EFFECT OF ORAL LOW DOSE CLONIDINE PREMEDICATION ON POSTOPERATIVE PAIN IN PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY: A RANDOMIZED PLACEBO CONTROLLED CLINICAL TRIAL

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EFFECT OF ORAL LOW DOSE CLONIDINE PREMEDICATION ON POSTOPERATIVE PAIN IN PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY: A RANDOMIZED PLACEBO CONTROLLED CLINICAL TRIAL (Abstract): This study evaluated the effect of oral low dose clonidine premedication on postoperative pain and hemodynamic status of the patients during abdominal hysterectomy under general anesthesia. Methods: This study is a randomized, placebo controlled double-blinded clinical trial. After approval of the study protocol by the Ethics Committee 60 patients were recruited and written informed consents were obtained. Two hours before surgery, patients in the treatment group (n=30) received a single oral dose of 100 microgram of clonidine and those in the placebo group received an oral dose of placebo (n=30). The severity of postoperative pain was assessed at 2nd, 6th, 12th and 24th hours after the operation using the visual analog scoring system (VAS score). Also the total dose of administered analgesics during 24 hours after the surgery and the interval between the surgery and the first request of analgesic were compared between the two groups. Systolic blood pressure and pulse rate were recorded during the surgery and at the post anesthesia care unit. Drug related adverse effects were also evaluated. Results: Postoperative pain VAS during 24 hours after the surgery was significantly (P=0.001) lower in clonidine group (3.86±0.89) compared to the placebo group (4.86±0.93). Also, the interval between surgery and the first request of analgesic in clonidine group was4.13±3.27 hours on of longer duration (P=0.02) compared to 2.88±3.74 hours in placebo group. The mean heart rate and systolic blood pressure were lower in the clonidine group. Conclusion: A single oral 100 µg dose of clonidine administered 2 hours before abdominal hysterectomy significantly reduces the severity of postoperative pain. Keywords: POSTOPERATIVE PAIN, CLONIDINE, HYSTERECTOMY

Prevention and treatment of postoperative pain and associated complications like nausea and vomiting are critical issues in postoperative care. Unless managed adequately, acute postoperative pain can adversely affect the outcome of surgery and may lead to a condition of chronic pain. Opiates such as morphine are the standard drugs used to alleviate postsurgical pain. However, although opiates produce antinociception through their µ receptor agonist activity, they also activate the N-methyl-d-
aspartate (NMDA) receptor, resulting in hyperalgesia and the development of tolerance to opiates. In addition, opiates have several side effects which can result in significant complications including hyperalgesia. For these reasons we prefer to use adjuvant drugs that alleviate pain and reduce postoperative consumption of the opioids.

Postoperative pain management is accomplished by different methods including the systemic (oral, intramuscular, or intravenous), regional (epidural or intrathecal), or transdermal administration of analgesic agents, and less commonly cutaneous electrical stimulation (1, 2).

Although the mechanisms responsible for the genesis of acute pain are not completely understood, it is believed that sensitization of the neurons in the dorsal horns of the spinal cord contributes significantly to postoperative pain. Acute pain is known to trigger a cascade of messages from the spinal cord and the release of amino acids and neuropeptides from afferent fibers. The resulting stimulation of the NMDA receptor causes hyperstimulation of the spinal dorsal horn neurons and prolongation of postoperative pain (3, 4). In patients with history of ischemic diseases, postoperative pain increases the sympathetic tone and enhances the risk of myocardial ischemia and myocardial infarction (5). Consequently, morbidity and mortality are increased. Hysterectomy is one of the most prevalent surgeries in women and is the definite treatment for abnormal uterine bleeding (AUB) because it yields the most satisfactory results compared to alternative therapies. Abdominal hysterectomy with or without salpingo-oophorectomy is associated with moderate to severe pain (6).

Clonidine is an alpha-2-adrenergic receptor agonist (7) used chiefly as an anti-hypertensive agent. Through stimulation of the α-2 receptor and the negative feedback at the presynaptic neurons, significant reductions in the sympathetic activity occur at the level of the heart, the kidneys, and the peripheral blood vessels lowering cardiac output, vascular resistance, and blood pressure. Clonidine is also effective in the prevention of vascular headaches by blocking vasomotor reflexes. In addition, clonidine is used in the treatment of dysmenorrhea and the control of opioid withdrawal symptoms. It is also used as an adjuvant in the management of attention deficit hyperactivity disorder (ADHD). Its half-life is 12-16 hours and its side effects include drowsiness, sedation, headache, vertigo, nausea and vomiting.

The aim of the present study is to corroborate and expand the observations reported in previous studies (8, 9; 10, 11, 12) which evaluated the use of clonidine as a premedication in the management of postsurgical pain.

**MATERIAL AND METHODS**

After approval by our institutional Ethics Committee, the study was registered in the Iranian registry of clinical trials (http://irct.ir) as IRCT201108202963N3. Sixty women with ASA physical status I or II who were candidates for abdominal hysterectomy under general anesthesia were recruited in this randomized, double blinded placebo controlled clinical trial. Randomization was done by an epidemiologist using a computer generated table of random numbers. Patients were randomly allocated to either the placebo group or the clonidine group (30 patients each). Sample size estimation was based on α=0.05 and β error=0.8 and based on previ-
ous studies $S=2$. Assuming possible 10% loss to follow-up, 30 patients were needed for each group. The patients with chronic pain, opium addiction, or allergy to clonidine were excluded from the study. At the beginning of the study, patients in the two groups were similar in terms of age, body weight, systolic blood pressure and heart rate (tab. I). Two hours before surgery patients received a single oral dose of either placebo or 100 µg of clonidine. The drug administration occurred under supervision of an anesthesiologist who was not aware of patients’ group assignment. Induction and maintenance of anesthesia was with 2 mg/kg propofol and also 2 mg/kg atracurium and then infusion of propofol 150 microgram/kg/h and O2 – N2O 50% - 50% for all patients. 5 mg morphine was given to all patients after induction of anesthesia. After administration of 0.5 mg /kg atracurium IV, patients were intubated. All surgeries were done by same surgeon using the same surgery method. The intensity of postoperative pain was evaluated by researcher using patient’ self report and quantified using a 10 cm visual analog scale (VAS) where zero indicates no pain at all and a score of 10 indicates very severe, intolerable pain. VAS was recorded at 2nd, 6th, 12th and 24th hour after the operation. Morphine was the only analgesic drug used in the first 24 hours after surgery. If the VAS score was more than 4, a 5 mg morphine dose was administered intramuscularly to maximum dose of 5 mg/6 hours. The two groups were compared with respect to the total dose morphine administered during the first 24 hours after the surgery and the time interval between the end of surgery and the first request of analgesia. Systolic blood pressure and heart rate were recorded before induction of anesthesia, immediately, 5 minutes, and 30 minutes after laryngoscopy and intubation and also at the end of the surgery and in the post anesthesia care unit (PACU). Patients were also monitored for drug related side effects. All measurements and data records were done by a resident of anesthesiology who was not aware of patients’ group assignment. Statistical analyses were performed using SPSS 15.5 software and differences were evaluated using Students’ T-test, Mann Whitney and Fishers exact tests. P-values <0.05 indicate statistically significant differences.

### RESULTS

A total of 71 patients were evaluated for the study, 11 patients were excluded before randomization because they did not meet the inclusion criteria and 60 patients were recruited and randomly assigned to the placebo or the clonidine group (30 patients per group).

VAS scores at the 2nd and 6th hours after the operation were not significantly different between the groups (P>0.05), but at the 12th and the 24th hours after the operation the VAS scores were significantly lower in the clonidine group (tab. II).

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Patients’ ages, body weights, and hemodynamics at the beginning of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clonidine</td>
</tr>
<tr>
<td>Age</td>
<td>45.86 ± 4.06</td>
</tr>
<tr>
<td>Body Weight</td>
<td>64.56 ± 13.29</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>116 ± 11</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>91 ± 16</td>
</tr>
</tbody>
</table>

NS = not significant
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Compared to placebo group, the patients in the clonidine group had lower mean heart rate and mean systolic blood pressure before induction of anesthesia, immediately after laryngoscopy and 5 minutes after tracheal intubation (P<0.05). Also mean systolic blood pressures at the 30th minute after tracheal intubation was lower in the clonidine group (P<0.05) (tab. III). Although VAS scores at 12th and 24th hours after the operation were 10% and 20% lower in the patients who received clonidine, the consumption of opioid in the first 24 hours after the operation was not different (fig. 2). The time interval between the end of operation and 1st request for analgesia was 40% longer in the clonidine group (4.13±3.27 hours in clonidine group vs. 2.88±3.74 hours in placebo group, Mann-Whitney Test, P=0.02). No difference was detected between the two groups in terms of the common side effects related to clonidine, and none of the patients had pruritus or bleeding at the field of surgery.

### Table II

**Mean ±SD of VAS pain scores at different times after surgery.**

<table>
<thead>
<tr>
<th>Measurement Time</th>
<th>2nd hour after surgery</th>
<th>6th hour after surgery</th>
<th>12th hour after surgery</th>
<th>24th hour after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>6.76±1.33</td>
<td>6.20±0.71</td>
<td>5.83±0.91</td>
<td>3.86±0.89</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.43±1.5</td>
<td>6.6±1.1</td>
<td>6.46±1.16</td>
<td>4.86±0.93</td>
</tr>
<tr>
<td>P-Value</td>
<td>NS</td>
<td>NS</td>
<td><strong>0.023</strong></td>
<td><strong>0.001</strong></td>
</tr>
</tbody>
</table>

Repeated measures

### Table II

**Mean ±SD of Pulse Rate and Systolic Blood Pressure (SBP) and related P-Values in study groups**

<table>
<thead>
<tr>
<th>Time</th>
<th>Before anesthesia induction</th>
<th>Immediately after larygoscopy</th>
<th>5 minute after intubation</th>
<th>30 minutes after intubation</th>
<th>End of surgery</th>
<th>Recovery room</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>81±11.9</td>
<td>82.5±19.41</td>
<td>77.4±12.11</td>
<td>74.96±11.62</td>
<td>75.9±10.25</td>
<td>78.7±10.07</td>
</tr>
<tr>
<td>Placebo</td>
<td>92.4±14.32</td>
<td>95.3±14.85</td>
<td>82.5±12.21</td>
<td>75.8±11.92</td>
<td>77.6±10.68</td>
<td>79.3±9.89</td>
</tr>
<tr>
<td>P</td>
<td><strong>0.001</strong></td>
<td><strong>0.002</strong></td>
<td><strong>0.045</strong></td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SBP (mmhg)</td>
<td>115.89±15.09</td>
<td>114.9±22.13</td>
<td>110.5±16.15</td>
<td>115.1±16.34</td>
<td>120.4±12.83</td>
<td>121.3±11.35</td>
</tr>
<tr>
<td>Placebo</td>
<td>131.7±12.72</td>
<td>133.3±18.82</td>
<td>122.2±16.23</td>
<td>123.3±13.06</td>
<td>124.6±10.15</td>
<td>124.6±10.45</td>
</tr>
<tr>
<td>P</td>
<td><strong>0.001</strong></td>
<td><strong>0.001</strong></td>
<td><strong>0.003</strong></td>
<td>0.015</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Repeated measures, NS = not significant
Fig. 1. Flow of the study

Fig. 2. The number of patients requiring analgesia at different time points after surgery

**DISCUSSION**

Perioperative pain is thought to involve multiple mechanisms, including sensitization of peripheral somatic and visceral nociceptive nerve terminals as well as cen-
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central neurons, nociceptive transduction, and loss of local and descending inhibition of neurons in the brainstem and spinal cord (13).

There is ample evidence that perioperative systemic administration of α2-agonists decreases postoperative opioid consumption, pain intensity, and nausea (14). Alpha2-agonists inhibit the release of P substance in dorsal root neurons (15). Also stimulation of α2-adrenoceptors in neural terminals may decrease pain by preventing norepinephrine release (16).

The results of the present study demonstrate that a single oral dose of clonidine (100 µg) administered two hours before surgery can lower postoperative pain scores at 12th and 24th hours after the operation in the women who underwent abdominal hysterectomy. Time interval between the end of surgery and need for first dose of analgesic was significantly longer without notable side effects. Heart rate and systolic blood pressure after laryngoscopy and intubation were lower in the patients who received clonidine compared to those who received placebo. Surprisingly the patients in the clonidine group had lower incidence of nausea than those in the placebo group.

Hidalgo MP et al in 2005 showed that three doses of 100 µg clonidine (at the night before surgery and first hour and 24 hours after surgery) can decrease post hysterectomy pain (8). In this study the patients received a total of three 100-g doses of clonidine compared to a single dose in our study. Hidalgo and co-workers did not discuss possible complications that might be associated the higher dose of clonidine.

In a study in 2006 administration of 2-4 mg/kg oral clonidine as premedication in children can decrease postoperative pain and anxiety (9). These results were confirmed by Toru Goyagi et al. In this study after adding oral clonidine to epidural morphine, postoperative pain was decreased without any complications (10). In a study in 2007 Persec J concluded that administration of clonidine before surgery will decrease postoperative pain more than administration of clonidine after surgery or placebo (17). Our study supports this conclusion. However, in our study there was no significant difference between groups with respect to the total consumption of morphine. This difference may be due to lack of cooperation by the nursing staff on the ward who may inject the analgesic without considering VAS score.

Clonidine can decrease stress response and improve the patient’s hemodynamic status by decreasing the level of circulating catecholamine. Our study shows that clonidine decreases systolic blood pressure (SBP) and Heart rate (HR) during surgery and recovery.

Shivering Singh et al in 2011 concluded that in patients who were candidates for laparoscopic cholecystectomy, 150 µg oral clonidine as premedication administered 90 minutes before the induction of anesthesia can improve the patient’s hemodynamics and prolong the time between surgery and the first request for analgesia (11). Nausea is one of the most prevalent complications after surgery. In our study nausea and vomiting occurred at a significantly lower rate in the clonidine group, but the two groups were similar with respect to other adverse effects. In this respect our results were similar to the findings reported by Farmery et al (12).

In our study the administration of morphine was based on the patient’s request,
and there was no significant difference in morphine consumption between the two groups at any point during the first 24 hours after surgery.

The long lasting effect of clonidine despite its 12 hours half-life may be due to its diverse actions modifying not only the adrenergic component to pain perception but also the neurohumoral response to tissue injury (18). A study in China on rats showed that the effects of clonidine were blocked by the α2-adrenoceptor antagonist yohimbine and partially reversed by the μ-opioid receptor antagonist naloxone (19).

CONCLUSION
A single oral dose of 100 μg of clonidine as a premedication in patients undergoing abdominal hysterectomy improves perioperative hemodynamic stability and reduces postoperative pain intensity without any considerable side effects. Clonidine is likely to play an increasing role in clinical practice in perioperative pain management.

CONFLICT OF INTEREST
This study was financially supported by the Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The study is part of Fayezah Niknam dissertation required for graduation as General Practitioner. Other authors declare no conflict of interest.

REFERENCES

NEWS

IS INTRAOPERATIVE HISTOLOGY IMPORTANT IN PREDICTING INFECTION IN PATIENTS UNDERGOING REVISION ELBOW ARTHROPLASTY?

A recent study by Ahmadi and co. brings new informations regarding the role of intraoperative histology in the diagnosis of infection in patients undergoing revision elbow arthroplasty. In the study were included 296 consecutive revision elbow procedures, from which 227 intraoperative histology and operative samples for culture were obtained. The number of procedures with histology read as consistent (acute inflammation) was 33 (14.5%). Intraoperative cultures were positive in 39 procedures (17.2%). Intraoperative histology was considered true positive (both histology and cultures positive) in twenty arthroplasties (8.8%), true negative (both histology and cultures were negative) in 175 arthroplasties (77.1%), false positive (the histology was positive but the culture was negative) in thirteen arthroplasties (5.7%), and false negative (the histology was negative but the culture was positive) in nineteen arthroplasties (8.4%). With regard to intraoperative histology, the sensitivity was 51.3%, the specificity was 93.1%, and the accuracy was 85.9%. The positive predictive value was 60.6% and the negative predictive value was 90.2%. The study concluded that intraoperative histology had a high specificity and negative predictive value, but a low sensitivity and positive predictive value for predicting infection in the setting of revision elbow arthroplasty and it should be used in conjunction with other studies to definitively establish the diagnosis of infection in the setting of revision elbow arthroplasty. (Ahmadi S, Lawrence TM, Morrey BF, Sanchez-Sotelo J. The value of intraoperative histology in predicting infection in patients undergoing revision elbow arthroplasty. J Bone Joint Surg Am. 2013; 95:1976-1979).

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