To compare the efficacy of intravenous pre treatment with Inj Ondansetron 4mg, and Inj Lignocaine 40 mg, preceded by venous occlusion, for reducing pain on injection of Propofol in adult surgical patients.

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Abstract: Propofol is the most frequently used IV anaesthetic today. Induction of anaesthesia with propofol is associated with several side effects with pain during intravenous injection being major among them. In view of the above consideration, this clinical study was performed to assess the comparative effects of lignocaine and ondansetron pretreatment to decrease pain on propofol injection. A hundred ASA physical status I & II patients, both male and female posted for various elective surgeries under general anaesthesia were studied. The patients were divided into two groups of fifty each: Group I: Received lignocaine (40 mg) as pretreatment and Group II: Received Ondansetron 4 mg (0.1 mg kg⁻¹) as pretreatment. The patients in both groups were comparable with respect to demographic and hemodynamic parameters. Both lignocaine and Ondansetron were found to decrease the injection pain significantly i.e. 74% of patients in each group did not experience pain at all. Hence ondansetron is found to be as effective as lignocaine to decrease pain on injection of propofol.

Key words: Propofol, Ondansetron, Lignocaine, Induction, Pain.

INTRODUCTION:

The international association for the study of pain defines pain as an “unpleasant sensory and emotional experience associated with acute or potential tissue damage or described in terms of such damage.” The development of intravenous anesthetics has been an important component of anesthetic management for more than 70 years. Propofol, introduced clinically in 1977, is an alkyphenol compound that has some advantages over thiopental. Propofol with its attractive kinetic properties like titratable level of anesthesia, absence of cumulation, rapid and clear headed recovery and minimal side effects is an ideal agent for induction of anaesthesia[1, 2]. Kay and Rolly confirmed its potential as an anaesthetic agent and is being used for clinical purpose since 1982 [3].

It is known to cause severe, sharp, stinging or burning pain on injection that can be distressing to the patient. This pain is considered to be clinically unacceptable as it can cause agitation and interfere with smooth induction of anaesthesia. Incidence of pain on injection of propofol varies from 3-85% in adults. The pain on injection of propofol can be immediate or delayed in nature. The immediate pain probably results from direct irritant effect whereas delayed pain results from indirect effect via the kinin cascade, which occurs 10-20 seconds later [4].

Intravenous lignocaine, local anaesthetic, has been well documented to reduce the incidence and severity of pain on injection of propofol [2, 8, 9]. It is considered superior to other drugs but cannot reduce the incidence and severity of pain on intravenous injection of propofol, in all situations. Ondansetron is widely used as an antiemetic drug. In animal experiments, Ondansetron administered intrathecally reduces the nociceptive responses of dorsal horn neurons[22] Ye et al. Found, in rats that Ondansetron is approximately 15 times more potent as local anaesthetic than lignocaine, and this property probably contributes to its antiemetic action [23]. Although ondansetron does not have this aromatic moiety, it has the ability to block Na channels. Peripheral 5-HT3 receptors involve nociceptive pathways. Recently, Ondansetron has demonstrated binding at the opioid µ receptors in humans and exhibits agonist activity [24]. As a result of its multifaceted actions as a Na channel blocker, a 5-HT3 receptor antagonist, and µ-opioid agonist, Ondansetron may potentially be used to alleviate pain produced by a drug similar to propofol.

In this study we are comparing lignocaine and Ondansetron in decreasing pain on injection of propofol during intravenous induction of anaesthesia.

MATERIALS AND METHODS:

Following institutional ethical committee approval and written informed consent, a prospective randomized control study was conducted on 100 patients, who were scheduled to undergo various surgeries under general anesthesia. The study population was divided into 2 groups of 50 each, Group I: received 4mg i.e. 2ml of Ondansetron and Group II: received 40 mg i.e. 2ml of 2 % Lignocaine. The Inclusion criteria for the study included patient between age group of >16 and <60 years admitted for surgery under ASA grade I and II and weighing between 40kg-80kg. Exclusion criteria included ASA grade III and IV, patients who were allergic to propofol, lignocaine and ondansetron and who are not able to communicate. Patients who have received any analgesic or sedation 24hrs prior to surgery were also excluded from the study.

After explaining the anesthetic procedure to the patients, informed written consent was taken to include them in the study. All patients were prescribed 0.5 mg of alprazolam and ranitidine 150 mg orally the previous night. Patients were advised to be nil oral from 12 am onwards on the previous day of surgery. On arrival of patient to operating room, a 20 gauge i.v cannula was inserted at the dorsum of hand after ECG, non invasive blood pressure and pulse oximeter monitoring were instituted. No analgesic drugs were given before induction.. Patients were already been informed about the scale for propofol injection pain advocated by Mc Crirrick and Hunter. The patients recived 2 mL of the pretreatment solution prepared at room temperature Ondansetron 4mg and Lignocaine 40mg for a period of 5 s while the venous drainage was occluded manually at midarm by an assistant . The occlusion was released after 1 min, and one fourth of the total calculated dose of propofol 2mg/kg of body weight was administered for a period of 5 s. During a 10-second pause before the induction of
anesthesia, patients were questioned about the pain intensity on injection which was explained to them during Pre-anesthetic evaluation and before injection of propofol injection. Induction of anesthesia was continued with propofol. Tracheal intubation was facilitated with Inj Vecuronium, and anesthesia was maintained with inhaled technique supplemented with Fentanyl.

Mc Crirrick and Hunter scale (Table 1) was used to evaluate pain of propofol injection. No response to questioning was graded as 0 or none, pain reported in response to questioning only without any behavioral signs was graded as 1 or mild, pain reported in response to questioning and accompanied by behavioural sign or pain reported spontaneously without questioning was graded as 2 or moderate in severity and finally strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears was graded 3 and severe. The heart rate and SpO2 were monitored continuously. Blood pressure was recorded every 5 minutes for the first 15 minutes, every 5 minutes for the rest of the operation. The following parameters were studied: Pain during induction and PR, BP, SPO2 & ECG recordings before induction, during induction, intra operatively at 5min, 10min, 15min and post operatively.

RESULT:

A Comparative clinical anesthesia study with 100 patients, randomized into two groups, Group I: received 4mg ie 2ml of Ondansetron and Group II: received 40 mg ie 2ml of 2% Lignocaine. Aims and objectives of the study were to decrease pain on propofol injection during induction of anesthesia and to compare the efficacy of lignocaine and Ondansetron in reducing the pain on injection of propofol.

Data was collected and statistical analysis was performed as explained in the methodology of the study. In both lignocaine and Ondansetron groups, the age distribution ranged from 18-60 yrs with a mean age for lignocaine group being 30.92 and for Ondansetron group being 37.26. The difference in age between both groups is not statistically significant as suggested by P value of 0.042. Majority of cases in both groups were females, 62% in lignocaine group and 60% in Ondansetron group. The sex difference between the groups is statistically insignificant as suggested by P value of 0.838. In the study 58% of patients in lignocaine group and 62% of patients in Ondansetron group belong to ASA I PS and 42% of patients in lignocaine group and 38% of patients in Ondansetron group belong to ASA II PS. The difference between two groups with regard to distribution of ASA physical status is not significant. Mean weight in lignocaine group is 49.76 and mean weight in Ondansetron group is 46.68. The difference between two groups with regards to distribution of weight of patients is not significant. The Heart rate, Blood pressure and SPO2 in both groups were compared before induction, during induction intra operatively at 5min, 10min, 15min, post operative period and is not statistically significant.

Comparing pain during propofol injection, 54% in lignocaine group and 60% in Ondansetron group did not have pain, 34% in lignocaine group and 24% in Ondansetron group had mild pain, 10% in both groups had moderate pain, 2% in lignocaine group and 6% in Ondansetron group had severe pain. But difference between two groups is statistically insignificant as suggested by p value of 0.942
DISCUSSION:

Research is a continuous process. Efforts are being made to develop an induction agent for anaesthesia which will fulfill all qualities of an ideal induction agent. Propofol is a fast acting agent and its action wears off quickly making it useful for day care procedures. But it is also associated with side effects like myoclonus, apnoea, hypotension and pain on injection [26]. The most worrying side effect which has been most extensively studied is pain on injection of propofol. The incidence of pain varies from 30-90% of patients. Various studies have been conducted for decreasing propofol injection pain. The initial preparation of 2% emulsion with castor oil, ethanol, soya oil were studied. As a result of the high incidence of pain and other reactions it was reformulated in 10% w/v soya bean oil, egg phosphatide and glycerol [25].

Scott et al suggested that vein size is an important factor in causation of pain on injection of propofol. They noted that there was no pain when propofol was injected in the antecubital veins. This is because the drug is injected in the bloodstream with no contact with sensitive walls of veins. However, it is not feasible to choose the antecubital fossa vein routinely to avoid propofol injection pain as the IV site in antecubital fossa is relatively uncomfortable to patients and has a tendency to occlude. For this study, we preferred a larger size vein on the dorsum of hand so that elicitation of pain and hence its alleviation can be compared with respect to two agents i.e lignocaine and Ondansetron.

Speed of injection is also an important determinant of pain on injection because high rate of injection causes rapid clearance of drug preventing release of kininogens from vascular endothelium. In a study conducted in 1985, it was reported that slowing the speed of injection gave more comfort. Though there were conflicting opinions regarding speed of injection and pain, in our study, 1/4th of the induction dose of propofol (2.5mgkg-1) was given slowly over 30 seconds in both the groups to find out the efficacy of pre treatment in alleviating the injection pain.

Also it was found that by giving propofol at 4°C, the incidence of injection pain could be significantly reduced from 46% to 23% and the efficacy of drug was unaltered. The cold temperature caused relative inactivation of the kinin cascade. In our study, the drug was kept at room temperature before administering to patient. The drug was aspirated in plastic syringes, uncontaminated with any other agent and injected into vein through 20G cannula.

Though many methods of alleviating or reducing the intensity of pain on injection of propofol have been studied, the most commonly drug used for pre treatment was lignocaine. Several doses of lignocaine were studied. In an attempt to find out optimal amount of lignocaine necessary to reduce pain, Than et al showed that a propofol emulsion containing 0.05% lignocaine is effective in reducing propofol injection pain [30]. The dose of lignocaine used in our study was 2% which was found to be effective.

Ondansetron is a widely used antiemetic drug. In animal experiments, Ondansetron administered intrathecally reduces nociceptive responses of dorsal horn neurons. In a experiment conducted in rats it is found that Ondansetron is approximately 15 times more potent as local anaesthetic than lignocaine[23] Ondansetron is found to have μ opioid agonist action. So Ondansetron
may be potentially used to decrease pain produced by propofol[24]. Ondansetron is routinely used in our hospital as a pre medication for prevention of PONV at a dose of 0.1mgkg\(^{-1}\). In this study we compared the effect of lignocaine and Ondansetron in reducing pain on propofol injection and found a good relief of pain.

Pretreatment to decrease propofol pain on injection had been tried in different ways ie either given as IV before propofol or given with a tourniquet 29 similar to Bier’s block or pretreatment drug mixed with propofol. In a systematic literature search done by Picard et al, they found that lignocaine given with a tourniquet was most effective method to decrease pain [28]. In our study, we occluded manually which was maintained for one minute duration during pre treatment and released prior to propofol injection. In this study we avoided any kind of IV premedication (other than the study drugs) which may cause irritation or analgesia before injection of propofol.

The best way to assess pain in clinical setting is by verbal response or its derivative, The VAS appears to be more sensitive to smaller changes in effect over time than are categorical measures[31]. In our study we chose four point verbal categorical scoring system as advocated by Mccrirrick and Hunter6 because it is simple and readily understood by patients and many previous studies reporting pain on injection of propofol have used either all or none or categorical scoring systems, thus allowing easier comparison with literature. Also we were concerned that the appropriate hand eye coordination required for a VAS might not be present in all patients during the rapidly changing state of consciousness of anaesthesia induction. Hence we chose four point verbal categorical scoring for pain assessment in our study. In our study, distribution of age ranged between 18-60 yrs with the mean age of lignocaine group being 30.92 and for Ondansetron group being 37.26. Majority of patients in both groups were females, 62% in lignocaine group and 60% in Ondansetron group. The sex difference between the groups is statistically insignificant. The distribution of weight and ASA PS between the groups are statistically insignificant. Hence demographic characteristics are similar and comparable in both groups.

Clinically, it is a fact that female experiences greater pain intensity, with or without related distress, and shows heightened sensitivity to experimentally induced pain compared to that of males[32-35]. The proposed reason of gender difference in propofol-induced pain is firstly due to the mechanical effect that male has larger sized veins than female while another factor suggested is the difference of pain sensitivity observed between the gender and this emphasizes the necessity of specifying the patients’ gender while investigating propofol-associated withdrawal. In our study, among the patients who experienced pain, majority were females and severity of pain was also more in them.

The heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation and ECG were recorded during pre induction, induction, intra operatively at 5min, 10min, 15min and post operatively. Changes in all these parameters showed similar pattern in both groups and are statistically insignificant. Thus both lignocaine and Ondansetron did not cause any significant hemodynamic disturbances in our study. Even in patients who experienced pain on propofol injection, increase in heart rate was not significant enough to cause hemodynamic instability.
Out of 50 patients of each study group, 54% in lignocaine group and 60% in Ondansetron group did not have pain, 34% in lignocaine group and 24% in Ondansetron group had mild pain, 10% in both groups had moderate pain, 2% in lignocaine group and 6% in Ondansetron group had severe pain. Thus both Ondansetron 0.1mg kg\(^{-1}\) and lignocaine 0.1mg kg\(^{-1}\) significantly reduced pain on propofol injection but there was no statistical significance between the two groups. Majority had only mild pain. They reported pain only on questioning. But there was no statistical difference between the two groups. This is comparable with the study of Ambesh et al who found that Ondansetron decreased pain in almost 50% of patients. Our results also resemble study of Kang et al who showed in their study that about 60% of patients did not have pain after pretreatment with Ondansetron. Though in our study same dose of lignocaine significantly reduced pain, but effect was not pronounced as the previous study in preventing pain from propofol injection\(p=0.033\).12

Regarding other side effects, 3 patients in lignocaine group and 2 patient in Ondansetron group had myoclonic movements following propofol injection. Study done by Ambesh et al had a higher incidence of myoclonic movements in both control and Ondansetron groups [37]. There was no evidence of thrombophlebitis post operatively in form of pain, edema, wheal and flare in both groups at injection site.

CONCLUSION:

Propofol is an IV induction agent which produces a good quality of anesthesia and rapid recovery. However, it often has the disadvantage of causing pain or discomfort on injection. Various methods have been tried to alleviate the pain on propofol injection. In our study we compared between pretreatment with lignocaine and Ondansetron to decrease the injection pain. We conclude that Ondansetron 4mg(0.1mgkg\(^{-1}\)) decreases the injection pain significantly. Ondansetron 4mg (0.1mgkg\(^{-1}\)) and lignocaine 40 mg (2%) are equally effective in alleviating pain of propofol injection and there was no significant hemodynamic changes caused by both drugs.

Table No. 1. McCrirrick and Hunter scale of evaluation of propofol injection pain

<table>
<thead>
<tr>
<th>Degree of Pain</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (0)</td>
<td>No response to questioning.</td>
</tr>
<tr>
<td>Mild (1)</td>
<td>Pain reported in response to questioning only without any behavioral signs.</td>
</tr>
<tr>
<td>Moderate(2)</td>
<td>Pain reported in response to questioning and accompanied by Behavioral sign or pain reported spontaneously without questioning.</td>
</tr>
<tr>
<td>Severe (3)</td>
<td>Strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears.</td>
</tr>
</tbody>
</table>

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Table 2: Comparison of Pain During Induction In Study Groups

<table>
<thead>
<tr>
<th>PAIN_IND</th>
<th>Lignocaine</th>
<th></th>
<th>Ondan</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>% within</td>
<td>Count</td>
<td>% within</td>
<td></td>
<td>Count</td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>54.0%</td>
<td>30</td>
<td>60.0%</td>
<td>57</td>
<td>57.0%</td>
</tr>
<tr>
<td>Mild</td>
<td>17</td>
<td>34.0%</td>
<td>12</td>
<td>24.0%</td>
<td>29</td>
<td>29.0%</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
<td>10.0%</td>
<td>5</td>
<td>10.0%</td>
<td>10</td>
<td>10.0%</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>2.0%</td>
<td>3</td>
<td>6.0%</td>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100.0%</td>
<td>50</td>
<td>100%</td>
<td>100</td>
<td>100%</td>
</tr>
</tbody>
</table>

Contingency Coefficient – 0.063  P-0.942

Graph 1: Comparison of Pain During Induction With Propofol

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