Postoperative Analgesia After Panhysterectomy, Addition of Clonidine to Bupivacaine: Boon for the Patients
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Abstract

Introduction: Postoperative period after panhysterectomy is very painful as there is too much tissue handling. In the practice of regional anesthesia neuraxial, opioids have been used extensively as an adjuvant to bupivacaine to enhance the potency and duration of sensory and motor block produced by bupivacaine with satisfactory results. However, delayed respiratory depression by opioids has prompted further research to develop nonopioid analgesics. This study was undertaken to assess the degree of sensory and motor block and postoperative analgesia provided by low dose 50 μg intrathecal clonidine admixed with 0.5% hyperbaric bupivacaine as compared to bupivacaine alone in patients undergoing a total abdominal hysterectomy. Materials and Methods: Hundred adult patients of American Society of Anesthesiologist Class 1 and 2 were randomly allocated to Group A and Group B. Group A patients received 15 mg 0.5% hyperbaric bupivacaine with 50 μg clonidine intrathecally. Group B patients received 15 mg 0.5% hyperbaric bupivacaine with normal saline. Observation and Results: The mean duration of motor block was significantly higher in Group A (270.80 ± 66.0 min) as compared to Group B (184.60 ± 72.03 min), with statistically significant difference. There was also statistically significant difference in the duration of sensory block between Group A (290.20 ± 80.27 min) and Group B (190.83 ± 86.90 min). The duration of postoperative analgesia was significantly higher in Group A as compared to Group B (541.06 ± 130.64 min and 252.80 ± 84.10 min respectively). Conclusion: Addition of intrathecal clonidine 50 μg to bupivacaine (15 mg, 0.5%) prolongs the duration of sensory and motor block and duration of analgesia, thus produces an effective spinal anesthesia and good postoperative analgesia for longer duration and reduced postoperative analgesic requirement.

Keywords: Bupivacaine, clonidine, postoperative analgesia

INTRODUCTION

Neuraxial anesthesia greatly expands the anesthesiologist’s armamentarium. In the hands of skilled anesthesiologists safe and satisfactory anesthesia can be achieved below the level of umbilicus to the mutual satisfaction of patients, surgeons, and anesthesiologists. However, with local anesthetic alone, duration of sensory and motor block does not last beyond 2.5–3.0 h. Many drugs such as opioids have been used in the past to enhance the effect of local anesthetics. As opioids are associated with catastrophic adverse events like respiratory depression, therefore search continues for an ideal agent.

Clonidine has been introduced with newer hopes. Low-dose clonidine as an adjuvant has been used previously with bupivacaine in spinal anesthesia. Several studies conducted have found clonidine (1 μg/kg) as safe dose with spinal bupivacaine. We conducted this study to evaluate the effect of 50 μg intrathecal clonidine as an adjuvant to bupivacaine on the duration of sensory block, motor block, and postoperative analgesia in panhysterectomy.

MATERIALS AND METHODS

After approval of Institutional Ethical Committee, prospective randomized double-blind trial was carried out in 100 normotensive adult patients of American Society of Anesthesiologist (ASA) physical status 1 and 2 undergoing a total abdominal hysterectomy. Exclusion criteria:

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patients of ASA Class 3 and 4, patients with significant cardiovascular, renal, hepatic dysfunction, morbidly obese patients and patients having an allergy to either clonidine or bupivacaine or having a contraindication to subarachnoid block. After taking written informed consent, patients were randomly allocated to two groups by computer-generated randomization. Group A patients received injection bupivacaine 15 mg with 50 μg clonidine, and Group B patients received injection bupivacaine 15 mg with normal saline. All patients were fasted overnight (as per fasting guidelines) and premedicated with tablet diazepam 5 mg and ranitidine 150 mg night before surgery. In the morning patients were wheeled into operation theater, monitors attached and baseline parameters (electrocardiogram, SPO₂, noninvasive blood pressure [NIBP], and heart rate [HR]) recorded. An intravenous line was established with 18-gauge cannula and patients were preloaded with 500 ml Ringer lactate. Under strict aseptic precaution lumbar subarachnoid block was given in L2–L3 interspace Group A patients received 15 mg 0.5% hyperbaric bupivacaine with 50 μg clonidine intrathecally. Group B patients received 15 mg 0.5% hyperbaric bupivacaine with normal saline. The anesthesiologists performing the block and collecting the data were unaware of the drug injected. Fall in mean arterial pressure of >20% from the baseline value was treated with 3 ml aliquots of injection mephentermine, and injection atropine was given in increments of 0.3 mg in case of bradycardia (pulse rate <20% from the baseline value). HR and NIBP were recorded after every 5 min initially and then after every 15 min. After completion of surgical procedure patients were observed in the postoperative ward for degree of postoperative analgesia, postoperative motor block, and return of sensory sensation. Degree of postoperative analgesia was assessed using modified Bromage score [6, 12, 18, and 24 h] (0 is no pain, and 10 is maximum imaginable pain) at 1, 2, 4, 6, 12, 18, and 24 h [Table 1]. The postoperative motor block was assessed using modified Bromage score [Table 2]. Return of sensory sensation was assessed by cold perception using ice packs. Duration of analgesia was calculated from onset of sensory block to the demand for first rescue analgesic.

**Statistical analysis**

Student’s t-test (paired and unpaired).

Sample size:

\[
n = \frac{(Z_\alpha + Z_\beta)^2}{d^2} (\sigma_1^2 + \sigma_2^2)
\]

Taking \(\sigma_1 = 1.28\), \(\sigma_2 = 1.46\), \(d = 1.28\)

Significant level

\(\alpha = 5\%\)

\(\beta = 10\%\)

Power = 90%

Sample size comes out to be \(n = 25\) per group

\(\sigma_1 =\) Standard deviation of Group 1

\(\sigma_2 =\) Standard deviation of Group 2

\(d =\) Mean standard deviation

\(\alpha =\) Type I error (5%)

\(\beta =\) Type II error (10%)

Power = (100−\(\beta\)) i.e., 90%.

The values were represented in number (%) and mean ± standard deviation. To compare the change in a parameter at two different time intervals paired t-test was used.

The level of significance was assessed by \(P\) value \((P < 0.05)\) was considered as significant.

**Observation and Results**

Patients were comparable to each other in terms of demographic characteristics [Table 3].

There was no statistically significant difference in mean HR in both groups at all-time interval [Table 4].

Mean systolic blood pressure remained at lower level in Group A, but statistically significant difference was seen only at 60 and 75 min [Table 5].

Mean diastolic blood pressure was comparable in both groups till 40 min and thereafter diastolic blood pressure remained at

**Table 1: Visual analog scale**

| Grade | Criteria | Degree of block (%) |
|-------|----------|---------------------|
| I     | Free movement of legs and feet | Nil (0) |
| II    | Just able to flex knees with free movement of feet | Partial (33) |
| III   | Unable to flex knees, but with free movement of feet | Almost complete (66) |
| IV    | Unable to move legs or feet | Complete (100) |

**Table 2: Description of the Bromage score for motor block**

| Grade | Criteria | Degree of block (%) |
|-------|----------|---------------------|
| I     | Free movement of legs and feet | Nil (0) |
| II    | Just able to flex knees with free movement of feet | Partial (33) |
| III   | Unable to flex knees, but with free movement of feet | Almost complete (66) |
| IV    | Unable to move legs or feet | Complete (100) |

**Table 3: Demographic profile**

| Characteristic | Study group \((n=50), n (%)\) | Control group \((n=50), n (%)\) | Statistical significance |
|----------------|--------------------------------|--------------------------------|--------------------------|
| Mean age±SD (years) | 42.26±11.91 | 48.52±12.18 | 1.552 0.124 |
| ASA Grade II | 50 (100) | 50 (100) | 0 (1) |
| Mean weight (kg) | 59.6±8.30 | 59.70±9.60 | 0.056 0.956 |
| Mean height (cm) | 160.46±7.37 | 162.32±8.37 | 1.179 0.241 |

ASA=American Society of Anesthesiologist, SD=Standard deviation
significantly lower level in Group A [Table 6]. However, none of the patients required therapeutic intervention.

The mean duration of motor block was significantly higher in Group A (270.80 ± 66.0 min) as compared to Group B (184.60 ± 72.03 min), with statistically significant difference [Table 7]. There was also statistically significant difference in the duration of sensory block between Group A (290.20 ± 80.27 min) and Group B (190.83 ± 86.90 min). The duration of postoperative analgesia was significantly higher in Group A as compared to Group B (541.06 ± 130.64 min and 252.80 ± 84.10 min, respectively). Except for 4 h time interval, at all the time intervals the mean VAS in the control group was significantly higher as compared to that in study group [Table 8].

**Table 4: Comparison of mean heart rate in two groups**

| Time interval (min) | Mean±SD (n=50) | Statistical significance |
|---------------------|-----------------|-------------------------|
| Study group         | Control group   | t           | P         |
| Baseline            | 90.32±9.78      | 88.26±16.73 | −1.116    | 0.267    |
| 5                   | 97.22±13.20     | 94.46±18.85 | −0.811    | 0.419    |
| 10                  | 93.30±18.14     | 88.48±19.51 | −1.280    | 0.204    |
| 15                  | 86.64±11.92     | 88.66±17.28 | 0.007     | 0.994    |
| 20                  | 86.86±11.51     | 86.70±18.27 | −0.092    | 0.927    |
| 25                  | 86.60±9.36      | 86.98±18.66 | −0.230    | 0.818    |
| 30                  | 88.84±17.90     | 83.80±15.82 | −1.490    | 0.139    |
| 35                  | 82.32±11.36     | 81.40±16.78 | −0.109    | 0.911    |
| 40                  | 82.96±13.16     | 79.50±13.68 | −1.289    | 0.200    |
| 45                  | 80.54±9.85      | 85.52±22.86 | 1.364     | 0.176    |
| 60                  | 81.25±9.26      | 79.72±15.66 | −0.210    | 0.834    |
| 75                  | 78.92±15.56     | 84.10±17.35 | 1.572     | 0.119    |
| 90                  | 79.54±11.50     | 84.56±15.83 | 1.814     | 0.073    |

SD=Standard deviation

**Table 5: Comparison of mean systolic blood pressure in two groups at different time**

| Time interval (min) | Mean±SD (n=50) | Statistical significance |
|---------------------|-----------------|-------------------------|
| Study group         | Control group   | t           | P         |
| Baseline            | 133.76±15.83    | 132.80±20.00 | −0.266    | 0.791    |
| 5                   | 128.42±16.64    | 129.32±20.40 | 0.242     | 0.809    |
| 10                  | 124.92±21.35    | 114.82±37.93 | −1.641    | 0.104    |
| 15                  | 125.84±21.34    | 120.94±25.65 | −1.038    | 0.302    |
| 20                  | 124.02±14.99    | 120.96±22.25 | −0.806    | 0.422    |
| 25                  | 119.76±19.45    | 120.68±20.03 | 0.233     | 0.816    |
| 30                  | 118.90±10.84    | 116.88±18.78 | −0.659    | 0.512    |
| 35                  | 118.26±12.04    | 119.86±15.95 | 0.566     | 0.573    |
| 40                  | 114.88±11.98    | 118.78±16.57 | 1.349     | 0.181    |
| 45                  | 112.62±10.99    | 115.58±11.58 | 1.753     | 0.083    |
| 60                  | 111.63±11.28    | 115.98±10.52 | 2.007     | 0.047    |
| 75                  | 108.10±10.89    | 118.52±12.29 | 4.443     | <0.001   |
| 90                  | 111.86±23.67    | 118.02±11.63 | 1.641     | 0.104    |

SD=Standard deviation

**Table 6: Comparison of mean diastolic blood pressure in two groups**

| Time interval (min) | Mean±SD (n=50) | Statistical significance |
|---------------------|-----------------|-------------------------|
| Study group         | Control group   | t           | P         |
| Baseline            | 81.76±10.89     | 83.60±8.76 | 0.881     | 0.380    |
| 5                   | 76.10±12.82     | 81.54±11.14 | 2.275     | 0.025    |
| 10                  | 76.42±13.17     | 75.72±9.00 | −0.310    | 0.757    |
| 15                  | 77.46±15.60     | 72.74±11.91 | −1.634    | 0.105    |
| 20                  | 76.68±15.02     | 74.18±8.21 | −0.620    | 0.537    |
| 25                  | 75.32±11.37     | 72.48±7.19 | −1.503    | 0.136    |
| 30                  | 72.40±11.56     | 71.60±8.77 | −0.412    | 0.681    |
| 35                  | 73.30±10.39     | 73.90±13.10 | 0.677     | 0.500    |
| 40                  | 68.87±9.86      | 71.88±11.64 | 1.391     | 0.167    |
| 45                  | 69.38±9.74      | 73.62±11.11 | 2.030     | 0.045    |
| 60                  | 66.88±9.96      | 72.84±9.31 | 3.091     | 0.003    |
| 75                  | 66.62±11.08     | 73.68±10.03 | 3.340     | 0.001    |
| 90                  | 66.38±11.68     | 74.38±10.04 | 3.673     | <0.001   |

SD=Standard deviation

**Table 7: Comparison of duration of sensory block, motor block, and postoperative analgesia**

| Landmarks          | Mean±SD (n=50) | Statistical significance |
|--------------------|-----------------|-------------------------|
| Study group        | Control group   | t           | P         |
| Duration of motor block (min) | 270.80±66 | 184.60±72.03 | 6.738     | <0.001   |
| Duration of sensory block (two segment regression time) (min) | 290.20±80.17 | 190.83±86.90 | 6.014     | <0.001   |
| Duration of analgesia (min) | 541.06±130.64 | 252.80±84.10 | 13.263    | <0.001   |

SD=Standard deviation

**DISCUSSION**

The α2 adrenergic agonist clonidine has variety of different actions, including the ability to potentiate the effect of local anesthetics. α2 adrenergic receptors are present within both presynaptic and postsynaptic terminals of primary afferent nociceptor neurons within the dorsal horn of spinal cord.[4] The analgesic effect following administration of intrathecal clonidine is mediated spinally through activation of postsynaptic α2 adrenergic receptors in the substantia gelatinosa of spinal cord and it acts by blocking conduction in type C and A-delta fibers.[5,6] In our study, duration of sensory and motor block was significantly prolonged by the addition of 50 μg of clonidine to bupivacaine intrathecally. We also found that clonidine augmented analgesic effect of bupivacaine significantly, extending which is reflected in prolonged time to first analgesic request and lower VAS score at different time intervals.
Dobrydnjov et al.\cite{1} reported that addition of 15–30 mcg clonidine to bupivacaine prolonged the time to first analgesic request and decreased postoperative pain with minimal risk of hypotension. In another study Dobrydnjov et al.\cite{5} evaluated the postoperative analgesic effect of equal doses (150 mcg) of oral or intrathecal clonidine. He opined that addition of clonidine to bupivacaine intrathecally prolonged the duration of postoperative analgesia and reduced the morphine consumption postoperatively.

However, contrasting results were found in studies conducted by Cordoso et al. who added 30 mcg of clonidine to hyperbaric bupivacaine and sufentanil in combined spinal-epidural analgesia and found no significant change in the duration of postoperative analgesia by addition of such small dose of clonidine.

Sethi et al. conducted study to assess the efficacy of analgesic effect of low dose (1 mcg/kg) intrathecal clonidine as an adjuvant to 12.5 mg 5% hyperbaric bupivacaine. The maximum dose of clonidine used was 70 mcg. They found that the patients in clonidine group had significant fall in mean arterial pressure and HR. However, no therapeutic intervention needed. They concluded that addition of clonidine to bupivacaine significantly prolonged the duration of spinal analgesia as compared to bupivacaine alone. Studies conducted by Kaabachi et al.,\cite{2} Elia et al.\cite{3} and Saxena et al.\cite{4} similarly showed that addition of various doses of clonidine to bupivacaine intrathecally significantly prolongs the duration of analgesia of bupivacaine.

When hemodynamic parameters were compared, we did not notice any change in HR by addition of 50 μg clonidine to 15 mg bupivacaine intrathecally. Though diastolic blood pressure remained at lower level in Group A (after 40 min) as compared to Group B, therapeutic intervention was required in none of the patients. Clonidine has U-shaped hemodynamic dose-response curve.\cite{6} Studies using very low dose (15–30 mcg) intrathecal clonidine found no hemodynamic instability, however, in the studies using 100–150 mcg clonidine significant bradycardia and hypotension was observed.\cite{7} Nishiyama and Hanaoka\cite{8} used still higher dose of clonidine (300–450 mcg) and found relative hemodynamic stability suggesting a pressure effect on the peripheral sites.

### Conclusion

On the basis of the observations made during this study and their analysis, it is concluded that the duration of sensory block and motor block were significantly higher in clonidine group as compared to control group. The mean VAS at different time intervals was significantly lower in clonidine group as compared to control group. The clonidine group had significantly prolonged the duration of analgesia and good hemodynamic stability.

The findings in this study suggested that addition of intrathecal clonidine 50 μg to bupivacaine (15 mg, 0.5%) produces an effective spinal anesthesia and prolonged postoperative analgesia and thus reduced postoperative analgesic requirement. As quality and duration of pain relief following panhysterectomy was improved, patient became ambulatory earlier, and postoperative recovery was improved.

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### Conflicts of interest

There are no conflicts of interest.

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### Table 8: Comparison of visual analog scale score at different time intervals

| Time interval (h) | Study group Mean±SD (n=50) | Control group Mean±SD (n=50) | Statistical significance |
|-------------------|---------------------------|-----------------------------|-------------------------|
| 1                 | 0.00±0.00                 | 0.00±0.00                   | t=0.0                           |
| 2                 | 0.00±0.00                 | 0.34±1.10                   | t=2.177 p=0.031              |
| 4                 | 0.50±1.27                 | 0.78±1.50                   | t=1.003 p=0.280             |
| 6                 | 0.40±1.12                 | 1.72±2.23                   | t=3.735 p<0.001             |
| 12                | 0.36±0.82                 | 2.08±2.30                   | t=4.989 p<0.001             |
| 18                | 0.27±0.85                 | 1.22±1.88                   | t=3.293 p=0.001             |
| 24                | 0.02±0.15                 | 1.06±1.82                   | t=4.022 p<0.001             |

SD=Standard deviation
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