

## 50% magnesium sulphate versus 2% lignocaine for amelioration of pain on injection of propofol – A single blind study

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Received: 19<sup>th</sup> October, 2018

Accepted: 9<sup>th</sup> January, 2019

### Abstract

**Introduction:** Propofol has surmounted its place in day care and ambulatory surgeries. However pain on propofol injection (POPI) still remains bothersome to most patients. Umpteen measures have been tried with variable results. In our study, 50% Magnesium sulphate with its unique and advantageous clinical profile was compared with the proven control, intravenous local anaesthetic 2% lignocaine to test their efficacy in reducing propofol induced pain.

**Aims:** To compare pre-treatment of intravenous 50% magnesium sulphate and intravenous 2% lignocaine (preservative free) as an effective method in controlling POPI.

**Settings and Design:** A sample of 100 patients of age 15-60 years belonging to ASA I and II posted for elective surgeries performed under general anaesthesia were allotted randomly into two groups.

**Methods and Material:** In Group M, 50% MgSO<sub>4</sub> 1ml (500mg) and in Group L, 2% Lignocaine 1ml (20mg) was used administered. The patients were observed for pain on injection at 5, 10, 15 and 20 s with injection of propofol. Pain was assessed using a four point scale. Quantitative data collected was assayed using chi-square test.

**Results:** There was no significant difference in the pain scores between both the groups (P value=0.6463).

**Conclusions:** 50% MgSO<sub>4</sub> is equally effective as 2% lignocaine in prevention of POPI and is a useful alternative for the same. No significant side effect were noted with the use of these drugs.

**Keywords:** Propofol, Pain, Lignocaine, Magnesium sulphate.

### Introduction

Propofol has gained immense popularity as an induction drug for most of surgical procedures done under general anaesthesia, adding a virtual death knell to most of the drugs used primitively like thiopentone. Propofol has stood steadfast and become an indispensable choice of induction because of its rapid onset, short duration of action, easy titration, and favourable side effect profile.<sup>1</sup>

However, POPI has remained a deterrent in grading propofol as an ideal induction drug. The incidence of pain varies between 28% and 90% in adults during induction of anaesthesia and may be severe.<sup>2</sup> The cause of POPI is still being unknown. Predictive factors like site of injection, calibre of the vein, rapidity of injection, buffering effect of blood, temperature of propofol and concomitant use of drugs such as local anaesthetics, opiates, etc., seem to affect the incidence of pain.<sup>2</sup>

Countless measures have been tried to counter the POPI ranging from drugs to distraction techniques. Pharmacological measures include lignocaine, ketamine, inhalational agents, opioids, anti-emetics, muscle relaxants etc. Pre-treatment with thiopentone, propofol, NSAIDs, other analgesics, steroids, ephedrine, antihistaminic and magnesium sulphate have been tried with varied success rates. Various non-pharmacological methods like distraction by counting, alkalization, rapid injection, cooling with or without lignocaine, larger vein, decreased concentration of propofol 0.5%, venous occlusion while injecting propofol etc. have been tried.<sup>5</sup>

Lignocaine has stood the test of time and is the most common and preferred choice to prevent POPI. The most effective dose for lignocaine with venous occlusion was 60 mg in one study where microemulsion propofol was used<sup>6</sup> whereas 40 mg is the most commonly used dose when premixed with 200 mg of propofol. Addition of 20mg lignocaine (1ml) to propofol syringe significantly reduced POPI to 32% as compared to low doses of lignocaine (i.e. 5mg, 10mg) or a placebo like saline (73%).<sup>7</sup> The efficacy of lignocaine lies in mechanisms other than local anaesthesia including the change in pH.<sup>8</sup>

Magnesium sulphate is a versatile drug with antiarrhythmic properties, anaesthetic adjunct, perioperative analgesic, muscle relaxant, anti-emetic, anti-shivering, anaesthetic and analgesic sparing properties. Magnesium has a high therapeutic index and cost effectiveness.<sup>9</sup> Magnesium being an NMDA antagonist with anti-nociceptive properties can also decrease POPI.<sup>2</sup> Magnesium also has a vasodilatory effect mediated by endothelium-derived nitric oxide which decreases POPI.<sup>10,11</sup> Nitric oxide donors protect vascular endothelium from ischemia and reperfusion-mediated endothelial dysfunction. Considering the numerous advantages magnesium sulphate brings in intra-operatively and postoperatively, we hypothesize that magnesium sulphate is equally efficacious to lignocaine and serve as a better alternative in treating POPI. We planned a study to compare 50% magnesium sulphate (1ml) in reducing POPI versus 2% lignocaine (1ml) given prior to injecting propofol.

## Materials and Methods

After obtaining necessary permission from our hospital's Ethics Committee and written informed consent from the patients, a prospective double blinded randomised controlled study was conducted on a sample of patients of American Society of Anaesthesiologists (ASA) physical status I and II aged between 18-60 years who underwent elective surgeries under general anaesthesia over a period of one year. Sample size was calculated based on previous studies. Considering incidence as per previous studies as 9% and standard deviation 1.96 at 5% level of significance and 8% error, a sample size of 49.16 was derived, which was rounded off to 50 in each group. Patients with thin dorsal veins and those with pre-existing cannula >24 hours, uncooperative patients and patients showing overt anxiety on the operating table, hypertensive patients, patients with cardiovascular risk factors, allergy to any of study drugs were excluded from the study. Patients were randomised into two groups M (n=50) and group L (n=50) using computer generated random sequence table.

Group M received 50% magnesium sulphate (500 mg, 1ml) and group L 2% lignocaine (22mg,1ml) with a lag period of 20s prior to the injection of propofol. The study drugs were prepared in identical syringes by an anaesthesiology resident blinded to the study group. The investigator was unaware of the identity of administered drug.

Patients underwent thorough pre-operative evaluation, routine investigations and good rapport was established with the patient to alleviate anxiety. Patient were explained in the pre-operative room about the study being performed and consent taken, the scale being used to measure POPI and the expected responses. Uniform premedication and monitoring was instituted in all patients. A specially designed pro-forma was used to collect the data which included patient's particulars, indication for surgery, the anaesthetic details, intra-operative monitoring details, observation for side effects etc.

After instituting standard monitoring (electrocardiogram lead II, non-invasive arterial blood pressure, and pulse oximetry), an 18-gauge cannula was inserted into the forearm dorsal vein with I.V fluid on flow. Patient were premedicated with Inj Glycopyrrolate 0.004mg/kg and Inj Midazolam 0.3mg/kg. No other analgesic drugs were added at this juncture. No venous occlusion tourniquet was used in our study. Patients in Group M received intravenous 50% Magnesium sulphate (500mg=2mmol of Magnesium) 1 ml 20 seconds prior to propofol injection. Patients in Group L received 1 ml of 2% Lignocaine (20mg) 20 seconds prior to propofol injection. Propofol stored at the temperature of 4° C (2mg/kg) was then administered with the IV flow at the rate of 1ml/s without interruption by an infusion pump. The patients were observed for pain on injection at 5(P5), 10(P10), 15(P15) and 20(P20) seconds with the injection of propofol (PO being just before propofol injection). Any behavioural signs such as facial grimacing, arm withdrawal, or tears were note.

Pain on injection was assessed using a scale used by McCrirrick and Hunter in their study.<sup>12</sup>

0 = no pain

1 = mild pain (pain reported only in response to questioning & without any behavioural signs)

2 = moderate pain (pain reported in response to questioning and accompanied by a behavioural sign, or pain reported spontaneously without questioning)

3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm Withdrawal or tears) McCrirrick Hunter score of 1 and more was considered as presence of pain.

Injection fentanyl (2ug/kg) IV and Injection Vecuronium (0.1mg/kg) was given following administration of propofol and noting the responses achieved. Intra-operatively routine maintenance and monitoring of anaesthesia was continued.

Side effects and complications like hypotension, bradycardia, allergy, anaphylaxis, post-operative nausea and vomiting, if any were noted.

Chi square test was used to analyse categorical data like age, gender and ASA grade. Data collected was subjected to standard statistical analysis and analysed using Chi-square test. The intra group differences of the cardiovascular variables recorded over time were analyzed using the repeated-measures ANOVA and intergroup mean values with t-test. Statistical significance was defined as  $P < 0.05$ . Minitab® Inc18.1, Coventry, United Kingdom was used for data tabulation and analysis.

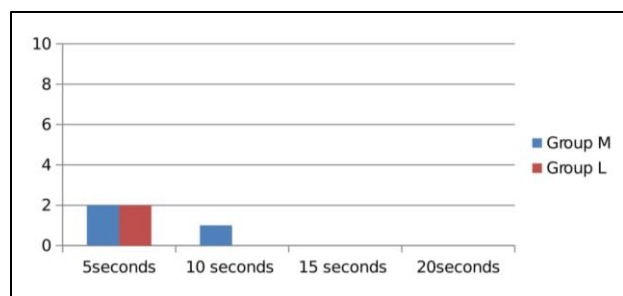
## Results

The two groups were comparable with respect to demographic characteristics (Table1). Most of the surgeries were related to ear, nose and throat with a view to maintain uniformity. Age distribution ranged between 18-60 years with the mean age of group M being 32.38 +14.82 and for group L being 35.02 +13.8. Majority of patients in both groups were females, 60% in lignocaine group and 62% in magnesium sulphate group. The age and sex difference between the groups is statistically insignificant. The distribution of weight and ASA physical status between the groups are also statistically insignificant.

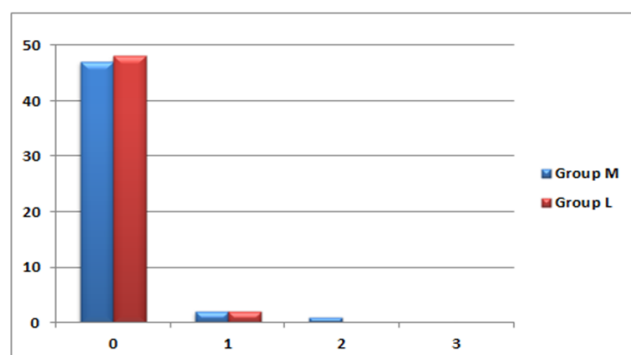
The primary objective of study was the study of incidence of pain in both the groups. Secondary objectives included the severity of pain and any complications when lignocaine and magnesium sulphate was used. Severity of pain was assessed by the scoring system as used by McCrirrick and Hunter scale.

Three patients in Group M (6%) and two patients in Group L (4%) had pain. The difference between the two groups weren't significant. ( $p=0.6463$ )

The pain on injection at 5, 10, 15 and 20 seconds after injection of propofol is as depicted in the Fig. 1. The difference of intensity of pain at different time intervals in two groups wasn't significant as shown in Fig. 2.



**Fig. 1: The pain on injection at 5, 10, 15 and 20 seconds after injection of propofol**



**Fig. 2: The difference of intensity of pain at different time intervals**

**Table 1: Demographic profile of the patients**

Demographics	Group M (N=50)	Group L (N=50)
Sex (M/F)	19/31	20/30
ASA(I/II)	46/4	45/5
Weight(kg)	56.16 ± 7.00	56.20 ± 7.66
Age(years)	32.38 ± 14.82	35.02 ± 13.8

## Discussion

Propofol has been a popular choice as an intravenous inducing agent owing to its faster and smoother induction, good quality of anaesthesia and rapid recovery profile.<sup>13</sup> Pain on propofol injection (POPI) remains the most common side effect followed by myoclonus, apnoea and hypotension. The incidence of POPI is very high with varied statistics due to many contributory factors for POPI. Incidence of 30-80% covers most of the patients when no pre-treatment is given.<sup>14-16</sup>

Magnesium, at doses of 500mg, has showed promising results in previous studies in decreasing POPI<sup>15</sup> as compared to placebo. Very few studies have compared its efficacy to lignocaine.

Hence we conducted a non-inferiority study comparing these two drugs in hundred patients using 500mg magnesium and 20mg lignocaine with the primary objective being incidence of pain. The incidence of pain in slightly higher with magnesium sulphate (6%) compared to lignocaine (4%) though the difference wasn't significant. The intensity of pain though varied at different time intervals, the difference between the two groups wasn't

significant. Intraoperative hemodynamics remained stable and was comparable in both the groups. No side effects or complications were noted in both the groups.

Previous studies showed incidence decreased from 37.5% to 17.5% with use of lignocaine.<sup>16</sup> Lignocaine acts by direct action of local anaesthetic on vascular smooth muscle. The exact mechanism by which lignocaine reduces propofol-induced pain remains unclear. It is possible that lignocaine pre-treatment in the present study may have induced bradykinin generation associated with activation of the plasma kallikrein-kinin system.<sup>6</sup> One systematic review noted that there is no obvious dose-response relationship within the dose range of 20-100mg lignocaine and that the lignocaine-tourniquet method is undeniably effective and simple to perform.<sup>17</sup> Another study showed that pre-treatment with lignocaine 20mg with or without venous occlusion for 60 sec significantly reduced pain (only 32% had pain) during injection of propofol but a highly significant negative dose-response relationship between the dose of lignocaine and the severity of pain.<sup>21</sup> Hence we chose lowest dose of lignocaine 20mg as the control arm to test effectiveness of Magnesium sulphate.

We inferred magnesium sulphate being efficacious for varied uses, can also be used as an alternative to lignocaine for POPI when better intraoperative and postoperative hemodynamics are desired. The mechanism of the analgesic effect of magnesium is not very clear. Blockade of calcium channels could be one of the possible causes. The second possible explanation for the analgesic action of magnesium is its antagonism of the NMDA receptor which is coupled to an ion channel permeable to K<sup>+</sup> and Ca<sup>++</sup>. Magnesium blocks NMDA receptor currents in a voltage-dependent manner by blocking the receptor channel.<sup>18</sup> The third possible explanation is Magnesium has a vasodilatory effect mediated by endothelium-derived nitric oxide.<sup>10,11</sup> Nitric oxide donors protect vascular endothelium to from ischemia and reperfusion-mediated endothelial dysfunction. Various dosages of the drug have been used in the earlier studies with variable results with doses ranging from 10mg/kg upto 1g, with 500mg being most commonly used. Hence we used 500mg (2mmol of Magnesium) as our study drug dose.<sup>19,20</sup>

In our study, among the 5 patients who experienced pain, majority i.e. 3 of them were females. Based on previous research, females are known to experiences greater pain intensity, with or without related distress, and show heightened sensitivity to experimentally induced pain compared to that of males.<sup>22</sup> The possible explanation for the gender difference in propofol-induced pain is firstly due to the mechanical effect that males have larger sized veins than females while another factor is the difference in pain sensitivity observed between the genders. This is the reason for emphasis on specifying the patient's gender while investigating propofol-associated withdrawal.

Incidence of POPI (5%) in our study was significantly less compared to other studies<sup>5</sup> where pre-treatment was given as we undertook several other non-pharmacological precautions to avoid POPI such as avoiding anxious patients, maintaining temperature of propofol at 4° C, use of

wide bore 18 G cannula, use of MCT/LCT propofol, a lag period of 20s prior between test drug and propofol and avoiding the use of tourniquet (which we believed could confound our results of pain assessment) In the last 10 years, only in three clinical trials, the incidence of POPI was 0%; in one study, three drugs (fentanyl, lignocaine, and sevoflurane) were used whereas in the other study, very high dose of ketamine (1 mg/kg) was used. Moreover, in the third clinical trial, combination of lignocaine 40 mg and remifentanyl 2 mcg/kg was premixed with propofol before use.<sup>5</sup> During our study, we followed our routine induction protocol. Incidence of POPI was considerably less in our study also considering the fact that we gave the entire induction dose rather than 1/4th or 1/3rd induction dose as done in previous studies. Our results would have definitely differed if we had done so.

Though we had no complications and side effects in our patients as most of the patients were healthy, magnesium sulphate has proven itself to be a versatile drug<sup>9</sup> which can serve as a good option in high risk cases.

### Conclusion

Magnesium sulphate 500mg given as pre-treatment 20 seconds prior to propofol injection in standardised conditions can serve as a versatile alternative to lignocaine 20mg in preventing POPI with favourable intraoperative and postoperative clinical effects.

**Conflict of Interest:** None.

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**How to cite this article:** Venugopal TB, Mitrageotri MV, Gopalakrishna K. 50% magnesium sulphate versus 2% lignocaine for amelioration of pain on injection of propofol – A single blind study. *Indian J Clin Anaesth* 2019;6(1):77-80.