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Volume 6 (6 issues) will be published in 2019
pISSN: 2349-8471, eISSN: 2455-6238

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INDIAN JOURNAL OF ANESTHESIA AND ANALGESIA

March-April 2022
Volume 9 Number 2

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Original Article

Indian Journal of Anesthesia and Analgesia
Volume 9 Number 2 March-April 2022
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.9222.8

A Comparative Study of 0.1% Ropivacaine with Fentanyl and 0.1% Ropivacaine with Clonidine for Epidural Labour Analgesia

Varalakshmi Karasala[1], Mukesh Somvanshi[2], Archana Tripathi[3], Upendra Kumar[4]

Author's Affiliation: [1]Post Graduate Student, [2,3]Senior Professor, [4]Medical Officer, Department of Anesthesiology and Critical Care, Government Medical College and AG Hospitals, Kota, Rajasthan 324005, India.

Abstract

Background: Pain relief in labour has always been surrounded with myths and controversies. Hence providing effective and safe analgesia during labour has remain an ongoing challenge. This study was undertaken to compare fentanyl and clonidine with ropivacaine in epidural labour analgesia.

Methods: A total of 60 term parturients with uncomplicated pregnancy, vertex presentation, posted for on-demand epidural labour analgesia were divided into two groups. Group RF (n=30) patients received 10ml solution comprising 0.1% ropivacaine with fentanyl 20mcg. Group RC (n=30) patients received 10ml of 0.1% ropivacaine with clonidine 60mcg. Characteristics of the block, onset and duration of analgesia and total analgesic requirements were noted. Pain and overall satisfaction scores were assessed with a 10-point visual analogue scale. Mode of delivery and neonatal APGAR scores were recorded.

Result: At baseline, groups were matched demographically, haemodynamically as well as for intensity of pain. A significant difference among groups in VAS was observed from 120min intervals and lowest values were in group RC. No significant difference was observed in haemodynamic parameters, mode of delivery and expulsive efforts. Total analgesic dose and top up dose requirement was more in group RF. Six percent of patients in group RF and 10 percent of patients in group RC developed nausea.

Conclusion: Ropivacaine 0.1% was effective in decreasing labour pain without any motor blockade. Clonidine was superior to fentanyl as an adjuvant in labour without any significant feto-maternal adverse effects.

Keywords: Ropivacaine, fentanyl, clonidine, epidural labour analgesia.

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Corresponding Author: Upendra Kumar, Medical Officer, Department of Anesthesiology and Critical Care, Government Medical College and AG Hospitals, Kota, Rajasthan 324005, India.
E-mail: drupendra1010@gmail.com
Received on: 29.01.2022, **Accepted on:** 28.02.2022

Introduction

The labour is reported to be one of the most painful experiences in a women's life. Pain relief in labour has always been surrounded with myths and controversies. Hence providing effective and safe analgesia during labour has remain an ongoing challenge. Advances in the field of labour analgesia have tread a long journey from the days of ether and chloroform in 1847 to the present day practice of comprehensive programm of labour pain management using evidence based medicine.

Ropivacaine is an amide local anaesthetic with a chemical structure similar to bupivacaine. A number of studies[1-3] suggested that ropivacaine is associated with less CNS and CVS toxicity and produces less motor block than bupivacaine and these qualities make ropivacaine advantageous for management of painless labour. Reduction in the concentration of local anaesthetics and addition of adjuvants like opioids and non opioids has been advocated to improve the results and minimize risks in epidural labour analgesia. This allows the patient to be ambulatory with preservation of motor function and subjective somatic sensation of lower limbs.

Several studies[4,5] have shown that addition of clonidine/fentanyl improves the quality of anaesthesia, reduces the dose requirement of local anaesthetic agent and provided better haemodynamic stability. Hence this study was undertaken to compare the effects of addition of fentanyl or clonidine added to 0.1% ropivacaine for epidural labour analgesia when given as intermittent top up doses.

Methods

After institutional ethical committees approval and written informed consent, the present study was conducted on sixty term parturient of ASA grade 1 or 2 with singleton pregnancy in vertex presentation and parturient in active labour with cervical dilatation 3-6 cm requesting pain less labour were included in the study. Exclusion criteria were: ASA grade 3 and 4, patient refusal, bleeding disorders, thrombocytopenia, history of allergy to local anaesthetics, hypovolaemia, local sepsis, patient with antepartum haemorrhage, severe eclampsia, cephalopelvic disproportion, and cervical dilatation>6cm. This double blind study was conducted on 60 patients who were randomly divided into 2 groups of 30 patients each.

Group RF (n=30): Patients were administered 0.1% ropivacaine 10 ml and fentanyl 20 mcg.

Group RC (n=30): Patients were administered 0.1% ropivacaine 10 ml and clonidine 60mcg. After confirming the active first stage of labour and cervical dilatation 3-6 cm, epidural block was performed after proper positioning of the patient. An intravenous access was secured and at least 500 ml of ringer lactate solution was given. Standard monitoring were applied like ECG, NIBP, pulse oximetry. Under all aseptic precautions, epidural space was identified in sitting position with midline approach using 18 gauge Tuohy's needle in L3-4 or L4-5 interspace with loss of resistance to air technique and after confirmation of epidural space, catheter was threaded cephalad 3 to 4 cms into epidural space and patient had been shifted in supine position with wedge under left buttock. After negative aspiration for blood and CSF, a test dose of 3ml of lignocaine 1.5% with 1:2,00,000 adrenaline was administered through the catheter to exclude intravenous or subarachnoid catheter placement.

Five minutes after administering the test drug, 10 ml of study drug of either 0.1% ropivacaine with fentanyl 20mcg or 0.1% ropivacaine with clonidine 60mcg was given. Following 10 min of drug administration, patient was asked to lift legs straight without flexing the knees. When patient was able to lift legs easily without bending knees, she was asked to take a trial walk.

Next top up doses were given on demand. Before giving each top up dose, aspiration was done. Following every top up dose, patients were monitored carefully for 10 min to detect any weakness or inadequate analgesia. When analgesia was inadequate (VAS>3), top up was repeated upto maximum of 20 ml at a time. The study was ended at the time of vaginal delivery, assisted or not, or when the decision was made to perform a caesarean delivery.

Parturient's vital parameters like pulse, blood pressure, respiratory rate, VAS score, motor power grade, foetal heart rate and any side effects or complaints were noted before block and after block at 0, 15, 30, 45, 60, 90, 120, 150 and 180 min interval. Mode of delivery was recorded and neonates were evaluated by means of Apgar score at 1 and 5minutes. Total analgesic dose of local anaesthetic and total number of top up doses were also recorded. After delivery epidural catheter was removed. Parturient were interviewed a day after delivery for satisfaction level and quality of analgesia on four point scale (Excellent, Good, Fair and Poor). Statistical analysis of data was done using Student's 't test and Chi-square test. Ap–

value less than 0.05 was considered as statistically signifcant.

Results

As shown in table no 2, demographic and obstetric variables were comparable in both groups. The difference in onset of analgesia was not significant statistically. At baseline no significant difference was observed in VAS score between the groups, however, VAS score was significantly less from 120min in group RC than group RF.

Table 1: Modified Bromage score.

Grade	
0	Normal movement in hip, knee and foot, No motor block
1	Weakness in hip muscles, Inability to raise extended leg
2	Weakness in knee muscles, Inability to flex knee
3	Motor block of hip, knee, Inability to flex ankle joint

Table 2: Demographic and obstetric characteristics.

Variables	Group RF	Group RC
Age (yr)	24.26± 3.63	23 ± 3.1
Weight (kg)	67.73 ± 3.88	69.77 ± 4.5
Height (cm)	158.20 ± 2.37	158.97± 2.72
Duration of labor (min) First stage	208± 70.03	224 ± 63.38
Second stage	43 ± 14.57	46 ± 15.67
Onset of analgesia (min)	22.17 ± 1.70	21.87 ± 1.80
Duration of effective analgesia(min)	65.33 ±7.30	107.67 ±4.50
Level of sensory block	T8 (T7-T9)	T8 (T7-T9)
Mode of delivery, no (%) Vaginal delivery	28 (93.33)	26 (86.67)
Forceps delivery	2(6.67)	4(13.33)
Cesarean delivery	0	0
Total dose of Study drug (mg)	R=38.77 ±8.20 F=20	R=24.37 ± 6.57 C=60
Total number of top up doses	3.4±1.13	1.9±0.52
APGAR Score at 1 min	8.33 ± 1.06	8.6 ± 0.49
5 min	9.83 ± 0.79	10
Patient satisfaction, no (%) Excellent	3(10)	24 (80)
Good	26 (86.67)	6(20)
Fair	1 (3.33)	0
Poor	0	0

Values are expressed as mean ± SD, no (Percentage) and median (range), Group RF vs RC

R=Ropivacaine, F=fentanyl, C=Clonidine

Table 3: Motor block.

Bromage Score Grade	Group RF no (%)	Group RC no (%)
0	30 (100)	30 (100)
1	0	0
2	0	0
3	0	0

The difference in duration of analgesia was statistically significant in both groups (p<0.05). This duration of analgesia was significantly prolonged in group RC than group RF. According to modified Bromage scale (Table 1), none of the parturient developed motor block in both groups (Table 3).

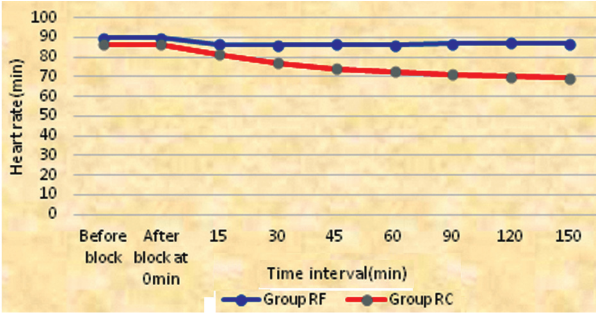

Fig. 1: Heart rate per min.

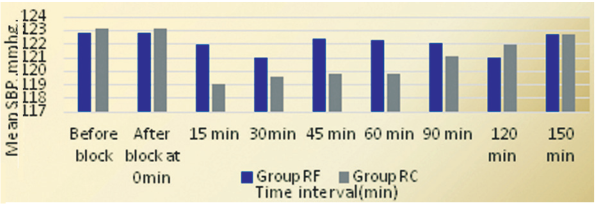

Fig. 2: Systolic blood pressure (mmhg).

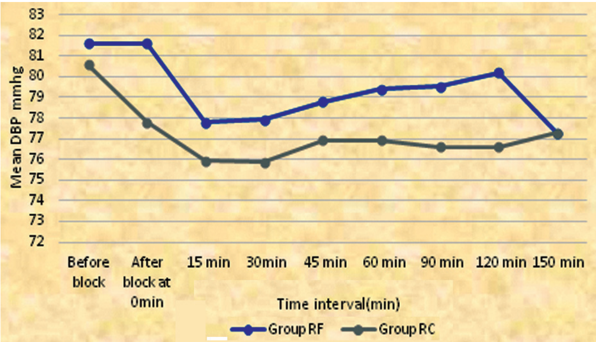

Fig. 3: Diastolic blood pressure (mmhg).

At all the time intervals during the study heart rate was less in group RC when compared with group RF (Fig. 1). However, the difference in heart rate was statistically insignificant at all the time except at 150min after epidural at which heart rate was significantly lower in group RC compared to group RF. The mean systolic and diastolic blood pressure decreased slightly after the initial dose of the drug until 15-30 minutes, thereafter remained stable in both groups (Fig. 2 and 3). The changes in the value of mean systolic and diastolic blood pressure in the two groups were statistically insignificant ($p<0.05$).

The difference in total dose of study drugs used in this study was statistically significant (Table 2). The difference in mean total number of top up doses was statistically significant in both groups (Table 2). No significant difference was observed among groups for mode of delivery (normal, forceps assisted or cesarean). A significantly higher nuber of patients had excellent patient acceptance in group RC as compared to group RF (Table 2).

None of the patient had APGAR score <7 at 1min and 5min interval (Table 2). On comparing adverse effects six percent of patients in group RF and ten percent of patients in group RC developed nausea and two patients had vomiting in group RC. Only one patient in group RF and two patients in group RC developed retention of urine and two patients in group RF and one patient in group RC had pruritus.

Discussion

Safe foetal outcome without any adverse maternal effect is the chief goal of pain relief during labour and lumbar epidural analgesia is the most efficient and widely employed modality for this. Of all the available methods of labour analgesia, epidural analgesia is the most effective form of analgesia and satisfies the basic requirements of labour analgesia by fulfilling the objective of decreasing the pain of labour without affecting other sensations such as a desire to push and to allow normal walking while preserving the tone of pelvic floor muscles as well as retaining the sensation of the baby's head in the vagina; thus allowing labour to proceed unhindered. Thus it is considered as gold standard in obstetric care.

Ropivacaine has been used in neuraxial, epidural and subarachnoid anaesthesia. It has a profile similar to bupivacaine but with less neuro and cardi-toxic effect.[6] Opioids are the most widely used class of adjuvant to epidural local anaesthetic in labour analgesia practice. Fentanyl and remifentanyl are the two most commonly used opioid for this purpose. The dose of fentanyl used in our study was 2mcg/ml of drug solution in loading bolus.

Clonidine being alpha-2 agonist, is known to increase the effectiveness of local anaesthetic agent in epidural labour analgesia in many studies.[7,8] The dose of clonidine used in our study was 1mcg/kg in loading bolus, which approximates to 50-70mcg/kg clonidine in loading bolus. Previous studies[9] have shown that clonidine used in doses greater than 100mcg have been associated with maternal and foetal bradycardia, maternal hypotension while doses less than 30mcg are ineffective in increasing the potency of local anaesthetics, but 60mcg clonidine is effective in labour analgesia when given with local anaesthetics. So we used the clonidine in 60mcg/kg dose as obese and malnourished patients were excluded from our study.

The VAS score of the two groups were comparable at baseline and throughout the labour and no significant difference was found between the groups except at 120min. Although, at 120min the difference in VAS was statistically significant, however, it was clinically insignificant as at 120min the mean VAS in both groups was less than 2 which was clinically acceptable grade of analgesia. Thus we can say that both drug solutions used in our study were able to achieve adequate and acceptable analgesia in laboring females.

At all the time intervals during the study, patient remained stable haemodynamically in both groups. The results of our study correlates with Ahirwar A et al.[10] We preloaded the patients to avoid any hypotension due to sympathectomy and it seems that preloading is adequate to prevent any episode of hypotension associated with initiation analgesia. No patient in any of the group required vasopressor for treatment of hypotension: therefore we can say that there is no risk of hypotension with the use of epidural analgesia with the drug combinations used in our study.

In group RF, two patients required instrumental vaginal delivery while in group RC instrumentation was required in four patients. The rate of normal vaginal delivery in group RF and group RC were 93% and 87% respectively. Previous studies[11,12,13] found that the rate of spontaneous delivery was similar in both fentanyl and clonidine groups which is also seen on our study.

As shown in table 2, the total dose of ropivacaine required and the total number of top up doses required were less in group RC than in group RF. Thus clonidine seems to be more effective as it reduced the total dose of ropivacaine and total number of top up doses required during first and second stage of labour. The dose sparing effect of clonidine on ropivacaine was also proven by Kumari I et al[14] and Topcu I et al.[15]

Conclusion

Thus we conclude that both drug combinations of 0.1% ropivacaine with fentanyl and 0.1% ropivacaine with clonidine were effective in controlling labour pain and 0.1% concentration of ropivacaine was sufficient for labour analgesia without causing any motor weakness which can affect the ambulation of the patient or the maternal expulsive efforts.

The addition of fentanyl and clonidine can decrease the requirement of ropivacaine and helps in the reduction of local anaesthetic toxicity. Clonidine and fentanyl does not cause any adverse foetal or maternal outcomes. Thus in our study, we found that both fentanyl and clonidine have dose sparing effect on 0.1% ropivacaine with stable haemodynamics and no significant feto-maternal adverse effects. However, clonidine is better than fentanyl in dose sparing effect with longer effective duration of analgesia, better quality of analgesia and excellent patient acceptance for epidural labour analgesia.

References

1. David C. Campbell, Rhonda M. Zwack, Lesley-Ann L. Crone, Ray W. Yip. Ambulatory labor epidural analgesia: bupivacaine versus ropivacaine. Anesth Analg 2000; 90: 1384–9.
2. P. D. W. Fettes, C. S. Moore, J. B. Whiteside, G. A. Mcleod, J. A. W. Wildsmith. Intermittent vs continuous administration of epidural ropivacaine with fentanyl for analgesia during labour. Br J Anaesth 2000; 97: 359–64.
3. Firoz Satpathy, Archana Tripathi, Mukesh Somvanshi, Pallavi Huilgol. A comparative study of 0.1% ropivacaine with fentanyl and 0.1% bupivacaine with fentanyl for epidural labour analgesia. Ind J Anesth Analg.2020;7:41-5.
4. Helene Finegold, Gordon Mandell, Sivam Ramanathan. Comparison of ropivacaine 0.1%-fentanyl and bupivacaine 0.125% -fentanyl infusions for epidural labour analgesia. Can J Anesth 2000; 47(8): 740–45.
5. Meister GC, D' Angelo R, Owen M, Nelson KE, Gaver R. A comparison of epidural analgesia with 0.125% ropivacaine with fentanyl versus 0.125% bupivacaine with fentanyl during labor. Anesth Analg 2000;90:632-7.
6. Scott DB, LeeA, Fagan D, Bowler GMR, Bloomfield P and Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989;69:563-9.
7. Claes B, Soetens M, Zundert AV, Datta S. Clonidine added to bupivacaine-epinephrine-sufentanyl improves epidural analgesia during childbirth. Reg Anesth Pain Med.1998;23(6):540-47.
8. Aveline C, Metaoua SE, Masmoudi A, Boelle PY, Bonnet F. The effect of clonidine on the minimum local analgesic concentration of epidural ropivacaine during labour. Anesth Analg. 2002;95(3):735-40.
9. Roelants F. The use of neuraxial adjuvant drugs (neostigmine, clonidine) in obstetrics. Curr Opin Anaesth. 2006;19(3):233-37.
10. Ahirwar A, Prakash R, Kushwaha BB, Gaurav A Chaudhary AK, Verma R,et al. Patient Controlled Epidural Labour Analgesia (PCEA): A comparison between ropivacaine, ropivacaine-fentanyl, ropivacaine-clonidine. J Clin Diagn Res 2014;8:GC09-13.
11. Ismet T, E Tuna, T Selcen, K Oznar, I Rusen, S Melek. The Comparison of Efficiency of Ropivacaine and Addition of Fentanyl or Clonidine in Patient Controlled Epidural Analgesia for Labor. The Int J Anesth.2006;(11):2.
12. Smedvig JP, Soriede E, Gjessing L. Ropivacaine 1mg/ml, plus fentanyl 2mcg/ml for epidural analgesia during labour. Acta Anaesthesiol Scand.2001;45(5):595-99.
13. Celleno D, Capogna G, Costantino P, Zangrillo A. Comparison of fentanyl with clonidine as adjuncts for epidural analgesia with 0.125% bupivacaine in the first stage of labor. Int J Obstetr Anesth. 1995;4(1):26-9.
14. Kumari I, Sharma K, et al., Comparison of Ropivacaine 0.2% with or without clonidine 1mcg/kg for epidural labor analgesia: A randomized controlled study. J Anaesthesiology pharmacol 2018;34;B-22.
15. Topcu I, Erincler T, Tekin S,Karaer O, Isik R, Sakarya M. The comparision of efficiency of ropivacaine and addition of fentanyl or clonidine in patient controlled epidural analgesia for labour.Internet J Anesthesiol 2006;11:1-7.

Original Article

Indian Journal of Anesthesia and Analgesia
Volume 9 Number 2 March-April 2022
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.9222.9

Effect of Dexmedetomidine as an adjuvant to Ropivacaine in Supraclavicular Brachial Plexus Block

Vijeta Khandelwal[1], Himanshu Nagar[2]

Author's Affiliation: [1]Associate Professor, [2]Postgraduate Student, Department of Anesthesiology and Critical Care, Government Medical College and AG Hospitals, Kota, Rajasthan 324001, India.

Abstract

Aims: A study was performed to evaluate the effect of dexmedetomidine added to ropivacaine on Supraclavicular brachial Plexus block characteristics, postoperative analgesia, haemodynamics and sedation.

Methods: Sixty patients, of ASA grade I & II of either sex, aged 21 to 60 years, who were undergoing various bony orthopaedic surgeries on the upper limb under supraclavicular brachial plexus block were randomly allocated in to two equal groups of 30 patients each to recieve 29 ml ropivacaine 0.75% plus 1ml saline (group R) and 29 ml ropivacaine 0.75% plus dexmedetomidine 1µg/kg body weight in 1ml saline (group RD) in supraclavicular brachial plexus block. Onset and duration of sensory blocks and motor blocks, duration of analgesia, perioperative haemodynamic parameters, VAS and sedation scores were assessed.

Results: Both groups were comparable with regard to demographic data. The onset of sensory and motor block were significantly earlier in group RD as compared to group R. Duration of motor block and analgesia were significantly longer in group RD as compared to group R. Sedation score were significantly higher in group RD. Though HR, NIBP and Respiratory rate were significantly decreased in group RD, however all patients remained haemodynamically stable.

Conclusion: Dexmedetomidine (1µg/kg) is a good adjuvant to ropivacaine (0.75%) has faster onset, early and prolonged duration of sensory and motor blockade and increased duration of analgesia, with arousable sedation in supraclavicular brachial plexus block for upper limb surgeries.

Keywords: Dexmedetomidine, Ropivacaine, supraclavicular block.

How to cite this article:

Vijeta Khandelwal, Himanshu Nagar/Effect of Dexmedetomidine as an adjuvant to Ropivacaine in Supraclavicular Brachial Plexus Block/Indian J Anesth Analg. 2022;9(2):69-73.

Corresponding Author: Himanshu Nagar, Postgraduate Student, Department of Anesthesiology and Critical Care, Government Medical College and AG Hospitals, Kota, Rajasthan 324001, India.

E-mail: hnagarforyou@gmail.com, **Received on:** 28.02.2022, **Accepted on:** 02.04.2022

Introduction

The use of peripheral nerve block for orthopaedic surgery has increased during the last few decades, with increasing demand for post operative pain relief, early & efficient rehabilitation, with reduce morbidity and mortality.[1] Brachial plexus block is a popular and widely employed regional anaesthesia technique for upper limb surgery which avoids unwanted effect of general anaesthesia. It is an excellent alternative for hemodynamic compromised & too ill patients. Supraclavicular brachial plexus block provides satisfactory surgical condition like complete motor & sensory block.[2] Brachial plexus block, is blocked at the level of distal trunk/division.

Besides all local anaesthetics bupivacaine[3] is more frequently used, because of its higher potency and prolonged duration of action. but disadvantage of cardiotoxicity, especially with inadvertent injection into subclavian artery. A long acting local anaesthetic drug, ropivacaine[4] was approved for clinical use in 1996. Ropivacaine is an amino-amide local anaesthetic (LA) effective for both intraoperative anaesthesia and post-operative analgesia. For peripheral nerve blockade, ropivacaine is comparable to bupivacaine and levobupivacaine.[5] However, the lower lipid solubility of ropivacaine gives greater sensory and motor differential blockade and reduces the potential for CNS and cardiotoxicity. Many techniques are used to improve the quality of brachial plexus block like adding an adjuvant, use of ultra sound guided block[6] or insertion of a catheter.[7] In order to avoid catheter complications, adding an adjuvant would be our choice for prolonging the duration of nerve block.

Alpha-2-adrenergic[8] agonists were chosen for their sedative, analgesic, antihypertensive and antiemetic properties along with decreased requirement of local anaesthetics drugs. Dexmedetomidine[9] a selective alpha-2 agonist, with affinity eight times that of clonidine, also has been shown to prolong the sensory and motor duration when added as an adjuvant to local anaesthetic in peripheral nerve block. Thus it is worthy to evaluate the effect of addition of dexmetomidine as adjuvant to Ropivacaine for supraclavicular brachial plexus block.

Materials and Method

After obtaining institutional ethical committee approval patients were explained about the anaesthesia technique and written informed consent was taken. this randomized double blind study was conducted on sixty patients of ASA grade I and II, aged between 21 and 60 years, of either sex, who were undergoing various bony orthopaedic surgeries on the upper limb under supraclavicular brachial plexus block. All the patients were considered otherwise healthy and not have any other medical treatment. Patients were kept NBM for 6-8 hours prior to surgery.

An IV line was secured in the unaffected limb and ringer lactate was started. Standard monitorings were applied using multiparameter monitor and preoperative baseline readings for heart rate, NIBP, pulse oximetry, ECG were recorded. The patients were randomly divided into two group 30 patients in each. Before the procedure, visual analogue scale (VAS) on 0-10 cm was explained to the patient. The supraclavicular block was performed at Midclavicular point, external jugular vein and subclavian artery pulsation were identified.

About 2cm above the midclavicular point just lateral to subclavian artery pulsation, a 24 gauge 1.5 inches short beveled needle was introduced and directed caudal and medially until paraesthesia was encountered, Group R (n=30) received 0.75% Ropivacaine 29 ml + 1ml saline Group RD (n = 30) received 0.75% Ropivacaine 29ml + 1μg/kg of Dexmedetomidine with1ml saline. Sensory block was assessed by the pin prick method at every 1 minute after completion of drug injection in the dermatomal areas corresponding to median nerve, radial nerve, ulnar nerve and musculocutaneous nerve, Sensory onset was defined as a dull sensation to pin prick, Complete sensory block was considered as complete loss of sensation to pin prick, Duration of sensory block defined as Ropivacaine administration to complete resolution of anesthesia, block will be graded as Grade 0:Sharp pin felt, Grade 1: Analgesia, dull sensation felt, Grade 2: Anaesthesia, no sensation felt.

Table 1: Modified Bromage scale.

Grade	Criteria
0	No motor block
1	Unable to raise extended legs
2	Unable to flex knee
3	Unable to flex ankle and foot

Onset of motor blockade, Peak motor block, and. Duration of motor block was determined at each 1 minute according to a modified Bromage scale for upper extremities on a 3-point scale (Table 1). The block was considered incomplete when any of the segments supplied by median, radial, ulnar and musculocutaneous nerve did not have analgesia even after 30 min of drug injection. In this case, general anaesthesia was given. Hemodynamic variables such as heart rate, blood pressure, respiratory rate and oxygen saturation were recorded at 0 min, 5 min, 10 min, 20 min, 30 min and then every 30 min after the block intraoperatively and every 30 min post-operatively. Sedation of the patients was assessed by Ramsay Sedation Score. All patients were observed for postoperative analgesia.

Pain intensity was measured using a 10 cm Visual Analogue Scale (VAS) on 0 to 10 points (0=no pain and 10=worst pain), VAS was recorded post-operatively every 30min till the score of 4 or >4. The rescue analgesia was given in the form of inj. Paracetamol 15mg/kg IV at the visual analogue scale ≥4 and the time of administration were noted. All patients was observed for any side-effects like nausea, vomiting, dryness of mouth and complications like pneumothorax, hematoma & ropivacaine toxicity and treated with appropriate measures. All data were tabulated and analyzed and results were expressed as mean ± standard deviation. All observations were analysed using Student t-test and Chi square test. P-value <0.05 was considered statistically significant.

Results

The demographic data were comparable between the two groups (Table 1). The onsets of the sensory block and motor block were significantly earlier in group RD as compared to group R (Table. 2).

Table 2: Patients variables.

Parameters	Group R	Group RD
Age (years)	32.36±8.55	31.16 ±7.44
Weight (kg)	67.16±5.93	66.90±6.07
Sex (M:F)	24 : 06	25 : 05
Onset of sensory block (min)	13.6±2.47	9.53±2.65
Onset of motor block (min)	19.43±3.95	11.46 ±2.98
Duration of sensory block (min)	303.33±39.52	441.66±74.07
Duration of motor block (min)	278.66±44.77	407.33±53.09
Duration of analgesia (min)	344 ±52.06	685.33±90.02

Values are Mean±SD or number ; p <0.05 significant.

Onset and peak of sensory & motor blockade was faster in group RD as compare to group R. Duration of sensory & motor blockade was longer in group RD than in group R. Prolonged duration of analgesia was observed in group RD than Group R (Table 3). In 24 hr post block period consumption of rescue analgesic was significantly lower in RD group than in group R. Sedation was higher in group RD than group R.

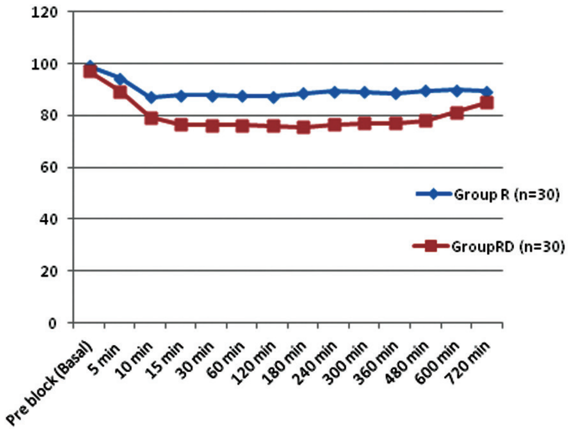

Fig. 1: pulse rate per min.

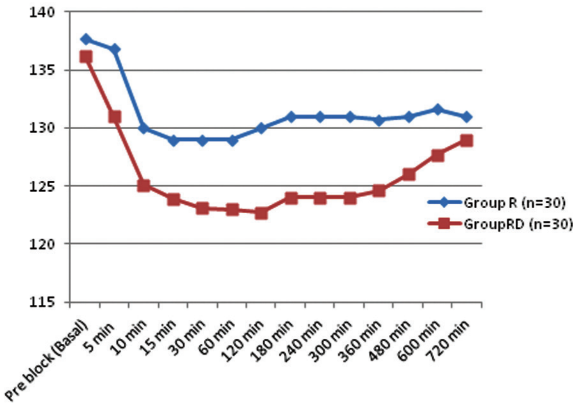

Fig. 2: Systolic Blood pressure (mmHg).

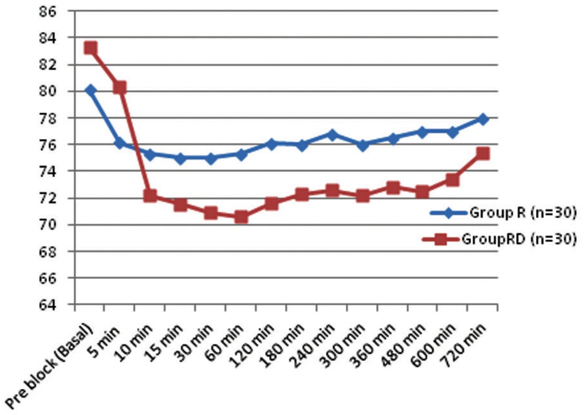

Fig. 3: Diastolic blood pressure (mmHg).

The VAS score was more decreased and remained significantly at low level in group RD as compared to group R after the block & difference was statistically significance (P<0.05) fall in pulse rate, SBP, DBP and respiratory rate was much more in

RD group than R group and remained significantly low (P<0.05). Hemodynamical stability was seen in both groups but patients in group RD were more stable than group R. No significant side effects or complications were seen in both groups.

Table 3: Sedation Score.

Time	Group R		Group RD	
	mean	SD	mean	SD
Pre block (Basal)	1.06	0.24	1.03	0.18
Post block at				
5 min	1.8	0.4	1.96	0.17
10 min	2	0	2.2	0.44
15 min	2	0	2.53	0.49
30 min	2	0	2.53	0.49
60 min	2	0	2.5	0.5
120 min	2	0	2.3	0.45
180 min	2	0	2.13	0.33
240 min	2	0	2.1	0.2
300 min	2	0	2	0
360 min	2	0	2	0
480 min	2	0	2	0
600 min	2	0	2	0
720 min	2	0	2	0

Discussion

Alpha-2 adrenergic agonists like dexmedetomidine have property to produce analgesia and sedation when used as an adjuvant in regional anaesthesia. The faster onset of action of local anaesthetics, rapid establishment of both sensory and motor blockade, prolonged duration of analgesia and stable cardiovascular parameters makes these agents a very effective adjuvant in regional anaesthesia.

The results of our study indicate that Dexmedetomidine when added to Ropivacaine 0.75% prolongs the duration of sensorimotor blockade and duration of analgesia perioperative sedation in brachial plexus supraclavicular block by blocking the hyperpolarization-activated cation (Ih) current, α2-adrenoceptor agonist enhances hyperpolarization and inhibits subsequent action potentials.

In the present study, onset time of sensory and motor blocks were significantly earlier in patients who received dexmedetomidine as adjuvant. Similar results were reported by Nema et al (2014)[10] where the onset was earlier in dexmedetomidine group and the result was statistically significant. prolonged duration of analgesia with prolong sensory and motor block with addition of dexmedetomidine in brachial plexus block was also found by Bharti et al (2015)[11] Santosh et al (2016)[12] and vinit et al (2017)[14] in their studies.

Effectiveness of dexmedetomidine as sedation scores were significantly higher as it produced good sedation in significant number of the patients result of our study correlates with Sharma et al (2016).[13] They found better sedation scores in dexmedetomidine group and 24 hr post block period consumption of rescue analgesic was significantly lower in RD group than in group R, where Mean consumption of rescue analgesic in RD group & R group was 2±0.06 & 3.3±0.6 respectively and difference was statistically highly significant (P>0.0001) Nema et al (2014)53 also found that the cumulative analgesia consumption in 24 hr was significantly reduced.

Decrease in pulse rate, SBP, DBP and respiratory rate in both groups, but in RD group much decrease in pulse rate, SBP, DBP and respiratory rate as compared to R group supposed to be due to systemic absorption of dexmedetomidine from the site of drug administration which cause low sympathetic state[13], better control over pain (low VAS score) & sedation. The result of our study coincides with Bharti et al (2015)[11] and Sharma et al (2016).[13] They found that there is a significant decrease in mean pulse rate, SBP, DBP and respiratory rate in patients receiving dexmedetomidine as an adjuvant to local anaesthetics in femoral nerve block. Side effect profile of the dexmedetomidine was favourable as none of the patient in RD group had profound deep sedation or respiratory depression.

Conclusion

We conclude that dexmedetomidine is a good adjuvant in supraclavicular brachial plexus block for upper limb surgeries has faster onset, early and prolonged duration of sensory and motor blockade and increased duration of analgesia, without any significant side effects.

References

1. Danninger T, Opperer M, and Stavros G Memtsoudis. Perioperative pain control after total knee arthroplasty: An evidence based review of the role of peripheral nerve blocks. World J Orthop 2014; 5(3): 225–232.
2. Pathak RG, Satkar AP, Khade RN. Supraclavicular brachial plexus block with and without Dexamethasone–A Comparative Study. Int J Sci Res Pub, 2012; 2(12):1-7.
3. Scott DB, Jebson PJR, Boyes RN. Pharmacokinetic study of the local anaesthetics bupivacaine

(marcain) and etidocaine (duranest) in man Br J Anaesth 1973; 45(10):1010-1012.

4. Kuthiala G and Chaudhary G. Ropivacaine: A review of its pharmacology and clinical use Indian J Anaesth 2011; 55(2): 104–110.
5. Kulkarni SB, Pimpare M, Govardhane BT. Comparison of levobupivacaine with ropivacaine for supraclavicular brachial plexus block. Int J Res Med Sci 2016 ; 4(9) : 3789-3796.
6. Coventry DM, Ultrasound-guided brachial plexus blocks.British journal anaesthesia. Contin Educ Anaesth Crit Care Pain 2014; 14(4):185-191.
7. Bowens C, Sripada R. Regional Blockade of the Shoulder: Approaches and Outcomes. Anesthesiology Res Prac, 2012; 2012: 971963.
8. Giovannitti JA, Thoms Sean M, Crawford JJ. . Alpha-2 Adrenergic Receptor Agonists: A Review of Current Clinical Applications Anesth Prog. 2015; 62(1): 31–38.
9. R, Brown HC, Mitchell DH Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc Bayl Univ Med Cent 2001; 14(1):13–21.
10. Nema N, Badgaiyan H, Raskaran S, Kujur S, Vaskle P, Mujalde M. Effect of addition of dexmedetomidine to Ropivacaine hydrochloride (0.75%) in brachial plexus block through supraclavicular route in upper limb surgeries: A clinical comparative study. J Evol Med Dent Sci 2014; 3(55):12612-621.
11. Bharti N, Sardana DK, Bala I. The Analgesic Efficacy of Dexmedetomidine as an Adjunct to Local Anesthetics in Supraclavicular Brachial Plexus Block: A Randomized Controlled Trial. Anesth Analg. 2015; 121(6):1655-1660.
12. Singh AV, Singh S. Effects of Clonidine as an Adjuvant to Ropivacaine for Brachial Plexus Block Via Axillary Approach International Journal of Interdisciplinary and Multidisciplinary Studies (IJIMS), 2015; 2(5):45-50.
13. Sharma B, Sunny R, Swami AC, Lata S. Effect of addition of dexmedetomidine to ropivacaine 0.2% for femoral nerve block in patients undergoing unilateral total knee replacement: A randomised double-blind study; 2016; 60(6):403-408.
14. Khemka V, Jadeja P.D. Comparative study of Ropivacaine with Dexmedetomidine versus Ropivacaine alone in supra clavicular brachical plexus block for upper limb surgery. Int J Sci Stud 2017;5 (6):74-80.

Original Article

Indian Journal of Anesthesia and Analgesia
Volume 9 Number 2 March-April 2022
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.9222.10

Intraperitoneal Instillation of Ropivacaine 0.375% with Dexmedetomidine vs Ropivacaine 0.375% with Clonidine for Postoperative Analgesia in Laproscopic Cholecystectomy: A Comparative Study

Nazma Jabeen[1], K Yugandhar[2], S Kiran Kumar[3]

Author's Affiliation:

[1]Post Graduate Student, [2]Associate Professor, [3]Professor, Department of Anesthesiology, Mamata Medical College, Khammam 507002, Telangana, India.

Abstract

Introduction: Laproscopic Cholecystectomy is a standard technique for symptomatic cholelithiasis. It is most commonly performed day care surgery. On the day of surgery pt experiences vague abdominal and shoulder pain. As the discharge is delayed due to lack of adequate analgesia, provision of adequate analgesia is of utmost importance.

Objective: To compare the efficacy of postoperative analgesia after intraperitoneal instillation of 0.375% Ropivacaine with Dexmedetomidine vs 0.375% Ropivacaine with Clonidine

Materials and Methods: 40 patients posted for laproscopic cholecystectomy were randomly divided into two groups A and B. Group A received 20 ml of 0.375% Ropivacaine with 1mcg/kg of Dexmedetomididne and Group B received 0.375% Ropivacaine with 1mcg/Kg Clonidine intraperitoneally through the 10mm supraumbilical port before closure. Pain was recorded on Visual Analog Scale at frequent intervals for 24 hrs postoperatively and categorised as either mild, moderate or severe. Inj. Diclofenac 75mg iv was administered as rescue analgesic in pts with moderate to severe pain.

Results: PostoperativeVAS score showed a statistically significant difference between both groups with lower values in Group A compared to Group B. (P< 0.05). The amount of rescue analgesia used was also less with dexmedetomidine as adjuvant.

Conclusion: Ropivacaine 0.375% with 1mcg/kg Dexmedetomidine provided better postoperative analgesia and significantly less requirement of rescue analgesia as compared to 0.375% Ropivacaine with 1mcg/kg clonidine.

Keywords: Ropivacaine; Intraperitoneal instillation; Laproscopic cholecystectomy; Dexmedetomidine; Clonidine.

How to cite this article:

Nazma Jabeen, K Yugandhar, S Kiran kumar/Intraperitoneal Instillation of Ropivacaine 0.375% with Dexmedetomidine vs Ropivacaine 0.375% with Clonidine for Postoperative Analgesia in Laproscopic Cholecystectomy: A Comparative Study/Indian J Anesth Analg. 2022; 9(2): 75-79.

Corresponding Author: Nazma Jabeen, Post Graduate Student, Department of Anesthesiology, Mamata Medical College, Khammam 507002, Telangana, India.

Email: nazmajabeen440@gmail.com, **Received on:** 13.01.2022, **Accepted on:** 22.01.2022

Introduction

Laparoscopic cholecystectomy is a treatment of choice in treating Gall Bladder disease. It has improved surgical outcomes in reduced pain, recovery duration, morbidity, better cosmetic results, and shorter hospitalization. However, it is a minimally invasive procedure; the pain has been mentioned as a major complaint and a reason for delayed postoperative recovery. The origin of pain after laparoscopic cholecystectomy is multifactorial with different pain components secondary to different pain mechanisms: Somatic Pain - Pain from the incisional site, Visceral Pain - pain from abdominal trauma due to gall bladder removal and referred shoulder pain - due to diaphragmatic irritation caused by residual CO_2 in the peritoneal cavity.[1]

Recently the use of local anesthetics for postoperative pain relief after laproscopic cholecystectomy has become a popular technique, and it is part of a multimodal approach to postoperative pain management.[2] The main advantage of using local anaesthetics is that it provides adequate analgesia without any considerable side effects, unlike opioids which may delay recovery.[3]

Intraperitoneal (IP) instillation of local anaesthetic agents alone or in combination with opioids [(4)] and α-2 agonists such as clonidine and dexmedetomidine has been found to reduce postoperative pain following laparoscopic surgeries.[5] The present study was carried out to compare the efficacy of postoperative analgesia after intraperitoneal instillation of 0.375% Ropivacaine with Dexmedetomidine vs 0.375% Ropivacaine with Clonidine in patients undergoing laparoscopic cholecystectomy.

Materials and Methods

After taking approval from the Institutional Ethical Committee and informed consent from the patient and their close relatives; This Comparative prospective randomised controlled double-blind hospital-based study was conducted on 40 patients of ASA grade I & II, 18 to 65 years of age & both sexes undergoing elective laparoscopic cholecystectomy. Patients with any chronic medical illness, allergic to study drugs, pregnant and lactating women are excluded from the study.

The patients were randomly allocated to two groups by a computer generated random number table and group assigned by sealed opaque envelope technique. Blinding was ensured by having an independent anesthesiologist not participating in the study to prepare the study drug in a ready to inject form for a total volume of 20 mL.

Group A received 20 ml of 0.375% Ropivacaine with 1mcg/kg of Dexmedetomidine, and Group B received 0.375% Ropivacaine with 1mcg/Kg Clonidine intraperitoneal through the 10mm supraumbilical port before closure.

General anaesthesia was administered to all patients. Inj. Glycopyrrolate (0.2 mg) and Inj. midazolam (0.03 mg/kg) were given as premedication. General anaesthesia was induced with Inj. Propofol and Inj. Fentanyl (2 µg/kg). Tracheal intubation was facilitated with Inj. Vecuronium (0.06 mg/kg). Anaesthesia was maintained with O_2 and air (50-50%) and isoflurane at 1 Minimum Alveolar Concentration (MAC).

Muscle relaxation was maintained by additional doses of Inj. Vecuronium as and when required. All patients received Inj. Ranitidine and Inj. Ondansetron as antiemetics. Monitoring included heart rate, respiratory rate, continuous ECG, NIBP, SpO_2, and $EtCO_2$. All surgeries were performed in Trendelenburg position. Intra-abdominal pressure of CO_2 was kept stable at 10-12 mmHg in all cases. A volume of 20 ml drug solution was given as an Intraperitoneal instillation site through the umbilical port.

The quality of analgesia was determined by a visual analogue scale (VAS) for 24 hrs. Postoperative pain scores were recorded by independent resident doctors at ½ hr, 1 hr, 2 hrs, 4 hrs, 8 hrs, 12 hrs, and 24 hrs. Postoperative analgesia was standard in all groups. When VAS score was >4, patients were given Diclofenac sodium (75 mg IV). Time to first request of analgesia, the total dose of analgesic required in the first 24 hrs, and any adverse effects such as nausea and vomiting and shoulder tip pain were noted.

Statistical analysis was performed using SPSS software version 12. Continuous data were described as mean±standard deviation (SD), and Categorical data were presented as absolute numbers or percentages. Continuous variables were compared using Student's independent t-test. Chi-square tests were used to match the demographic data of two groups. All data were presented as mean±SD, percentage (%), or number.

Results

There were no significant differences among the two groups regarding patient demographics and operative data (Table 1).

Table 1: Demographics and clinical characteristics of study participants.

Variable	Group A (n=20)	Group B (n=20)	P-value
Age (years)	44.7±11.4	41.0±12.1	0.242
Sex (Male/Female) (n)	12/8	13/7	0.419
Weight (kg)	64.2±12.9	61.0±12.1	0.185
BMI (kg/m2)	26.4±2.8	26.4±4.2	0.746
ASA PS (I/II) (n)	11/9	14/6	0.428
Duration of surgery (min)	70.6±23.7	76.2±32.3	0.296
Duration of anaesthesia (min)	99.8±27.0	106.4±36.9	0.158

Heart rate

In this study there was no significant difference in the heart between the groups at various time intervals. The results were shown in table 2.

Table 2: Comparison of heart rate between the groups.

Heart rate (BPM)	Group A(n=20)	Group B (n=20)	P value
½ hr	88.4±17.7	86.5±16.1	0.56^{NS}
1 hr	68.8±16.3	70.1±15.8	0.87^{NS}
2 hr	75.1±17.8	73.6±16.5	0.92^{NS}
4 hrs	74.7±16.8	72.5±15.1	0.75^{NS}
8 hrs	70.5±12.4	71.7±14.2	0.65^{NS}
12 hrs	72.1±11.2	73.4±10.2	0.34^{NS}
24 hours	75.7±9.1	76.3±8.8	0.45^{NS}

The data are represented as mean ± SD.* denotes p value < 0.05. NS- Non-significant

Systolic blood pressure (SBP)

There was no significant difference in the baseline systolic blood pressure between the groups (p=0.65). Further, the SBP was significantly lower at 1 hour (p=0.005), 2 hour (p=0.002) in group A as compared to the group B. Meanwhile, at 4 and 8 hours there was no significant change in SBP between the groups. The results were shown in table 3.

Table 3: Comparison of Systolic blood pressure (SBP) between the groups.

SBP	Group A(n=20)	Group B (n=20)	P value
½ hr	135.3±18.0	133.3±15.4	0.65^{NS}
1 hr	128.2±14.7	134.3±20.6	0.005*
2 hr	124.1±18.5	130.6±13.6	0.002*
4 hrs	122.0±19.2 8	125.6±15.	0.08^{NS}
8 hrs	121.0±18.56	123.6±12.76	0.12^{NS}
12 hrs	128.2±14.7	134.3±20.6	0.005*
24 hours	121.7±11.6	130.6±10.12	0.001*

The data are represented as mean ± SD.* denotes p value <0.05. NS-Non-significant.

Diastolic blood pressure (DBP)

There was no significant difference in the systolic blood pressure between the groups at various time intervals. The results were shown in table 4.

Table 4: Comparison of Diastolic blood pressure (DBP) between the groups.

DBP	Group A(n=20)	Group B (n=20)	P value
½ hr	80.8±14.6	79.2±11.0	0.65^{NS}
1 hr	78.2±14.8	77.2±11.1	0.78^{NS}
2 hr	77.2±15.7	76.4±11.3	0.62^{NS}
4 hrs	79.4±13.7	80.9±13.3	0.71^{NS}
8 hrs	80.5±14.65	80.2±15.25	0.76^{NS}
12 hrs	81.2±12.12	83.7±15.6	0.61^{NS}
24 hours	82.6±11.45	84.6±16.12	0.54^{NS}

The data are represented as mean ± SD.* denotes p value < 0.05. NS-Non-significant.

The mean VAS scores of group A were significantly lower at all time intervals except till the 2nd hr postoperatively when compared to group B (p<0.05) (Table 2). At 24th hr, the difference between VAS scores of the two groups was statistically significant (p<0.05) (Table 5).

Table 5: Comparison of postoperative VAS scores at various time intervals between the groups.

VAS score	Group A (n=20)	Group B (n=20)	P-value
½ hr	0.25±0.44	0.33±0.47	0.465^{NS}
1 hr	1.58±0.59	1.83±0.54	0.054^{NS}
2 hr	2.10±0.67	2.23±0.66	0.404^{NS}
4 hrs	1.48±0.71	4.13±0.72	0.000*
8 hrs	1.75±0.87	2.35±0.74	0.012*
12 hrs	1.98± 0.76	4.25±1.12	0.001*
24 hours	1.67±0.54	2.86±0.98	0.001*

The values are expressed as mean ± SD. * p-value <0.05, NS-Non-significant

The time to requirement of the first rescue analgesia was 487.7±40.96 minutes in group A as compared to 242.5±19.84 minutes in group B (p<0.05) (Table 6). The mean total consumption of Inj. Diclofenac in group A was at an average of 61.88±37.55 mg, while in group B, it was 183.75±44.78 mg, which was statistically significantly high (p=0.00) (Table 6). All patients received rescue analgesia in group B at various time intervals, whereas only 60% of the patients in group A received rescue analgesia.

Table 6: Comparison of rescue analgesic requirements.

Variable	Group A (n=20)	Group B (n=20)	P-value
Number of patients given rescue analgesia (%)	12 (60%)	20 (100%)	0.001*
Meantime for the first dose (minutes)	487.7±40.96	242.5±19.84	0.001*
Mean total dose (mg) in 24 hrs	61.88±37.55	183.75±44.78	0.001*

The values are expressed as mean ± SD. * p-value <0.05, NS-Non- significant.

Discussion

Laparoscopy is a minimally invasive procedure; a certain degree of pain is still experienced by patients. Pain can be multifactorial, arising from the incision site (somatic pain), from the surgical site (visceral pain), and due to pneumoperitoneum (referred pain).[6] Out of the different regimens proposed for postoperative pain, such as intravenous NSAIDS, opioids, and local infiltration, Intraperitoneal infiltration of local anaesthetic has been chosen by many surgeons as an effective modality. The rationale for this route is that visceral nociceptive conduction is blocked.

The local anaesthetic inhibits nociception by affecting nerve membrane associated proteins and by inhibiting the release and action of prostaglandins and other agents that sensitise the nociceptors and contribute to inflammation. However, absorption from a large peritoneal surface may also occur, and this may be a further mechanism of analgesia. Local anaesthetics have been administered into the peritoneal cavity during laparoscopic cholecystectomy[6], and the main advantage of using local anaesthetics is that they do not have the adverse effect of opioids, which may delay recovery and discharge from the hospital.

Bupivacaine has been used most widely for treating postoperative analgesia after laparoscopic cholecystectomy. Ropivacaine, a new long-acting amide local anaesthetic, is chemically related to bupivacaine, but it has been shown to be less toxic to cardiac and central nervous systems.[8]

Dexmedetomidine is a highly lipophilic α2 agonist. Its antinociceptive effect occurs at the dorsal root neuron level. Here, it blocks the release of substance P in the nociceptive pathway through the action of inhibitory G protein, which increases the conductance through K+ channels.[9] Dexmedetomidine enhances both central and peripheral neural blockade by local anaesthetics.[10] Its peripheral neural blockade is due to its binding to α2a-AR antibody. Because of the high lipophilic nature of dexmedetomidine, it acts over the peritoneal neural receptors and blocks the nociceptive stimuli.

Memis et al.[11] in 2005, studied the effects of tramadol and clonidine added to Intraperitoneal bupivacaine on postoperative pain in total abdominal hysterectomy and found it to be better than bupivacaine alone. Only few studies in literature have examined the analgesic effect of Intraperitoneal dexmedetomidine.

Ahmed et al.[12] compared meperidine or dexmedetomidine in combination with bupivacaine (0.25%) in gynecological laparoscopic surgery and concluded that dexmedetomidine group significantly decreased postoperative analgesic requirement. Results of our study correlate with the above study.

On analysis of mean scores, it was observed that group 1 had better pain relief till 24 hrs postoperatively and this was statistically significant (P=0.05), except at ½ hr, at 1 hr, and 2 hrs postoperatively when pain scores were not statistically different.

Shukla et al. had done the same study in laparoscopic cholecystectomy and concluded that Intraperitoneal instillation of dexmedetomidine in combination with bupivacaine gives better pain relief and reduces analgesic requirement as compared to bupivacaine alone [(13).]

Table 3 shows that in group 2, patients required the first dose of rescue analgesia by 242.5±19.84 minutes, whereas in group 1, analgesia stayed for nearly 487.7±40.96 minutes. However, the VAS score in group 2 was low after 4th hr; this may be due to the administration of diclofenac to these patients after 4th hr postoperatively.

In patients receiving ropivacaine and dexmedetomidine, only few patients required the second dose of rescue analgesia. The mean dose of Diclofenac consumption was significantly higher in group 2 (183.75±44.78 mg) than in group 1 (61.88±37.55 mg). These findings suggest that adding dexmedetomidine to ropivacaine intraperitoneal significantly decreases analgesic requirement. The above results were in agreement with that of Memis et al.[14] and Ahmed et al.[15] but on contrast, Memis et al.[14] in their study found higher doses in clonidine group than tramadol group. In the present study, dexmedetomidine shows better results which might be due to its high selectivity than clonidine

Conclusion

Intraperitoneal instillation of ropivacaine and dexmedetomidine combination is an easy and effective mode of providing postoperative analgesia in laparoscopic cholecystectomy for a longer period and is superior to ropivacaine with clonidine without any significant increase in adverse events.

References

1. Schirmer BD, Edge SB, Dix JA, Hyser MJ, Hanks JB, Jones RS. Laparoscopic cholecystectomy. Treatment of choice for symptomatic cholelithiasis. Annals of surgery. 1991 Jun;213(6):665.
2. Barazanchi AW, MacFater WS, Rahiri JL, Tutone S, Hill AG, Joshi GP, Kehlet H, Schug S, Van de Velde M, Vercauteren M, Lirk P. Evidence-based management of pain after laparoscopic cholecystectomy: a PROSPECT review update. British journal of anesthesia. 2018 Oct 1;121(4):787-803.
3. Cha SM, Kang H, Baek CW, Jung YH, Koo GH, Kim BG, Choi YS, Cha S Cha YJ. Peritrocal and intraperitoneal ropivacaine for laparoscopic cholecystectomy: a prospective, randomised, doubleblind controlled trial. Journal of Surgical Research. 2012 Jun 15;175(2):251-8.
4. Kucuk C, Kadiogullari N, Canoler O, Savli S. A placebo-controlled comparison of bupivacaine and ropivacaine instillation for preventing postoperative pain after laparoscopic cholecystectomy. Surg Today 2007;37(5):396-40.
5. Kholi AV, Ishaq S, Bhadral N, Gulati S, Manhas R. Comparison of Efficacy of Clonidine Vs Dexmedetomidine on Hemodynamic Changes in Laproscopic Cholecystectomy. JK Science. 2017 Apr 1;19(2):70-5.
6. Kim TH, Kang H, Park JS, Chang IT, Park SG. Intraperitoneal ropivacaine instillation for postoperative pain relief after laparoscopic cholecystectomy. J Korean Surg Soc 2010;79:130-6.
7. Møiniche S, Jørgensen H, Wetterslev J, Dahl JB. Local anesthetic infiltration for postoperative pain relief after laparoscopy: A qualitative and quantitative systematic review of intraperitoneal, port-site infiltration and mesosalpinx block. Anesth Analg 2000;90(4):899-9.
8. Moller R, Covino BG. Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Anesthesiology 1990;72(2):322-9.
9. Kamibayashi T, Maze M. Clinical uses of alpha2 - Adrenergic agonists. Anesthesiology 2000;93(5):1345-9.
10. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand 2006;50(2):222-7.
11. Memis D, Turan A, Karamanlioglu B, Tükenmez B, Pamukçu Z. The effect of tramadol or clonidine added to intraperitoneal bupivacaine onpostoperative pain in total abdominal hysterectomy. J Opioid Manag 2005;1(2):77-82.
12. Ahmed B, Elmawgoud AA, Dosa R. Antinociceptive effect of (α-2 adrenoceptor agonist) dexmedetomidine vs meperidine, topically, after laproscopic gynecologic surgery. J Med Sci 2008;8:400-4.
13. Shukla U, Prabhakar T, Malhotra K, Srivastava D, Malhotra K. Intraperitoneal bupivacaine alone or with dexmedetomidine or tramadolfor postoperative analgesia following laparoscopic cholecystectomy: A comparative evaluation. Indian J Anaesth 2015;59(4):234-9.
14. Memis D, Turan A, Karamanlioglu B, Tükenmez B, Pamukçu Z. The effect of tramadol or clonidine added to intraperitoneal bupivacaine on postoperative pain in total abdominal hysterectomy. J Opioid Manag 2005;1(2):77-82
15. Ahmed B, Elmawgoud AA, Dosa R. Antinociceptive effect of (α-2 adrenoceptor agonist) dexmedetomidine vs meperidine, topically, after laproscopic gynecologic surgery. J Med Sci 2008;8:400-4.

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Original Article

Indian Journal of Anesthesia and Analgesia
Volume 9 Number 2 March-April 2022
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.9222.11

The Use of Intravenous Sodium Bicarbonate in the Treatment of Metabolic Acidosis with Septic Shock

Vijaya Kumar HN[1], Satish Kumar Madabhavi[2]

Author's Affiliation:
[1]Associate Professor, [2]Junior Resident, Department of Anesthesiology, Bangalore Medical College and Research Institute, Bangalore, Karnataka 560002, India.

Abstract

Background: Acute metabolic acidemia, defined as a decrease in blood pH originating from a primary reduction in bicarbonate concentration that is accompanied by an appropriate secondary reduction in PaCO2 and is present for up to a few days, can impair hemodynamics and increase mortality, particularly when severe (arterial blood pH<7.20). Septic shock constitutes an important cause of morbidity and mortality in the critically ill patient. The Surviving Sepsis Campaign recommends against treatment with bicarbonate in patients with lactic acidosis due to hypo perfusion when pH is >7.15 but does not explicate what should be done in cases with lower pH.

Methodology: Prospective randomized, Double-blind controlled study was conducted in ICU of Bangalore Medical College and Research Institute, Bangalore for a period of 4 months (November 2020 to February 2021). Sample size calculation was based on previous prospective, randomized double bind, controlled study by Jung B et al, calculated to be 27 in each group.

Results: Mean age of subjects in Study group was 43.7 ± 14.0 years and in control group was 43.3 ± 17.1 years. A statistically significant difference was found in mean final pH and HCO3 levels and with respect to need for ventilation and Multi Organ Dysfunction Syndrome among the groups.

Conclusion: Metabolic acidosis is a common acid-base disorder and its management should be directed by the current guidelines of therapy. Rational treatment of metabolic acidosis in sepsis is directed towards addressing the underlying causes of acidosis and optimizing tissue oxygen delivery through optimization of cardiopulmonary parameters. Limitations of the previous studies prevent reaching definite conclusions and further investigations are required in order to ensure the validity of this therapeutic approach.

Keywords: Metabolic acidemia; Septic shock; Sodium Bicarbonate; Multi Organ Dysfunction Syndrome.

How to cite this article:

Vijaya Kumar HN, Satish Kumar Madabhavi/The Use of Intravenous Sodium Bicarbonate in the Treatment of Metabolic Acidosis with Septic Shock/Indian J Anesth Analg. 2022; 9(2): 81-86.

Corresponding Author: Satish Kumar Madabhavi, Junior Resident, Department of Anesthesiology, Bangalore Medical College and Research Institute, Bangalore, Karnataka 560002, India.

Email: drsatishkumarjm@gmail.com, **Received on:** 23.11.2021, **Accepted on:** 30.11.2021

Introduction

Acute metabolic acidemia, defined as a decrease in blood pH originating from a primary reduction in bicarbonate concentration that is accompanied by an appropriate secondary reduction in $PaCO_2$ and is present for up to a few days, can impair hemodynamics and increase mortality, particularly when severe (arterial blood pH < 7.20).[1]

Septic shock constitutes an important cause of morbidity and mortality in the critically ill patient. Metabolic acidosis, including lactic acidosis, is part of the underlying pathophysiology in sepsis and is related to poor prognosis. Septic shock is life threatening condition caused by a severe localized or system-wide infection causing organ failure and dangerously low blood pressure that requires immediate medical attention.[2]

The treatment of metabolic acidosis is based on control of the underlying pathophysiologic process and reversal of organ dysfunction. Etiologic treatment is essential in metabolic acidosis, but optimization of oxygen delivery to tissues and reduction of tissue oxygen demand through sedation and mechanical ventilation are parts of the therapeutic strategy. Severe acidemia in sepsis contributes to hemodynamic instability, which is the result of reduced myocardial contractility, arterial vasodilation, and impaired responsiveness to catecholamine. the effect of alkaline therapy on vasopressor requirements and hemodynamic profile in severe acidosis (pH ≤ 7.15) is unknown.[3]

Despite lack of data on the effect of bicarbonate therapy, many intensivists attempt to alkalinize blood with intravenous administration of sodium bicarbonate as part of the treatment of sepsis. However, the benefit of bicarbonate administration in metabolic acidosis in sepsis is controversial and remains a matter of debate in clinical practice.[4]

The Surviving Sepsis Campaign recommends against treatment with bicarbonate in patients with lactic acidosis due to hypo perfusion when pH is >7.15 but does not explicate what should be done in cases with lower pH (9). In daily practice sodium bicarbonate is frequently prescribed in patients with severe acidemia (pH <7.15).[6]

Replacement of sodium bicarbonate to patients with sodium bicarbonate loss due to diarrhea or renal proximal tubular acidosis is useful, but there is no definite evidence that sodium bicarbonate administration to patients with acute metabolic acidosis with septic shock.[7] Hence this study was undertaken to evaluate the use of intravenous sodium bicarbonate in the treatment of metabolic acidosis with septic shock in terms of changes in Arterial blood pH, Need for vasopressor agents, Frequency of multiple organ dysfunction, Duration of mechanical ventilation, Duration of ICU and hospital stay and Reduction in mortality.

Material and Methods

Prospective randomized, Double-blind controlled study was conducted in ICU of hospitals attached to Bangalore Medical College and Research Institute, Bangalore for a period of 4 months (November 2020 to February 2021).

Patients in the age 18-60 yrs, presenting with metabolic acidosis and septic shock. (Arterial blood pH < 7.201 and Systolic blood pressure i.e SBP < 80 mm of Hg2), admitted to ICU or emergency ward and Patients with intra-abdominal sepsis and who need explorative laparotomy were included.

Patients with confirmed diagnosis of Multi Organ Dysfunction, Diabetic Keto-Acidosis and Chronic Kidney Disease. Post cardiac arrest, Bleeding and coagulation disorders, Neurological and Epileptic disorders were excluded from the study.

Sample size calculation was based on previous prospective, randomized double bind, controlled study by Jung B et al[4], assuming equal variance and minimum expected difference will be 10 in two groups.

Sample size is calculated using the formula, n = $n = 2\,(Z_\alpha + Z_{1\text{-}\beta})^2\, \sigma^2/d^2$

Where $Z\alpha$ = Standard table value for 95% confidence interval =1.96

$Z_{1\text{-}\beta}$ = Standard table value for 80% power = 0.84, σ = standard deviation = 13

d = expected difference between the two mean heart rates = 10

$n = 2(1.96+ 0.84)^2\,(13)^2/(10)^2 = 26.4992$

n-27 in each group

Methodology

Written informed consent was obtained from relatives of all patients. Patients were divided into 2 groups, study and control group consisting of 27 patients in each group. Randomization was done using numbers generated from www.randomization.org. The study drug syringes were prepared by a physician not involved in the patient care. Patient, treating physician and nurses will not be aware of study drug. Study group (S)-received intravenous Injection Sodium bicarbonate 75meql in 0.45% Normal saline bolus and maintenance fluid for 24hrs till target pH of >7.3 and bicarbonate of > 18mmol. Control group(C)- received placebo 0.9% normal saline.

In study, each patient received sodium bicarbonate (1 mmol/kg infused over 15 minutes) and equimolar sodium chloride sequentially in random order. After sodium bicarbonate administration, arterial pH, serum bicarbonate, and arterial blood partial CO_2 pressure ($PaCO_2$) increases, while plasma ionized calcium decreases.

Both sodium bicarbonate and sodium chloride transiently increases pulmonary capillary wedge pressure and cardiac output, mean arterial pressure and hemodynamic responses to sodium bicarbonate increases and sodium chloride remains the same. While control group will receive 0.9% normal saline along with vasopressor agents to maintain mean blood pressure.

Efficacy Parameters measured

- Hemodynamic parameters- HR, SBP, DBP, SP02, ETCO2 every 60 minutes.
- Arterial blood gas analysis every day
- Time since admission to develop metabolic acidosis and septic shock
- Number of days on mechanical ventilator / ICU stay
- Requirement of sodium bicarbonate.

Statistical analysis

Software: SPSS version 20 (IBM SPSS Statistics) was used to analyze data. Representation of data: Categorical data was represented in the form of Frequencies and proportions. Continuous data was represented as mean and SD. *Tests of Significance:* Chi-square test was used as test of significance for categorical data.

Independent Student t test was used as test of significance to identify the mean difference between two quantitative variables. Paired t test was used as the test of significance for paired data such as before and after treatment for quantitative data. p value (Probability that the result is true) <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Results

Table 1: Profile of subjects.

		Group				P value
		Study Group		Control Group		
		Count	%	Count	%	
Age	Mean ± SD	43.7	14.0	43.3	17.1	0.924
Sex	Female	4	14.8%	5	18.5%	0.715
	Male	23	85.2%	22	81.5%	

Mean age of subjects in Study group was 43.7 ± 14.0 years and in control group was 43.3 ± 17.1 years. There was no significant difference in age and gender distribution between two groups.

Table 2: Vital signs between two groups.

	Group				P value
	Study Group		Control Group		
	Mean	SD	Mean	SD	
HR	111.0	9.1	112.4	10.9	0.590
SBP	98.9	6.1	98.3	8.0	0.776
DBP	53.8	5.6	53.0	5.7	0.616
SPO_2	100.0	0.2	99.8	0.5	0.082

In the study there was no significant difference in mean HR, SBP, DBP and SPO_2 between two groups.

In the study there was no significant difference in mean pH between two groups at admission. However, there was significant difference in mean final pH between two groups. Mean pH was high in Study group compared to control group.

Table 3: PH and HCO_3 comparison between two groups at Admission and after treatment.

		Group						P value
		Study Group			Control Group			
		Mean	SD	P value with in group	Mean	SD	P value with in group	
PH	Initial	7.2	0.0		7.2	0.1		0.939
	Final	7.4	0.0	<0.001*	7.3	0.1	<0.001*	0.007*
HCO3	Initial	13.8	1.8		13.7	2.2		0.945
	Final	18.9	1.1	<0.001*	17.3	1.8	<0.001*	<0.001*

In the study there was no significant difference in mean HCO_3 between two groups at admission. However, there was significant difference in mean final HCO_3 between two groups. Mean HCO_3 was high in Study group compared to control group.

Table 4: Mean Number of Days on Ventilation between Cases and Controls.

Parameters	Cases		Controls		p value
	Mean	SD	Mean	SD	
No. of days on ventilation	2.6	0.3	3.1	1.1	0.041*

Note:* significant at 5% level of significance ($p<0.05$)

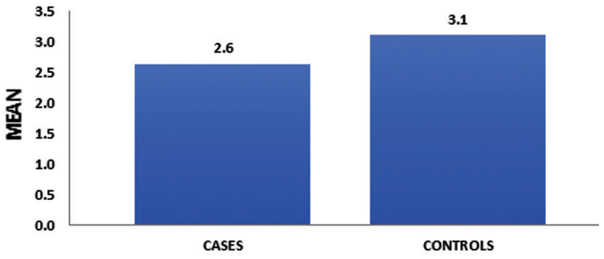

Fig. 1: Mean Number of Days on Ventilation between Cases and Controls.

Table 5: Distribution of IV Drugs between Cases and Controls.

IV Drugs	Cases		Controls		P Value
	N	%	N	%	
Noradrenaline	5	18.5%	6	22.2%	
Noradrenaline+ Vasopressin	1	3.7%	3	11.1%	0.576
Noradrenaline+ Vasopressin+ Adrenaline	0	0.0%	2	7.4%	

Note:*significant at 5% level of significance ($p<0.05$).

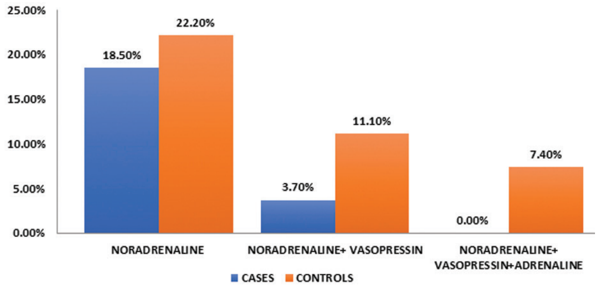

Fig. 2: Distribution of IV Drugs between Cases and Controls.

Table 6: Incidence of Mods Between Cases and Controls.

Parameters	Cases		Controls		p value
	N	%	N	%	
MODS	3	11.1%	12	44.4%	0.021*

Note:* significant at 5% level of significance ($p<0.05$).

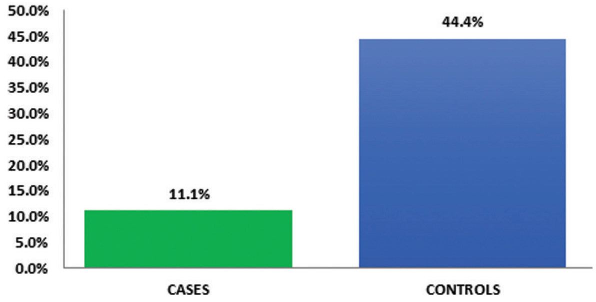

Fig. 3: Incidence of Mods Between Cases and Controls.

Table 7: Outcome distribution between two groups.

		Group			
		Study Group		Control Group	
		Count	%	Count	%
Outcome	Alive	25	92.6%	21	77.8%
	Death	2	7.4%	6	22.2%

$\chi^2 = 2.348$, df =1, p =0.125

In Study group mortality rate was 7.4% and in Control group mortality rate was 22.2%. However, there was no statistically significant difference in outcome between two groups.

Discussion

The present study was conducted at BMCRI Bengaluru including 27 study subjects in study group and control group respectively. Sepsis is considered to be one of most serious and very fatal disease seen among the patients who are admitted in ICU . The presence of metabolic Acidosis reflects the severity of the underlying disease and the progression of the patient condition towards worse. The treatment of the metabolic acidosis will help in the recovery of the patients . Causes of metabolic acidosis include sepsis, cardiogenic shock, severe hypoxemia, hepatic failure, and intoxication. Most of these conditions share similar pathogenic mechanisms, including reduced oxygen delivery to cells and impaired oxygen consumption in cell mitochondria, yet some conditions are due to more complex derangements.

In the present study nearly 85.2% of the subjects in study group were male and 81.5% subjects in control group were also male with mean age of 43.7+ 14 years in study group and 43.3+ 17.1 years in control group. In the study done by Samir Jaber et al[11] the median age among study subjects was 65 years in control and 66 years in study group with majority of the subjects being male (59% in study group and 63% in control group). The vital parameters in both the groups were found to be comparable between both the study subjects and the p value was also found to be statistically insignificant.

The Ph of the study subjects was found to be 7.2 in the initial set up in both the groups and it was increased to 7.4 in study group and 7.3 in the control group. There was statistical significant improvement in Ph between study and control group on bicarbonate supplementation. The Bicarbonate level also found to be increased from 13.8 to 18.9 in study group and 13.7 to 17.3 in control group with significant statistical association between both the groups.

In the study done by Cooper et al[12] in the study group increased arterial pH from 7.22 to 7.36 with $p < 0.001$ and serum bicarbonate increased from 12 to 18 mmol/L, $P < 0.001$. In Another study done by Ahn et al[13] in the Sodium bicarbonate group had significant effect on pH (6.99 vs.6.90, P = 0.038) and bicarbonate levels (21.0 vs. 8.0 mEq/L, P = 0.007) when compared with placebo group. In the study done by Mintzer et al[14] sodium bicarbonate corrections lowered base deficit from 7.6 ± 1.8 to 3.4 ± 2.1 mmol l(-1) ($P < 0.05$), and increased median (±SD) pH from 7.23 ± 0.06 to 7.31 ± 0.05 ($P< 0.05$) . All these studies were found to be comparable to the present study findings and showed that sodium bicarbonate supplementation had better and significant impact on Ph and HCO_3 level among the subjects with metabolic acidosis.

The number of days on ventillations was also found to be more in control group 3.1+1.1 in control group and 2.6+0.3 days in study group with significant p value of 0.04 in the present study which is comparable to the findings of study done by El Solh et al[8] where among bicarbonate group the median time to liberation of mechanical ventilation was reduced (10 days [95% CI, 5.0 to 13.0] vs. 14 days [95% CI, 9.0 to 19.0], p = 0.02) and the length of intensive care unit stay was shorter (11.5 days (95% CI, 6.0 to 16.0) vs. 16.0 days (95% CI, 13.5 to 19.0), p = 0.01). In the study done by Jung Et al 4 there was found to be no difference in length of ICU stay or mortality in pts receiving sodium bicarbonate compared with those who received routine solutions.

Among the subjects in the present study acute Kidney injury was seen in 11.1% of the subjects and 44.4 % of the control groups. Chen et al[10] also opined that dysfunctional organs was less in bicarbonate group when compared to normal group. Zhang et al[15] studied 1718 septic patients (1218 controls and 500 patients who received sodium bicarbonate) and reported no significant mortality change in the overall population (hazard ratio [HR], 1.04; 95% CI, 0.86 to 1.26; p = 0.67], but bicarbonate proved to be beneficial in patients with acute kidney injury (HR, 0.74; 95% CI, 0.51 to 0.86; p = 0.021). In Kim H J et al[16] study suggest that unlike the overall population of patients with metabolic acidosis, those suffering from concomitant acute kidney injury may experience improved outcomes and a reduced rate of mortality from enrolment to day 28 with sodium bicarbonate infusion therapy.

Conclusion

Metabolic acidosis is a common acid-base disorder and its management should be directed by the current guidelines of therapy

Rational treatment of metabolic acidosis in sepsis is directed towards addressing the underlying causes of acidosis and optimizing tissue oxygen delivery through optimization of cardiopulmonary parameters.

Available evidence suggests that the severity of metabolic acidosis in these conditions reflects the gravity of the underlying illness rather than being itself a contributor to mortality.

Recent studies have suggested that metabolic acidosis might contribute to worsening kidney disease and sodium bicarbonate supplementation has been proposed as a renoprotective strategy. However, limitations of these studies prevent reaching definite conclusions and further investigations are required in order to ensure the validity of this therapeutic approach.

References

1. Kraut JA, Madias NE. Intravenous Sodium Bicarbonate in Treating Patients With Severe Metabolic Acidemia. Am J Kidney Dis. 2019 Apr;73(4):572-575.
2. Velissaris D, Karamouzos V, Ktenopoulos N, Pierrakos C, Karanikolas M. The Use of Sodium Bicarbonate in the Treatment of Acidosis in Sepsis: A Literature Update on a Long Term Debate. Critical Care Research and Practice. 2015;2015:1–7.
3. Ghauri SK, Javaeed A, Mustafa KJ, Podlasek A, Khan AS. Bicarbonate Therapy for Critically Ill Patients with Metabolic Acidosis: A Systematic Review. Cureus. 2019;11(3):e4297.
4. Jung B, Rimmele T, Le Goff C, Chanques G, Corne P, Jonquet O, et al. Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. a prospective, multiple-center study. Crit Care. 2011;15(5):R238.

5. Halperin ML, Kamel KS. Some Observations on the Clinical Approach to Metabolic Acidosis. J Am Soc Nephrol. 2010 Jun 1;21(6):894-897.
6. Kooter AJ, Nanayakkara PW. Sodium bicarbonate for critically ill patients with metabolic acidaemia, treatment or window dressing? J Emerg Crit Care Med 2018;2:74.
7. Adeva-Andany MM, Fernández-Fernández C, Mouriño-Bayolo D, Castro-Quintela E, Domínguez-Montero A. Sodium Bicarbonate Therapy in Patients with Metabolic Acidosis. Di Iorio BR, editor. The Scientific World Journal. 2014 Oct 21;2014:627673.
8. El-Solh AA, Abou Jaoude P, Porhomayon J. Bicarbonate therapy in the treatment of septic shock: a second look. Internal and Emergency Medicine. 2010 Aug 1;5(4):341–7.
9. Kim HJ, Son YK, An WS. Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: a retrospective analysis. PLoS One. 2013;8(6):e65283.
10. Chen X, Ye J, Zhu Z. [The use of sodium bicarbonate in stages in treating hypoperfusion induced lactic acidemia in septic shock]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2013 Jan;25(1):24–7.
11. Samir Jaber, Catherine Paugam, Emmanuel Futier, Jean-Yves Lefrant, Sigismond Lasocki, Thomas Lesco et al . Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial.The Lancet .2018 ;6736(18):31080-8.
12. Cooper DJ, Walley KR, Wiggs BR, Russell JA. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. Ann Intern Med 1990; 112: 492–98.
13. Ahn S, Kim Y-J, Sohn CH, Seo DW, Lim KS, Donnino MW, Kim WY: Sodium bicarbonate on severe metabolic acidosis during prolonged cardiopulmonary resuscitation: a double-blind, randomized, placebo-controlled pilot study. J Thorac Dis. 2018, 10:2295-2302.
14. Mintzer JP, Parvez B, Alpan G, LaGamma EF: Effects of sodium bicarbonate correction of metabolic acidosis on regional tissue oxygenation in very low birth weight neonates. J Perinatol. 2015, 35:601-6.
15. Zhang Z, Zhu C, Mo L, Hong Y: Effectiveness of sodium bicarbonate infusion on mortality in septic patients with metabolic acidosis. Intensive Care Med. 2018, 44:1888-1895.
16. Kim HJ, Son YK, An WS: Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: a retrospective analysis. PLoS One. 2013, 8:65283.

References for Statistical Methods

1. Dakhale GN, Hiware SK, Shinde AT, Mahatme MS. Basic biostatistics for post-graduate students. Indian J Pharmacol. 2012;44(4):435-442.
2. Sunder Rao P S S, Richard J: An Introduction to Biostatistics, A manual for students in health sciences, New Delhi: Prentice hall of India. 4th edition. 2006; 86-160.
3. Elenbaas, RM, Elenbaas, JK, Cuddy, PG. Evaluating the medical literature, part II: Statistical analysis. AnnEmerg Med. 1983; 12:610–620.

Review Article

Indian Journal of Anesthesia and Analgesia
Volume 9 Number 2 March-April 2022
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.9222.12

Over View of Oliceridine Newer Opioid Analgesic

Anurita Konnur[1], Yoganarasimha N[2], Kripa Anand[3]

Author's Affiliation: [1]Post Graduate, [2]Professor, [3]Senior Resident, Department of Anesthesiology, BGS Global Institute of Medical Sciences, Bengaluru, Karnataka, 560060, India.

Abstract

Pain relief requires a balance between adequate analgesia and risk of adverse effects. Opioids remain the cornerstone for managing moderate to severe pain, but are associated with opioid-induced respiratory depression (OIRD) and gastrointestinal complications. Opioids exert their analgesic effects predominantly via G-protein signaling, however, adverse effects including OIRD are mediated by the β-arrestin pathway. Oliceridine is the first of a new class of biased opioid agonists that preferentially activate G-protein signaling over β-arrestin, which would theoretically improve analgesia and reduce the risk of adverse effects. Oliceridine is approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe acute pain. The efficacy of Oliceridine was mainly established in two randomized controlled Phase III clinical trials of patients experiencing moderate to severe pain after bunionectomy (APOLLO-1) and abdominoplasty (APOLLO-2). The results of the APOLLO studies demonstrate that Oliceridine, when administered via patient-controlled analgesia (PCA) demand boluses of 0.35mg and 0.5mg, provides superior analgesia compared to placebo, and is equianalgesic to PCA morphine 1mg demand boluses, without significant difference in the incidence of respiratory complications. However, these studies were designed to evaluate analgesic efficacy, and it is still uncertain if Oliceridine has a better safety profile than conventional opioids. Although several post hoc analyses of pooled data from the trials reported that Oliceridine was associated with lower OIRD and gastrointestinal complications compared to morphine, prospective studies are needed to elucidate if biased agonists such as Oliceridine reduce the risk of adverse effects compared to conventional opioids.

Keywords: TRV130; Biased ligand; Opioid agonist; Mu-opioid receptor.

How to cite this article:

Anurita Konnur, Yoganarasimha N, Kripa Anand/Over View of Oliceridine Newer Opioid Analgesic/Indian J Anesth Analg. 2022; 9(2): 87-92.

Corresponding Author: Anurita Konnur, Post Graduate, Department of Anesthesiology, BGS Global Institute of Medical Sciences, Bengaluru, Karnataka, 560060, India.

E-mail: dranurita85@gmail.com, **Received on:** 02.03.2022, **Accepted on:** 02.05.2022

Introduction

Opioids remain the cornerstone for analgesic management of moderate to severe acute pain, which affects approximately 75% of postoperative patients. Optimal pain relief requires a balance between providing adequate analgesia versus the risk of analgesia-related adverse effects. On one hand, inadequate analgesia has been associated with prolonged hospitalization, impaired recovery, and increased risk of developing chronic pain.[2]

Conversely, excessive opioid use is associated with nausea, vomiting, sedation, constipation, and opioid-induced respiratory depression (OIRD).[3–5] In particular, OIRD results from a combination of central respiratory depression, sedation, and airway obstruction, potentially leading to hypoxemia, hypercapnia, and cardiorespiratory arrest.[6,7]

The incidence of OIRD ranges from 0.04% to 41%, depending on the diagnostic criteria,8 and places a significant population at risk of morbidity or mortality.[9] In the last decade, opioid utilization has risen dramatically with concomitant increase in related mortality and adverse effects, which has prompted the search for novel drugs with improved analgesic efficacy and adverse effect profiles.

Severe acute pain occurs through nociceptive signalling involving both ascending and descending spinal pathways, in which nerve conductance is mediated in part by the action of opioid receptors. Opioid receptors are seven-transmembrane G-protein-coupled receptors (GPCRs), of which the μ-opioid receptor subtype is predominantly targeted by and is responsible for the effects of opioid agonists. However, due to the ability of some opioid agonists to bind to other targets, as well as activation of additional downstream pathways from opioid receptors such as those involving β-arrestin, the beneficial analgesic effects of opioids are coupled with severe adverse effects such as constipation and respiratory depression.

Oliceridine (formerly known as TRV130) is a "biased agonist" at the μ-opioid receptor by preferentially activating the G-protein pathway with minimal receptor phosphorylation and recruitment of β-arrestin. By acting as a biased agonist, oliceridine provides comparable analgesia compared with traditional opioids such as [morphine] at a comparable or decreased risk of opioid-related adverse effects such as constipation and respiratory depression.

Opiod Receptor Classification and Location

Receptor	CNS location	Response on activation
Mu	Brain (laminae III and IV of the cortex, thalamus, periaquadectal gray), spinal cord(substantia gelatinosa)	Mu1: Supraspinal analgesia, physical dependence. Mu2: Respiratory depression, miosis, euphoria, reduced gastrointestinal motility, Physical dependence.
Kappa	Brain (hypothalamus, periaquadectal gray, claustrum), spinal cord(substantia gelatinosa)	Spinal analgesia, dieresis, dysphoria, sedation, miosis, depersonalization and derealization
Delta	Brain (pontine nucleus, amygdale, olfactory bulbs, deep cortex)	Analgesia may be associated with mood change.

Chemistry

Molecular structure: N-[(3-methoxythiophen-2-yl)methyl]-2-[(9R)-9-pyridin-2-yl-6-oxaspiro[4.5] decan-9-yl]ethanamine.

Molecular weight : 386.6g\mmol.

Mechanism of Action

Oliceridine acts as a "biased agonist" at the μ-opioid receptor by preferentially activating the G-protein pathway with minimal receptor phosphorylation and recruitment of β-arrestin.[A218026, A218031] Competetive binding assays and structural modelling suggest that the binding site for oliceridine on the μ-opioid receptor is the same as for classical opioids. [A218026, A216961] However, molecular modelling supports a model whereby oliceridine binding induces a different intracellular conformation of the μ-opioid receptor, specifically due to a lack of coupling with transmembrane helix six, which confers the specificity for G-protein over β-arrestin interaction. [A216961].

Numerous in vitro,in vivo and clinical studies support the view that this biased agonism results in comparable analgesia compared with traditional opioids at a comparable or decreased risk of opioid-related adverse effects such as constipation and respiratory depression. [A218026, A218031, A218051, A218056, A218061, A218066, A218071, L15516].

Oliceridine is a biased μ-opioid receptor agonist that acts through downstream signalling pathways to exert antinociceptive analgesia in patients experience severe acute pain. [A218026, A218031, A218036, A218041, A218046, L15516] Results from multiple clinical studies[A218051, A218056, A218061, A218066, A218071, L15516] and simulation data [A218076, A218081] demonstrate that oliceridine exerts significant analgesic benefits within 5-20 minutes following administration but dissipates quickly with a half-life between one and three hours. [A218051, A218056, A218061, A218066, A218071, L15516] Despite an improved adverse effect profile over conventional opioids [A218051, A218056, A218061, A218066, A218071, L15516], oliceridine carries important clinical warnings.

Oliceridine has the potential to cause severe respiratory depression, especially in patients who are elderly, cachectic, debilitated, or who otherwise have chronically impaired pulmonary function.

Pain perception follows a complex pathway initiated in primary sensory neurons, subsequently transmitted to the spinal cord dorsal horn and through ascending axons to multiple regions within the thalamus, brainstem, and midbrain, and finally relayed through descending signals that either inhibit or facilitate the nociceptive signalling. [A218041, A218046].

Opioid receptors are seven-transmembrane G-protein-coupled receptors (GPCRs) that can be divided into μ, κ, δ, and opioid-like-1 (ORL1) subtypes,[A218031, A218046].

However, the μ-opioid receptor is predominantly targeted by and is responsible for the effects of traditional opioids. [A218046].

GPCRs in the inactive state are bound intracellularly by a complex consisting of a Gα, β, and γ subunit together with guanosine diphosphate (GDP). Activation of the GPCR through extracellular agonist binding catalyzes the replacement of GDP with guanosine triphosphate (GTP), dissociation of both Gα-GTP and a βγ heterodimer, and subsequent downstream effects.[A218046].

In the case of the μ-opioid receptor, the Gα-GTP directly interacts with the potassium channel Kir3 while the dissociated Gβγ subunit directly binds to and occludes the pore of P/Q-, N-, and L-type Ca2+ channels.

Furthermore, opioid receptor activation inhibits adenylyl cyclase, which in turn reduces Camp-dependent Ca^{2+} influx. By altering membrane ion conductivity, these effects modulate nociceptive signalling and produce an analgesic effect. [A218036, A218041, A218046] In addition to the G-protein pathway, μ-opioid receptor activation can also result in downstream signalling through β-arrestin, which results in receptor internalization and is associated with negative effects of opioid use including respiratory depression, gastrointestinal effects, and desensitization/tolerance.[A218026, A218031, A218036, A218041, A218046].

Pharmacokinetic Properties

Oliceridine is primarily metabolized in liver by CYP3A4 and CYP2D6 in vitro, with minor contributions from CYP2C9 and CYP2C19. [L15516] None of oliceridine's metabolites are known to be active. [A218046, L15516] Metabolic pathways include N-dealkylation, glucuronidation, and dehydrogenation. [L15516]. Oliceridine has a half-life of 1.3-3 hours while its metabolites, none of which are known to be active, have a substantially longer half-life of 44 hours.[L15516].

Absorption

Oliceridine administered as a single intravenous injection of 1.5, 3, or 4.5 mg in healthy male volunteers had a corresponding Cmax of 47, 76, and 119 ng/mL and a corresponding AUC0-24 of 43, 82, and 122 ng*h/mL.[A218051] Simulations of single doses of oliceridine between 1-3 mg suggest that the expected median Cmax is between 43 and 130 ng/mL while the expected median AUC is between 22 and 70 ng*h/mL.[A218081]. Oliceridine has a mean steady-state volume of distribution of 90-120 L.[L15516].

Oral Bioavailibility

Distribution

Oliceridine is approximately 77% bound to plasma proteins. [L15516].

Elimination

Approximately 70% of oliceridine is eliminated via the renal route, of which only 0.97-6.75% of an initial dose is recovered unchanged. The remaining 30% is eliminated in faeces.[L15516].

Indications

Management of acute pain

Contraindications

- Acute or severe Bronchial Asthma in an unmonitored setting.
- Known or suspected gastrointestinal obstruction, including paralytic ileus.
- Known hypersensitivity to Oliceridine.

Dosage, Administration and Storage

Available as 30mg\30ml vial for Patient Controlled Analgesia.

Cumulative daily dose should not exceed 27mg.

Stored at controlled room temperature 20-25 degree celcius

Protect from freezing and light.

Toxicity

Symptoms of oliceridine overdose are variable but can include respiratory depression, airway obstruction, pulmonary edema, bradycardia, hypotension, muscle flaccidity, cold skin, and somnolence progressing to either stupor or coma. Miosis is commonly observed but in cases of severe hypoxia, mydriasis may be observed instead. Oliceridine overdose may be fatal. In case of overdose, the establishment of a protected airway followed by the institution of assisted or controlled ventilation is a high priority; in case of cardiac arrhythmias or arrest, additional supportive measures may be immediately required. Supportive treatment, including oxygen, vasopressors, and the administration of an opioid antagonist such as naloxone may be applied but should be tailored to the individual patient's condition. [L15516].

Addiction Liability None

Precautions

- Addiction, Abuse and misuse
- Life threatening respiratory depression
- Prolonged use of opioid analgesics during pregnancy-Neonatal opioid withdrawal syndrome
- Potential for QT prolongation with daily dose > 27mg
- Adrenal insufficiency
- Severe hypotension

Conclusion

Oliceridine is a biased agonist at mu opiod receptor, used to treat severe acute pain with less adverse effects caused by morphine like respiratory depression and constipation.

References

1. DeWire SM, Yamashita DS, Rominger DH, Liu G, Cowan CL, Graczyk TM, Chen XT, Pitis PM, Gotchev D, Yuan C, Koblish M, Lark MW, Violin JD: A G protein-biased ligand at the mu-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine. J Pharmacol Exp Ther. 2013 Mar;344(3):708-17. doi: 10.1124/jpet.112.201616. Epub 2013 Jan 8. [PMID:23300227].
2. Manglik A, Lin H, Aryal DK, McCorvy JD, Dengler D, Corder G, Levit A, Kling RC, Bernat V, Hubner H, Huang XP, Sassano MF, Giguere PM, Lober S, Da Duan, Scherrer G, Kobilka BK, Gmeiner P, Roth BL, Shoichet BK: Structure-based discovery of opioid analgesics with reduced side effects. Nature. 2016 Sep 8;537(7619):185-190. doi: 10.1038/nature19112. Epub 2016 Aug 17. [PMID:27533032].
3. Ok HG, Kim SY, Lee SJ, Kim TK, Huh BK, Kim KH: Can oliceridine (TRV130), an ideal novel micro receptor G protein pathway selective (micro-GPS) modulator, provide analgesia without opioid-related adverse reactions? Korean J Pain. 2018 Apr;31(2):73-79. doi: 10.3344/kjp.2018.31.2.73. Epub 2018 Apr 2. [PMID:29686804].
4. Azzam AAH, McDonald J, Lambert DG: Hot topics in opioid pharmacology: mixed and biased opioids. Br J Anaesth. 2019 Jun;122(6):e136-e145. doi: 10.1016/j.bja.2019.03.006. Epub 2019 Apr 19. [PMID:31010646].
5. Urits I, Viswanath O, Orhurhu V, Gress K, Charipova K, Kaye AD, Ngo A: The Utilization of Mu-Opioid Receptor Biased Agonists: Oliceridine, an Opioid Analgesic with Reduced Adverse Effects. Curr Pain Headache Rep. 2019 Mar 18;23(5):31. doi: 10.1007/s11916-019-0773-1. [PMID:30880365].
6. Soergel DG, Subach RA, Burnham N, Lark MW, James IE, Sadler BM, Skobieranda F, Violin JD, Webster LR: Biased agonism of the mu-opioid receptor by TRV130 increases analgesia and reduces on-target adverse effects versus morphine: A randomized, double-blind, placebo-controlled, crossover study in healthy volunteers. Pain. 2014 Sep;155(9):1829-35. doi: 10.1016/j.pain.2014.06.011. Epub 2014 Jun 19. [PMID:24954166].
7. Viscusi ER, Webster L, Kuss M, Daniels S, Bolognese JA, Zuckerman S, Soergel DG, Subach RA, Cook E, Skobieranda F: A randomized, phase 2 study investigating TRV130, a biased ligand of the mu-opioid receptor, for the intravenous treatment of acute pain. Pain. 2016 Jan;157(1):264-72. doi: 10.1097/j.pain.0000000000000363. [PMID:26683109].
8. Singla N, Minkowitz HS, Soergel DG, Burt DA, Subach RA, Salamea MY, Fossler MJ, Skobieranda F: A randomized, Phase IIb study investigating oliceridine (TRV130), a novel micro-receptor G-protein pathway selective (mu-GPS) modulator, for the management of moderate to severe acute pain following abdominoplasty. J Pain Res. 2017 Oct 6;10:2413-2424. doi: 10.2147/JPR.S137952. eCollection 2017. [PMID:29062240].
9. Singla NK, Skobieranda F, Soergel DG, Salamea M, Burt DA, Demitrack MA, Viscusi ER: APOLLO-2: A Randomized, Placebo and Active-Controlled Phase III Study Investigating Oliceridine (TRV130), a G Protein-Biased Ligand at the mu-Opioid Receptor, for Management of Moderate to Severe Acute

Pain Following Abdominoplasty. Pain Pract. 2019 Sep;19(7):715-731. doi: 10.1111/papr.12801. Epub 2019 Jun 24. [PMID:31162798].

10. Viscusi ER, Skobieranda F, Soergel DG, Cook E, Burt DA, Singla N: APOLLO-1: a randomized placebo and active-controlled phase III study investigating oliceridine (TRV130), a G protein-biased ligand at the micro-opioid receptor, for management of moderate-to-severe acute pain following bunionectomy. J Pain Res. 2019 Mar 11;12:927-943. doi: 10.2147/JPR.S171013. eCollection 2019. [PMID:30881102].
11. Fossler MJ, Sadler BM, Farrell C, Burt DA, Pitsiu M, Skobieranda F, Soergel DG: Oliceridine, a Novel G Protein-Biased Ligand at the mu-Opioid Receptor, Demonstrates a Predictable Relationship Between Plasma Concentrations and Pain Relief. II: Simulation of Potential Phase 3 Study Designs Using a Pharmacokinetic/Pharmacodynamic Model. J Clin Pharmacol. 2018 Jun;58(6):762-770. doi: 10.1002/jcph.1075. Epub 2018 Feb 2. [PMID:29393971].
12. Fossler MJ, Sadler BM, Farrell C, Burt DA, Pitsiu M, Skobieranda F, Soergel DG: Oliceridine (TRV130), a Novel G Protein-Biased Ligand at the mu-Opioid Receptor, Demonstrates a Predictable Relationship Between Plasma Concentrations and Pain Relief. I: Development of a Pharmacokinetic/ Pharmacodynamic Model. J Clin Pharmacol. 2018 Jun;58(6):750-761. doi: 10.1002/jcph.1076. Epub 2018 Feb 7. [PMID:29412458].
13. Schneider S, Provasi D, Filizola M: How Oliceridine (TRV-130) Binds and Stabilizes a mu-Opioid Receptor Conformational State That Selectively Triggers G Protein Signaling Pathways. Biochemistry. 2016 Nov 22;55(46):6456-6466. doi: 10.1021/acs.biochem.6b00948. Epub 2016 Nov 7. [PMID:27778501].
14. Chen XT, Pitis P, Liu G, Yuan C, Gotchev D, Cowan CL, Rominger DH, Koblish M, Dewire SM, Crombie AL, Violin JD, Yamashita DS: Structure-activity relationships and discovery of a G protein biased mu opioid receptor ligand, [(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro-[4.5] decan- 9-yl]ethyl})amine (TRV130), for the treatment of acute severe pain. J Med Chem. 2013 Oct 24;56(20):8019-31. doi: 10.1021/jm4010829. Epub 2013 Oct 14. [PMID:24063433].
15. FDA Approved Drug Products: Olinvyk (oliceridine) injection.
16. FDA Briefing Document: Oliceridine.
17. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin. 2014;30(1):149–160. doi:10.1185/03007995.2013.860019 [PubMed] [CrossRef] [Google Scholar].
18. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017;10:2287–2298. doi:10.2147/JPR.S144066 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
19. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain. 2002;3(3):159–180. doi:10.1054/jpai.2002.123652 [PubMed] [CrossRef] [Google Scholar].
20. Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. Science. 2018;361(6408):eaau1184. doi:10.1126/science.aau1184 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
21. Bedene A, Lijfering WM, Niesters M, et al. Opioid prescription patterns and risk factors associated with opioid use in the Netherlands. J Pain. 2019;2(8):e1910223. doi:10.1001/ jamanetworkopen.2019.10223 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
22. Cashman JN, Dolin SJ. Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. Br J Anaesth. 2004;93(2):212–223. doi:10.1093/bja/ aeh180 [PubMed] [CrossRef] [Google Scholar].
23. Macintyre PE, Loadsman JA, Scott DA. Opioids, ventilation and acute pain management. Anaesth Intensive Care. 2011;39(4):545–558. doi:10.1177/0310057X1103900405 [PubMed] [CrossRef] [Google Scholar].
24. Gupta K, Nagappa M, Prasad A, et al. Risk factors for opioid-induced respiratory depression in surgical patients: a systematic review and meta-analyses. BMJ Open. 2018;8(12):e024086. doi:10.1136/ bmjopen-2018-024086 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
25. Kessler ER, Shah M, Gruschkus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. Pharmacotherapy. 2013;33(4):383–391. doi:10.1002/ phar.1223 [PubMed] [CrossRef] [Google Scholar].

Drug Bank

Studies

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Case Report

Indian Journal of Anesthesia and Analgesia
Volume 9 Number 2 March-April 2022
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.9222.13

Segmental Thoracic Spinal for Modified Radical Mastectomy in Carcinoma of Breast

Bindu Kapu[1], K Yugandhar[2], S Kiran kumar[3]

Author's Affiliation: [1]Post Graduate, [2]Associate Professor, [3]Professor, Department of Anesthesiology, Mamata Medical College, Khammam, Telangana, Andhra Pradesh 507002, India.

Abstract

Segmental Thoracic spinal anaesthesia for modified Radical Mastectomy in patients with compromised Pulmonary Function Test provides good hemodynamic stability, adequate intraoperative and postoperative analgesia, with patient satisfaction. Here, we present a 60 years old patient with carcinoma of breast posted for Modified Radical Mastectomy under Segmental Thoracic Spinal Anaesthesia.

Keywords: Segmental; Levobupivacaine; Mastectomy; Spinal; Thoracic.

Introduction

General anesthesia is currently the conventional technique used for surgical treatment of breast cancer. The drawbacks of general anesthesia include inadequate pain control due to lack of residual analgesia, high incidence of nausea and vomiting, and prolonged hospital stay. Breast surgery is associated with a high incidence of postoperative pain, it is estimated that over more than 50 % of women suffer chronic pain after surgery. Regional anesthesia is a good alternative to general anesthesia for breast cancer surgery, providing superior analgesia and fewer side effects related to a standard opioid-based analgesia. Regional anesthesia decreases operative stress, provides beneficial hemodynamic effects especially for critically ill patients and decreases postoperative morbidity and mortality. It also reduces post-operative nausea and vomiting and provides prolonged post-operative sensory block, minimizing narcotic requirements.

Case Report

A 60 years old female came to our institute with chief complaints of lump in the right breast gradually increasing in size since 6 months. On examination, a lump of size 9×6cms with irregular surfaces, fixed to skin, with enlarged axillary lymph nodes were noticed. FNAC report revealed presence of malignant cells. In the Preoperative assessment, she has history of smoking since 20 yrs with 3 pack years stopped 1 month back. On examination,

How to cite this article:

Bindu Kapu, K Yugandhar, S Kiran kumar/Segmental Thoracic Spinal for Modified Radical Mastectomy in Carcinoma of Breast/Indian J Anesth Analg. 2022; 9(2): 93-94.

Corresponding Author: Bindu Kapu, Post Graduate, Department of Anesthesiology, Mamata Medical College, Khammam, Telangana, Andhra Pradesh 507002, India.

Email: bindu.chowdary94@gmail.com, **Received on:** 01.08.2021, **Accepted on:** 22.01.2022

vitals are stable with SpO2-96% at room air, Chest was clear with equal bilateral air entry, Chest x-ray showed hyperlucent lung fields, PFT's revealed severe obstruction with poor reversibility, 2D Echo revealed EF-60% with no abnormalities. All investigations were within normal limits. The patient was scheduled for surgery under ASA-II.

On the day of surgery, high risk consent was taken and patient shifted to OR. Standard ASA monitors connected and baseline monitoring done. IV line secured with 18G cannula. In sitting position, under strict aseptic precautions, Spinal anaesthesia was performed via para-median approach, at T5-T6 space with 27G spinal needle, 1 ml of levobupivacaine 0.5% with 50μg fentanyl was given. Spinal level assessed and fixed at C6. Oxygen mask with 4l/min was kept, Emergency cart with airway access was kept ready, surgery lasted for 2hrs uneventfully and patient was shifted to the postoperative care unit.

Discussion

Segmental thoracic spinal anesthesia have introduced for cardiac surgery in adults and children in the early 1990's. Spinal anaesthesia decreases operative stress, provides beneficial hemodynamic effects with lower incidence of nausea and vomiting, minimizing opioid requirements and decreases postoperative morbidity and mortality. The dose of the anaesthetic is very low, compared to lumbar spinal anaesthesia, given the highly specific block to only certain nerve segments. Successful use of this technique, avoids tracheal intubation minimising postoperative pulmonary complications.

Conclusion

Segmental Thoracic Spinal anaesthesia provides a better option in high risk cases of Modified Radical Mastectomy in providing good analgesia, maintaining hemodynamic stability and faster recovery and early discharge from hospital.

References

1. Elakany MH, Abdelhamid SA. Segmental thoracic spinal has advantages over general anesthesia for breast cancer surgery. Anesth Essays Res. 2013;7(3):390-395. doi:10.4103/0259-1162.123263.
2. Kejriwal AK, Begum S, Krishan G, Agrawal R. Laparoscopic Cholecystectomy under Segmental Thoracic Spinal Anesthesia: A Feasible Economical Alternative. Anesth Essays Res. 2017;11(3):781-783. doi:10.4103/0259-1162.174467.
3. Mahmoud AA, Hussein HA, Girgis K, Kamal AM, Nafady HA. The novel use of spinal anesthesia at the mid-thoracic level: a feasibility study. Egypt J Cardiothorac Anesth 2014;8:21-6.
4. Shatri G, Singh A. Thoracic Segmental Spinal Anesthesia. [Updated 2021 Jul 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK572087/.

Letter to Editor

Management of troublesome Intrathecal fentanyl induced pruritis.

SP Sharma, Sunny Eapen, Dheeraj Kumar

[1]HOD, [2]Consultant in Anesthesiology, [3]Classified Specialist, Department of Anesthesiology and Critical Care, Military Hospital, Jaipur, Rajsthan 302006, India.

Sir,

Combination of intrathecal local analgesic and opioid are commonly used for neuraxial blocks. This combination gives excellent intraoperative as well as postoperative analgesia. Pruritus is a troublesome side-effect of intrathecal opioids. Sometimes it may be more unpleasant than pain itself. We would like to share our experience in a 58 years old ASA-II female weight 62 kg a case of intertrochanteric fracture femur right side posted for open reduction and internal fixation under sub-arachanoid block received 3 ml (15 mg bupivacaine) and 25 µg fentanyl mixture for procedure and post operative pain relief.[1]

Spinal needle 25G quincke needle was used to give spinal anaesthesia in sitting position in mid line. After free flow of cerebrospinal fluid, 0.5% bupivacaine (heavy) 3 ml and 25 µg fentanyl was injected in the L3-L4 subarachnoid space. 90 minutes after sub arachanoid block patient began to complain of itching all over the body. Injection hydrocortisone succinate 200 mg IV was given. Patient maintained all the vitals within normal limit during the procedure and she was shifted to ward for close monitoring.

Next day in the morning at 0300 hrs patient developed tachypnea (RR-35-40/min) and tachycardia (HR-140-160/min). Blood pressure was 146/96 mmHg and maintaining Spo2 at 92% with oxygen 8L/min. Patient complained of generalised pruritis without any rashes. In spite of giving injections of hydrocortisone, pheniramine and propofol, pruritis did not subside. In view of continuing pruritis, infusion naloxone was started at rate of 0.5µg/kg/hr. After 4 hours, patient was comfortable and maintaining all vitals within normal limit. Rest of the post-operative period was uneventful and patient was highly satisfied with the relief of generalised pruritis. We have used infusion of naloxone at 0.25 to 1 µg/kg / h is the most efficient for controlling pruritis.[2-4]

It shows that low dose of intravenous naloxone is very effective in reversing the pruritis due to intrathecal administration of fentanyl without affecting the analgesia.

A large variety of drugs has been evaluated in the treatment of fentanyl induced pruritus.[5,6] Among them, many drugs are including antihistamines, 5-hydroxytryptamine 3-receptor antagonists, opiate-antagonist, propofol, non-steroidal anti-inflammatory drugs (NSAIDs), and droperidol. In conclusion, naloxone is an effectively therapeutic strategy to prevent opioid-induced side effects, such as pruritus in low dose without affecting the analgesia.

References

1. Malhotra A, Singh U, Singh MR, Sood D, Grewal A, Mahajan A. Efficacy of premixed versus succedent administration of fentanyl and bupivacaine in subarachnoid block for lower limb surgeries: A randomised control trial. Indian J Anaesth 2020;64:175-9.
2. Wang R, Xing WY, Guo NM, et al Effects of naloxone on side effects of epidural analgesia with opioids. Inner Mongolia Med J 2013; 45:990–991.
3. Kyriakides K, Hussain SK, Hobbs GJ. Management of opioid-induced pruritus: A role for 5-HT3 antagonists? Br J Anaesth 1999;82:439–41
4. Miller JL, Hagemann TM. Use of pure opioid antagonists for management of opioid-induced pruritus. Am J Health Syst Pharm. 2011;68:1419–25
5. Reich A, Szepietowski JC. Opioid-induced pruritus: An update. Clin Exp Dermatol. 2010;35:2–6.
6. Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth. 1995;42:891–903.

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Standard journal article

[1] Flink H, Tegelberg Å, Thörn M, Lagerlöf F. Effect of oral iron supplementation on unstimulated salivary flow rate: A randomized, double-blind, placebo-controlled trial. J Oral Pathol Med 2006; 35: 540–7.

[2] Twetman S, Axelsson S, Dahlgren H, Holm AK, Källestål C, Lagerlöf F, et al. Caries-preventive effect of fluoride toothpaste: A systematic review. Acta Odontol Scand 2003; 61: 347–55.

Article in supplement or special issue

[3] Fleischer W, Reimer K. Povidone-iodine antisepsis. State of the art. Dermatology 1997; 195 Suppl 2: 3–9.

Corporate (collective) author

[4] American Academy of Periodontology. Sonic and ultrasonic scalers in periodontics. J Periodontol 2000; 71: 1792–801.

Unpublished article

[5] Garoushi S, Lassila LV, Tezvergil A, Vallittu PK. Static and fatigue compression test for particulate filler composite resin with fiber-reinforced composite substructure. Dent Mater 2006.

Personal author(s)

[6] Hosmer D, Lemeshow S. Applied logistic regression, 2nd edn. New York: Wiley-Interscience; 2000.

Chapter in book

[7] Nauntofte B, Tenovuo J, Lagerlöf F. Secretion and composition of saliva. In: Fejerskov O,

Kidd EAM, editors. Dental caries: The disease and its clinical management. Oxford: Blackwell Munksgaard; 2003. pp 7–27.

No author given

[8] World Health Organization. Oral health surveys - basic methods, 4th edn. Geneva: World Health Organization; 1997.

Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979–2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): 7–18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

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