ORIGINAL RESEARCH

Impact of Clonidine on Hemodynamic Parameters When Combined with Alkalinized 0.2% Ropivacaine

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ABSTRACT
Several surveys carried out during the past 15 years have reported a high incidence of patients (30 to 75%) complaining of moderate to severe pain after surgery. During recent years, there has been a tremendous increase in our understanding of acute pain physiology and the importance of pain relief which has led to the development of new analgesic drugs and techniques to combat postoperative pain. There are several strategies for postoperative pain relief. Intravenous opioids are commonly used in surgical patients. They can lead to respiratory depression, nausea, vomiting, and tolerance. Also, they need to be used cautiously in patients having hepatic and renal disease. Parenteral NSAIDs provide inadequate pain relief for major surgery; they also produce adverse effects on the gastrointestinal system, renal system, and coagulation. In addition, NSAIDs can cause urticaria and bronchoconstriction. There is a growing conviction that multi-modal perioperative analgesia has advantages over the use of a single modality. A combination of local anesthetics and opioids given by intrathecal/extradural route has been advocated. There are very few studies that analyses the effects of the addition of clonidine to alkalinized 0.2% ropivacaine. Therefore, these drugs have been used in the present study to determine the time of onset and duration of analgesia after a single shot epidural dose of the drug, to observe the Ramsay sedation scoring for any sedative effects of the drug, and to determine the visual analog scale scoring for pain as expressed by the patients.
Keywords: Clonidine, ropivacaine, sadation, visual analog scale

INTRODUCTION

Postoperative pain relief aims to provide subjective comfort, in addition to inhibiting trauma-induced nociceptive impulses to blunt autonomic and somatic reflex responses to pain and subsequently enhance restoration of the physiologic function of the operated region.

There has been a renewed interest in regional techniques for intraoperative anesthesia and postoperative analgesia Epidural and intrathecal local anesthetics have been used most commonly for this purpose. Local anesthetics reversibly block nerve impulses and are the mainstay of regional anesthesia. Local anesthetics can be divided into two main groups, esters (e.g. cocaine, procaine, chloroprocaine, tetracaine) and the more commonly used amides (e.g. lidocaine, prilocaine, bupivacaine). The newer amides, ropivacaine, and levobupivacaine, are single enantiomers [1]. Alkalinization of local anesthetics increases the non-ionized component and allows faster penetration of nerves. This should make the onset of the block quicker, but the literature is controversial, with some studies unable to demonstrate a difference when bicarbonate is added to bupivacaine 0.5% or lidocaine 2% for epidurals [2].

There is a risk of precipitation when bicarbonate solutions with concentrations of 1–8.4% are used [3], therefore there are limitations to the addition of sodium bicarbonate to local anesthetics. There are very few studies that analyze the effects of the addition of clonidine to alkalinized 0.2% ropivacaine, therefore, these drugs have been used in the present study to better understand their analgesic effects.

Ropivacaine is less lipophilic than bupivacaine, which together with its stereoselective properties, contributes to ropivacaine having a significantly higher threshold for cardiotoxicity and CNS toxicity than bupivacaine[4]. Ropivacaine is believed to have a lower incidence of clinical cardiac side effects than bupivacaine as shown by Graf BMetal(2002)[5].

Efforts were made to increase the efficacy and duration of ropivacaine as a post-operative analgesic and To improve epidural analgesia epinephrine was tried by Niemi G, Breivik Het al (2002).[6]

The present study aimed to observe the influence of the addition of epidural clonidine to alkalinized ropivacaine 0.2% for postoperative pain relief to observe the onset and duration of analgesia, hemodynamic parameters as heart rate, blood pressure (MAP), Ramsay sedation scoring for any sedative effects of the drug. And to determine the visual analog scale (VAS) scoring for pain as expressed by the patients.

MATERIAL AND METHODS

This prospective study was conducted on 90 adult patients of the American Society of Anaesthesiologists (ASA) physical status I-II, aged 18 to 60 years, scheduled for elective or emergency abdominal surgery in SRN hospital associated with MLN Medical College, Allahabad over one year. Informed consent from the patients and approval from the institutional ethics committee was obtained. Patients were randomly assigned to one of the three groups, using a "Slips of paper in a box" technique consisting of 30 patients in each group. Double blinding was assured for patients as well as for the performers. After randomization, patients were allocated to one of the following groups, receiving epidural drugs for postoperative pain relief.

Group A: Patients received plain ropivacaine 0.2% (10ml+1ml normal saline);

Group B: Patients received alkalinized ropivacaine 0.2% (20ml 0.2% ropivacaine mixed with 0.1 ml 7.5% sodium bicarbonate of which 11 ml is taken);

Group C: Patients received alkalinized ropivacaine 0.2% and clonidine 37.5mcg

Time durations were assessed as follows:

'0' min = the time when the full single shot epidural analgesic dose was given.

Onset time = '0' min to VAS score of ≤ 2

Total duration = onset time to when the patient started complaining of pain or VAS score of ≥3. Subsequently, when the patient again complained of pain with a VAS score of ≥3, a repeat dose of the epidural drug was given to provide full pain benefit to the patient. Assessment of postoperative analgesia was recorded by VAS (0 - 10) at 30 min, 1, 2, 4, 8, 12 and 24hrs. The duration of analgesia after the 1st shot of epidural analgesia was recorded and epidural analgesia was continued to give full pain relief benefit to the patient. The sedation score was evaluated by using the Ramsay sedation scale mentioned below:

1= Anxious, agitated or restless or both.
2= Cooperative, oriented and tranquil.
3= Responding to commands only.
4= Brisk response to light glabellar tap or loud auditory stimulus.
5= Sluggish response to light glabellar tap or loud auditory stimulus.
6= No response to light glabellar tap.

Maximum sedation score was noted. Heart rate & blood pressure (mean arterial pressure) were measured at30mins, 1 hr, 2 hrs, 4hrs, 8hrs, 12hrs and 24hrs.

- Heart rate <50 was considered bradycardia and treated with incremental doses of Inj. Atropine 0.6 mg i.v.
- A decrease in Mean arterial pressure >20% of the baseline is considered hypotension and treated with incremental doses of Inj. Mephentermine 6 mg i.v.
- For nausea and vomiting Inj. Ondansetron 4mg i.v. was given.
- Diclofenac sodium 75 mg i.m.wasgiven if VAS scores were>3 or if requested by the patient..

The patients graded their satisfaction regarding analgesia (very satisfied, mildly satisfied, or not satisfied).

STATISTICAL ANALYSIS

Comparison of quantitative data between groups was done using ANOVA, unpaired t-test, and within groups by student's paired t-test. Qualitative data like the requirement of rescue analgesia were compared by contingency table analysis.

RESULTS

The mean time for onset of adequate analgesia (vas score <= 3) was 24.2 ±3.96 min in group A, 8.06 ±1.63 min in group B, and 7.5 ±1.16 min in group C, which was statistically comparable among all the groups ($p<0.05$) (Table 1).

Table 1: Comparison and analysis of onset of analgesia (VAS =<3)

Demographic Profile	Group A (Mean±SD)	Group B (Mean±SD)	Group C (Mean±SD)	p value
Time of onset (min)	24.2±3.96	8.06±1.63	7.56±1.16	<0.05

The onset of analgesia was much faster in group B & group C when compared to group A ($p<0.05$ in both comparisons) which was statistically significant (Table 1).

VAS Score

In comparison with Group A & Group B, Group C had lower VAS scores during the latter part of the study (8 – 24 hrs) (Table 2)

Table 2: Comparison and analysis of Visual Analog Scale Scores

	Group A	Group B	Group C	p value (ANOVA)
AT T0 Min	6.73±1.65	6.65±1.35	7.23±1.1	> 0.05
After 30 min	0.6±0.62	1.06±0.73	1.06±0.78	<0.05
After 1 hr	0.83±0.64	0.63±0.49	0.4±0.49	< 0.05
After 2 hr	0.56±0.5	0.33±0.47	0.26±0.42	<0.05
After 4 hr	0.5±0.62	0.56±0.56	0.56±0.5	> 0.05
After 8 hr	1.5±0.97	1.23±0.62	1.06±0.69	> 0.05
After 12 hr	5.5±1.88	2.76±1.52	1.66±0.36	<0.05
After 24 hr	7.1±0.80	6.2±1.24	1.83±1.39	<0.05

Inference: Statistically, there was no difference in VAS of patients amongst the three groups

Sedation score

No significant sedation was observed in any of the groups (p>0.05, ANOVA) (Table 3).

Table 3: Comparison of Maximum Sedation Score in three groups

N = 30	Group A	Group B	Group C
Mean ± SD	1.62 ±0.41	1.75 ± 0.49	1.77± 0.50
Range	1– 3	1 – 3	1– 3

Heart Rate

The baseline heart rate was comparable among the 3 groups. Intragroup analysis showed no significant change in heart rate occurred from the baseline in any of the groups following epidural injection upto a period of 24 hrs (p>0.05, repeated measures ANOVA) (Table 4)

Table 4: Comparison and analysis of Heart Rate (bpm)

Duration	Group A	Group B	Group C	p value (ANOVA)
Baseline	80.63±7.84	82.9±8.92	88.06±8.7	0.07
AT T0 Min	85.2±6.18	84.46±8.09	87.63±11.29	> 0.05
After 30 min	79.94±7.75	81.7±6.81	83.33±8.63	>0.05
After 1 hr	79.96±7.72	79.2±5.28	80.3±7.93	> 0.05
After 2 hr	79.86±7.514	76.16±5.61	78.33±7.42	>0.05
After 4 hr	79.76±7.28	75.4±4.40	77.7±7.14	> 0.05
After 8 hr	79.63±7.17	77.7±4.5	78.3±9	> 0.05
After 12 hr	79.33±7.63	79.4±4.88	80.23±8.08	>0.05
After 24 hr	79±7.37	80.53±7.87	78.7±14.7	>0.05

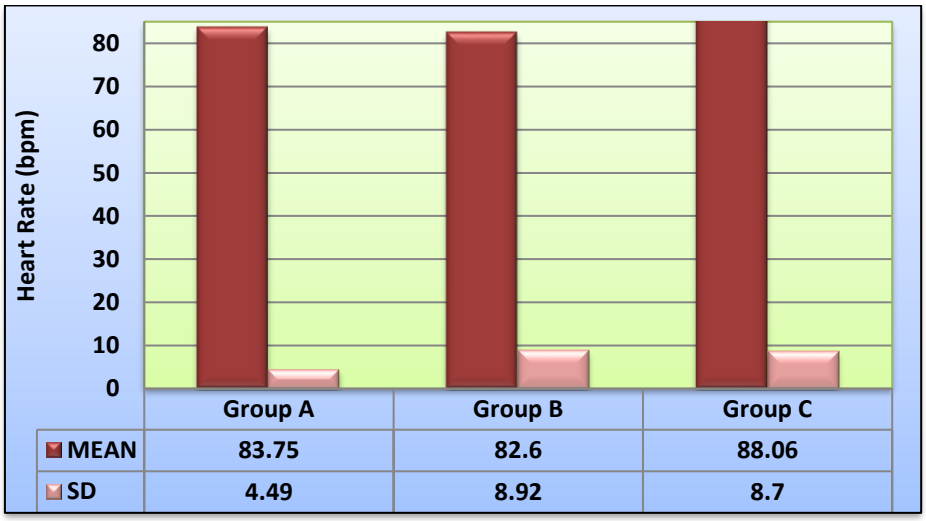

Figure 1: Bar Diagram showing Comparison and analysis of Baseline Heart Rate (bpm)

*Inference: Statistically, there was no difference in the baseline Heart rate of patients amongst the three groups

Blood pressure

Table 5: Comparison and analysis of Mean Arterial Pressure (mm Hg)

Duration	Group A	Group B	Group C	p value (ANOVA)
Baseline Range	90.06±8.9 72-99	92.8±9.58 80-99	94.66±8.67 78-90	0.77
AT T0	87.53±6.96 70-99	90.03±7.6 82-98	92.9±7.3 88-98	> 0.05
AT T 30 min	86.73±6.22 70-97	87.06±7.44 78-95	90.16±7.26 90-98	> 0.05
AT T1 hr	81.03±7.76 66-97	83.7±6.56 75-97	86.9±6.43	>0.05
At T2 hrs	81.2±6.5 72-97	80.53±6.1 68-94	83.5±6.49 86-96	> 0.05
At T4 hrs	82.83±7.08 72-99	82±5.07 70-92	81.36±6.41 86-94	> 0.05
AT 8 hrs Range	87.06±6.41 67-97	87.43±6.20 75-95	79.5±6.63 68-96	> 0.05
AT 12 hrs	91.6±4.12 68-97	93.5±3.64 78-86	77.06±6.23 70-94	> 0.05
AT T24 hrs	94.83±3.30 98-98	93.66±3.91 78-87	88.8±4.05 80-98	>0.05

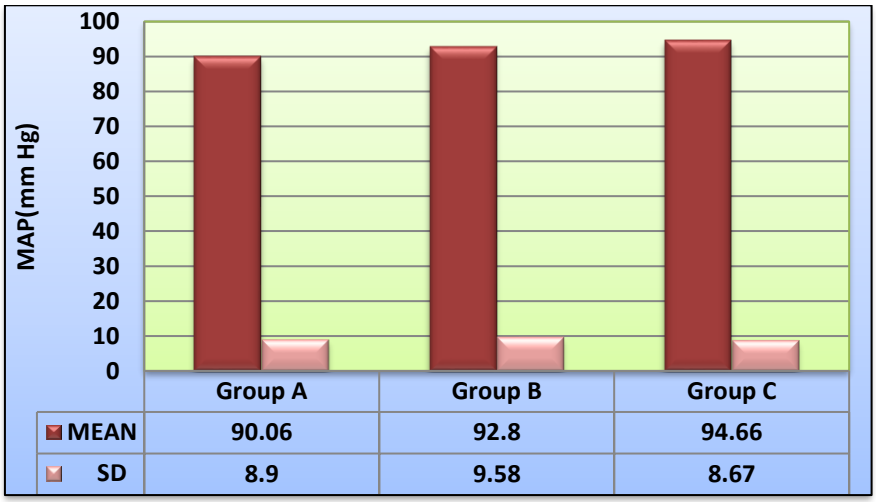

Figure 1: Bar Diagram showing Comparison and analysis of Baseline Mean Arterial Pressure (mm Hg)

*Inference: Statistically (p>0.05) there was no difference in Baseline MAP of patients amongst the three groups.

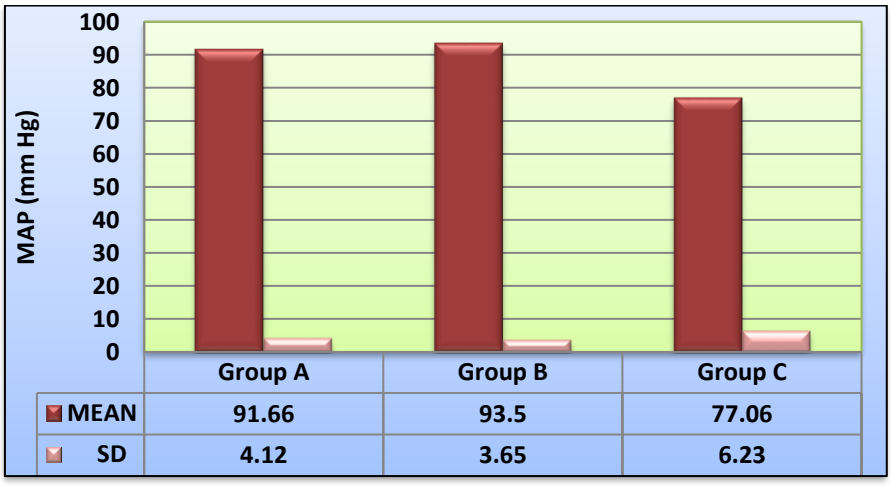

Figure 2: Bar Diagram showing Comparison and analysis of Mean Arterial Pressure (mm Hg) AT T12 hr

*Inference: Statistically (p>0.05) there was no difference in MAP at T12 amongst the three groups.

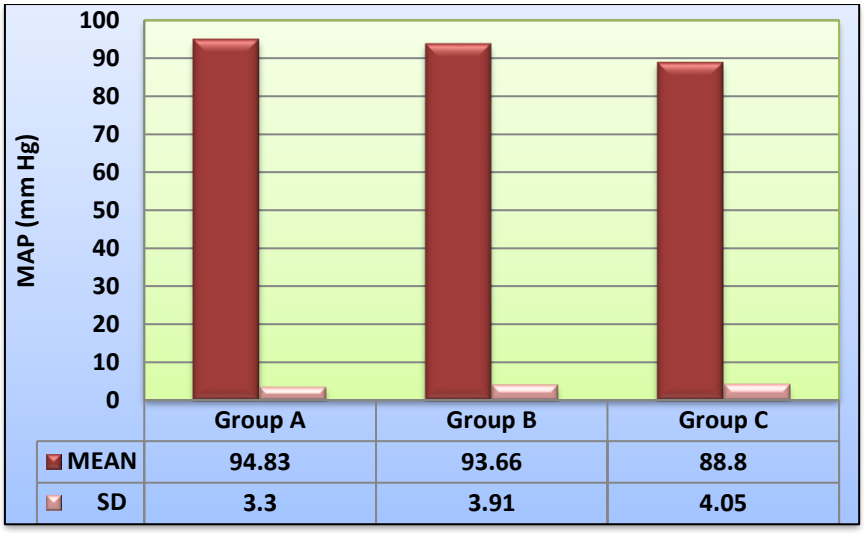

Figure 3: Bar Diagram showing Comparison and analysis of Mean Arterial Pressure (mm Hg) AT T24 hr
*Inference: Statistically (p>0.05) there was no difference in MAP at T24 amongst the three groups.

The duration of analgesia (time for request of rescue analgesic) was significantly prolonged in group C, with the duration of analgesia being 10.46±1.96 hrs in group A, 10.5±1.16 hrs in group B, and 26.7±1.96 hrs in group C (Table 7).

Table 6: Comparison of Age & weight in three groups

Demographic Profile	Group A	Group B	Group C	p value (ANOVA)
Age(yrs) (Mean±SD) Range (yrs)	40.76±11.13 23-60	44.06±13.02 20-60	41.4±10.25 21-60	0.508
Wt.(kg) (Mean±SD) Range (kg)	55.75±4.40 50-62	55.5±3.74 50-62	56.65±4.03 50-62	0.645

*Inference: Statistically (p>0.05) there was no difference in age and weight of patients amongst the three groups.

Table 7: Comparison and analysis of duration of Surgery

Demographic Profile	Group A	Group B	Group C	p value (ANOVA)
Duration of surgery (min) (Mean±SD)	130.66±44.58	139.5±57.88	141.6±250.55	>0.05

*Inference: Statistically (p>0.05) there was difference in the duration of Surgery amongst the three groups which was statistically insignificant.

Table 8: Comparison and analysis of onset of analgesia (VAS =<3)

Demographic Profile	Group A	Group B	Group C	p value (ANOVA)
Time of onset(mins) (Mean±SD)	24.2±3.96	8.06±1.63	7.56±1.16	<0.05

Inference: Statistically (p<0.05) there was difference in the onset of analgesia amongst the three groups which was statistically significant.

Comparison and analysis of onset of analgesia, Comparison of VAS scores between group B and Group C, difference in sedation score in three groups and Comparison of level of satisfaction in three groups were shown in table 8, 9, 10 and 11 respectively.

Table 9: Comparison of VAS scores between group B and Group C

	T value	P value
At T 1 hr	6.55	<0.05
At T 2hr	6.36	<0.05
At T 4hr	6.23	<0.05
At T 8 hr	5.09	<0.05

Inference: There was a difference in the intragroup analyses of VAS scores from 1 to 8 hrs and this difference

was statistically significant.($p<0.05$)

Table 10: Comparison of Maximum Sedation Score in three groups

N = 30	Group A	Group B	Group C
Mean ± SD	1.62 ±0.41	1.75 ± 0.49	1.77± 0.50
Range	1– 3	1 – 3	1– 3

Table 11: Comparison of level of satisfaction in three groups

N = 30	Satisfied	Mildly Satisfied	Not Satisfied
Group A	28	1	1
Group B	29	1	0
Group C	29	1	0

Adverse effects and complications

- Nausea and vomiting was observed in 2 patients in group A, 1 patients in group B and 3 patients in group C that was statistically not significant($p>0.05\%$) and all these patients were successfully treated with inj. Ondansetron 4 mg i.v.
- No patient in any group had other side effects like hallucination, disorientation, shivering, temporary or permanent neurological deficit.
- Bradycardia was seen in no patients in any of the groups.

DISCUSSION

Optimal pain relief following surgery cannot be achieved by a single drug or method without major strain on equipment or surveillance systems. Multimodal or balanced analgesia is defined as the use of two or more analgesic drugs or techniques in combination. At present, multimodal analgesia is the most effective treatment of postoperative pain. The rationale of balanced analgesic approach is achievement of sufficient analgesia due to additive or synergistic effects between different analgesics with concomitant reduction of side effects.

Local anaesthetics are the commonest agents used for regional anaesthesia and also for postoperative analgesia. The efficacy of the local anaesthetic can be enhanced by using adjuvants like Opioids, α2 agonists and by alkalinisation of local anesthetics.

In the present study we evaluated the effects of addition of clonidine to alkalinized 0.2% ropivacaine in single shot epidural for post operative analgesia in abdominal surgeries under general anaesthesia. In this study the onset & duration of analgesia after administration of these drugs epidurally& hemodynamic parameters postoperatively were evaluated in all the groups. In addition, the degree of sedation, quality of analgesia & any complications associated were evaluated.

The studies done by Niemi [7] and Negri et al [8] reported significant sedation with clonidine. The sedative effect of clonidine is dose-dependent and is said to be due to its action on the locus coeruleus. The dose of clonidine used in our study was 37.5mcg, which was lower than the dose used in the above studies. Hence, the lower dose of clonidine used in this study may explain the absence of sedative effects. The quality of block was superior in patients of the study group (group C) when compared with the other two groups (group B & group A) with consistently lower VAS scores during 1-8 hrs of the postoperative period. These findings were in concurrence with those of Claes et al [9], Huang et al [10] and Klimscha et al [11].

There was no significant difference in Mean Arterial Pressure values in between the three groups. Incidence & duration of hypotension was comparable between the three groups. Bradycardia was not seen in any of the patients. This again may be due to the fact that a lesser dose of 37.5mcg was administered to the patients because Filos KS et al [12]. concluded that even though epidural clonidine provided effective post operative analgesia but it wasn't without significant hypotension and bradycradia. That they had used 300 mcg of clonidine epidurally may have something to do with it. There have been studies though which have shown that epidural clonidine is more hemodynamically stable [11].

The quality of block was superior in patients of the present study group (Group C) when compared with the other two groups (Group B & Group A) with consistently lower VAS scores during 1-8 hrs of the postoperative period. These findings were in concurrence with those of Brigitte Claes, et al [13] Huang et al [10] and Klimscha et al [11].

CONCLUSION

The purpose of this study was to evaluate and compare the analgesic and hemodynamic effects of the addition of clonidine to single-shot epidural alkalinized 0.2% ropivacaine for postoperative analgesia in patients undergoing abdominal surgeries under general anesthesia. 90 adult patients were divided randomly into three groups as follows:

The time to onset of analgesia was reduced in patients receiving alkalinized ropivacaine (group B & group C). The addition of clonidine to alkalinized 0.2 % ropivacaine however did not further reduce the time of onset of analgesia when compared with the group administered alkalinized 0.2 % ropivacaine alone. Duration of analgesia was significantly increased in patients receiving alkalinized 0.2%

ropivacaine and clonidine. Alkalinized ropivacaine alone did not increase the duration of analgesia significantly when compared with the control group. None of the groups had significant sedation. The study group with clonidine also did not show significant sedation. This may be because a lesser dose of clonidine was used in the study.

We concluded that the addition of 37.5mcg of clonidine to single shot epidural epidural with alkalinized 0.2% ropivacaine for post-operative analgesia in patients undergoing abdominal surgeries, effectively prolonged the duration of analgesia.

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