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# ONDANSETRON V/S METACHLOPRAMIDE FOR ALLEIVATION OF PROPOFOL PAIN. A RANDOMISED CONTROL STUDY

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## ABSTRACT

Background and Aims: Propofol is widely used for induction of anaesthesia, pain during its injection remains a concern. A number of techniques have been adopted to minimise propofol induced pain. Various $5HT_3$ antagonists have shown to reduce propofol induced pain, metachlopramide is shown to have analgesic effect and reduce the use of opioids. Both drugs are used commonly for prevention of postoperative nausea and vomiting. A randomised controlled study was conducted to compare the efficacy of ondansetron and metachlopramide in terms of attenuation of propofolinduced pain during induction of anaesthesia. Methods: 100 adult patients aged 20–70 years posted for various elective surgical procedures under general anaesthesia were randomly assigned to two groups of 50 each. Group O received 4 mg of ondansetron, Group M received 10mg of metachlopramide. After intravenous pre-treatment of study drug, manual occlusion of venous drainage was done at mid-arm for 1 min. This was followed by administration of propofol (1%) after release of venous occlusion. Pain was assessed with a four-point scale. Unpaired Student's t-test and Chi-square test/Fisher's exact test were used to analyse results. Results: Demographic data in both the groups were comparable and there was no statistical significance.VRS and VASwere lower in group M compared to group O. Priming with either ondansetron or metachlopramide mostly alleviated pain of initiation of propofol injection where 17 patients in group O and 36 in group M had no pain. 16 patients in group O whereas only 8 patients in group M had mild pain. VRS of 2 was noted in 11 patients with group O and 3 patients in group M. Priming with 10 mg metachlopramide provided significantly better analgesia compared to ondansetron 4mg with p value of 0.002.

**KEYWORDS:** Ondansetron, metachlopramide, pain, propofol.

## INTRODUCTION

Propofol is a short acting anaesthetic agent used extensively due to smooth induction and rapid recovery. It is the agent of choice for day care anesthesia, total intravenous anaesthesia, for sedation in intensive care units, and as an agent for maintenance of anaesthesia.[1,2] Pain on injection of propofol is a concern for anaesthesiologist as it is an important cause of patient dissatisfaction.[3] The mechanism whereby Propofol causes pain is still not very clear. Many factors influence causing pain on intravenous injection like intrinsic drug property (e.g. osmolarity, emulsion composition, temperature, injection volume and pH of the formulation), injection procedure itself (speed of administration, concentration the aqueous phase, speed of IV carrier fluid, use of local anesthetics, and the blood's buffering capacity[4-6]). Various techniques including pharmacological and nonpharmacological are tried to reduce propofol injection pain. The most commonly studied technique is venous occlusion together with the use of various drugs such as lidocaine, antiemetics, nonsteroidal anti-inflammatory drugs, β-blockers, and opioids.

Ondansetron is a specific 5-hydroxytryptamine (5-HT3) receptor antagonist. It has been shown that ondansetron produces numbness when injected under the skin and has local anesthetic effect that is ~15 timesmore potent than lidocaine.[7] In practice, ondansetron is routinely administered as premedication toprevent postoperative nausea and vomiting. Metachlopramide is a benzamide with both central and peripheral anti-emetic actions. In addition metachlopramide has local anesthetic properties similar to lidocaine.[8] A study done by Maroof et al[9] showed that10mg of metachlopramide along with venous occlusion was effective in relieving pain on injection of propofol. The aim of this randomized double-blinded study was to compare the effectiveness of ondansetron, metachlopramide pretreatment in preventing propofol pain.

## MATERIALS AND METHODS

This prospective randomised study was conducted after obtaining institutional ethical committee approval from Decembe r2019 to March 2020. It included 100 adult patients of American Society of Anaesthesiologists physical status class I–II, aged 20 -70 years. Written informed consent was taken, routine fasting guidelines were followed. The procedure was explained to patients during the preanesthetic visit and once again before propofol injection in the operation room. Patients with psychological disease or communication problems; neurological diseases, allergy to propofol, 5-HT3 receptor antagonists were excluded from the study. Patients were randomly classified into two equal groups using computer-generated random numbers (50 in each group): group O received 4-mg (2ml) ondansetron as pretreatment medication and group M received 10mg (2 ml) metachlopramide as pretreatment before intravenous administration of propofol . Tab alprazolam 0.5 mg and tab ranitidine 150 mg was given as a premedication on the night before the day of the surgery. In the operation theatre, all the test drugs were prepared in a 2 cc syringes by a separate anaesthesiologist. Heart rate, noninvasiveblood pressure, and peripheral $O_2$ saturation were monitored in all patients. An 18-G cannula was intravenously inserted on the dorsum of the patient's nondominant hand and normal saline was infused at 200ml/hr, while the venous drainage was occluded by tourniquet to arm, the test drug (either ondansetron or metachlopramide), loaded in 2cc syringe, was given over 5 sec. The compression was released exactly after 1 minute and one-fourth the calculated induction dose of propofol (2mg/kg) given slowly over 5 sec. Patients were interviewed immediately after propofol injection about the pain by using VAS scores and VRS (Verbal rating scores). Heart rate (HR) and mean arterial pressure (MAP) were noted as baseline, just after test drug injection, after $1/4^{th}$ dose of propofol and full dose of propofol injection respectively.

VRS is a four-point verbal rating scale: 0=no pain (negative response to questioning), 1=mild pain (pain reported only in response to questioning without any behavioral signs), 2=moderate pain (pain reported in response to questioning accompanied by a behavioral sign or pain spontaneously reported without questioning), and3=severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears).[10] VRS is easy to comprehend. The VRS also is consistently sensitive to treatments that are known to have an impact on pain intensity.[11]

## RESULTS

**Age**

| Group | N | Mean | Std. Deviation | t test p value |
|---|---|---|---|---|
| Group O | 50 | 34.38 | 12.295 | .362 |
| Group M | 50 | 36.68 | 12.799 | NS |

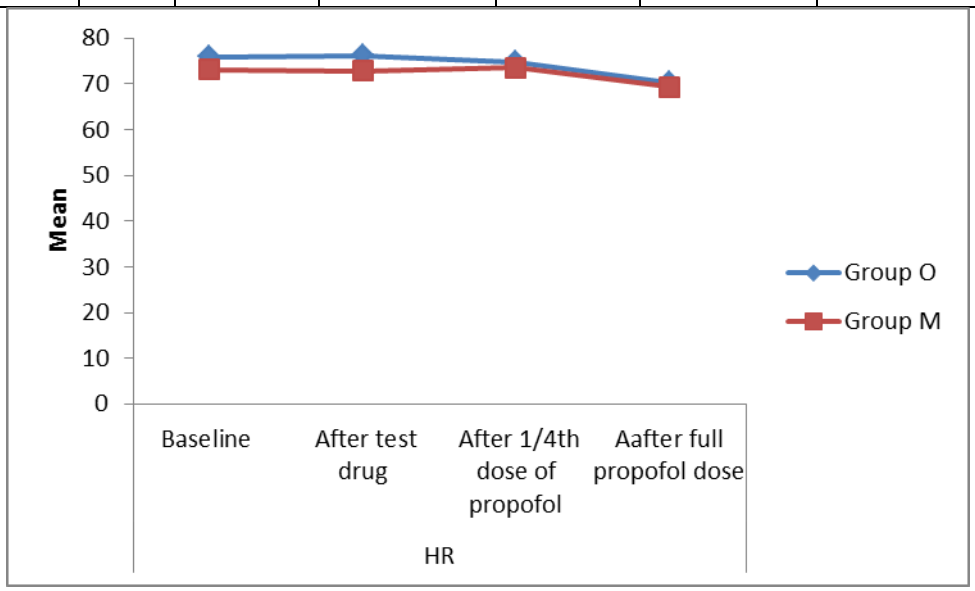
**Table 1: Demographic data.**

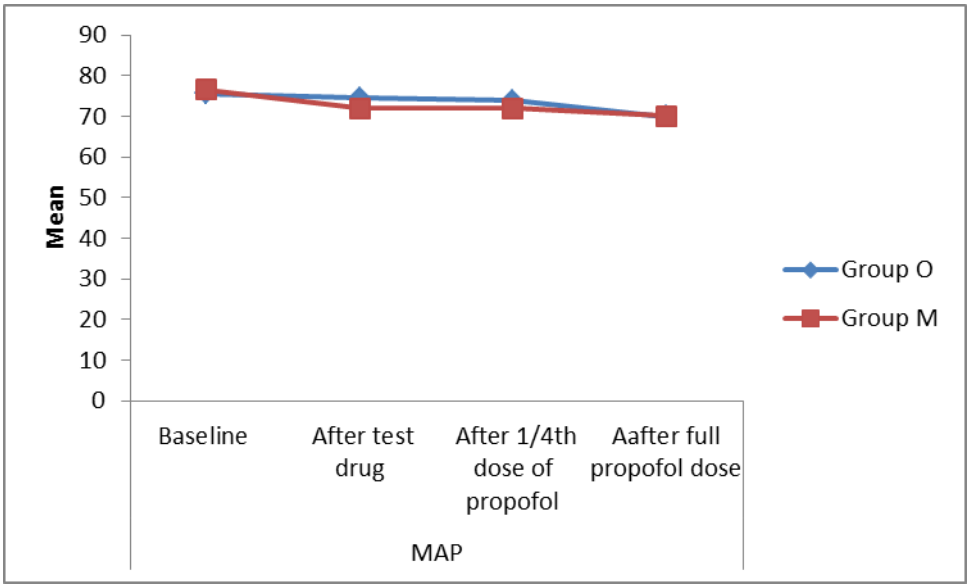
| | | Group | | | | |
|---|---|---|---|---|---|---|
| | | **Group O** | | **Group M** | | **P value** |
| | | **Count** | **Column N %** | **Count** | **Column N %** | |
| Sex | F | 31 | 62.0% | 30 | 60.0% | .838, NS |
| | M | 19 | 38.0% | 20 | 40.0% | |
| | Total | 50 | 100.0% | 50 | 100.0% | |
| ASA | 1 | 33 | 66.0% | 34 | 68.0% | .832,NS |
| | 2 | 17 | 34.0% | 16 | 32.0% | |
| | | | | | | |
| | Total | 50 | 100.0% | 50 | 100.0% | |

**Table 2: VAS and VRS scores.**

| | | **Group** | | | | p value |
|---|---|---|---|---|---|---|
| | | **Group O** | | **Group M** | | |
| | | **Count** | **Column N %** | **Count** | **Column N %** | |
| VAS | 2 | 8 | 16.0% | 27 | 54.0% | .0001 HS |
| | 3 | 9 | 18.0% | 12 | 24.0% | |
| | 4 | 11 | 22.0% | 8 | 16.0% | |
| | 5 | 12 | 24.0% | 3 | 6.0% | |
| | 6 | 10 | 20.0% | 0 | 0.0% | |
| | Total | 50 | 100.0% | 50 | 100.0% | |
| VRS | 0 | 17 | 34.0% | 36 | 72.0% | .002 HS |
| | 1 | 16 | 32.0% | 8 | 16.0% | |
| | 2 | 11 | 22.0% | 3 | 6.0% | |
| | 3 | 6 | 12.0% | 3 | 6.0% | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Total | 50 | 100.0% | 50 | 100.0% | |




Demographic data in both the groups were comparable and there was no statistical significance. With respect to VRS and VAS, scores were lower in group M compared to group O. Priming with either ondansetron or metachlopramide mostly alleviated pain of initiation of propofol injection where 17 patients in group O(34%) and 36 in group M (72%) had no pain.16 patients (32%) in group O whereas only 8 patients (16%) in group M had mild pain. VRS of 2 was noted in 11 patients (22%) with group O and 3 patients (6%) in group M. Severe pain (VRS 3)was seen in 6 patients (12%) in group O and 3 patients (6%) in group M. Priming with 10 mg metachlopramide provided significantly better analgesia compared to ondansetron 4mg with p value of 0.0007. All patients showed significant decrease of heart rate and MAP throughout the study period compared to baseline measures with nonsignificant difference between studied groups (Graph 1 and 2)

## DISCUSSION

Propofol is an hindered phenol that is characteristically dissimilar to any other drug used in anaesthesia.[12] There are immediate and delayed components of pain.The initial component involves immediate stimulation of nociceptors and free nerve endings.[13] and seems to be mainly related to the concentration of free drug within the aqueous phase of the emulsion.[14] There are several methods to reduce the pain caused by propofol injection including increasing the infusion rate, adding opioids, aspirin and lignocaine, cooling or diluting the propofol,pretreatment with small dose of propofol itself, ketamine, thiopentone, opiates, nonsteroidal anti-inflammatory drugs, esmolol/metoprolol, magnesium, a flash of light, clonidine/ephedrine combination, dexamethasone, and metachlopramide, all have been investigated to reduce pain on injection of propofol with variable results.

$5HT_3$ receptor antagonists bind to opioid μ-receptor thus acting as agonists and also sodium channel blockade activity similar to local anaesthetics. In addition, 5-$HT_3$ receptors are involved in the nociceptive pathway and this may be the mechanism of these drugs analgesic effect. There are currently seven types of 5-$HT_3$ receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron, alosetron, tropisetron and ramosetron).[15] and these drugs exhibit different affinity for receptors.

Metachlopramide is a potent antagonist of Dopaminergic $D_2$ receptor at low doses, at higher doses it poses $5HT_3$ receptor antagonist activity. Clinical studies also have reported analgesic effects of the drug, I.V. metachlopramide 20 mg was at least as effective as atropine 0.5 mg plus morphine 20 mg s.c. in relieving acute pain in ureterolithiasis.[16] However, in a study.[17] in which patients underwent total hip replacement under intrathecal analgesia supplemented with intrathecal morphine, metachlopramide 1 mg\ kg i.v. followed by an infusion of 1.5 mg\ kg over 9 hours decreased the need for postoperative analgesics and prolonged the pain-free time. This suggests that metachlopramide may exert a true analgesic action in the clinical setting.

Metachlopramide in doses >20 mg has been associated with dystonic and extrapyramidal reactions.[18,19] However, in this study, patients received metachlopramidein doses of 10 mg.

Although metachlopramide, in common with morphine, may alter the influx of calcium ions across the membrane to produce a generalized analgesic effect, the mechanism whereby it prevents local pain is unknown. However, investigation in patients undergoing second trimester abortion, showed that morphine requirements were reduced significantly by i.v. metachlopramide. The authors speculated that the drug reduced "spasm" in the Fallopian tubes and it may be on this basis that venous pain is attenuated.[20]

Metachlopramide 10 mg priming dose was found as effective as lidocaine for reduction of propofol injection pain with aneffect superior to 2.5 and 5 mg metachlopramide.[21] These finding go in hand with Fujii & Nakayama.[22] who found that the combination of lidocaine/metachlopramide is more effective than lidocaine alone for reducingpain on injection of propofol in a peripheral vein. Our study showed significant pain relief with 10mg metachlopramide in acceptance with Fuji study.

The obtained results concerning the pain alleviating effect of metachlopramide could be attributed to the facts that serotonin, (5-hydroxytryptamine [5-HT]), is a biological amine found in the brain and spinal cord and has a role in neurotransmission[23], animal studies indicated that 5-$HT_3$ antagonists reduce nociceptive responses of dorsal horn neurons when administered intrathecally by altering the 5-$HT_3$ nociceptive receptors and this effect can be attributed to the antagonism to the stimulatory action of serotonin at 5-$HT_3$receptors that are involved in the nociceptive pathways.[24] Also, Ye et al.[25] found 5- $HT_3$ antagonists to be 15 times potent than lidocaine as a local anaesthetic when injected under the skin in equal amounts. Moreover, 5-$HT_3$ antagonists had been found to have sodium channel blocking action. Furthermore, ondansetron has been shown to bind to opioid μ-receptors in humans and exhibit agonist activity.[26] These properties, as a central, local, and chemical antinociceptive drug, have been postulated to explain the superior results obtained by metachlopramide priming that were comparable to xylocaine. In support of the obtained results multiple studies reported similar effect with other 5-$HT_3$; Memis et al.[27] found tramadol or ondansetron are equally effective in preventing pain from propofol injection. Dubey & Prasad.[28] reported that granisetron pretreatment may be used to reduce the incidence of pain on injection of propofol. Ma et al.[29] investigated the alleviation effect of vein pretreatment with granisetron/lidocaine combination on propofol injection-induced pain and reported pain in 84% of patients received placebo, 46% with lidocaine alone, 52% with granisetron alone and 24% with granisetron/ lidocaine combination and concluded that pretreatment with granisetron/ lidocaine is effective in attenuating pains during intravenous injection of propofol.Our study correlates with other studies with 17 patients having no pain, 16 complained of mild pain, whereas 11 patients had moderate pain and only 6 patients had severe pain in group O. Mohammadreza Safavi et al., found that addition of metoclopromide 10 mg to lidocaine for intravenous regional anaesthesia in trauma patients decrease intraoperative and postoperative analgesic requirement till 24 h, decreased onset of sensory and motor block, increased duration of sensory and motor block, reduced tourniquet induced pain, prolonged the rescue time for analgesic use, and finally enhance the patients and surgeons satisfaction without triggering significant adverse effects.[30] Our study showed similar results.

## CONCLUSION

Our study showed reduction in propofol pain with both ondansetron 4mg and metachlopramide 10mg. Metachlopramide is better drug in relieving propofol pain as both VRS and VAS were significantly lower in this group.

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