Effect of Oral Clonidine on Hemodynamic Response During Surgery

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ABSTRACT

Clonidine is an alpha 2-adrenoceptor agonist. It has recently, however, found a new and possibly significant role in anaesthesia and the treatment of pain. Diazepam has been used as a drug for premedication for years but oral clonidine has not been used as premedication even though it is cheaper and has longer postoperative analgesic effect. This prospective, double blind randomized study was conducted in department of anaesthesiology, institute of medicine, TUTH. A total 60 consecutive patients scheduled for abdominal gynaecological surgeries were randomized to clonidine or diazepam premedication group and received these drug one hour before surgery planned under spinal anaesthesia. Intraoperative haemodynamic changes in terms of blood pressure, heart rate, oxygen saturation, were recorded.

Hypotension was occurred in 9(15%) in clonidine group and 10(16.7%) in diazepam group, (p value> 0.05). During surgery, bradycardia was noted in 6(10%) vs. 3(5%) patient in diazepam and clonidine group respectively (p value >0.05). Nausea, shivering, restlessness were other side effects seen during surgery in both clonidine and diazepam group (33.33% vs. 36.66%). Although few more cases of nausea (1 vs. 5) with clonidine and few more cases of restless (3 vs. 7) were noted with diazepam , the overall difference was not statistically significant between two groups (p value >0.05). Oral clonidine premedication had similar hemodynamic response to diazepam. It is cheaper and has longer postoperative analgesic effect as well as similar sedative effect.

Key words: Clonidine, intraoperative haemodynamic change, blood pressure

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INTRODUCTION

Clonidine is an alpha 2-adrenoceptor agonist. It was synthesized in 1960s and has been used for over 20 years to treat hypertension. It has recently, however, found a new and possibly significant role in anaesthesia and the treatment of pain. Clonidine is a direct-acting alpha-adrenergic agonist with a strong preference for the alpha-2 receptor. It acts centrally to produce inhibition of sympathetic vasomotor centers by inhibiting release of norepinephrine in the medulla. Sympathetic tone is reduced, thus decreasing systemic blood pressure. When used for the acute or chronic management of hypertension, the reduction in sympathetic tone decreases systemic vascular resistance, heart rate, and blood pressure.

Clonidine is rapidly and completely absorbed by the oral route, reaching peak plasma level in 60 to 90 minutes. One of the major side effects of clonidine as an antihypertensive agent is its significant sedative property. This is thought to be mediated by stimulation of alpha-2 receptors in the locus ceruleus, the area of the brain that modulates wakefulness. This characteristic limits clonidine's use as an antihypertensive agent but is an attractive quality to the anesthesiologist due to its perioperative sedation. Its sedative effects, combined with anxiolysis and a favorable haemodynamic profile at low doses, makes clonidine a good preoperative medication. In fact, the anxiolytic effects of clonidine and benzodiazepines have been demonstrated to be comparable.

Diazepam has been used as a drug for premedication for years but clonidine has not been used as premedication even though it is cheaper and has longer postoperative analgesic period. This double blind, randomized study is designed to evaluate postoperative analgesic effect of oral clonidine premedication vs. oral diazepam premedication in spinal anaesthesia with hyperbaric 0.5% bupivacaine.

This study was aimed to compare the intraoperative haemodynamic changes between oral clonidine and diazepam premedication in spinal anaesthesia with bupivacaine in abdominal gynaecological surgeries.

MATERIALS AND METHODS

After obtaining approval from institutional ethics committee, this prospective and randomized study was carried out in 60 ASA grade I and II patients scheduled for elective abdominal gynaecological surgeries in the operation theatre of Tribhuvan University Teaching Hospital (TUTH), Institute of Medicine, Maharajgunj, Kathmandu, Nepal since first Baisakh 2065 to first Falgun 2065.

INCLUSION CRITERIA

• Patients of ASA I & II grading.
• All patients aged between 18-60 years for elective abdominal gynaecological surgeries.
• Patients with controlled hypertension (BP<140/90mmHg) on antihypertensive drug other than clonidine.

EXCLUSION CRITERIA

• Patients of ASA physical status more than II and contraindicated for neuraxial block.
• Concomitant intake of clonidine and /or diazepam.
• Patients with acute or chronic liver, renal disease.

All patients were assessed one day before surgery as routine pre-anaesthetic check-up. The procedure, alternative methods and possible complications were explained to the patient in her own language. Informed and written consent was taken. All patients were premedicated with single dose diazepam 0.2mg /kg at bed time and advised for nil per orally from midnight the day before surgery. Patient was transferred to operation theatre preparation room on the day of operation. Base line blood pressure, heart rate and oxygen saturation were recorded. IV cannulation was done by 18G cannula. Patients were divided
randomly into two groups. Group 1 (clonidine) and Group 2 (diazepam), each consisting of 32 patients. Randomization was accomplished by using sealed envelope method. Group 1 (clonidine) received 0.004mg/kg of oral clonidine and Group 2 (diazepam) received 0.2mg/kg diazepam as premedication one hour before subarachnoid injection with sip of water.

Systemic blood pressure, heart rate, ECG and SpO2 were monitored in operation theatre. Spinal anaesthesia was given and time of spinal anaesthesia delivered was recorded.

Electrocardiogram, blood pressure and heart rate were monitored by the automated oscillographic method and were recorded every 5 minutes till the end of surgery. Hypotension was considered as a 20% decrease in baseline systolic BP or BP<80mmHg and was treated with mephentermine 6mg at incremental dose. Bradycardia was considered as heart rate <50/min, which was treated with atropine 0.3mg with incremental doses. Side effects like nausea, vomiting, shivering were managed with ondansetron 8mg intravenously. The time interval between delivery of bupivacaine and patient received first dose of pethidine as analgesic was recorded.

RESULTS

A total number of sixty four patients were included in this study and were randomized to clonidine and diazepam premedication groups. Four patients were excluded, (one case converted to general anaesthesia due to inadequate level of block, two cases received opioid intraoperatively due to complaining of pain and fourth case excluded as the plan of surgery was changed). Therefore data of sixty patients was analyzed in this study.

| Table–1  Characteristics of the patient |
|-------------------------------|-------------------|-----------------|
|                               | Clonidine         | Diazepam        | p value |
| Mean + SD Age(Yrs)           | 39.93 + 11.47     | 37.70 + 12.72   | >0.05(NS) |
| Mean + SD Weight (Kg)        | 56.10 + 5.79      | 59.00 + 6.63    | >0.05(NS) |
| Mean + SD Baseline SBP(mmHg) | 113.56 + 10.08    | 110.93 + 12.28  | >0.05(NS) |
| Mean + SD Baseline DBP(mmHg) | 75.03 + 8.16      | 73.13 + 10.42   | >0.05(NS) |
| Mean + SD baseline HR (Per minute) | 81.16 + 8.51    | 83.53 + 10.04   | >0.05(NS) |

| Table-2  Distribution of subject according to ASA physical status. |
|---------------------------------|------------------|----------------|
|                                | Clonidine        | Diazepam       |
|                                | Number           | Percentage     | Number | Percentage |
| ASA 1                           | 24               | 40.0%          | 27     | 45.0%      |
| ASA 2                           | 6                | 10.0%          | 3      | 5.0%       |
| Total                           | 30               | 50.0%          | 30     | 50.0%      |

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Percentage</th>
<th>Number</th>
<th>Percentage</th>
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<tr>
<td>Clonidine</td>
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<td>45.0%</td>
</tr>
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<td>diazepam</td>
<td>27</td>
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<td>5.0%</td>
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<tr>
<td>Total</td>
<td>51</td>
<td>85.0%</td>
<td>9</td>
<td>15.0%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Clonidine</th>
<th>Diazepam</th>
<th>p value</th>
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</thead>
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<td>ASA Physical Status</td>
<td>ASA 1</td>
<td>ASA 2</td>
<td>Total</td>
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<td>30</td>
<td>30</td>
</tr>
<tr>
<td>diazepam</td>
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<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

There were higher number of ASA 2 status patients in clonidine premedication Group 6 than diazepam 3 but the difference was not statistically significant. p value 0.4716(>0.05).
Table 3  Haemodynamic parameters (Hypotension)

<table>
<thead>
<tr>
<th>Group</th>
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<th>Hypotension</th>
<th></th>
<th></th>
<th>p value</th>
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<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Number</td>
<td>9</td>
<td>21</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>15.0%</td>
<td>35.0%</td>
<td>50.0%</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Number</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>0.781</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>16.7%</td>
<td>33.3%</td>
<td>50.0%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Number</td>
<td>19</td>
<td>41</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>31.7%</td>
<td>68.3%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Hypotension was occurred in 9 (15%) in clonidine group and 10 (16.7%) in diazepam group, There is no significant difference between two groups. Chi square value is 0.077 and p value 0.781 (>0.05).

Fig. 1 Distribution of hypotension during surgery

Table 4  Haemodynamic parameters (Bradycardia).

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>Bradycardia (HR&lt;50)</th>
<th></th>
<th></th>
<th>p value</th>
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<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Number</td>
<td>3</td>
<td>27</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>5.0%</td>
<td>45.0%</td>
<td>50.0%</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Number</td>
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<td>24</td>
<td>30</td>
<td>0.4708</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>10.0%</td>
<td>40.0%</td>
<td>50.0%</td>
<td></td>
</tr>
<tr>
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<td>51</td>
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<tr>
<td></td>
<td>Percentage</td>
<td>15.0%</td>
<td>85.0%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

During surgery, bradycardia was noted in 6 (10%) vs. 3(5%) patient in diazepam and clonidine group respectively. There is no significant difference between two groups. Chi square value is 0.52 and P value 0.4708 (>0.05).

Hypertension and tachycardia were not noted in all 60 cases during surgery.
Table - 5 Side effects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Nausea</th>
<th>Shivering</th>
<th>*No Side effects</th>
<th>Restless</th>
<th>&gt;1 side effect</th>
<th>Total</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Clonidine</td>
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<td>2</td>
<td>20</td>
<td>3</td>
<td>0</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>8.3%</td>
<td>3.3%</td>
<td>33.3%</td>
<td>5.0%</td>
<td>0.0%</td>
<td>50.0%</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Number</td>
<td>1</td>
<td>3</td>
<td>18</td>
<td>7</td>
<td>1</td>
<td>30</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>1.7%</td>
<td>5.0%</td>
<td>30.0%</td>
<td>11.7%</td>
<td>1.7%</td>
<td>50.0%</td>
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<tr>
<td>Total</td>
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<td>6</td>
<td>5</td>
<td>38</td>
<td>10</td>
<td>1</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Percentage</td>
<td>10.0%</td>
<td>8.3%</td>
<td>63.3%</td>
<td>16.7%</td>
<td>1.7%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

*No side effects other than haemodynamic.

Nausea, shivering, restlessness were other side effects seen during surgery in both clonidine and diazepam group (33.33% vs. 36.66%). Although few more cases of nausea (1 vs. 5) with clonidine and few more cases of restless (3 vs. 7) were noted with diazepam, there is no significant difference between two groups. Chi square value is 5.57 and p value 0.2326 (>0.05).

Table-6 Time of first dose analgesia.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean(+SD) time of first dose of analgesia(min.)</th>
<th>t-test</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>261.90 + 33.03</td>
<td>15.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diazepam</td>
<td>135.60 + 31.86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean +/- SD time of first dose analgesia was (261 + 33.03) min in clonidine premedication group which was statistically significantly prolonged than diazepam premedication group (135.60 + 31.86) minutes. p value <0.001.

DISCUSSION

Intrathecal clonidine has been shown to be effective in opioid-tolerant patients and has been used extensively in the treatment of chronic and intractable pain, neuropathic pain, and cancer pain. Oral administration is both simpler and cheaper than intrathecal administration and is suitable for use as a premedication. Its sedative effects, combined with anxiolysis and a favorable hemodynamic profile at low doses, makes clonidine a good preoperative medication. In fact, the anxiolytic effects of clonidine and benzodiazepines have been demonstrated to be comparable. Clonidine has further advantage of producing sedation and prolongs postoperative analgesic period, decreases total post operative opioids consumption, but the major side effect, i.e. antihypertensive effect, limits its use as premedication agent.

Study showed pressure responses to noradrenaline and phenylephrine are enhanced by clonidine premedication. Clonidine easily crosses blood–brain barrier and therefore may interact with alpha–adrenergic receptors at spinal and supraspinal sites within the central nervous system. In addition previous studies suggest that clonidine may also affect peripheral sensory nerves as a sole agent or in combination with local anaesthetics.

Clonidine premedication in a dose of 5 mcg/kg may be particularly well suited for elderly patients. To pursue this approach, sedation, intraocular pressure (IOP), and the hemodynamic profile of two doses of oral clonidine premedication were compared in 60 elderly patients, aged 65–82 year, who underwent elective ophthalmic surgery under local anesthesia. Results suggest that a dose of 150 µg of clonidine, given orally 90–120 min preoperatively to elderly patients is as effective as a dose of 300 mcg in decreasing IOP perioperatively, without causing excessive hemodynamic depression and sedation.

Clonidine easily crosses blood–brain barrier and therefore may interact with alpha –adrenergic receptors at spinal and supraspinal sites within the central nervous system. In addition previous studies suggest that clonidine may also affect peripheral sensory nerves as a sole agent.
or in combination with local anaesthetics. Pre-
medication with 4-5 mcg/ kg oral clonidine was
compared with 0.20-0.25mg/kg oral diazepam.
Duration of sensory blockade by bupivacaine and
fentanyl spinal anaesthesia as significantly pro-
longed in clonidine group.

The analgesic effect of clonidine is mediated by
the same central alpha 2 adrenoreceptors that
mediated its hypotensive effects.

In our study, premedication with oral clonidine 4
mcg/kg was compared with oral diazepam 0.20
mg/kg for patients undergoing surgery under spi-
nal anaesthesia with hyperbaric bupivacaine. In-
traoperative haemodynamic changes were simi-
lar in both groups, but clonidine group had longer
postoperative analgesic period. This result is
consistent with the study done in 1992, by Ota K,
Namiki K, Ujike Y & Takahashi I. They concluded
that sensory analgesia of spinal tetracaine was
prolonged by oral clonidine premedication be-
cause of its capacity to prolong sensory blockade
& its potent sedating properties.

In our study, duration of sensory block following
spinal anaesthesia with 0.5% hyperbaric bupi-
vacaine was significantly prolonged when the
patients were premedicated with oral clonidine.
The result is consistent with the findings of study
done by Singh H, George YG and Paul FW in
which oral clonidine prolonged the duration of tet-
racaine’s sensory & motor block.

Some other studies 16-20 showed patients treat-
ed with clonidine before and 24 hours after sur-
gery had a larger reduction of anxiety and pain
levels after surgery, reduced the heart rate peri-
operatively and enhanced sleepiness immediate-
ly after surgery.

Bradycardia and hypotension are adverse effects
of alpha 2-adrenergic agonists. However, these
effects prevent tachycardia and hypertension.
Risk of cardiac ischemia is reduced by blunting
the sympathetic activity on the cardiovascular
system after surgical stress and emergence from
anesthesia. Thus, clonidine may be an alterna-
tive therapy in patients with cardiac risk factors
who are undergoing noncardiac surgery. In this
study, neither clinically significant hypotension
nor use of larger doses of vasopressor drugs
was observed. Clonidine decreases opioid use
and lowers hormonal response while maintain-
ing stable hemodynamics in patients undergoing
CABG.

These results suggest oral clonidine could be a
better therapeutic alternative to other preopera-
tive sedatives. Further studies are necessary to
compare its effects with other anxiolytics on post-
operative outcomes in other cardiac and noncar-
diac surgeries.

**CONCLUSIONS**

Oral clonidine premedication had similar hemo-
dynamic response to diazepam. It is cheaper
and has longer postoperative analgesic effect
as well as similar sedative effect. Further stud-
ies are needed to support its use in coronary
artery bypass and other orthopedic, paediatric
and general surgeries.
REFERENCES