International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

A Comparative Evaluation of Dexmedetomidine and Clonidine as an Adjuvant to Ropivacaine in Epidural Anaesthesia for Intraoperative and Postoperative Sedation and Analgesia

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Abstract: ***Background: This prospective randomized double blind study was carried out to evaluate and compare the effect of dexmedetomidine and clonidine as an adjuvant to ropivacaine in epidural anaesthesia. Method: Ninety patients (ASA grade I and II), were randomly allocated into three groups of 30 patients in each. Group A (R) received 17 ml of 0.75% ropivacaine + 2ml saline (control), group B (RD) received dexmedetomidine 1.5µg/kg in 2ml+ 17 ml of 0.75% ropivacaine and group C (RC) received clonidine 2µg/kg in 2ml+17 ml of 0.75% ropivacaine in epidural anaesthesia. All three groups were evaluated in terms of onset of analgesia, duration of analgesia, motor block, sedation and any untoward side effects. Results: Onset of analgesia (sensory block) was earlier in group B (8.13±2.02 mins) than group A (12.13±3.37 mins) and group C (9.86±2.84 mins) (p<0.05). Similarly, onset of maximum sensory block and maximum motor block were shorter in group B (13.6±2.36 mins &17.23±3.30 mins respectively) as compared to group A (18.06±3.16 mins &21.23±3.74 mins respectively) and group C (15.76±3.39 mins &19.66±3.74 mins respectively) (p <0.05). Duration of analgesia was 284.7±28.22 mins, 341.33±29.06 mins and 312.6±27.68 mins in group A, B and C respectively as well as intro-operative sedation score was also higher in group B as compared to group A&C (p<0.05). Conclusion: Alpha-2 adrenergic agonists particularly dexmedetomidine when used as an adjuvant with ropivacaine significantly prolong the duration of sensory and motor blockade and duration of analgesia.***

Keywords: Dexmedetomidine, Clonidine, Ropivacaine, Alpha 2 agonist, Epidural anaesthesia

1. Introduction

Acute postoperative pain management is a key aspect of postoperative care as acute pain regardless of its site can adversely affect nearly every organ function and so affects the postoperative morbidity and mortality [1]. Effective control of per operative pain also represents an important concept of post-operative recovery as it serves to blunt autonomic, somatic and endocrine stress responses to surgery with resultant potential for decrease in per operative morbidity.

Regional anaesthesia have always been preferred technique to provide both intraoperative and postoperative analgesia as it avoids complications associated with intubation and general anaesthesia and offered several benefits to the patients, the top three from the patient's point of view are staying awake, early family contact and early food intake [2]. Epidural blockade is one of the most useful and versatile procedures in modern anesthesiology as it can reduce the adverse physiologic responses to surgery such as autonomic hyperactivity, cardiovascular stress, tissue breakdown, increased metabolic rate, pulmonary dysfunction and immune system dysfunction [3-6].

Epidural bupivacaine has been used since long but it is highly cardio toxic. Recently ropivacaine became better alternative in choice of LA, due to long duration of action and less cardiovascular effects [6]. Very slow recovery of Na^+ channel blockade after a cardiac action of bupivacaine, which is the hallmark of bupivacaine, is considerably faster with ropivacaine. However, the negative inotropic potency of ropivacaine on isolated cardiac tissue appears to be considerably less than that of bupivacaine [7]. Adding adjuvants to LA have proven better and faster onset of blockade, prolonged duration of action and postoperative analgesia with lower consumption of local anaesthetic. Adjuvants like opioids can perform these activities but as to their certain side effects like pruritus, urinary retention, nausea and vomiting, newer adjuvants are being considered.

The alpha-2 adrenergic agonists (eg. clonidine and dexmedetomidine) have both analgesic and sedative properties. They provide stable hemodynamic effects and avoid opioids side effects when used as an adjuvant in regional anaesthesia [8].

Dexmedetomidine has higher selectivity for alpha-2 adrenergic receptors with an affinity of eight times greater than clonidine [9, 10]. The elimination half-life of dexmedetomidine is approximately 4 times shorter than clonidine, which makes it a more useful drug when most rapid changes are required in the progression of this state, as well as in postoperative sedation and intensive care.

Dexmedetomidine is a lipophilic agent, so it is rapidly absorbed into the bloodstream, causing systemic effects even after subarachnoid administration [11]. The anaesthetic and analgesic requirement gets reduced to a huge extent by use of these drugs because of their analgesic property and augmentation of local anaesthetic effects [12, 13]. In this study, we compared the analgesic and sedative properties of dexmedetomidine and clonidine as an adjuvant to epidural ropivacaine for lower abdomen and lower limb surgeries.

2. Materials and Methods

In this prospective randomized double blinded study 90 patients belonging to ASA grade I and II, aged between 20-60 years after taking informed and written consent for elective lower abdomen and lower limb surgeries and randomly divided into three groups comprising 30 patients in each group by using envelope method. (Figure1)

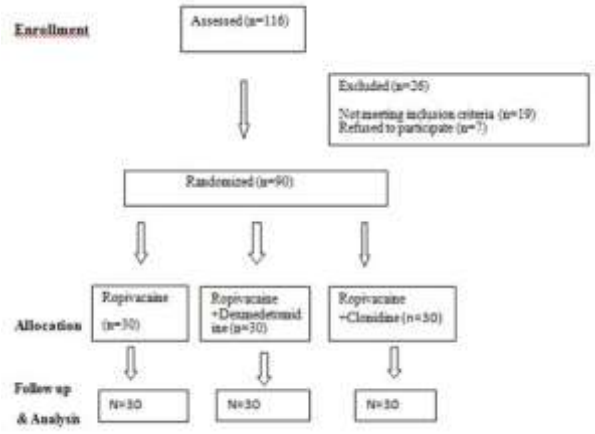

Figure 1: Consort flow diagram

Group A (R) received 17 ml of 0.75% ropivacaine +2ml saline (control), group B (RD) received combination of dexmedetomidine 1.5µg/kg in 2ml+ 17 ml of 0.75% ropivacaine and group C (RC) received combination of clonidine 2µg/kg in 2ml+17 ml of 0.75% ropivacaine in epidural anaesthesia.

Patients with haematological disease, bleeding or coagulation test abnormalities, psychiatric diseases, diabetes, history of drug abuse and allergy to local anaesthetics of amide group, any local sepsis or deformity of spinal lumber region are excluded. There was no significant difference in demographic data between three groups.

After arriving in operating room, routine monitoring including continuous ECG, NIBP and SpO2 were applied and baseline vital parameters were recorded prior to epidural block. Intravenous (IV) access was secured with 18G cannula and a crystalloid solution was started.

Under aseptic precautions, lumber epidural block performed at L2-L3 space with 18G Toughy epidural needle (Epi kit ®) in lateral decubitus position with a pillow under the shoulder. The epidural space identified by loss of resistance technique with LOR syringe, catheter secured into epidural space and a test dose of 3cc of 2% lignocaine HCL solution containing adrenaline 1:2,00,000 injected, after 5 minutes patients received drugs according to their groups. Routine general anaesthesia equipments and anaesthesia work station, Bain's circuits, laryngoscope, endotracheal tubes, oxygen mask, drugs required for general anaesthesia and emergency drugs kept ready as a protocol. Hypotension (SBP fall >20% of baseline) treated with injection mephentermine and bradycardia (HR<55bpm) with injection atropine. IV fluid was given as per body weight and operative loss requirement.

Onset of analgesia/sensory block was assessed by pinprick test using 22G hypodermic needle after completion of injection till complete loss to pinprick sensation, and it was assessed every 5 mins up to 20 mins after epidural block. The grading of pin-prick test was done as score 0=normal sensation, 1= Blunted sensation and 2= absence of sensation.

Motor blockade effect was assessed by using modified Bromage scale every 5mins after completion of epidural injection till 30 mins, then every 1hr interval up to 6-8 hrs post-operatively.

Modified Bromage scale-

0	No block
1	Inability to raise extended legs
2	Inability to flex legs
3	Inability to flex ankle and foot

Sedation score was recorded just before the initiation of surgery and thereafter every 20mins during the surgical procedure, grading of sedation was done by using five point scales (1-alert and wide awake, 2-arousable to verbal command, 3-arousable with gentle tactile stimulation, 4-arousable with vigorous shaking and 5-unarousable).

Duration of analgesia was recorded using VAS (visual analogue score) estimated on 0-10 cm scale after completion of surgery at time interval of 15mins,30mins,60mins and then every 1hrs interval up to 6-8 hrs postoperatively, it was taken from completion of injection to administration of first rescue analgesic dose to the patient and rescue analgesic dose with injection tramadol 100mg IV was administered by nursing staff whenever VAS score of ≥ 3 was recorded any time during the observation period of 6-8 hrs postoperatively. Any untoward effects such as nausea, vomiting, hypotension and bradycardia etc were recorded per operatively.

3. Statistical analysis

All data compiled systemically and statistical analysis was done using the statistical Package for Social Sciences (SPSS version 17). Normally distributed continuous variables were analysed with student t'test, while abnormally distributed data were presented as median (95% conf. interval) and categorical variables were analysed with 'CHI_SQUARE' test and ANOVA (analysis of variance) test. Value of $p<0.05$ was considered significant while $p<0.001$ was considered highly significant.

4. Results

There was clinically insignificant difference in the demographic data between the three groups. (Table-1) Mean

time to onset of analgesia/sensory block was earlier in group B (8.13±2.02mins) than group A (12.13±3.37mins) and group C (9.86±2.84mins) which was statistically highly significant (p<0.001) in group A vs B and significant (p<0.05) in group A vs C and group B vs C.

Table 1: Demographic Variables

Variables	*Group A(R)(n=30)*	*Group B(RD)(n=30)*	*Group C(RC)(n=30)*
Age(years)	42.4±9.93	40.1±9.66	41.2±9.45
Weight(kg)	55.8±8.19	57±8.2	55±8.5
Sex(M/F)	12/18	13/17	11/19
ASAgrade(I/II)	24/6	23/7	25/5
Type of surgery(LAS/LLS)	20/10	21/9	20/10
Duration of surgery(mins)	90.33±11.54	93.67±13.53	92.67±11.23

Data are represented in mean±SD except for sex, ASA grade and type of surgery
M/F-Male/Female, ASA- American Society of Anaesthesiologists

Similarly, mean onset of maximum motor block was 21.23±3.74 mins in group A, 17.23±3.30 mins in group B and 19.66±3.74 mins in group C which was also highly significant (p<0.001) in group A vs B and significant (p<0.05) in group B vs C and non significant (p>0.05) in group A vs C. Mean time to attain maximum sensory level was earlier in group B (13.46±2.36 mins) as compared to group A (18.06±3.16 mins) and group C (15.76±3.39 mins) that was statistically significant (p<0.05) in group A vs B and group B vs C.

Intra-operative sedation score observed in three groups (table-2) and sedation score 3 (arousable with gentle tactile stimulation) observed in 37% of patients in group B in comparison of 17% of patients in group C. All patients in group A were alert and wide awake (sedation score 1). The results were statistically significant (p < 0.05).

Table 2: Comparative analysis of sedation score

Sedation score scale	Group A(n)	Group B(n)	Group C(n)
1	30(100%)	5(17%)	10(33%)
2	0	14(46%)	15(30%)
3	0	11(37%)	5(17%)
4	0	0	0
5	0	0	0

In our study maximum level of sensory block was also observed, and it was T7-8 in group A (53% of patients), T5-6 in group B (70% of patients) and T6-7 in group C (63% of patients). The difference was statistically significant (p <0.05).

Duration of analgesia was assessed by using VAS score after completion of surgery. The time of first rescue analgesia (VAS score ≥3) was recorded. The mean duration of analgesia was 284.7±28.22 mins, 341.33±29.06 mins and 312.66±27.68 mins in group A, B and C respectively. The difference was highly significant (p<0.001) between group A and B, significant (p<0.05) between group A and C as well as between group B and C. (Figure 2)

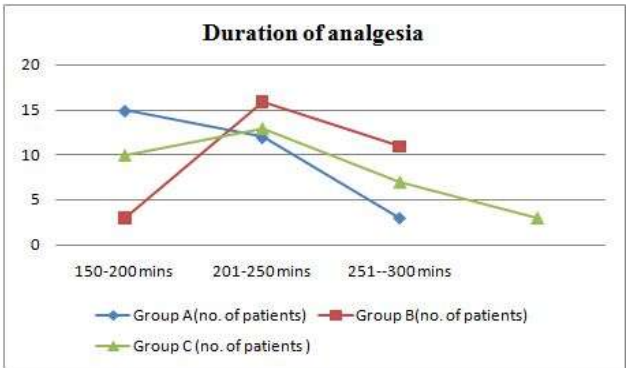

Figure 2: Comparison of duration of analgesia among three groups

Duration of motor block was assessed by using modified Bromage scale. Mean duration of motor block was 244.8±22.56 mins in group B which was more than mean duration of motor block in group A (204.7±30.44 mins) and group C (227.67±28.71 mins). The difference was highly significant (p<0.001) between group A and B, significant (p<0.05) between group A and C as well as between group B and C.

Table 3: Rescue analgesia needed in intra-operative period

Type of supplementation	Group A(n)	Group B(n)	Group C(n)
Not required	23	27	28
Drug through epidural catheter	4	2	1
I.V. anaesthesia	3	1	1
E.T. anaesthesia	0	0	0

Incidence of side effects were comparable in all three groups (p >0.05) except dry mouth which was higher in group B and group C in comparison of group A.

5. Discussion

Alpha-2 agonists are being extensively evaluated as an alternative adjuvant in regional anaesthesia with emphasis on opioid related side effects such as respiratory depression, nausea, urinary retention and pruritis [14-16]. The pharmacologic properties of α-2 agonists have been extensively studied and have been employed clinically to achieve the desired effects in regional anaesthesia [17-19, 8]. Epidural administration of these drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis [4, 5]. Clonidine has been used successfully over the last decade for this purpose but introduction of dexmedetomidine has further widened the scope of α-2 adrenergic agonists in regional anaesthesia in terms of rapid onset of action of local anaesthetics, rapid establishment of both sensory and motor blockade, prolonged duration of analgesia in postoperative period as well as better sedative effect during intra-operative period [20-22]. Therefore, we decided to compare analgesic efficacy of clonidine and dexmedetomidine during intra-operative and postoperative period as well as sedative effects as an adjuvant to epidural 0.75% ropivacaine.

In our prospective double blinded study it was observed that dexmedetomidine provide faster onset, prolonged duration and excellent sensory and motor blockade along with better sedation, stable hemodynamic when epidurally administered

with ropivacaine as compared to clonidine and control group.

The results of our study in terms of onset of analgesia coincide with the study done by Bajwa SJ et al. [8] where the onset was earlier in dexmedetomidine group (8.52 ± 2.36 mins) as compared to clonidine group (9.72 ± 3.44 mins). Bajwa SJ et al. [20] compared ropivacaine 0.75% versus ropivacaine 0.75% with 75µg clonidine for elective caesarean section and found similar result of early onset of analgesia in clonidine group.

The results are also comparable to those of Salgado PF et al. [23] who compared 20 ml ropivacaine 0.75% and ropivacaine+dexmedetomidine 1µg/kg and found earlier onset of analgesia in dexmedetomidine group. In contrast to our study, Kaur S et al. [24] showed that mean time taken for onset of sensory was 14.182 ± 6.02 min in plain ropivacaine group and 12.536 ± 4.172 min in ropivacaine+ dexmedetomidine group and difference among the two groups was not statistically significant (P = 0.115).

Similarly, time to attain maximum sensory level and maximum level of sensory block in our study coincide with study done by Bajwa SJ et al. [8] in which they found time to attain maximum sensory level was shorter in dexmedetomidine group in comparison with clonidine group (13.14±3.96 versus 15.80±4.86 mins).

In contrast to our study, Kaur S et al. [24], Salgado PF et al. [23] observed insignificant difference in time to reach maximum sensory block on addition of dexmedetomidine to ropivacaine. Also Kaur S et al. [24], Salgado PF et al. [23], Bajwa SJ et al. [20] found similar results that addition of dexmedetomidine or clonidine increases maximum level of sensory block.

In our study duration of analgesia was longer in group B (341.33±29.06 mins) as compared to group A (284.7±28.22 mins) and C (312.66±27.68 mins), same results were found in Bajwa SJ et al. [8] study (342.88±29.16 and 310.76±23.76 mins in dexmedetomidine and clonidine group respectively) but there was no control group and Kaur S et al. [24], (535.18 ± 19.85 mins in ropivacaine+dexmedetomedine group and 375.20 ± 15.97 mins in plain ropivacaine group).

Similar results of prolonged duration of analgesia with addition of dexmedetomidine epidurally found by Vasupalli R et al. [25], Anand VG [26], Bajwa SJ et al. [27], Salgado PF et al. [23], Shah PJ et al. [28], and AM et al. [22] in their studies.

Addition of clonidine with ropivacaine also has prolonged duration of analgesia in our study (310.76±23.76 mins) that coincides with the studies of and Agrawal S et al. [29], Bajwa SJ et al. [20], Bajwa SJ et al. [30] and Landau R et al. [16].

In our study mean onset of maximum motor block was 21.23±3.74 mins, 17.23±3.30 mins 19.66±3.74 mins in group A, B and C respectively. It was found that addition of dexmedetomidine to ropivacaine results in early onset of motor block as compared to ropivacaine plain ($p<0.001$) or combined with clonidine ($p<0.05$) when compared statistically.

Mean duration of motor block in our study was 244.8±22.56 mins in group B which was more than mean duration of motor block in group A (204.7±30.44 mins) and group C (227.67±28.71 mins). These results of our study coincide with Bajwa SJ et al. [8] study, they found that in comparison to clonidine, dexmedetomidine causes early onset of motor block (17.24 mins versus 19.52 mins) and prolong duration of block (246.72 versus 228.44 mins). Kaur S et al. [24] found comparable results of time to complete motor block (27.34±5.970mins versus 25.73±4.172 mins, p= 0.123) in plain ropivacaine and ropivacaine+dexmedetomedine group respectively, and prolong duration of motor block (385.92±17.719mins) in dexmedetomidine+ropivacaine group as compared to plain ropivacaine group (259.80±15.486min) (p=0.00).

Our study clearly indicate significant effectiveness of epidural dexmedetomidine for intraoperative sedation as depicted in table-2, and the results coincides with Bajwa SJ et al. [8] , Kaur S et al. [24], Salgado PF et al. [23], Vieira AM et al. [22], Bajwa SJ et al. [27] and Anand VG [26].

The anesthetic and the analgesic requirement get reduced to a large extent by the use of α2 agonists because of their analgesic properties and augmentation of local anesthetic effects as they cause hyperpolarization of nerve tissues by altering transmembrane potential and ion conductance at locus coeruleus in the brainstem [8]. Sedation is due to action on locus coeruleus, which inhibit the release of norepinephrine [12-13]. Sedation after epidural α2 agonists is due to its systemic absorption and vascular redistribution to higher centers [31-33]. Sedation is an add on advantage for regional anesthesia to bring down the stress associated with the surgery.

Dexmedetomidine is a highly selective α2 adrenergic agonist with an affinity of 8 times greater than clonidine and hence allows the use of higher doses with less α1 effect. There is no such study which has compared the dose equivalence of these drugs, but the observations of various studies have stated that the dose of clonidine is 1.5−2 times higher than dexmedetomidine when used in epidural route [8]. Neuraxial clonidine enhances the action of local anesthetics, increases the intensity and duration of analgesia. It is known to have sedative properties, and the side effects are hypotension and bradycardia [34].

6. Conclusion

Alpha-2 adrenergic agonists (dexmedetomidine and clonidine) significantly prolong the duration of sensory and motor blockade and duration of analgesia. Dexmedetomidine is better adjuvant than clonidine as far as patient comfort, stable cardio-respiratory parameters, intraoperative and postoperative analgesia is concerned, and it provide superior sedative and anxiolytic effect during surgery under regional anaesthesia.

7. Acknowledgement

No financial assistances/funding used
No conflict of interest

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