A randomized clinical study to compare pre-emptive analgesic efficacy of clonidine and diclofenac sodium in patients undergoing major surgeries at a tertiary care hospital

Prachi Jain1*, Uma Bhosale2, Shashank Desai1

INTRODUCTION

Major surgery is any invasive operative procedure in which a more extensive resection is performed; they are usually done under spinal anesthesia. Spinal anesthesia is an economical and simple technique but it comes with disadvantages like limited duration of analgesia leading to post-operative pain.1 It is important to achieve a better post-operative analgesia for inhibiting autonomic and somatic reflexes that arise in response to pain and restore

ABSTRACT

Background: Pre-emptive analgesia is a method to achieve analgesia even before exposure to a noxious stimulus. The purpose of pre-emptive analgesia is to reduce pain caused due to surgical incision triggered inflammatory mechanism activation; and to ensure a good post-operative pain control so that there is no development of chronic pain. Clonidine is an α2 adrenergic agonist thus it decreases the sympathetic outflow, while Diclofenac is a non-steroidal anti-inflammatory agent. Our literature review showed that both clonidine (150 μg) and diclofenac are efficacious pre-emptive analgesics. Literature review also revealed that there is no study available to compare pre-emptive analgesic efficacy as well as safety of oral clonidine with diclofenac, therefore present study was designed to compare pre-emptive analgesic efficacy of these two drugs.

Methods: This randomized clinical study included 100 patients from surgical departments, of either sex, between 18 to 70 years age and of American society of anesthesiologists (ASA) I/II grade. Patients were randomly allocated to two groups and received either of the treatments 30 minutes prior to induction of anesthesia. Pain scores were recorded using visual analog scale, facial rating scale and behavioral rating scale at awakening and at 1, 2, 4, 6 and 24 hours. Postoperative analgesic requirement over 24 hours was recorded. Data were analyzed using OpenEpi statistical softwares.

Results: Significantly lower pain scores were observed in clonidine group as compared to Diclofenac at 4 and 6 hours (p<0.05) on all the pain scales. Clonidine group also required less postoperative analgesic as compared to diclofenac (p<0.05).

Conclusions: Study results are strongly suggestive of greater pre-emptive analgesic efficacy of clonidine over diclofenac in major surgeries done under spinal anesthesia.

Keywords: Pre-emptive analgesia, Clonidine, Diclofenac, VAS, Aldrete’s scale
function by allowing the patient to cough, breathe more easily.2

Pre-emptive analgesia is an antinociceptive treatment which helps to develop premature analgesia even before exposure to a noxious stimulus. The purpose of pre-emptive analgesia is to reduce pain caused due to surgical incision triggered inflammatory mechanism activation; and to ensure a good post-operative pain control so that there is no development of chronic pain.3

The concept of preemptive analgesia has now become popular and some drugs such as opioid, local anesthetics, and nonsteroidal anti-inflammatory drugs have been demonstrated for their preemptive effect in previous studies.4 Various modalities have been tried but side-effects produced by them limits their use.

Clonidine is an α2 adrenergic agonist and since α2 has an inhibitory effect on descending pain pathway, it decreases the sympathetic outflow in brain and spinal cord. Owing to this, it produces effects including sedation, analgesia, hypotension, and bradycardia. There is wide use of clonidine through various routes including intrathecal or intravenous administration in order to prolong the duration of spinal anesthesia without any adverse effects.5,6 Our literature review showed that clonidine (150 μg) is an efficacious pre emptive analgesic and can be used safely along with spinal anesthesia.7 Diclofenac is a non-steroidal anti-inflammatory agent and is an established pre-emptive analgesic.8 Literature review also revealed that there is no study available to compare pre-emptive analgesic efficacy as well as safety of oral clonidine with diclofenac.

**Aim and objectives**

Aim and objectives of the study were: to evaluate the pre-emptive analgesic efficacy of single dose clonidine in the patients undergoing major surgeries, to compare the pre-emptive analgesic efficacy of clonidine and diclofenac sodium, and to estimate and compare the total postoperative analgesic consumption and post anaesthetic care unit (PACU) stay in both the groups.

**METHODS**

**Study type**

A prospective randomized study was conducted.

**Study place**

The study was conducted at a tertiary care hospital and medical college in Pune

**Study period**

The duration of the study was from December 2017 to June 2019.

**Inclusion criteria**

It included 100 patients, of either sex, between 18 to 70 years of age, having American society of anesthesiologists (ASA) grade I and II, from departments of surgery, obstetrics and gynecology and orthopedics undergoing major surgeries.

**Exclusion criteria**

Patients with diabetic complications and other diseases like congestive cardiac failure, arrhythmias, ischemic heart disease, uncontrolled hypertension, and stroke; cancer, renal, hepatic disease, bleeding diathesis, allergic to the study drugs pregnant or lactating females and those who were simultaneously involved in other trials, not willing to give consent were excluded from study.

**Procedure**

All patients were assessed preoperatively the day before surgery. Study protocol was explained. Subjects were randomly assigned to either of the two groups using a computer-generated table of random numbers to receive medications. With 50 subjects in each group, group A was given clonidine (oral 100 μg tablet) 30 minutes prior to surgery and group B was given diclofenac (oral 100 mg tablet) 30 minutes prior to surgery.9,10 Premedication with injection (inj) ondansetron (4 mg intravenously) and inj glycopyrrolate 0.04 mg/kg intravenous (i.v.) followed by induction of spinal anesthesia was done as per standard protocol. After completion of surgery, patients were transferred to post anesthetic care unit and from where they were transferred to their respective wards. Baseline and post-operative vital parameters such as pulse rate, respiratory rate, mean arterial pressures and saturation of peripheral oxygen (SpO2) were recorded. Postoperative level of analgesia was noted on visual analog scale (VAS), facial rating scale (FRS) and behavioral rating scale (BRS) at 1, 2, 4, 6 and 24 hours. Rescue analgesic (diclofenac 75 mg) was given if patient complained of pain or pain score was more than 4. Post-operative analgesic requirement for 24 hours was recorded. Duration of postoperative anesthesia care unit (PACU) stay was recorded by using modified Aldrete’s scoring system; patients with score >9 were shifted to the ward.

**Ethical approval**

The protocol of study was approved by institutional ethics committee and written informed consent was obtained from each participant.

**Statistical analysis**

Sample size calculation was done by using OpenEpi statistical software with 95% confidence level, 80% power. Parametric data was analyzed using unpaired t test. Nonparametric data was analysed using Mann Whitney U test. Data was analyzed by using Open Epi statistical
RESULTS

In the present study entitled “A randomized clinical study to compare pre-emptive analgesic efficacy of clonidine and diclofenac sodium in patients undergoing major surgeries at a tertiary care hospital”, was conducted after taking permission from institutional ethics committee (IEC). Total 100 patients fulfilling selection criteria were enrolled and results were as follows.

As presented in Table 1, the mean age of group A was 50.08±8.48 years and mean age of group B was 50.22±9.18 years. There were 30 males and 20 females in group A while 31 males and 19 females in group B.

As per the study protocol, vital parameters were observed, and no significant differences were found in both the groups as shown in Table 2.

When compared between two groups, it was found that pain scores on VAS, FRS, and BRS were statistically significant at 4 and 6 hours. The incidence of nausea and vomiting was 4 and 6 in clonidine and diclofenac groups, respectively (Table 3).

First rescue analgesia was required earlier in diclofenac group as compared to clonidine group. Frequency of rescue analgesic administration was higher in diclofenac group as compared to clonidine group. Both time and frequency of rescue analgesic administration showed statistical significance between the two groups. The present study showed that total diclofenac requirements were significantly less in the clonidine group. The PACU stay was the less in the clonidine as compared to diclofenac group and this difference between the 2 groups based on the PACU stay was statistically highly significant as shown in Table 4.

Table 1: Demographic profile (n=100).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean±SD)</td>
<td>50.08±8.48</td>
<td>50.22±9.18</td>
<td>0.74</td>
</tr>
<tr>
<td>Male: female</td>
<td>30:20</td>
<td>31:19</td>
<td>NS*</td>
</tr>
<tr>
<td>Type of operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal hysterectomy</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Open cholecystectomy</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>3</td>
<td>4</td>
<td>NS*</td>
</tr>
<tr>
<td>Vaginal hysterectomy</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Appendicectomy</td>
<td>22</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Varicose veins</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Unpaired t test used for inter-group comparison; *NS-statistically non-significant

Table 2: Vital parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Awakening 1 hour</th>
<th>Awakening 2 hour</th>
<th>Awakening 4 hour</th>
<th>Awakening 6 hour</th>
<th>2 hour</th>
<th>4 hour</th>
<th>6 hour</th>
<th>Baseline</th>
<th>Awakening 1 hour</th>
<th>Awakening 2 hour</th>
<th>Awakening 4 hour</th>
<th>Awakening 6 hour</th>
<th>2 hour</th>
<th>4 hour</th>
<th>6 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>84.04±7.27</td>
<td>63.52±3.96</td>
<td>66.34±1.89</td>
<td>70.28±2.30</td>
<td>78.18±5.05</td>
<td>84.38±6.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse rate</td>
<td>14.14±1.37</td>
<td>15.18±1.98</td>
<td>16.1±1.67</td>
<td>15.26±1.19</td>
<td>15.02±1.27</td>
<td>15.66±1.45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>99.14±0.83</td>
<td>98.76±0.87</td>
<td>99.16±0.74</td>
<td>98.88±0.82</td>
<td>98.90±0.81</td>
<td>98.98±0.82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>86.78±4.80</td>
<td>67.88±2.31</td>
<td>69.28±2.01</td>
<td>71.32±2.39</td>
<td>77.82±4.10</td>
<td>86.10±4.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>84.54±8.26</td>
<td>63.90±5.16</td>
<td>66.82±4.52</td>
<td>69.80±4.02</td>
<td>78.82±5.86</td>
<td>85.34±7.38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse rate</td>
<td>14.34±1.79</td>
<td>15.46±1.88</td>
<td>16.34±1.60</td>
<td>15.46±1.43</td>
<td>15.28±1.59</td>
<td>16.02±1.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>99.06±0.79</td>
<td>98.92±0.80</td>
<td>99.06±0.77</td>
<td>99.02±0.84</td>
<td>99.06±0.82</td>
<td>99.14±0.83</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>86.84±5.37</td>
<td>68.32±1.87</td>
<td>70.08±2.14</td>
<td>72.14±2.0</td>
<td>77.18±2.44</td>
<td>86.70±4.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Pain scores.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Awakening</th>
<th>1 hour</th>
<th>2 hour</th>
<th>4 hour</th>
<th>6 hour</th>
<th>24 hour</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>1.02±0.55</td>
<td>0.98±0.62</td>
<td>0.66±0.69</td>
<td>3.22±0.93</td>
<td>3.36±1.26</td>
<td>5.02±0.74</td>
<td>Nausea/vomiting-4</td>
</tr>
<tr>
<td>VAS</td>
<td>1.03±0.53</td>
<td>1±0.60</td>
<td>0.72±0.70</td>
<td>3.16±0.98</td>
<td>3.24±1.27</td>
<td>4.96±0.78</td>
<td></td>
</tr>
<tr>
<td>FRS</td>
<td>1.06±0.55</td>
<td>1.04±0.60</td>
<td>0.74±0.69</td>
<td>3.24±0.98</td>
<td>3.28±1.20</td>
<td>4.90±0.76</td>
<td></td>
</tr>
<tr>
<td>BRS</td>
<td>1.04±0.60</td>
<td>0.96±0.57</td>
<td>0.8±0.67</td>
<td>3.86±1.73</td>
<td>3.98±1.62</td>
<td>5.18±0.83</td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>1.04±0.60</td>
<td>0.96±0.57</td>
<td>0.8±0.67</td>
<td>3.84±1.75</td>
<td>3.92±1.45</td>
<td>5.06±0.82</td>
<td></td>
</tr>
<tr>
<td>VAS</td>
<td>1.04±0.60</td>
<td>0.96±0.57</td>
<td>0.8±0.67</td>
<td>3.84±1.75</td>
<td>3.92±1.45</td>
<td>5.06±0.82</td>
<td></td>
</tr>
<tr>
<td>FRS</td>
<td>1.05±0.60</td>
<td>0.96±0.57</td>
<td>0.8±0.67</td>
<td>3.94±1.67</td>
<td>3.90±1.47</td>
<td>5±0.81</td>
<td></td>
</tr>
<tr>
<td>BRS</td>
<td>1.05±0.60</td>
<td>0.96±0.57</td>
<td>0.8±0.67</td>
<td>3.94±1.67</td>
<td>3.90±1.47</td>
<td>5±0.81</td>
<td></td>
</tr>
</tbody>
</table>

Preemptive analgesia is a treatment that is intended to reduce the physiological consequences of nociceptive transmission provoked by the procedure. It is administered before the surgical procedure. Due to this—protective effect on the pain pathways, preemptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, it helps to reduce immediate postoperative pain and to prevent development of chronic pain. The demographic data was comparable between the two groups. No statistically significant differences were found between the groups with respect to age, sex distribution, type of surgery and duration of surgery. This allows us to evenly compare the results obtained. The mean baseline heart rate and mean arterial pressure were comparable between two groups (p>0.05). There was no significant change in hemodynamic parameters in both the groups and the difference in mean heart rate and mean arterial pressure between both the groups were statistically insignificant preoperatively and postoperatively (p>0.05). There was no significant change within the groups at different time intervals. According to a study, in patients undergoing laparoscopic cholecystectomy, premedication with oral clonidine 150 µg results in improved perioperative hemodynamic stability when compared to a placebo. Few studies have reported that clonidine increases perioperative circulatory stability in patients undergoing laparoscopic cholecystectomy and potentiate parasympathetic nervous system. In our study, no statistical significance is suggestive of hemodynamic stability with both clonidine and diclofenac. There was no significant change in respiratory rate and SpO2 between the two groups and the difference in mean respiratory rate and SpO2 of patients was statistically insignificant preoperatively and postoperatively both between and within groups (p value >0.05). According to a study, same dose of 100 µg Clonidine does not cause respiratory depression and produces adequate analgesia.

For postoperative pain assessment VAS, BRS and FRS were used. The VAS, BRS and FRS scores were lower in group A than group B at all set time points, with the difference reaching statistical significance at 4 and 6 hours. In a meta-analysis of randomized trials, patients receiving pre-emptive local anesthetic wound infiltration and nonsteroidal anti-inflammatory drug administration experienced a decrease in analgesic consumption, but no decrease in postoperative pain scores. Pre-emptive epidural analgesia did show a decrease in pain scores as well as analgesic consumption. In another study, the effects of diclofenac, paracetamol, and their combination on pain after tonsillectomy were compared. Two drugs combination caused less pain after surgery but there was no significant difference between the effects of diclofenac and paracetamol. Some other studies also investigated the effect of diclofenac on pain after tonsillectomy surgery or other surgeries, all of which indicated the pain-relieving effect of diclofenac and that less opioid consumption was required after surgery.

First rescue analgesia was required earlier in diclofenac group as compared to clonidine group. Frequency of rescue analgesic administration was higher in diclofenac group as compared to diclofenac group. Both time and frequency of rescue analgesic administration showed statistical significance between the two groups. After applying student’s t-test to both the groups at different time intervals, we found the difference between total rescue analgesic requirements to be statistically highly significant. The clonidine group required less rescue analgesic as compared to diclofenac group. Oral/ injectable diclofenac was used as a rescue analgesic. This finding is like earlier studies as mentioned above. According to a study, postoperative analgesic requirements were reduced when oral clonidine 150 µg was administered as a pre-medicant in patients undergoing laparoscopic cholecystectomy. The present study showed that total diclofenac requirements were significantly less in the clonidine group. NSAIDs are commonly used analgesics in surgical procedures for decreasing pain and opioid requirements. They are well established, effective, and inexpensive; however, inadequate analgesia and adverse renal, gastrointestinal, and hemostatic effects may limit their use in some groups of patients. This finding is like earlier studies as mentioned above. The PACU stay was the less in the clonidine as compared to diclofenac group and this difference between the 2 groups based on the PACU stay was highly significant. The side effects we observed in our study were the postoperative nausea and vomiting (PONV) where 4 patients of clonidine group and 6 patients of diclofenac group were affected. The difference between the post-operative vomiting episodes in the two groups is not statistically significant. All the subjects who suffered nausea and vomiting were treated by tablet ondansetron 4 mg orally. Factors like age and gender of patient, obesity, technique of anesthesia employed, presence of post-operative pain, use of opioids for pain management and

**DISCUSSION**

Preemptive analgesia is a treatment that is intended to reduce the physiological consequences of nociceptive transmission provoked by the procedure. It is administered before the surgical procedure. Due to this—protective effect on the pain pathways, preemptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, it helps to reduce immediate postoperative pain and to prevent development of chronic pain. The demographic data was comparable between the two groups. No statistically significant differences were found between the groups with respect to age, sex distribution, type of surgery and duration of surgery. This allows us to evenly compare the results obtained. The mean baseline heart rate and mean arterial pressure were comparable between two groups (p>0.05). There was no significant change in hemodynamic parameters in both the groups and the difference in mean heart rate and mean arterial pressure between both the groups were statistically insignificant preoperatively and postoperatively (p>0.05). There was no significant change within the groups at different time intervals. According to a study, in patients undergoing laparoscopic cholecystectomy, premedication with oral clonidine 150 µg results in improved perioperative hemodynamic stability when compared to a placebo. Few studies have reported that clonidine increases perioperative circulatory stability in patients undergoing laparoscopic cholecystectomy and potentiate parasympathetic nervous system. In our study, no statistical significance is suggestive of hemodynamic stability with both clonidine and diclofenac. There was no significant change in respiratory rate and SpO2 between the two groups and the difference in mean respiratory rate and SpO2 of patients was statistically insignificant preoperatively and postoperatively both between and within groups (p value >0.05). According to a study, same dose of 100 µg Clonidine does not cause respiratory depression and produces adequate analgesia.

For postoperative pain assessment VAS, BRS and FRS were used. The VAS, BRS and FRS scores were lower in group A than group B at all set time points, with the difference reaching statistical significance at 4 and 6 hours. In a meta-analysis of randomized trials, patients receiving pre-emptive local anesthetic wound infiltration and nonsteroidal anti-inflammatory drug administration experienced a decrease in analgesic consumption, but no decrease in postoperative pain scores. Pre-emptive epidural analgesia did show a decrease in pain scores as well as analgesic consumption. In another study, the effects of diclofenac, paracetamol, and their combination on pain after tonsillectomy were compared. Two drugs combination caused less pain after surgery but there was no significant difference between the effects of diclofenac and paracetamol. Some other studies also investigated the effect of diclofenac on pain after tonsillectomy surgery or other surgeries, all of which indicated the pain-relieving effect of diclofenac and that less opioid consumption was required after surgery.

First rescue analgesia was required earlier in diclofenac group as compared to clonidine group. Frequency of rescue analgesic administration was higher in diclofenac group as compared to diclofenac group. Both time and frequency of rescue analgesic administration showed statistical significance between the two groups. After applying student’s t-test to both the groups at different time intervals, we found the difference between total rescue analgesic requirements to be statistically highly significant. The clonidine group required less rescue analgesic as compared to diclofenac group. Oral/ injectable diclofenac was used as a rescue analgesic. This finding is like earlier studies as mentioned above. According to a study, postoperative analgesic requirements were reduced when oral clonidine 150 µg was administered as a pre-medicant in patients undergoing laparoscopic cholecystectomy. The present study showed that total diclofenac requirements were significantly less in the clonidine group. NSAIDs are commonly used analgesics in surgical procedures for decreasing pain and opioid requirements. They are well established, effective, and inexpensive; however, inadequate analgesia and adverse renal, gastrointestinal, and hemostatic effects may limit their use in some groups of patients. This finding is like earlier studies as mentioned above. The PACU stay was the less in the clonidine as compared to diclofenac group and this difference between the 2 groups based on the PACU stay was highly significant. The side effects we observed in our study were the postoperative nausea and vomiting (PONV) where 4 patients of clonidine group and 6 patients of diclofenac group were affected. The difference between the post-operative vomiting episodes in the two groups is not statistically significant. All the subjects who suffered nausea and vomiting were treated by tablet ondansetron 4 mg orally. Factors like age and gender of patient, obesity, technique of anesthesia employed, presence of post-operative pain, use of opioids for pain management and
elective surgical procedures also influence the incidence of PONV.

The limitation of this study is that the pre-emptive analgesic efficacy was studied only in patients operated under spinal anesthesia; patients operated under general anesthesia as well need to be studied. Furthermore, we have evaluated pre-emptive analgesic efficacy of single oral dose of 100 μg clonidine; the single highest safe dose needs to be evaluated to offer maximal post-operative pain control through practicing pre-emptive analgesia.

CONCLUSION

This study revealed that clonidine has better pre-emptive analgesic efficacy and safety as compared to diclofenac based on pain scores, frequency of rescue analgesic requirements, duration of PACU stay and adverse events.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES