Clonidine as an Adjuvant to Caudal Epidural Ropivacaine for Lumbosacral Spine Surgeries

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Abstract

Background: Caudal epidural analgesia is a proven technique for providing analgesia for spinal surgeries. Prolonged pain relief with no motor blockade is desired for early mobilization. Objective: The objective of this study is to compare the effect of adding 1 µg/kg of clonidine to injection ropivacaine 0.2% with respect to duration of analgesia, hemodynamic effects, and associated side effects. Methodology: In this prospective double-blind study, a total of 60 patients undergoing lumbosacral spine surgery were randomized to receive 25 cc caudal epidural injection of either ropivacaine 0.2% (Group R, n = 30) or a mixture of injection ropivacaine 0.2% and injection clonidine 1 µg/kg (Group RD, n = 30) under general anesthesia after the patient was positioned prone for surgery. Visual analog scale (VAS) scores, heart rate, blood pressures, and time to rescue analgesia and sedation score were recorded at regular intervals for the first 24 h. Results: Mean VAS scores were significantly lower in the RC Group for up to 12 h following the caudal block. The time to first rescue analgesic was prolonged in the RC group compared to the R Group, and it was statistically significant. No clinically significant hemodynamic changes were noted in either of the groups. No other side effects were seen in both the groups. Conclusion: These results suggest that injection clonidine is an effective additive to injection ropivacaine for caudal epidural analgesia in lumbosacral spine surgeries.

Keywords: Analgesia, caudal epidural, hemodynamic

Introduction

Caudal analgesia is a good, reliable, and easy method to provide intraoperative and postoperative analgesia. However, the single shot caudal analgesia is short in duration so the use of catheter injection may be used to prolong the analgesia time but it is associated with infection.[1]

Many additives were used in combination with local anesthetics in caudal block to prolong the postoperative analgesia.[1] To study the efficacy of clonidine in terms of quality and duration of analgesia, they produce when added to caudal by single-shot technique, this study was designed to compare the intraoperative hemodynamics, postoperative analgesia, postoperative sedation, and postoperative side effects of clonidine as an adjuvant to ropivacaine in caudal analgesia.

Pain due to lumbar disc herniation is the result of direct nerve root compression and an associated inflammatory response.[2] Persistent postoperative nerve root pain is thought to be due to peridural fibrosis and arachnoiditis. Peridural fibrosis is initiated by the inflammation associated with compression and then promoted by surgical trauma to overlying paraspinal muscles.[3]

Tissue injuries cause an increase in the excitability of dorsal neurons in the central nervous system, which is a normal physiologic response, and contribute to pain in the postoperative pain.[4]

Insufficient management of postoperative spinal surgery pain leads to reduced intestinal motility, retention of urine, delayed ambulation, with a subsequent increase in thromboembolic complications, and cardiopulmonary morbidity.[5]

Control of pain during intraoperative and postoperative period is important in patients as poor pain control may result in morbidity and mortality.[6] Caudal epidural anesthesia/analgesia is the most widely employed technique
for various surgical procedures within the distribution of T10–S5 dermatome,[7,8] and it is easier to perform caudal procedure in prone position.

Single-shot caudal block provides analgesia for 2–4 h; however, this can be further prolonged by adding adjuvants such as opioids, ketamine, α2 agonists, and adrenaline. Clonidine a selective α2-agonist with safe pharmacokinetic profile is a good neuraxial adjuvant.[9]

The anesthetic and the analgesic requirement get reduced to a huge extent by the use of clonidine as adjuvants because of their analgesic properties and augmentation of local anesthetic effects as they cause hyperpolarization of nerve issues by altering transmembrane potential and ion conductance at locus ceruleus in the brainstem.[10] The stable hemodynamics and the decreased oxygen demand due to enhanced sympathoadrenal stability make them very useful pharmacologic agents.[11]

**Methodology**

The study design was a prospective, double-blinded, and randomized controlled trial.

Sixty four patients physical status American Society of Anesthesiologists (ASA) Classes I and II between the age of 18 and 65 s who underwent patient’s lumbosacral surgeries were included in the study. Written informed consent was taken. They were allocated into any one of two groups of 30 patients each, by means of computer-generated randomization:

- Group R: Patients receiving caudal block with injected ropivacaine 0.2% 20 ml
- Group RC: Patients receiving ropivacaine 0.2% 20 ml + 1 µg/kg intravenous (IV) clonidine.

Patients with cardiac conductive disorders, hepatic insufficiency, renal impairment, psychiatric disorders, those with contraindications for a caudal block (skin infection at the injection site, bleeding diathesis, neurological disorders, and sacral anomalies), and a history of allergy to any of the study medications were excluded from the study. Patients who had undergone previous back surgeries were also excluded from the study. In the preoperative visit, the numerical visual rating scale for pain was explained to all patients, which ranges from 0 = no pain to 10 = worst imaginable pain.[12]

The demographic data (age, weight, and ASA status, type of operation, and duration of surgery) and hemodynamic parameters such as heart rate (HR) and mean blood pressure (MBP) were recorded before the block which was considered as the baseline and at regular intervals intraoperatively and postoperatively using standard monitoring such as pulse oximeter, HR, noninvasive blood pressure, electrocardiogram, and oxygen saturation.

After securing appropriate gauge IV cannula, anesthesia was induced with injection fentanyl 2 µg/kg, injection propofol 2 mg/kg, and endotracheal intubation facilitated by injection vecuronium 0.1 mg/kg and then turned prone for the surgery. Under strict aseptic precautions, sacral hiatus was identified by palpating sacral cornu. Twenty gauge IV cannula needle was introduced at 90° until a pop is felt and then angled down to enter the sacral hiatus in the cephalic direction. After negative aspiration for blood and cerebrospinal fluid, the study drugs were introduced into the caudal space according to allocation. Position in the epidural space was confirmed using loss of resistance technique. The anesthetist blinded to the contents of the syringe injected the same into the epidural space. Patients in the R Group were given 20 ml of 0.2% ropivacaine and patients in Group RC were given 1 µg/kg of injection clonidine with 0.2% injection ropivacaine. Moreover, surgeon was asked to wait for 15 min to put incision. IV paracetamol 1 g was given to all patients intraoperatively and the same was continued eight hourly for the first 24 h. Intraoperatively, HR and MBP were recorded. A fall of systolic blood pressure to <20% baseline was considered as hypotension. Bradycardia was considered when HR dropped to <60/min or <20% of baseline pulse and was treated with IV atropine sulfate 0.6 mg. All patients were observed in the post anesthesia care unit for the next 6 h. All patients were catheterized before starting of surgery as a routine protocol of neurosurgeons and were kept for 12 h. At the end of the operation, patients were placed back in the supine position and the trachea was extubated after reversal of the muscle relaxant by administration of mixed neostigmine 40 µg/kg with glycopyrrolate 10 µg/kg intravenously. Visual analog scale (VAS)[13] was used for the assessment of postoperative pain relief at immediate postoperatively, 30 min, 1, 2, 4, 8, 12, and 24 h by a trained nurse. At VAS score of ≥4, rescue analgesia was given in the form of injection tramadol 50 mg IV. Duration of analgesia is defined as the time taken from the time of caudal anesthesia to the first request of rescue analgesia. Sedation score was assessed on a four point categorical scale as 0 = awake, alert; 1 = drowsy, not sleeping; 2 = asleep, arousable by verbal contact; 3 = asleep, not arousable by verbal contact.

Side-effects such as nausea, vomiting, respiratory depression, motor blockade (Bromage scale >1), deep sedation (Ramsay sedation scale [RSS] >3), shivering and hypotension, duration of surgery, and parameters were recorded and entered in pro forma sheets.

**Statistical methods**

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean ± standard deviation (SD) (minimum-maximum) and results on categorical measurements are presented in number (%). The significance is assessed at 5% level of significance. The following assumptions on data are made, assumptions: (1) Dependent variables should be normally distributed, (2) samples drawn from the population should be random, cases of the samples should be independent.

Student t-test (two-tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (intergroup analysis) on metric parameters.
Chi-square/Fisher’s exact test has been used to find the significance of study parameters on categorical scale between two or more groups, nonparametric setting for qualitative data analysis.

**Statistical software**
The statistical software, namely, SAS 9.2 (SAS Institute, Cary, NC, USA), Statistical Package for Social Sciences (SPSS version 15.0 IBM Corp, Armonk, NY), Statate L.P. 4905 Lakeway Drive, college station, Texas, USA), Medcalc 9.01 (American statistical association, Acacialaan 22, 8400 ostend, Belgium), Systat 12.0 (Systat Software, San Jose, CA 95131, USA) and R environment ver. 2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables, etc.

**Results**
There were no statistical differences between the two groups in terms of the demographic data (age, sex, weight, and height) of the patients [Table 1 and Figure 1]. In addition, there were no statistical differences between groups according to the duration of operation, duration of anesthesia, and ASA classification. There were no significant differences between groups in HR and MAP intraoperatively and postoperatively [Tables 2 and 3].

Postoperatively, pain score assessed using VAS score in Group RC had lower pain scores, which was statistically significant and the requirement of rescue medicine was lesser in Group RC. RC group required a longer time for the first postoperative analgesia than R Group, with a mean ± SD of 3.10 ± 3.23 and 2.97 ± 4.86 which was statistically significant ($P = 0.011* $) [Table 4] and VAS for pain was lower in the RC Group specially at, 4, 8, and 12 h than the R Group, shows statistically significant $P < 0.001$ [Table 5].

In both groups, the VAS score followed a decreasing trend from 0 to 240 min of postoperatively, the VAS score was stable, and this period was almost totally pain-free. After 240 min (4 h), the VAS score showed an increasing trend [Figure 2]. All the patients of either groups asked for additional drug when the average VAS score was $>4$. However, the mean VAS score was higher in the ropivacaine group at each time point.

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**Table 1: Baseline information of patients studied**

| Variables          | Ropivacaine | Clonidine | Total | $P$ |
|--------------------|-------------|-----------|-------|-----|
| Age (years)        | 43.83±13.15 | 43.97±13.15 | 43.90±13.04 | 0.969 |
| Gender (male:female) | 15:15     | 12:18    | 27:33 | 0.436 |
| Weight (kg)        | 59.80±9.59 | 56.10±11.82 | 57.95±10.83 | 0.188 |
| Height (cm)        | 158.43±8.67 | 158.20±7.61 | 158.32±8.09 | 0.912 |
| Time               | 2.28±0.81 | 2.17±0.98 | 2.23±0.89 | 0.636 |

**Table 2: Comparison of heart rate (bpm) in two groups of patients studied**

| HR (bpm) | Ropivacaine | Clonidine | Total | $P$ |
|----------|-------------|-----------|-------|-----|
| Preoperative | 87.87±13.14 | 93.23±13.40 | 90.55±13.43 | 0.123 |
| 1 h      | 82.70±12.25 | 82.83±14.28 | 82.77±13.19 | 0.969 |
| 3 h      | 77.93±13.01 | 78.17±13.60 | 78.05±13.19 | 0.946 |
| 5 h      | 73.97±12.75 | 74.83±11.53 | 74.40±12.06 | 0.783 |
| 10 h     | 71.37±13.09 | 73.17±9.36 | 72.27±11.32 | 0.543 |
| 15 h     | 70.47±13.43 | 70.37±9.59 | 70.42±11.57 | 0.974 |
| 30 h     | 69.40±14.15 | 66.57±8.24 | 67.98±11.57 | 0.347 |
| IPO      | 87.13±12.77 | 85.37±14.18 | 86.25±13.41 | 0.614 |
| Postoperative | 84.73±11.12 | 81.20±10.74 | 82.97±10.98 | 0.216 |
| 30 min   | 83.67±9.88  | 79.53±10.58 | 81.60±10.36 | 0.123 |
| 1 h      | 80.57±10.14 | 76.33±7.84  | 78.45±9.23  | 0.076* |
| 2 h      | 81.57±9.78  | 75.70±8.38  | 78.63±9.50  | 0.015* |
| 4 h      | 79.43±9.92  | 75.80±6.95  | 77.62±8.69  | 0.106 |
| 8 h      | 79.03±10.24 | 74.97±6.71  | 77.00±8.82  | 0.074* |
| 12 h     | 78.80±9.13  | 76.10±6.32  | 77.45±7.90  | 0.188 |
| 24 h     | 75.70±8.38  | 78.17±11.07 | 79.53±10.58 | 0.045* |

**Table 3: Comparison of mean blood pressure (mm Hg) in two groups of patients studied**

| MBP (mm Hg) | Ropivacaine | Clonidine | Total | $P$ |
|-------------|-------------|-----------|-------|-----|
| Preoperative | 105.80±15.25 | 102.33±14.73 | 104.07±14.97 | 0.374 |
| 1 h         | 96.93±15.98 | 88.93±14.15 | 92.93±15.50 | 0.045* |
| 3 h         | 89.37±15.25 | 85.53±13.29 | 87.45±14.31 | 0.304 |
| 5 h         | 86.67±14.17 | 81.17±11.07 | 83.92±12.91 | 0.099* |
| 10 h        | 84.93±12.79 | 79.47±11.97 | 82.20±12.59 | 0.093* |
| 15 h        | 85.17±13.31 | 79.63±10.34 | 82.40±12.14 | 0.077* |
| 30 h        | 81.93±11.69 | 77.43±12.10 | 79.68±12.01 | 0.148 |
| IPO         | 104.07±15.54 | 100.97±12.42 | 102.52±14.03 | 0.397 |
| Postoperative | 101.50±12.88 | 97.40±13.97 | 99.45±13.48 | 0.242 |
| 1 h         | 98.67±11.52 | 95.60±12.48 | 97.13±12.01 | 0.327 |
| 2 h         | 98.73±11.73 | 94.50±12.24 | 96.62±12.08 | 0.177 |
| 4 h         | 98.23±14.07 | 92.67±12.37 | 95.45±13.43 | 0.109 |
| 8 h         | 97.73±13.07 | 95.30±13.79 | 96.52±13.38 | 0.486 |
| 12 h        | 98.67±12.17 | 93.70±13.06 | 96.18±12.76 | 0.133 |
| 24 h        | 99.40±12.64 | 94.43±12.78 | 96.92±12.85 | 0.136 |

MBP=Mean blood pressure, IPO=Immediate post operative, *Moderately significant ($P = 0.01 < P ≤ 0.05$)
Nagappa, et al.: Caudal clonidine effect in spine surgeries

**Discussion**

Patients undergoing surgical laminectomy experience severe postoperative pain. Poorly controlled postoperative pain delays mobilization and physiotherapy, prolongs hospitalization, and increases days of recovery. Furthermore, it is associated with complications such as deep venous thrombosis, pulmonary embolism, and infection.

It has been shown that postlaminectomy pain can lead to pathological changes around the nerve tissues such as inflammation, edema, fibrosis, venous congestion, and also pressure on the posterior longitudinal ligament, decreased nutrient supply to the spinal nerve and nerve root, and central sensitization.

The primary mechanism of caudal epidural anesthesia is the spinal root block. It is a simple and quickly done procedure, allowing short turnover time while providing good surgical anesthesia and postoperative analgesia and more economical compared to interlaminar epidural block. When performed correctly there is little danger of neurological deficits.

In the report by Crighton, there was a 10% rate of technical failure because of an absent sacral hiatus due to wide anatomic variation in this region.

In addition, we are avoiding lumbar region, i.e., surgical site in our spine cases.

Clonidine acts, similar to local anesthetic, and their interaction with local anesthetics has been explained by three possible mechanisms first, clonidine blocks Ad and C fibers as a consequence of an increase in potassium conductance in isolated neurones, thus intensifying local anesthetic conduction block. Second, clonidine may cause local vasoconstriction, thus decreasing local anesthetic spread and removal around neural structures. This effect is mediated by drug action on postsynaptic α₂ receptors although there is little evidence of this mechanism with clinical doses.

The incidence of dry mouth and sedation (RSS SCORE) were statistically nonsignificant [Table 6]. All the patients of either interval and also the R Group needed rescue analgesia earlier than clonidine RC group [Figure 3].

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**Table 4: Time taken to give first dose of rescue analgesia in two groups of patients studied**

| Time taken for rescue analgesia | Ropivacaine (%) | Clonidine (%) | Total (%) |
|---------------------------------|-----------------|---------------|-----------|
| 0                               | 14 (46.7)       | 21 (70.0)     | 35 (58.3) |
| 1-6                             | 10 (33.3)       | 1 (3.3)       | 11 (18.3) |
| 6-12                            | 6 (20.0)        | 8 (26.7)      | 14 (23.3) |
| Total                           | 30 (100)        | 30 (100)      | 60 (100)  |

* Mean±SD 

* Moderately significant (*P* value: 0.01 < *P* ≤ 0.05), Significant, Chi-square test. SD=Standard deviation

**Table 5: Comparison of visual analog scale score in two groups of patients studied**

| Time                  | Ropivacaine (%) | Clonidine (%) | Total (%) | *P*
|-----------------------|-----------------|---------------|-----------|
| IPO                   | 0.00±0.00       | 0.00±0.00     | 0.00±0.00 | -        |
| 30 min                | 0.03±0.18       | 0.07±0.25     | 0.05±0.22 | 0.561    |
| 1 h                   | 0.20±0.55       | 0.07±0.25     | 0.13±0.43 | 0.233    |
| 2 h                   | 0.27±0.64       | 0.03±0.18     | 0.15±0.48 | 0.060*   |
| 4 h                   | 1.00±1.55       | 0.23±0.68     | 0.62±1.25 | 0.016*   |
| 8 h                   | 1.70±1.21       | 0.53±0.78     | 1.12±1.17 | <0.001** |
| 12 h                  | 1.43±0.73       | 1.00±0.83     | 1.22±0.80 | 0.036*   |
| 24 h                  | 0.73±0.69       | 0.57±0.50     | 0.65±0.61 | 0.290    |

VAS=Visual analog scale, IPO=Immediate post operative, + Suggestive significance (*P* value: 0.05 < *P* < 0.10)

**Table 6: RSS distribution in two groups of patients studied**

| RSS | Ropivacaine (%) | Clonidine (%) | Total (%) |
|-----|-----------------|---------------|-----------|
| 1   | 29 (96.7)       | 25 (83.3)     | 54 (90)   |
| 2   | 1 (3.3)         | 5 (16.7)      | 6 (10)    |
| Total | 30 (100)        | 30 (100)      | 60 (100)  |

*P*=0.195, Not significant, Fisher exact test. RSS=Ramsay sedation score

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**Figure 2**: VAS Score distribution in two groups at 4hr

**Figure 3**: Comparison of VAS Score in two groups of patients studied
clonidine combined with spinal local anesthetics or used in peripheral blocks intensifies and prolongs analgesia.\(^2\) Spinal α2 adrenergic agonists may also induce analgesia by activating spinal cholinergic neurones resulting in acetylcholine release.

Several mechanisms have been suggested for the clonidine-induced prolongation of caudal analgesia. The anti-nociceptive action is due to the direct suppression of the spinal cord nociceptive neurones by epidural clonidine. Another mechanism is that clonidine crosses the blood–brain barrier and interacts with α\(_2\) adrenoceptors at spinal and supraspinal sites to produce analgesia. Clonidine also suppresses neurotransmission in peripheral sensory a δ and C nerve fibers. The final mechanism suggested is pharmacokinetically mediated: Clonidine induces vasoconstriction through α-2b adrenoceptors located at the peripheral vascular smooth muscles.\(^25\) Both clonidine and dexmedetomidine are equally good as additives. The study by Bajwa et al. showed that sedation scores were highly statistically significant with administration of dexmedetomidine compared to clonidine and also not many studies using caudal route for spine surgeries.

Ropivacaine 0.2% was the choice of local anesthetic agent as it provides an advantage over bupivacaine with respect to safety index. Its selectivity toward sensory rather than motor blockade\(^27\) also makes it the desirable drug as it allows the surgeons to assess the motor system postoperatively.

In Taiwan, Chen et al.\(^28\) first reported the use of caudal block during a vaginal delivery HR and mean arterial pressure never fell down to more than 20% of the baseline values.\(^29\) Furthermore, the use of low concentration of ropivacaine (0.2%) decreased the chances of hypotension.

In our study, both the groups had lower VAS score; however, the addition of clonidine to caudal analgesia had greater response on VAS score as RC Group had lower VAS score for longer duration and the requirement of rescue analgesia was less.

The incidence of other side-effects such as nausea, vomiting, headache, and shivering were comparable in both groups and found to be statistically nonsignificant (\(P > 0.05\)). None of the patients showed respiratory depression or motor block in either group. Only one patient in clonidine group had bradycardia and treated with injection atropine 0.6 mg.

**Conclusion**

Clonidine in a dose of 1 µg/kg added to 0.2% ropivacaine for caudal analgesia, during lumbosacral surgeries, prolongs the duration of analgesia of ropivacaine, without any side effects. Caudal block, addition of clonidine 1 µg/kg to ropivacaine 0.2% resulted in better postoperative analgesia than ropivacaine 0.2% alone. This combination was not associated with sedation or motor block.

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**Conflicts of interest**

There are no conflicts of interest.

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