofol's quick onset of action and positive association with speedy recovery make it a common choice for use in general anesthesia. However, propofol causes injection site pain and is thus seldom used for inducing general anesthesia. Untreated individuals had a higher incidence ratio (between 28 and 90 percent) of propofol-induced pain (2).

No one knows why getting an injection of propofol hurts so much. Propofol's direct irritating impact, via activation of venous polymodal nociceptive receptors or free nerve endings, is thought to be responsible for the drug's acute vascular discomfort upon injection (3,4).

An indirect action through activation of the kallikrein- kinin cascade is hypothesized to be responsible for the delayed pain experienced 10-20 seconds after a propofol injection (5,6).

Several methods, including chilling the propofol, diluting the injected solution,

injecting into the great antecubital vein, and using topical nitroglycerin and lidocaine, have been used with varying degrees of success to lessen the discomfort of propofol injection (7). Pain medication after an injection of propofol often includes nonsteroidal anti-inflammatory medications (8), metoclopramide (9), narcotic drugs (10), and ketamine and magnesium sulfate (11).

Lidocaine, a common local anesthetic, works by decreasing the permeability of the neuron membrane to sodium ions, therefore preventing the start and conduction of nerve impulses. It is less painful to inject propofol when combined with the local anesthetic lidocaine, which also helps stabilize the kinin system (12). Scopolamine butyl bromide, or hyoscine butyl bromide, is an anticholinergic medicine used for the relief of a variety of cholinergic symptoms, including esophageal spasms, renal colic, and bladder spasms (13).

The 5HT3 receptor antagonist granisetron is widely used these days to reduce the risk of patients experiencing nausea and vomiting following surgery that required general anesthesia. Previous literature suggested that granisetron analogs, such as ondansetron, given intravenously might mitigate the discomfort associated with propofol injection (14). Our primary outcome will be to study the effects of lidocaine, hyoscine and granisetron drugs on reducing the pain of propofol injection during induction of general anesthesia. Our second outcome will be the severity of propofol induced injection pain, vital signs and adverse effects including: hypotension, bradycardia (<50 beats/min), physical movement and cough.

2. Patients and Methods:

This study was a comparative randomized double blind study conducted at Beni-Suef University hospital after obtaining approval by the department of Anesthesiology, surgical intensive care and pain management faculty of medicine, Beni-Suef University and after obtaining approval from the local research and ethical committee during the period from October 2021 to March 2022. Written informed consents were obtained from each patient before the surgery.

By utilizing sealed opaque numbered envelopes specifying the group each patient belonged to, an independent anesthesiologist randomly assigned patients to one of three groups of fifty patients each to receive the study medicine. The anesthesia residents who administered the research medication, oversaw general anesthesia, and collected data were all unaware of the study procedure since the solutions were made in identical syringes labeled study drug.

One hundred and fifty patients undergoing elective surgery with general anesthesia were randomly divided into three groups: -

- **Group A:** 50 patients received 2 ml of 2% iv lidocaine (Depocaine "ADWIC/El-Debeiky") in 0.9% normal saline to make a total of 5ml solution.
- **Group B:** 50 patients received 2 mg of iv. Granisetron (Granitryl "Egypharma") in 0.9% normal saline to make a total of 5ml solution.
- **Group C:** 50 patients received 20 mg of hyoscine butyl bromide (Buscopan "Boehringer Ingelheim") in 0.9% normal saline to make a total of 5 ml solution.

Inclusion criteria:

- Males and females with physical statuses I and II according to the American Society of Anesthesiology.
- Age between 20 and 60 years.
- Patients who will be receiving general anesthesia for elective procedures.

Exclusion criteria:

- Patients refused to give consent.
- Patients belonging to ASA Grade III and IV.
- Patients with history of drug allergy to propofol, lidocaine, granisetron or hyoscine.
- Significant respiratory, cardiac or systemic diseases.
- Patients on analgesics in the past 24 hours.
- Patients scheduled for emergency surgery.

Methods:

All patients were evaluated preoperatively with a comprehensive history, standard lab work, and a thorough physical. Patients with ASA scores of I and II were eligible for participation.

All patients had their resting heart rates (HR), noninvasive blood pressures

(NIBP), oxygen saturations (SpO2), ECGs, end-tidal carbon dioxide levels, and body temperatures recorded and monitored continuously.

The patient's non-dominant hand's dorsum was pierced with a 20-gauge cannula, and Normal Saline was fed into the veins at a rate of 100 ml/hr. After 2 minutes, the IV was disconnected and the patient's arm was lifted for 15 seconds to allow the venous blood to drain by gravity. Patients were briefed once again on what to expect from the surgery. The patient was not given any pain medication prior to receiving the propofol injection.

The forearm was tourniqueted around 10 cm below the cubital fossa. In order to boost the local concentration of the medication, venous occlusion was performed by squeezing the forearm with a tourniquet to 50 mmHg. The arm was occluded by a tourniquet at 50 mmHg for 60 seconds while the research drug (lidocaine, granisetron, or hyoscine, depending on the study group) was administered over 20 seconds. After 60 seconds, the tourniquet was deflated and the occlusion was lifted, and then a 25 percent dosage of propofol (1 percent w/v in lipid base) was given over a period of 20 seconds. The total dose was 2 mg/kg.

Assessment parameters and follow up:

As After giving the patient the medication, doctors observed his or her facial expressions for symptoms of pain or discomfort and enquired whether the patient was experiencing any pain.

An anesthesiologist who was unaware of the drug's identity assessed the level of discomfort. After 20 seconds, the patient was under the effect of Propofol, thus the pain intensity was rated at 0, 5, 10, 15, and 20 seconds only using a four-point verbal rating pain scale (15).

In our research, we opted for a 4-point verbal answer scoring (15) method over the Visual Analog Score (VAS) because of its reliability, ease of administration, and overall practicality. In addition, the frequent shifts in consciousness that occur during propofol induction may make VAS measurement impossible. We also took note of any adverse events including hypotension, bradycardia, hypoxemia, an allergic response, or even just feelings of nausea or vomiting.

Sample size calculation:

The sample size was calculated using G.power. To compare between the 3

studied groups, One-way ANOVA (F test) was used to compute the sample size at an effect size 0.0325, alpha error 0.05, power (95%), it was detected that the sample size was 150 with 50 subject in each group.

Data Analysis and Statistics:

Pearson's Chi-square test for independence of attributes/exact Fisher's test was used to compare groups based on categorical variables represented as numbers of patients or percentages of patients.

The Mann-Whitney U-test was used to compare continuous variables across groups, and the resulting means, medians, and standard deviations were calculated.

For this study, we used SPSS 20 (IBM) and set our alpha at 5%, therefore results with P values less than 0.05 were deemed significant.

Ethical consideration:

This study protocol was approved by the research ethics committee of Faculty of Medicine of Beni-Suef University number FMBSUREC/05122021/Ali. The study was done according the Declaration of Helsinki.

3. Results :

The study included 50 patients in each arm with mean age 33.4±9.1, 37.4±10.2, 35.3±10.6 years in Lidocaine, Granisterone, Hyoscine groups, respectively. There was no significant difference between the studied groups regarding their age, sex and ASA (P-value>0.05) (Table 1).

Table (1): Demographic data of the studied groups:

Items	Lidocaine (no=50)	Granisterone (no=50)	Hyoscine (no=50)	P-value
Age	33.4±9.1	37.4±10.2	35.3±10.6	0.147
Sex **Males** **Females**	 31(62.0%) 19(38.0%)	 26(52.0%) 24(48.0%)	 22(44.0%) 28(56.0%)	 0.196
ASA **I** **II**	 41(82.0%) 9(18.0%)	 41(82.0%) 9(18.0%)	 45(90.0%) 5(10.0%)	 0.440

This study showed that there was a significant difference between the studied groups regarding their heart rate at different times (P-value<0.05). As there was a significant increase in HR in hyoscine group than in lidocaine and Granisetron groups at 0,5,10,15,20 seconds (Table 2).

Table (2): Follow up of heart rate of the studied groups:

Items	Lidocaine (no=50)	Granisetron (no=50)	Hyoscine (no=50)	P-value
HR at 0 sec	69.6±9.1a	73±13.2a	82±15b	<0.001*
HR at 5 sec	69.8±9.4a	73.7±13.9a	100±15.2b	<0.001*
HR at 10 sec	70.7±9.5a	75.3±14.2a	110±15.2b	<0.001*
HR at 15 sec	71.8±9.9a	76.8±14.7a	110±15.2b	<0.001*
HR at 20 sec	73.1±10.3a	78.1±15.3a	110±15.2b	<0.001*

**P-value is significant *a: lidocaine and granisetron groups *b: hyoscine group*

Table 3 showed that there was no significant difference between the studied groups regarding their systolic and diastolic blood pressure at different times (P-value>0.05).

Table (3): Follow up of blood pressure of the studied groups:

Items	**Lidocaine (no=50)**	**Granisetron (no=50)**	**Hyoscine (no=50)**	**P-value**
SBP before induction	128.9±12.4	130.8±12.6	133.9±14.4	0.156
SBP after 1 minute	102.2±7.4	106.2±12.1	106.5±12.3	0.090
DBP before induction	79.8±9.8	81.8±10	81.5±9.470	0.540
DBP after 1 minute	66.7±8.2	68.9±12.5	67.2±12.5	0.545

P-value is significant

There was no significant difference between the studied groups regarding their pain score (verbal pain score) at 0 seconds (P-value>0.05). At 5, 10, 15 and 20 seconds of induction, there was a significant difference between the studied groups (P-value<0.05). The least pain was observed in lidocaine group followed by Hyoscine then Granisetron (Table 4).

Table (4): Follow up of pain (verbal response score) of the studied groups:

Pain	Lidocaine (no=50)	Granisetron (no=50)	Hyoscine (no=50)	P-value
at 0 sec				
No	47(94.0%)	43(86.0%)	43(86.0%)	
Mild	2(4.0%)	2(4.0%)	3(6.0%)	0.730(ET)
Moderate	1(2.0%)	3(6.0%)	2(4.0%)	
Severe	0(0.0%)	2(4.0%)	2(4.0%)	
at 5 sec				
No	47(94.0%)	32(64.0%)	40(80.0%)	
Mild	2(4.0%)	11(22.0%)	6(12.0%)	0.014*
Moderate	1(2.0%)	6(12.0%)	2(4.0%)	
Severe	0(0.0%)	1(2.0%)	2(4.0%)	
at 10 sec				
No	47(94.0%)	30(60.0%)	35(70.0%)	
Mild	2(4.0%)	16(32.0%)	11(22.0%)	0.002*
Moderate	1(2.0%)	4(8.0%)	4(8.0%)	
at 15 sec				
No	43(86.0%)	30(60.0%)	36(72.0%)	
Mild	7(14.0%)	17(34.0%)	14(28.0%)	0.014*
Moderate	0(0.0%)	3(6.0%)	0(0.0%)	
at 20 sec				
No	44(88.0%)	30(60.0%)	35(70.0%)	
Mild	5(10.0%)	5(10.0%)	5(10.0%)	0.0062*
Moderate	1(2.0%)	15(30.0%)	10(20.0%)	

P-value is significant

Table (5) showed that there was no significant difference between the studied groups regarding presence of hypoxia, post operative nausea and vomiting (P-value>0.05).

Table (5): Comparison between the studied groups regarding their effects on oxygen and side effects

Side effects	Lidocaine (no=50)	Granisetron (no=50)	Hyoscine (no=50)	P-value
Hypoxia (SPO_2<90%)	0(0.0%)	0(0.0%)	1(2.0%)	0.999(ET)
PONV	4(8.0%)	3(6.0%)	4(8.0%)	0.999(ET)
Allergic reaction	0(0.0%)	0(0.0%)	0(0.0%)	------

4. Discussion

Our study showed that the most effective drug in reducing pain induced by propofol was lidocaine followed by hyoscine then granisetron at all times. There was no significant difference between the studied groups regarding their pain score (verbal pain score) at 0 seconds. At 5, 10, 15 and 20 seconds of induction, there was a significant difference between the studied groups. The least pain was observed in lidocaine group followed by Hyoscine then Granisetron.

Matching with our results was the study of Sargın *et al.*, (2018) about the use Hyoscine N-butylbromide (HnBB) for preventing propofol injection pain. They reported that administration of 20 mg HnBB before propofol injection reduced the pain by 30% compared to placebo and this reduction was more than that of the study Ahmed *et al.*, (2012) who reported a reduction in the incidence of pain by 15% when using granisetron (16, 17).

In contrary to our study is that performed by Sangsungnern *et al.*, (2022) who compared pretreatment between 20 mg of HBB and 60 mg of lidocaine with use of tourniquet for venous occlusion and demonstrated that VAS pain score in patients receiving HBB were higher than those receiving lidocaine (18).

In contrary to our study is that performed by Bakhtiari *et al.*, (2021) they disagreed

with our results and concluded that opioids and 5 HT3 antagonists were the most effective drugs for management of propofol induced pain (19).

AbouSlemah, (2018) compared lidocaine to 5 HT3 antagonists but used ondansetron and found that it was more effective than lidocaine in reducing pain. The incidence of propofol induced pain was 26% with ondansetron pretreatment versus 34% with lidocaine pretreatment (20).

Several studies investigated the use of lidocaine in reducing the incidence of propofol induced pain with injection and revealed its efficacy. Wang *et al.,* (2020) compared between nalbuphine and lidocaine and found that 66% of patients had no pain with lidocaine and the remaining reported mild (25%) to moderate pain (9%). No cases complained from severe pain (21). Hunie *et al.,* (2020) compared between tramadol and lidocaine and found that both drugs were effective in reducing the propofol induced pain with no statistically significant difference between them. However, lidocaine treated patients had a lower incidence of pain 23.1% Vs 34.6% for tramadol (22). By contrast, 76% of patients in the lidocaine group reported no pain after the Valsalva maneuver with propofol injection, while 21% reported mild discomfort and 2% reported significant pain (Ahmed & Dubey, 2022). Valsalva maneuver with propofol injection was compared to lidocaine, with 76% of patients in the lidocaine group reporting no discomfort, 21% reporting mild pain, and 2% reporting significant pain (Ahmed & Dubey, 2022) (23). Lidocaine was shown to be more effective than ketamine in reducing the pain associated with injecting propofol, with 80% of patients in the lidocaine group reporting no pain, 17.1% reporting mild discomfort, and 2.9% reporting significant pain (25).

Adinehmehr *et al.,* (2018) compared the effect of granisetron and dexamethasone on intravenous propofol pain and found that both drugs were effective in controlling the pain but with better results of dexamethasone (24). Also, Banu *et al.,* (2017) mentioned in their study about the reduction of pain on injection of propofol comparing pretreatment with granisetron Vs lignocaine that there was no pain on injection of propofol in 25 out of 30 patients (27). The meta-analysis

performed by Zhou & Zhou, (2020) concluded that 5-HT3 receptor antagonists could effectively reduce moderate and severe propofol injection pain (26).

It is unclear how propofol causes injection discomfort. Injection pain seems to be related to several aspects, including as the size of the vein, the location of the injection, the rate of the injection, and the amount of propofol present in the aqueous phase (21)

There may be a kinin cascade effect at work when propofol injections cause pain. Bradykinin is produced as a consequence of propofol's indirect action on the endothelium, which activates the kinin-kallikrein pathway. The contact of propofol with vein nerve terminals is increased by bradykinin, leading to an increase in injection discomfort (28).

Adding lidocaine to propofol explains why patients reported less discomfort during injections. Propofol has the ability to stimulate the Kallikrein system after administration, resulting in dilated and more see-through blood vessels. When combined with lidocaine, propofol has a considerably easier time entering the bloodstream and reaching the free nerve terminals where it may block pain (29).

Injection pain might be caused by propofol's direct irritant impact on the inner wall of blood vessels, which would activate the nerve fibers responsible for pain transmission. In addition, the direct stimulation of afferent nerve terminals from propofol injection may be avoided because to lidocaine's role as a local anesthetic by blocking voltage-gated sodium channels, which in turn blocks action potential propagation. Consequently, lidocaine's immediate analgesic impact was more potent (30).

Abdominal discomfort and spasms in organs that contain smooth-muscle fibers are treated with hyoscine butyl bromide, an anticholinergic drug. Because of the nitrogen atom in its structure, it attaches to muscarinic receptors and prevents acetyl choline from entering the cell. Hyoscine butyl bromide is used as an analgesic for a variety of conditions, including but not limited to: acute ureteral and renal colic; stomach cramping and discomfort; dysmenorrhea; the termination of pregnancy; and the recovery period after laparoscopic sterilization (16).

By blocking the sodium channel and acting as a mu-opioid agonist, serotonin receptor antagonists may dull pain. In addition to preventing postoperative nausea and vomiting, ondansetron pretreatment was also effective in reducing the occurrence of pain upon injection of propofol (20).

As regards to the heart rate and blood pressure. All patients had normal SBP and diastolic blood pressure while there was a significant increase in HR in hyoscine group than in lidocaine and Granisetron groups.

Anjidani *et al.,* (2022) reported in their study about the Effect of Isometric Exercises and lidocaine 2% on Pain Relief during Intravenous Propofol Injection that all patients were hemodynamically stable having a normal heart rate, blood pressure and oxygen saturation (31).

The study of Hu *et al.,* (2022) about the use of lidocaine with propofol in patients undergoing gastroscopy found No significant differences in SBP, DBP, MAP, HR or RR between the control and lidocaine groups. They found that patients in lidocaine group were more stable in terms of hemodynamic parameters (32).

Hemodynamic stability was noted, and no significant alterations were documented, in research comparing the effectiveness of ketamine and lidocaine in alleviating the pain after propofol injection (Khadka & Sharma, 2021). Increases in heart rate and blood pressure were seen, although they were too brief to be considered clinically or statistically significant and may be related to discomfort (33).

The study of Adinehmehr *et al.,* (2018) comparing the effect of granisetron and dexamethasone on intravenous propofol pain reported similar results and found that all patients were hemodynamically stable regarding the HR, MAP and oxygen saturation. However, they observed a slight drop in HR after 3 minutes of induction (24).

Ahmed *et al.,* (2012) in their study about pre-treatment with granisetron in reduction of propofol injection pain that there was transient rise in heart rate in patients suffering from pain (17).

Matching with our results was the study of Sangsungnern *et al.,* (2022) found that the incidence of tachycardia in patients

received HBB was higher than patients received lidocaine. However, this tachycardia was self-limiting and did not progress to severe tachyarrhythmia (18).

Matching with our results was the study of Tytgat *et al.,* (2008) mentioned that tachycardia from HBB administration was mild and self-limiting (34).

In our study, only 8% of patients in lidocaine group and hyoscine group complained of postoperative nausea and vomiting vs 6% of patients in granisetron group. Hypoxia with SPO2 less than 90% were reported in 2% of patients only with hyoscine group. There was no significant difference between the studied groups regarding presence of hypoxia, post operative nausea and vomiting.

Post-operative nausea and vomiting may be attributed to propofol as demonstrated by the study of Chen *et al.,* (2019) who revealed that propofol was associated with PONV however, this adverse effect was significantly lower than volatile anesthesia (35).

The lower incidence of PONV in our study could be explained as lidocaine, granisetron and hyoscine all have anti-emetic effect with higher effect with granisetron.

The findings of Singh et al. (2018) corroborated ours; they reported that 5-HT3 receptor antagonists had a central antiemetic effect, decreasing the likelihood of intravenous anesthetic-related reflux and aspiration (36).

The study of Sai & Kamath, (2015) comparing granisetron to lignocaine in reducing propofol injection pain demonstrated that there were no incidences of adverse reaction to lignocaine, granisetron or propofol among the participants (37).

Wang *et al.,* (2020) also reported in their study that other than 2% of patients having hypoxia, post-operative follow up of all patients was free of complications. Weibel *et al.,* (2018) conducted a systematic review and meta-analysis on the use of intravenous lidocaine and reported that lidocaine infusion reduced the incidence of postoperative nausea and vomiting (21).

The study of Abitagaoglu *et al.,* (2020) about the effect of hyoscine butyl bromide on post-operative nausea and vomiting showed that PONV was significantly reduced with the use of HBB (36). Abbas *et al.,* (2018) explained this as HBB, a quaternary ammonium

compound, might be effective as an antiemetic as it is an antispasmodic with peripheral anticholinergic effects. It acts on the smooth muscles in the gastrointestinal, biliary, and genitourinary system reducing its motility. In addition to its analgesic effect (39).

5. Conclusions:

Our study showed that lidocaine was better than hyoscine and that hyoscine is better than gransteron in reducing the incidence of propofol injection pain with no effect on the hemodynamics of the patients and no major post-operative complications or adverse effects.

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