The influence of lidocaine, thiopental, fentanyl and normal saline in reducing the incidence and severity of pain following the infusion of Fresenius propofol 1%; a double blind randomized controlled clinical trial

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ABSTRACT
Propofol is one of the latest anesthetics widely used due to providing pleasant anesthesia and rapid recovery. Rapid and complete awakening after anesthesia and minimal vomiting and nausea during the recovery is one of the benefits of this drug. However, painful injection is one of the most undesirable features of this drug. The incidence of pain in adults during the injection of propofol has been listed between 28% and 91%. The aim of this double-blind, placebo-controlled study is to assess the extent and intensity of pain during intravenous injection of Fresenius propofol 1% and application of Mg 20 Lidocaine, Mg200 Sodium thiopental, 100 Mg fentanyl and 2 Cc normal saline before injection of Fresenius propofol to patients. This study is a double blind clinical trial which has been done on 261 patients, 15 to 55 years old with I, II ASA (American Society Anesthesiologist) who were candidate for elective surgery in 5th Azar Hospital in 1390. Patients were divided into 5 groups in order to evaluate pain intensity: 2 mg / kg of Fresenius Propofol 1% with lateral branches of long triglycerides (LCT) were injected to the first group (54 patients). 2 Cc of lidocaine 1% was injected to the second group (50 patients) prior to the injection of Fresenius propofol 1% (Frensenius kabi Austria Gmbh). The third group (48 patients) received 2 mL of normal saline 0.09% before injection of Fresenius propofol 1%. 50 Mg thioipental sodium was injected to the fourth group (54 patients) before injection of Fresenius Propofol 1%, and 100 micrograms of fentanyl was injected to the fifth group (55 patients), before injection of Fresenius Propofol 1%. 261 patients were examined in this study. Among them 4 patients were excluded due to the lack of inclusion criteria. Assessment of pain intensity between five groups was as follow: Group I (propofol), there were 13 patients (24.5%) without pain, 13 patients (24.5%) had mild pain, 15 patients (28.3%) had moderate pain and 12 patients (22.6%) experienced severe pain. Group II (propofol and lidocaine), 29 patients (59.2%) had no pain, 13 patients (26.5%) had mild pain, 7 patients (14.3%) had moderate pain and none of the patients experienced severe pain. Group III (propofol and normal saline), there were 9 patients (18.8%) without pain, 10 patients (20.8%) had mild pain, 14 patients (29.2%) moderate pain and 15 patients (31.3%) had severe pain. Group VI (propofol and thiopental sodium), 36 patients (53.7%) had no pain, 11 patients (20.4%) mild pain, 12 patients (21.0%) moderate pain and none of the patients experienced severe pain. Group V (propofol and fentanyl), 29 patients (41.1%) had no pain, 58 patients (22.6%) mild pain, 54 patients (21.6%) moderate pain and 2 patients (3.7%) had severe pain. In this study, injection of Lidocaine prior to Propofol reduced the patients’ pain and was in consistent with the results of Eriksson [1], Picard [2] and Rehom [3] studies. But with the difference that the doses used in these studies was on behalf of us. Evaluation the amount of pain derived from infusion of propofol along with thiopental reflected pain reduction which was compatible with Pollard [4] study. The results show that Thiopental and lidocaine reduce more effectively incidence and pain severity than other groups, especially severe pain from injection of propofol [5]. It seems that aforementioned drugs be more appropriate as an alternative method than other treatment to diminish propofol injection pain.

Key Word: propofol, injection pain, premedication

INTRODUCTION
Propofol is one of the newest anesthetics which have found wide application due to its huge benefits. Rapid and complete awakening after anesthesia and minimal vomiting and nausea during the recovery is
one of the benefits of this drug [5]. However, painful injection is one of the most undesirable features of this drug [6]. The incidence of pain in adults during the injection of propofol has been listed between 28% and 91% [7]. Pain intensity was 5/6±2/3 based on VAS measurement system (Visual Analog Scale) (0-10) which is indicative of a severe pain [8]. Numerous ways have been suggested and studied to reduce the incidence and severity during injection of propofol. The usage of different kinds of propofol emulsion [9, 10] as well as various drugs such as lidocaine [11], thiopental [12], alfentanil [13] and GraniNetron (ondansetron) [14] can be noted among these methods. In Iran, there are different propofol emulsions like Fresenius Propofol 1% with lateral branches of long triglycerides (LCT) and Lipuro propofol 1% with lateral branches of long and medium triglycerides (MCT/LCT) [15]. Nerve impulses are conducted through the reduction of nerve membrane permeability to sodium ions by lidocaine as a local anesthetic. This drug prevents membrane depolarization as well as spread of its action potential and conductance so the systemic absorption of the drug is very fast through the skin and mucosa [16]. Fentanyl is commonly used as a premedication because it is rapid, painless and short-acting. It is stable from cardiovascular point of view and releases a little amount of histamine [17]. Thiopental is from barbiturates which causes hypotension in patients but has the ability to efficiently protect the nerves and ICP control in patients [18]. Ondansetron is an antiemetic medicine which has been selected as an antagonist for Hydroxy-tryptamine type 3. This drug has a phenomenal effect on glands activity (stomach), in addition, it has the ability to reduce nausea and vomiting and its complications are negligible [19]. Other studies have reported that Lidocaine, sodium thiopental, fentanyl, ondansetron and normal saline and other drugs injection following injection of propofol reduces pain. The aim of this double-blind, placebo-controlled study is to assess the extent and intensity of pain during intravenous injection of Fresenius propofol 1% and application of Mg 20 Lidocaine, Mg200 Sodium thiopental, 100 Mg fentanyl and 2 Cc normal saline before injection of Fresenius Propofol to patients.

MATERIALS AND METHODS
This study is a double blind clinical trial which has been done on 261 patients 15 to 55 years old with I, II ASA (American Society Anesthesiologist) who were candidate for elective surgery in 5th Azar Hospital in 1390. Each of the patients entered the study with full consent. A history of drug abuse, alcohol consumption or any kind of analgesic 24 hours before surgery as well as history of neurological disease, chronic pain syndrome, Thrombophlebitis, progressive systemic disease (eg. advanced diabetes) and any different indications from propofol injection caused patients exclusion from the study. The method of measuring pain in patients was from zero to three based on VRS (Verbal Rating Scale) which has been developed by Ciriick and MC Hunter (0= without pain, 1= Feeling mild pain or discomfort, 2= Moderate pain expressed by the patient, 3= Severe pain associated with changing facial expressions, receding the hand or forearm or both. After arriving to the operating room, a No. 20 cannula will be inserted in the vein of the patient's non-dominant hand (Without injection of any local anesthetic) and is attached to the normal saline (Without the infusion). Patients were randomly divided into 5 groups and a table of random numbers was generated by computer. 2 mg / kg of Fresenius Propofol 1% with lateral branches of long triglycerides (LCT) were injected to the first group (54 patients). 2 Cc of lidocaine 1% was injected to the second group (50 patients) prior to the injection of Fresenius propofol 1% (Fresenius kabi Austria Gmbh). The third group (48 patients) received 2 mL of normal saline 0.09% before injection of Fresenius propofol1%. 50 Mg thiopental sodium was injected to the fourth group (54 patients) before injection of Fresenius Propofol 1%, and 100 micrograms of fentanyl was injected to the fifth group (55 patients), before injection of Fresenius Propofol 1%. The aforementioned drugs were injected in the dorsal hand vein. None of the patients received Premedication. And five to ten seconds after injection of 25% of induction dose, patients were asked about the pain during the injection. And their response was recorded. After decreasing the level of consciousness, the rest of the anesthetic medication was injected. Anesthesia procedure was similar for all patients. Propofol was kept at room temperature (21 °C). Patients and the colleagues, who completed the questionnaires, were unaware of the type of injection. Due to the same color and shape of the medicines due to the same color and shape of the medicines, understanding the content of the medications is not possible. The drug was prepared by one person and was administered by the other one. And the amount of pain and discomfort in patients' hands was recorded in the relevant questionnaire by the third person. The data was confidential, and analyzed through the SPSS 18 software. The sample size for each group was determined based on a statistical study. To determine the association between treatment procedures and pain, in the case of quality ratings; Kruskal - Wallis test and chi test was used in the case of classified data. To determine the extent of the effect of treatment methods, the relative error and its confidence interval are used. Mann-Whitney test was used for the comparison of two independent groups and in the case of quality rating. In all statistical tests, the significance level was 0.05.
RESULTS

261 patients were examined in this study. Among them 4 patients were excluded due to the lack of inclusion criteria. Demographic characteristics of patients (Age, sex and weight) were similar in all groups. Pain severity was scored from 0 to 3 (0= no pain, 1= mild pain, 2= moderate pain, 3= severe pain). All patients were assessed according to this scale. 116 patients (45.1%) had no pain, 58 patients (22.6%) had mild pain, 54 patients (21.0%) suffered from moderate pain and 29 patients (11.3%) had severe pain. In this regard, patients had significant differences (P>0.05) (Diagram 1).

Evaluation of pain intensity between five groups was as follow:
- First group (propofol) 13 patients (24.5%) without pain, 13 patients (24.5%) mild pain, 15 patients (28.3%) moderate pain, 12 patients (22.6%) severe pain.
- Second group (propofol and lidocaine): 29 patients (59.2%) without pain, 13 patients (26.5%) mild pain, 7 patients (14.3%) moderate pain and none of the patients experienced severe pain.
- Third group (propofol and normal saline), 9 patients (18.8%) without pain, 10 patients (20.8%) mild pain, 14 patients (29.2%) moderate pain and 15 patients (31.3%) had severe pain.
- Fourth Group (propofol and thiopental sodium), 36 patients (53.7%) no pain, 11 patients (20.4%) mild pain, 12 patients (21.0%) moderate pain and none of the patients experienced severe pain.
- Fifth Group (propofol and fentanyl), 29 patients (45.1%) without pain, 58 patients (22.6%) mild pain, 54 patients (21.6%) moderate pain and 2 patients (3.7%) severe pain (Diagram 2).
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DISCUSSION

Injection pain causes patient stress and interferes with a good anesthetic. The mechanism of pain during the injection of propofol is not yet known. But perhaps due to a direct stimulation, an immediate sensation of pain may occur, or an indirect effect related to the release of mediators, leads to the emergence of pain [16]. Delayed pain (after 10 to 20 seconds), is caused by an indirect effect on the endothelium (owing to the release of Cyanogens) [20]. Fat-soluble causes the increased activity of plasma’s kallikrein-kinin system which leads to production of bradykinin. These interactions cause dilation and increase permeability in the peripheral veins, lead to an increase in Aqueous phase of Propofol with the endothelium and free efferent nerve endings between the media and intima of vessel wall and eventually cause pain[21]. Finally we can say that Propofol is a kind of drugs which stimulates skin and mucus and the lining of the vein[22].

The analgesic effects of lidocaine for reducing pain following the injection of propofol are not only because of its topical analgesic effects but also lidocaine reduces the PH of propofol solution. And based on a hypothesis, PH reduction makes soluble propofol migrate to fat phase and the amount of propofol reduces in the aqueous phase and thus decreases pain severity [21, 23]. In this study, injection of lidocaine prior to propofol injection has caused pain reduction which is in accordance with Eriksson[1], Picard [2], and Roehm [3] studies. But with the difference that the doses used in their study were greater than ours. Pain assessment on injection of propofol associated with thiopental showed a pain reduction which was in accordance with Pollard study [4]. In our study, Propofol injection was not significant just in terms of pain intensity that is corresponded to Larsen study [24]. In surveys conducted on pain caused by injection of propofol with lidocaine none of the patients suffered from pain which is in accordance with Masto [25], but didn't match Krobbouban[26]. Since in our study higher doses of lidocaine were used compared to the two previous studies.

Table 1: Characteristics of study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Propofol</th>
<th>Group II Lidocaine</th>
<th>Group III Normal saline</th>
<th>Group IV Thiopental</th>
<th>Group V Fentanyl</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29±11.4</td>
<td>26.9±11.2</td>
<td>26.4±8.4</td>
<td>29</td>
<td>28.8±10.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>31/22</td>
<td>28/21</td>
<td>29/24</td>
<td>25/28</td>
<td>21/33</td>
<td>0.4</td>
</tr>
<tr>
<td>Weight</td>
<td>69±13</td>
<td>66±15</td>
<td>71±14</td>
<td>70±14</td>
<td>69±12</td>
<td>0.12</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>46/7</td>
<td>41/8</td>
<td>40/8</td>
<td>48/5</td>
<td>45/9</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Table 2: severity and incidence of pain following injection of pain

<table>
<thead>
<tr>
<th>Pain severity score</th>
<th>Group I Propofol</th>
<th>Group II Lidocaine</th>
<th>Group III Normal saline</th>
<th>Group IV Thiopental</th>
<th>Group V Fentanyl</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole patients</td>
<td>53</td>
<td>49</td>
<td>48</td>
<td>53</td>
<td>54</td>
<td>257</td>
</tr>
<tr>
<td>Patients with pain</td>
<td>40</td>
<td>29</td>
<td>29</td>
<td>17</td>
<td>24</td>
<td>130</td>
</tr>
<tr>
<td>None</td>
<td>13(24.5)</td>
<td>29(59.2)</td>
<td>9(18.8)</td>
<td>36(67.9)</td>
<td>29(53.7)</td>
<td>116(45.1)</td>
</tr>
<tr>
<td>Mild</td>
<td>13(24.5)</td>
<td>13(26.5)</td>
<td>10(20.8)</td>
<td>11(20.8)</td>
<td>11(20.4)</td>
<td>58(22.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15(28.3)</td>
<td>7(14.3)</td>
<td>14(29.2)</td>
<td>6(11.3)</td>
<td>12(22.2)</td>
<td>54(21)</td>
</tr>
<tr>
<td>Severe</td>
<td>12(22.6)</td>
<td>0</td>
<td>15(31.3)</td>
<td>0</td>
<td>2(3.7)</td>
<td>29(11.3)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

The results showed that Lidocaine and thiopental compared to other drugs caused more reduction in pain, especially pain from injection of propofol. And due to the better effects of lidocaine towards thiopental on patients' hemodynamic changes and because of low price and availability the consumption of this drug is recommended in combination with propofol.

REFERENCES


CITATION OF THIS ARTICLE