COMPARATIVE STUDY OF EFFICACY AND SAFETY OF INTRATHECAL DEXMEDETOMIDINE VERSUS INTRATHECAL CLONIDINE AS AN ADJUVANT WITH 0.5% HYPERBARIC BUPIVACAINE TOTAL ABDOMINAL HYSTERECTOMY PROCEDURES
Chanda Salame1, Anjali Bhure2, Gunjan Badawaik3, Ketaki Marodkar4, Sohal Parate5

HOW TO CITE THIS ARTICLE:
Chanda Salame, Anjali Bhure, Gunjan Badawaik, Ketaki Marodkar, Sohal Parate. “Comparative Study of Efficacy and Safety of Intrathecal Dexmedetomidine versus Intrathecal Clonidine as an Adjuvant with 0.5% Hyperbaric Bupivacaine total Abdominal Hysterectomy Procedures”. Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 16, April 21; Page: 4167-4175, DOI: 10.14260/jemds/2014/2414

ABSTRACT: INTRODUCTION: Newer α-2 agonistic agents have opened a new chapter in the history of postoperative analgesia. MATERIAL AND METHODS: Ninety adult patients of ASA grade I-II were randomly divided into three groups of thirty each. Groups A, B, C received hyperbaric bupivacaine 0.5% 3.4 ml intrathecally with normal saline 0.5 ml, with dexmedetomidine 15 µg, and with clonidine 75 µg respectively. Hemodynamic data, degree of motor block (modified bromage scale), time to reach sensory block to L1 level, time for two segment regression of sensory block and time to reach modified bromage 0, total duration of analgesia was assessed. RESULT AND CONCLUSION: Onset time of sensory and motor block was shorter in group B and group C compared to group A. Two segment regression time of sensory block was significantly higher in group B (122.60+17.44min) and group C (87.73+10.37min) as compared to group A(63.73+8.70min).Regression time to reach Modified bromage 0 was significantly high in group B (235.10+26.64min) and group C (226.70+45.85min)as compared to group A (174.53+22.03min). Total duration of analgesia was significantly prolonged in group B (346.26+41.63min) and group C (302.85+38.45min) as compared to Group A (162.80+39.55min). Heart rate and mean arterial pressure remained at lower level in group B and group C as compared to group A but that was not statistical significant. It can be concluded that though both clonidine and dexmedetomidine prolonged duration of sensory and motor block of bupivacaine, dexmedetomidine is better in terms of longer duration of action.
KEYWORDS: Dexmedetomidine, Clonidine, Hyperbaric Bupivacaine 0.5% (H).

INTRODUCTION: Adjuvant is a pharmacological agent added to a drug to increase or aid its effect. The use of adjuvant drugs for regional anesthesia is intended to prolong local anesthetic analgesia & avoid there toxic doses. Hence number of adjuvants, such as Clonidine, Dexmedetomidine, Midazolam, Opioids, Neostigmine and Magnesium Sulphate, has been studied to prolong the effect of spinal anesthesia.1-5

Dexmedetomidine & Clonidine both are alpha-2 agonist drugs. Clonidine is an alpha 2 adrenergic receptor agonist with a 200:1 ratio of alpha 2 : alpha 1 receptor while Dexmedetomidine is a selective, specific, potent α 2 – adrenergic agonist with a 1, 620:1 ratio of alpha2 : alpha1 receptor. Dexmedetomidine showed protective or growth promoting properties in tissues, including nerve cells from cortex and has a neuroprotective effect similar to methylprednisolone in spinal cord injury when used intrathecally.6-7

Clonidine has antihypertensive effects as well as the ability to potentiate the effect of local anesthetics. It can provide pain relief by an opioid-independent mechanism.8 Clonidine and
Dexmedetomidine were added in present study to find out whether the addition of Clonidine or Dexmedetomidine to bupivacaine changes its efficacy and to find out any change in the quality of sensory and motor block. The aim of our study was to evaluate the efficacy and safety of intrathecal administration of Dexmedetomidine vs. intrathecal Clonidine as an adjuvant with 0.5% Bupivacaine (heavy) in abdominal hysterectomies.

Our objectives were to compare onset & duration of sensory analgesia, onset & duration of motor block achieved with the use of individual drug, hemodynamic changes, depth of sedation, side effects related to drugs under study, post-operative assessment of pain by VAS (Visual Analogue Scale), number of rescue analgesic doses (Diclofenac injection) required in 1st 24 hours.

**MATERIALS & METHOD:** After approval of local institutional ethics committee, randomized double blind controlled study was carried out in 90 ASA I & II patients age between 30-60 years, weight between 50-80kg, height between 150-170cm, patient willing to participate in the study was included in the study, scheduled for elective abdominal hysterectomy procedures was divided into three groups of thirty each. Patients excluded from the study were patients with contraindications for spinal anesthesia, sensitivity to study drugs, recent onset of MI (<3 months), hypovolemic patient, patients with renal or hepatic impairment and patients on antihypertensive medications.

**Group A:** Intrathecal injection of 3.4 ml of 0.5 % Bupivacaine (heavy) + 0.5 ml 0.9% normal saline.

**Group B:** Intrathecal injection of 3.4 ml of 0.5 % Bupivacaine (heavy) + 15 µg Dexmedetomidine (0.5 ml).

**Group C:** Intrathecal injection of 3.4 ml of 0.5 % Bupivacaine (heavy) + 75 µg Clonidine (0.5ml).

The total volume injected was 3.9 ml in all the three groups.

Patients were enrolled after taking informed consent. Patients were explained about Visual analogue scale preoperatively and in the operating room. Baseline vitals like Heart rate, respiratory rate, ECG, oxygen saturation, non-invasive blood pressure were recorded. All patients were preloaded with 10ml/kg ringer lactate.

Patients were placed in sitting position on the operation table. With strict aseptic precautions, midline approach subarachnoid block was achieved in L3-L4 space with 23G disposable Quincke spinal needle. Drug was injected after free flow and clear aspiration of CSF. Patients were immediately placed in the supine position with no tilt given to the table. The onset of sensory analgesia was tested by pinprick. Sensory anesthesia was defined as loss of sensation to pin-prick with 23G hypodermic needle. Time taken for achievement of sensory anesthesia at L1 after intrathecal injection was recorded. Sensory anesthesia was recorded every 15 seconds initially for 5 minutes and then every minute for 15 minutes.

Time taken to achieve highest sensory level was noted. Time taken for onset of maximum motor blockade i.e. the time taken from the time of spinal to the time to achieve maximum grade of motor blockade was noted. Maximum grade of motor blockade achieved using modified Bromage score was also noted. Time to return of Modified Bromage score to zero was recorded.

Total duration of analgesia was defined as the time taken from the time of spinal anesthesia to the first request of rescue analgesia. Duration of motor blockade was defined as the time taken from the time of spinal anesthesia to the return of modified bromage score of grade 0. After intrathecal drug injection, hemodynamic data was recorded for every 2 minutes for first 10 minutes then every 5 minutes for next 30 minutes and then for every 15 minutes till the procedure was completed.
Hypotension (defined as a decrease in systolic blood pressure > 30% of the baseline value or systolic blood pressure < 90 mm Hg) was treated with intravenous boluses of 3 mg mephenteramine. Bradycardia (defined as a decrease in heart rate of < 20% of baseline value or 50 beat/min) was treated with boluses of 0.6 mg atropine. Respiratory depression (RR< 8 or SpO₂ < 95%) was noted. Occurrence of nausea, vomiting, pruritus and respiratory depression were recorded throughout the study duration.

Visual Analogue Scale (VAS) was used for assessment of post-operative pain relief at 30, 60, 90, 120, 180, 240, 300, 360, 420, 540, 720, 1080, 1440 minutes. Patient was explained about Visual analogue scale preoperatively. When VAS score was 3 or > 3, Inj. Diclofenac 75 mg. IM was given as rescue analgesia.

Level of sedation was assessed by Ramsay Sedation Score.

**STATISTICAL ANALYSIS:** Statistical analysis was carried out by one-way analysis of variance (ANOVA) and, if appropriate, followed by Tukey multiple comparison test. Nominal categorical data among study groups were compared using the chi-square test. P < 0.05 was considered to be statistically significant.

**OBSERVATION AND RESULTS:** In our study we found onset of sensory anesthesia at L1 was significantly early with Dexmedetomidine/Bupivacaine (2.00±0.03 min) as compared to Clonidine/Bupivacaine (2.23±0.43min) and Control group (2.90±0.54 min). Difference was statistically significant when study groups were compared to Control group (p< 0.05) (Table no.1).

However no statistically significant difference in onset of time was seen between Dexmedetomidine and Clonidine groups (p> 0.05). We found that that the spread of sensory block with intrathecal Dexmedetomidine was 100% at T4 level. We also found that the spread of sensory block with intrathecal Clonidine was 100% at T4 level. Peak sensory level achieved by Control group was T4 in 53.33% and T6 in 46.66% patients. In our study the two segment regression time in Dexmedetomidine group was (122.60±17.44 min), Clonidine group (87.73±10.73 min) and Control group (63.73±8.70 min).

Thus time for 2 segment regression is faster in Control group as compared to Dexmedetomidine and Clonidine. The difference was statistically significant (p< 0.05).

Total duration of analgesia, for Dexmedetomidine group was 346.26 ± 41.63 Clonidine group was 302.85 ± 38.45 and that of Control group was 162.80 ± 39.55. Hence, total duration of analgesia was significantly higher in Dexmedetomidine and Clonidine group as compared to Control group (p<0.05) (As shown in table no.1) which was statistically significant. Difference was also statistically significant between Dexmedetomidine and Clonidine groups (p<0.05).

The mean time for motor block Bromage grade 3 in Dexmedetomidine group was 4.73 ± 0.86; in Clonidine group was 5.33 ± 1.09 whereas for Control group it was 9.23 ± 1.38. The difference was statistically significant when study groups were compared to Control group (p<0.05) (Table no.1).

But the difference was not statistically significant between Dexmedetomidine and Clonidine groups (p> 0.05).

The mean time for return of Bromage score to zero for the Dexmedetomidine, Clonidine and Control groups were 235.10±26.64, 226.70±45.85, 119.17±6.97 respectively. Significantly high time was required in return of bromage score to zero in Dexmedetomidine group as compared to Control.
group (p<0.05) (Table no.1) which was statistically significant. The difference was not statistically significant between Dexmedetomidine and Clonidine groups (p> 0.05).

No difference in the pulse rate was observed between Dexmedetomidine and Clonidine and between Dexmedetomidine, Clonidine and Control group at majority of time points. (P>0.05).

We found that the mean SBP remained at lower levels from 20 min after drug administration till 45 min in dexmedetomidine and clonidine groups as compared to control group. But the overall systolic blood pressure changes were statistically insignificant in all three groups. Also change in mean systolic blood pressure at various interval from baseline between all the three groups was statistically insignificant at majority of times between all the three groups (P>0.05) (Graph no1).

Overall diastolic blood pressure changes were statistically insignificant in all three groups. Also change in mean diastolic blood pressure at various interval from baseline between all the three groups is statistically insignificant at majority of times between all the three groups (p>0.05) (Graph no.2).

No difference in mean respiratory rate and saturation was observed between three groups which was statistically insignificant (P>0.05).

In our study the mean VAS in Dexmedetomidine group ranges from a maximum of 3.46 ± 0.62 at 1080th min to a minimum of 0.03 ± 0.18 at 30th minute. The mean VAS in Clonidine group ranges from a maximum of 3.1 ± 0.40 at 720th min to a minimum of 0.00 ± 0.0 at 30th minute. The mean VAS in Control group ranges from a maximum of 3.13 ± 1.27 at 240th min to a minimum of 0.9 ± 0.30 at 30th minute.

Significant difference in the VAS scores was observed between Dexmedetomidine and Clonidine group and between Dexmedetomidine group and Control group at majority of time points which was statistically significant (P<0.05).

Mean time for first rescue analgesia, for Dexmedetomidine group was 393.46 ± 24.46 min compared to Clonidine it was 314.46 ± 38.92 min whereas for the Control group it was175 ± 39.26 min. Mean time for first rescue analgesia was significantly higher in Dexmedetomidine and Clonidine group as compared to Control group (p<0.05)and it was statistically significant. Difference was also statistically significant between Dexmedetomidine and Clonidine groups (p<0.05).

Rescue analgesic Diclofenac 75mg was administered I.M at VAS scores of 3 or more. In Control group 2-3 doses of rescue analgesic was required whereas Clonidine group (86.6%) required 1-2 doses of Diclofenac. In Dexmedetomidine group majority of the patient (90.0%) of patient required 1-2 doses in the 1st 24 hrs. The difference was statistically significant between study groups and Control group (p< 0.05).

In our study, we found Ramsay sedation score of Dexmedetomidine group was 2 in 56.67%, 3 in 23.33% and 4 in 20% of patients. In Clonidine group sedation score was 2 in 46.67%, 3 in 33.33% and 4 in 20%. The difference was not statistically significant between the study groups. In Control group sedation score was 1 in 40.0%, 2 in 60% of patients which was statistically significant when compared to study groups.

In our study we defined hypotension as a decrease of systolic B.P of more than 30% of baseline which was treated with I.V fluids and injection Mephenteramine hydrochloride 3mg I.V as required. Hypotension was observed in 10 (33.33%) patients in Dexmedetomidine group and was treated. In Clonidine group 11 (36.67%) patients had hypotension where all the patients were treated with one dose of inj. Mephenternine 3mg IV each after treating with IV fluids. In control
group hypotension was observed in 5 (16.67%) patients and was treated initially with IV fluids and then with a single dose of inj. Mephentermine 3mg IV each.

1(3.33%) patient in Dexmedetomidine had bradycardia. In Clonidine group 2 (6.67%) patients had bradycardia who were treated with a single dose of injection Atropine sulphate 0.6mg. None of the patients in control group had bradycardia requiring treatment with a single dose of injection Atropine Sulphate 0.6mg I.V. each. Intraoperative hypotension and bradycardia were not statistically significant with both the study groups when compared to control group.

**DISCUSSION:** Early onset of sensory and motor block with Dexmedetomidine/Bupivacaine than Bupivacaine alone correlated with study of Sunil BV\(^9\) et al in 2013 also with Clonidine/Bupivacaine than Bupivacaine alone correlated with study of H.Saxena\(^10\) et al in 2010.

Two segment regression time and total duration of analgesia is higher in Dexmedetomidine group than Clonidine and Control groups. This result is in accordance with the study of Rampal singh\(^11\) et al in 2012. They concluded that though both Clonidine and Dexmedetomidine prolonged duration of sensory block of Bupivacaine, Dexmedetomidine is better in terms of longer duration of action. Hala E A Eid\(^12\) et al in 2012 studied dose response study using intrathecal Dexmedetomidine 10mcg & 15mcg in arthroscopic anterior cruciate ligament reconstruction surgery found that 10mcg and 15mcg of intrathecal Dexmedetomidine produces dose dependent analgesia and concluded that 15mcg dose may be beneficial in patients undergoing prolonged lengthy complex surgical procedures.

Mean regression time to Bromage 0 motor block was significantly higher in Dexmedetomidine group than Clonidine and Control group. This result correlated with study of G. E. Kanazi et al in 2006.

Adjuvants have an additive or synergistic effect secondary to the different mechanisms of action of the local anesthetic and the \(\alpha_2\)-adrenoceptor agonist. The local anesthetic acts by blocking sodium channels whereas the \(\alpha_2\)-adrenoceptor agonist acts by binding to pre-synaptic C-fibers and post-synaptic dorsal horn neurons. Intrathecal \(\alpha_2\)-adrenoceptor agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons. This antinociceptive effect may explain the prolongation of the sensory block when added to spinal anesthetics.

We found that the change in mean heart rate at various intervals from baseline between all the three groups was statistically insignificant. This finding is in accordance with the study of G.E. Kanazi et al. Hypotension was observed in 10 patients of Dexmedetomidine group, 11 patients in Clonidine group and 6 patients in control group. All the patients were treated with one dose of inj Mephentermine 3mg IV each after treating with IV fluids.

One patient in Dexmedetomidine group while two patients in Clonidine group had bradycardia and were treated with a single dose of injection Atropine sulphate 0.6mg. Rampal Singh et al found 10/30 patients had hypotension in Clonidine group 9/30 patients in Dexmedetomidine group, 4/30 patients in Control group had hypotension which was not statistically significant. Also 6/30 patients in Clonidine group, 2/30 patients in Dexmedetomidine group, 4/30 patients in Control group had bradycardia which was not statistically significant.

Alpha 2 agonist stimulate alpha 2 receptor in brain and spinal cord and inhibit the neuronal firing, which leads to hypotension and bradycardia. All patients in our study were preloaded with
10ml/kg Ringers lactate. This could be the reason why even though patients had decrease in blood pressure, these findings were easily treatable and the results were not statistically significant.

In our study, we found Ramsay sedation score 2 was seen in 56.67% patients in Dexmedetomidine group and 46.67% in Clonidine group. Ramsay sedation score of 3 was seen in 23.33% in Dexmedetomidine group and 33.33% in Clonidine group. In Control group sedation score was 1 in 40.0% and 2 in 60% of patients which was statistically significant when compared to study groups. But the difference was insignificant between the study groups.

The sedation effect of alpha 2 agonist is postulated to be in the locus ceruleus (a bilateral nucleus that contains many adrenergic receptors) in the brainstem. The locus ceruleus is also the origination site for the descending medullospinal adrenergic pathway, which is known to be a key mechanism in regulating nociceptive neurotransmission.

Our study VAS were at significantly lower levels in Dexmedetomidine and Clonidine groups as compare to Control group. Asharaf Amin Mohamed et al in 2012 found that mean VAS score showed a significant reduction immediately postoperatively and at 12 hours postoperatively in Dexmedetomidine group than the control group.

Both Dexmedetomidine and Clonidine activates alpha 2- adrenoceptor in the spinal cord reducing transmission of nociceptive signals like substance P and produces analgesia. Kalso A. reported that as compared to Clonidine, the affinity of Dexmedetomidine to alpha 2 receptors is ten times greater and a much more effective analgesic agent than Clonidine.

The rescue analgesic Inj. Diclofenac 75mg was administered intramuscularly at VAS score more than 3. In Control group 2-3 doses of rescue analgesic was required. In Clonidine group 86.6% patients required 1-2 doses of Diclofenac. In Dexmedetomidine group, 90% of patients required 1-2 doses in the 1st 24 hrs.

None of the patient in the present study required supplementation with General anesthesia.

CONCLUSION: Based on the results obtained of our study, we conclude that the supplementation of Bupivacaine spinal block with intrathecal Dexmedetomidine (15mcg) or Clonidine (75mcg) leads to significant faster onset of sensory block and motor block. They also prolong the duration of sensory and motor block than Bupivacaine alone. Dexmedetomidine a newer alpha 2 agonist seems to be an attractive adjuvant to spinal bupivacaine which provides longer duration of sensory and motor block and post-operative analgesia when compared to clonidine. There was no significant change seen in the vital parameters (blood pressure, heart rate, respiratory rate and SpO2).

BIBLIOGRAPHY:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sensory block</td>
<td>2.90 + 0.54</td>
<td>2.00 + 0.03</td>
<td>2.23 + 0.43</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Two segment regression time</td>
<td>66.73 + 8.70</td>
<td>122.60 + 17.44</td>
<td>87.73 + 10.37</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Total duration of analgesia</td>
<td>162.80 + 39.55</td>
<td>346.26 + 41.63</td>
<td>302.85 + 38.45</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Onset of motor block</td>
<td>9.23 + 1.38</td>
<td>4.73 + 0.86</td>
<td>5.33 + 1.09</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Duration of motor block</td>
<td>119.17 + 6.97</td>
<td>235.10 + 26.64</td>
<td>226.70 + 45.85</td>
<td>P&lt;0.05</td>
</tr>
</tbody>
</table>

Table no.1: Comparison of parameters in three groups
Graph no. 1: Comparison of mean SBP in three groups at intraoperatively

Graph no. 2: Comparison of DBP in three groups at intraoperatively
Graph no. 3: Comparison of pain on VAS in three groups postoperatively