Original Research Article

Study of dexmedetomidine as an intrathecal adjuvant to ropivacaine for hemodynamic stability and for postoperative analgesia

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Abstract

Background: Various adjuvants that can be added to local anesthetics and administered in central neuraxial blockade are Opioids, α2 agonists, benzodiazepines. Knowledge and use of adjuvant drug therapy has rendered neuraxial analgesia more effective in the management of both acute and chronic pain conditions. α-2 adrenergic agonists have both analgesic and sedative properties when used as adjuvant in regional anaesthesia.

Aim: To study the effects of intrathecal dexmedetomidine added to ropivacaine for surgeries under spinal anesthesia.

Materials and methods: Clinical study conducted on 50 patients of ASA PS 1 and 2 in the age group of 18-50 years of either sex posted for elective lower limb orthopaedic and lower abdominal surgeries under spinal anaesthesia.

Results: Subjects among the age groups and the mean age of study population was 40 years (SD: ±11.5). 66% (n=33) of study population were male and 34% (n=17) were female. Most of the study population had healthy BMI. 76% (n= 38) of subjects belonged to ASA grade 1 and 34% (n=12) subjects belonged to ASA grade 2. The average duration of surgery was 94.4 min ± 34.4 min. Level of sensory block was T6 in 24 (48%) of subjects, T4 in 17 (34%) of subjects, T8 in 6 (12%) and T2 in 3 (6%) of subjects. The mean duration for onset of Sensory block was 4.12 minutes (SD: ± 1.69) and the mean duration for onset of motor block was 10.12 minutes (SD: ± 2.89). Hypotension was

observed in 3 patients after SAB (Fall in SBP > 20%) after 4 to 6 min. The mean RSS was 2.08 with SD 0.27. Side effects observed were mainly hypotension, nausea and shivering.
Conclusions: 5 microgram dexmedetomidine is alternative as an adjuvant to spinal ropivacaine in surgical procedures. It has excellent quality of postoperative analgesia with minimal side effects.

Key words

Dexmedetomidine, Intrathecal, Ropivacaine, Hemodynamic stability, Post-operative, Analgesia.

Introduction

The ASA "Practice guidelines for acute pain management in the peri-operative setting" [1-3] stresses on multimodal therapy with two or more analgesic agents or techniques used in combination for control of postoperative pain. The final aim of this aspect of therapy would be seen as the complete relief of postoperative pain with no treatment related side effects. In reality, all current therapies have unwanted side effects. The present aim of treatment may be regarded as time dependent maximization of comfort.

Adjuvant drugs are pharmacological agents possessing little pharmacological effect by themselves, but enhance or potentiate the action of other drugs when given at the same time. Adjuvant drugs modify LA effects and reduce side effects. Peri-operatively these drugs affect: Latency i.e. time of onset of LA block, Duration of analgesia i.e. duration of sensory and motor block, Quality of analgesia i.e. complete, incomplete (partial or patchy analgesia requiring supplemental drugs), Postoperatively adjuvant drugs affect analgesic gap i.e. time interval between subsequent doses administered, Quality of analgesia i.e. patient satisfaction, care provider's impression of pain relief.

Various adjuvants that can be added to local anesthetics and administered in central neuraxial blockade are Opioids, α2 agonists, benzodiazepines. Knowledge and use of adjuvant drug therapy has rendered neuraxial analgesia more effective in the management of both acute and chronic pain conditions. α-2 adrenergic agonists have both analgesic and sedative properties when used as adjuvant in regional anaesthesia [1-3]. Dexmedetomidine is a highly selective α2 agonist with 8 times greater affinity than clonidine. More clinical experience have been gained with regard to usage of clonidine compared to dexmedetomidine by intrathecal route. There are less studies available for these drugs as adjuvants to 0.75% Ropivacaine. Dexmedetomidine reduces opioids and inhalational anaesthetic requirement and have been wildly used for Intensive Care Unit sedation with haemodynamic stability. Intrathecal alfa-2 receptor agonists have anti-nociceptive action for both somatic and visceral pain. We study the use of intrathecal combination of dexmedetomidine (5 microgram) with isobaric ropivacaine in lower abdominal surgeries. The aim of this study was to evaluate haemodynamic effects intra-operatively as well as to notify the duration of postoperative analgesia. The primary outcomes studied were hemodynamic parameter changes- especially blood pressure and pulse changes intraoperative as compare to preoperative. The duration of pain relief define as the time from intrathecal administration of ropivacaine + dexmedetomidine to first request for supplementary analgesia by the patients. Postoperative analgesia consumption in total and maximum have been evaluated as secondary outcome by pain score (Visual Analogue Scale).

Materials and methods

This clinical study was conducted on 50 patients of ASA PS 1 and 2 in the age group of 18-50 years of either sex posted for elective lower limb orthopaedic and lower abdominal surgeries under spinal anaesthesia after taking informed consent at Osmania General Hospital, Osmania Medical College, Hyderabad over a period of 12 months. After approval from the hospital ethical

committee, a prospective study was carried out on 50 adult patients.

Inclusion criteria:

- ASA grade 1 and 2 patients
- Age group of 18 – 60 years
- Patients giving valid informed consent
- Those patients scheduled to undergo elective surgery under subarachnoid block.

Exclusion criteria:

- Patient refusal.
- Patients with gross spinal abnormality, localized skin sepsis, hemorrhagic diathesis, or neurological involvement / diseases.
- Head injury cases.
- Patient receiving alpha-2 adrenergic receptor antagonists, calcium channel blockers, ACE inhibitors, having dysarrhythmias on ECG, body weight more than 120 kg.

Method of study

Pre-anaesthetic check-up was carried out preoperatively with a detailed history, general examination and systemic examination, airway assessment, spinal column examination were done.

Details of present study process including potential side effects were explained to all patients and relatives and familiarised with visual analogue scale.

All routine laboratory examination was done in selected patients. Patient was shifted to the OT table; IV access was obtained on the fore arm with 18 G IV canula and co-loaded with lactated ringer solution 10 ml/kg. The monitors connected to the patient included non-invasive blood pressure, ECG, HR and pulse oximetry.

Under strict aseptic precautions lumbar puncture was performed with disposable Quincke's spinal needle (25G) at the L3-L4 space. If the spinal block failed, at the level of L3-L4, we changed the level to L2-L3.In case of failure at both levels the procedure was abandoned, general anaesthesia was administered and those patients were excluded from the study. All patients were given 3 ml of 0.75% Ropivacaine (22.5 mg) + Dexmedetomidine (5 µg).

Patients were monitored continuously using NIBP, pulse oxymeter and ECG. After Spinal anaesthesia oxygen (6 lts/min) by face mask was given. Fluid therapy was maintained with lactated ringer solution infused according to patients hemodynamics volume status. Vital parameters HR, NIBP, SPO2, RR, ECG at 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 75, 90, 105, 120, 240 min were monitored .

The onset of sensory block was tested by pin prick method using a hypodermic needle. The time of onset was taken from the time of injection of drug into SAS to loss of pin prick sensation. The highest level of sensory block and time was noted. The time for 2 dermatomal segment regression of sensory level was noted. The duration of sensory blockade was taken as time from onset to time to return of pinprick sensation to S1 (heel) dermatomal area.

Motor Blockade assessed by Bromage scale .The time interval between injections of drug into subarachnoid space, to the patient's inability to lift the straight extended leg was taken as onset time (Br.3). The duration of motor block was taken from time of injection to complete regression of motor block. (ability to lift the extended leg) (Br 0) as per **Figure – 1**.

Modified Bromage Scale:

- Grade 0 – Full flexion of knees and feet.
- Grade 1 – Just able to flex knees, full flexion of feet.
- Grade 2 – Unable to flex knees, but some flexion of feet possible.
- Grade 3 – Unable to move legs or feet.

Assessment of Sedation:

The level of sedation was evaluated introperatively and post operatively every 15 minutes using Ramsey level of sedation score.

1. Patient anxious, agitated, or restless.
2. Patient cooperative, oriented, tranquil alert.
3. Patient responds to commands.
4. Asleep, but with brisk response to light glabellar tap or loud auditory stimulus.
5. Asleep, sluggish response to light glabellar tap or loud auditory stimulus.
6. Asleep, no response.

Pain

Assessed by visual analogue scale, initially for every 1 hour for 2 hours, every 2 hours for next 8 hours and then every 4 hours till 24 hours. Inj tramadol 2 mg/kg iv (max 100 mg) was given as a rescue analgesic when VAS score was greater than / equal to 4 (**Figure – 2**).

Figure - 1: Bromage Scale for assessing motor block and degree of paralysis.

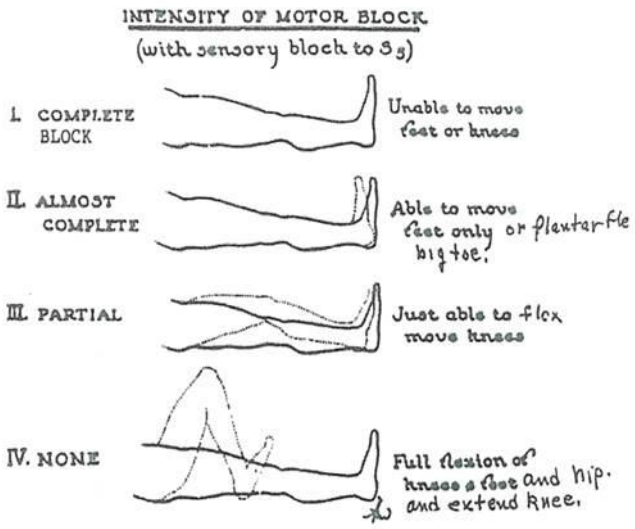
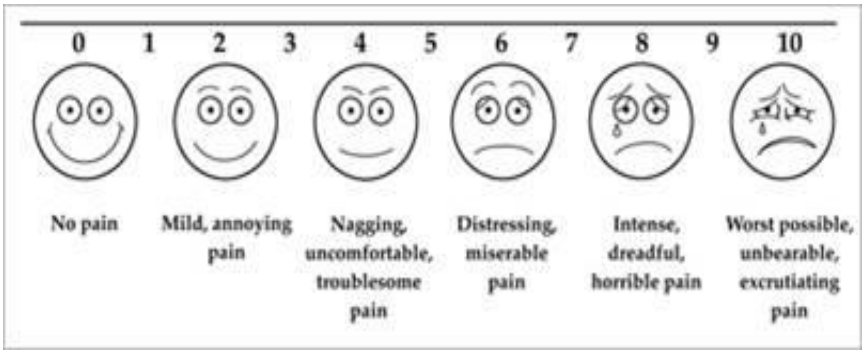


Figure – 2: Visual analogue scale.



Results

There was fair distribution of subjects among the age groups and the mean age of study population was 40 years (SD: ±11.5). 66% (n=33) of study population were male and 34% (n=17) were female. Most of the study population had healthy BMI. 76% (n= 38) of subjects belonged to ASA grade 1 and 34% (n=12) subjects belonged to ASA grade 2 (**Table – 1**).

The average duration of surgery was 94.4 min ± 34.4 min. Level of sensory block was T6 in 24 (48%) of subjects, T4 in 17 (34%) of subjects, T8 in 6 (12%) and T2 in 3 (6%) of subjects (**Table – 2**).

Table - 1: Demographic distribution of subjects.

Variable	Number of subjects	%
Age groups		
20-29yrs	15	30%
30-39yrs	13	26%
40-49yrs	13	26%
50-59yrs	9	18%
Sex wise distribution		
Males	33	66%
Females	17	34%
BMI		
underweight:18.5	2	4%
healthy:18.5-24.9	28	56%
overweight:25-29.9	20	40%
obese:30-34.9	0	0%
ASA grade		
1	38	76%
2	12	24%
3	0	0%
4	0	0%
Type of surgery		
Lower abdominal procedures	28	56%
Urological procedures	6	12%
Orthopedic procedures	16	32%

Table - 2: Variables in study.

Duration of surgery in min	Number of subjects	%
60	11	22
61-90	13	26
91-120	15	30
121-150	10	20
151-180	4	8
Level of block		
t2	3	6%
t4	17	34%
t6	24	48%
t8	6	12%

The mean duration for onset of Sensory block was 4.12 minutes (SD: ± 1.69) and the mean duration for onset of motor block was 10.12 minutes (SD: ± 2.89) as per **Figure – 3**.

Pulse rate in all the patients was maintained in normal range during the observation period. Mean pulse rate was 76 ±4.3 beats per min. Average mean systolic pressure was 117.7 ± 14.3 mm Hg and diastolic pressure 68.7± 4.6 mmHg .

However, when considered individually, Hypotension was observed in 3 patients after SAB (Fall in SBP > 20%). The hypotension was mainly observed after 4 to 6 mins after SAB.

Oxygen saturation was in the required normal levels.

The mean RSS was 2.08 with SD 0.27 (**Table – 3**). Side effects observed were mainly hypotension, nausea and shivering (**Table – 4**).

Table - 3: Ramsay sedation score in study.

Ramsay sedation score	Number of subjects	%
1	0	0%
2	46	92%
3	4	8%
4	0	0%
5	0	0%
6	0	0%

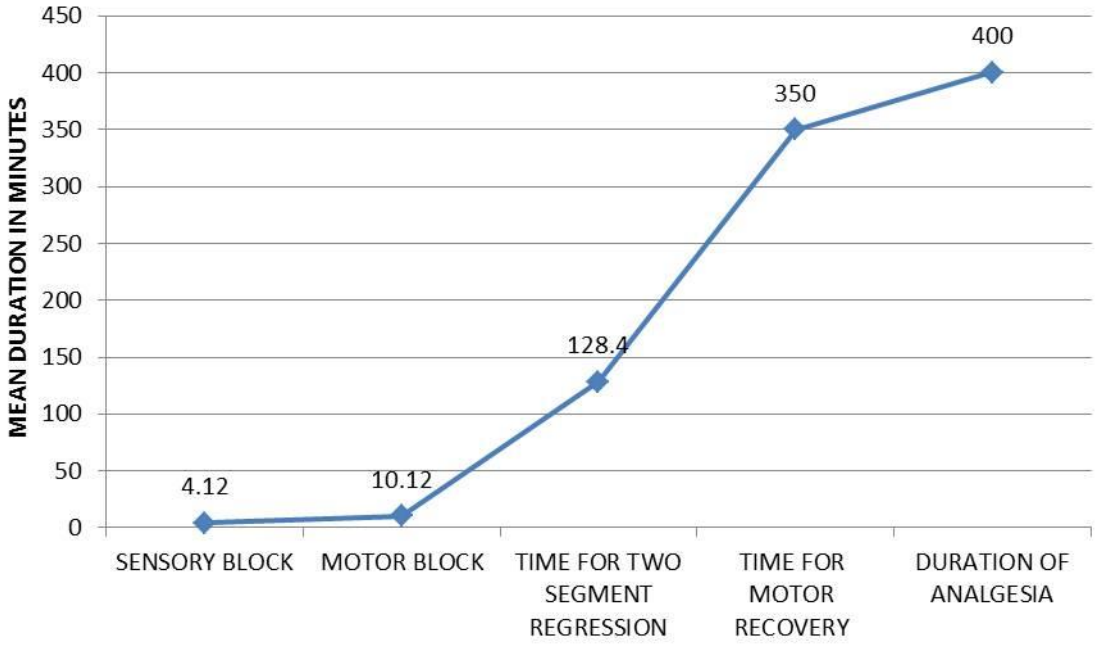
Table - 4: Side effects observed in study population.

Side effects	Number of subjects	%
Hypotension	2	4%
Bradycardia	0	0%
Nausea/Vomiting	2	4%
Shivering	1	2%

Discussion

Lower abdominal and lower limb surgeries may be performed under local, regional (spinal or epidural) or general anesthesia. Spinal block is still the first choice because of its rapid onset, superior blockade, low risk of infection as from catheter *in situ*, less failure rates and cost-effectiveness, but has the drawbacks of shorter duration of block and lack of adequate postoperative analgesia [4].

Figure - 3: Duration of study parameters in study.



Till recently Bupivacaine 0.5% Heavy was the only drug used for spinal anaesthesia after the discontinuation of Lidocaine in intrathecal use. Ropivacaine- another amino-amide local anaesthetic having all the advantages but with lower CNS and cardiac toxicity in comparison to Bupivacaine has been introduced [2] in Indian market. Ropivacaine is a first single enantiomer-specific compound, which has a reduced risk of cardiotoxicity, neurotoxicity, and rapid recovery of motor function. Ropivacaine is available as 0.75% isobaric and 0.5% isobaric for intrathecal anaesthesia and also 0.2% for infiltration anesthesia. Ropivacaine is in a way a new addition in our Indian field of local anaesthetics whose neuronal blocking potential seems to be equal or superior to Bupivacaine [5].

Onset of sensory block is the time lapse between drug administration and loss of cold sensation at T10 dermatome tested by hypodermic needle. Onset of motor block is the time lapse between drug administration and attainment of Bromage 3 scale .In our study the mean duration of onset of sensory block was 4.12 min and of motor block was 10.12 min. In study conducted by Shah A, et al. [6] onset of sensory block was 4.8 ± 1.2 sec similar to findings of our study Dhasmana Satish [7] conducted a double blind randomized control study of intrathecal ropivacaine 7.5 mg with dexmedetomidine 5mcg versus ropivacaine 7.5mg with clonidine 15 mcg by intrathecal route in patients undergoing TURP. The study showed onset of sensory block in dexmedetomidine group was 3.2 min and that of motor block was 4.4 min. The onset of motor block was faster in this study compared to our study as they defined onset as inability to raise legs on command and not according to bromage scale. In study conducted by Nitish Kumar Parmar, et al. [8] the mean duration of onset of sensory block was 4.03±0.69 min which closely correlates with our study.

In our study the mean peak sensory level was achieved in 12.92 min. Mean time for 2 segment regression was 128±15.7 min. In a study conducted by Dhasmana Satish [7], mean time for two segment regression was 133.40 ± 14.20 min. In another study conducted by Alka Shah [6], mean time to achieve maximum sensory block was 11.7 ± 1.7 min and mean time for two segment regression was 125.6 ± 16.5 similar to our study.

Similar prolongations were observed in a study conducted by Mahendru V [9] who compared dexmedetomidine, clonidine, fentanyl as adjuvants to hyperbaric bupivacaine. They concluded that intrathecal dexmedetomidine as adjuvant was associated with a prolonged motor and sensory blockade with a better postoperative analgesia and reduced requirement of rescue analgesia in first 24 hrs.

In our study the mean duration of motor recovery (bromage 3) was 350±50 min. The prolongation of motor effect might be caused by direct impairment of excitatory amino acid release from spinal interneurons. Nitish Kumar Parmar, et al. [8] studied the effect of intrathecal ropivacaine and dexmedetomidine and demonstrated that dexmedetomidine significantly prolongs the motor blockade (258.55±30.46 min). Gupta, et al. [10] observed that the total duration of motor blockade was prolonged in dexmedetomidine group as compared to fentanyl group (421±21 min vs. 149.3±18.2 min, P value<0.0001). Dharamsana S [7] observed duration of motor block to be 231±18 min which is lower than our findings. This may be explained by the fact that they used low dose of ropivacaine.

In another study conducted by Gupta, et al. [10], they observed that the total duration of motor blockade was prolonged in dexmedetomidine group as compared to fentanyl group (421±21 min vs. 149.3±18.2 min, P value<0.0001). Gupta R, et al. [11] also observed similar results. The mean systolic pressure in the study was 117.7 ± 14.3 mmHg and diastolic pressure 68.7 ± 4.6mmHg .Mean pulse rate was 76 ± 4.3.In our study only 2 cases of hypotension were noted where SBP fell more than 20% from the base line. However, there was no case of clinically severe hypotension observed in the study.

Klimscha W, et al. [12] found that intrathecal dexmedetomidine did not potentiate the effect of bupivacaine on blood pressure. This may be explained by the mechanism local anesthetics affect blood pressure. Local anesthetics reduce blood pressure by decreasing sympathetic outflow. Sympathetic blockade produced by intrathecal dexmedetomidine does not decrease blood pressure further presumably because the blockade produced by bupivacaine is nearly maximum. Eisenach, et al. [13], also found that addition of a low dose of alpha 2-agonist to a high dose of local anesthetics does not further affect the near-maximal sympatholysis.

Al-Ghanem, et al. [14] have reported the use of dexmedetomidine to be associated with a decrease in heart rate and blood pressure but in our study no significant hypotension and bradycardia was noted. The reason could be combination of dexmedetomidine with ropivacaine has been shown to be a better drug in terms of cardiovascular and haemodynamic control. Gupta R, et al. [11] conducted a study of Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia and demonstrated a no significant change in haemodynamic parameters.

Mahendru V [9], compared dexmedetomidine, clonidine, fentanyl as adjuvants to hyperbaric bupivacaine showed no significant changes in haemodynamic parameters and side effects both were comparable intra-operatively and postoperatively.

G. E. Kanazi [15], conducted study on effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. They observed that the mean arterial pressure, heart rate and level of sedation were similar in the three groups intra-operatively and post-operatively.

Dhasmana Satish [7], conducted a double blind randomized control study of intrathecal ropivacaine 7.5 mg with dexmedetomidine 5 mcg versus ropivacaine 7.5 mg with clonidine 15 mcg by intrathecal route in patients undergoing TURP. Cardiovascular parameters (SBP, DBP, MAP, HR) remained stable, similar results were obtained in the studies conducted by Al-Mustafa, et al. [14].

The mean duration of analgesia in our study was 400 min ± 58 min. Shah A, et al. [6] found that the analgesic effect of intrathecal ropivacaine was potentiated by intrathecal dexmedetomidine. The addition of 5 microgram of intrathecal dexmedetomidine prolonged the postoperative analgesic effect of ropivacaine by approximately 8 hours which co related well with our findings. In addition, dexmedetomidine – treated group required less postoperative analgesic in the first 24 hours after surgery. Nitish Kumar Parmar, et al. [8] observed that the duration of analgesia was significantly prolonged with the addition of dexmedetomidine as compared to ropivacaine alone (370.00±38.75 min and 174.77±22.31 min), respectively. Gupta R, et al. [11], found that duration of analgesia was significantly prolonged when dexmedetomidine was added to ropivacaine (478.4±20.9 minutes) as compared to plain ropivacaine (241.67±21.67 minutes) similar to findings in our study.

Dexmedetomidine is a partial agonist of the α_2 adrenoceptors that are found densely in the pontine locus ceruleus, which is an important source of sympathetic nervous system innervations of the forebrain and a vital modulator of vigilance. The sedative effects evoked by α_2 agonists most likely reflect inhibition of this nucleus. Tan J O [16] compared the dose-dependent effect of dexmedetomidine (5 mcg and 10 mcg) and found that all patients had mild sedation. Intrathecally administered -α2-agonist have a dose-dependent sedative effect.

The cause of sedation after intrathecal dexmedetomidine may be related to its systemic absorption and vascular redistribution to higher centers or cephalad migration in CSF

Sedation in our study was assessed by Ramsay sedation scale. The mean RSS was 2.08 ± 0.2

Bradycardia was observed in 6% (n=3), hypotension was observed in 4% (n=2) and nausea in 4% (n=2) of subjects. Only 1 person (2%) had shivering .Despite providing good sedation, dexmedetomidine does not cause significant respiratory depression, providing wide safety margins. Bradycardia, hypotension and sedation which are the most dreaded side effects of alpha adrenoceptors agonist was not that significant in our study which can be attributed to the usage of low dose of dexmedetomidine. No serious adverse effects were observed in studies conducted by Shah A, et al. [6], Nitish Kumar Parmar, et al. [8]. Our study adds to the growing body of evidence that dexmedetomidine can be effectively and safely used as an intrathecal adjunct to ropivacaine however our study was limited by its small sample size and larger randomized controlled studies are recommended to firmly establish the efficacy and safety of intrathecal dexmedetomidine.

Talke, et al. [17], observed in their study that α-2 adrenergic agents also have anti-shivering property. In our study shivering was noted in only 1 patient which is in agreement with this study. it was in the month of December and no fluid warmers were used for the case. Dexmedetomidine is available as preservative free ampoules in our country and hence appears suitable for intrathecal and epidural use by virtue of its properties to modify neural transmission in the nerve, spinal cord and CNS. Although no major neurological complications have been reported so far, larger studies are required to rule out any short term or long term adverse effects.

The anaesthesia was well accepted by surgeons and anaesthesiologist. Majority opined that the quality of anaesthesia and relaxation is good to excellent with the combination of ropivacaine and dexmedetomidine and the real benefits extended well into the post-operative period by way of quality post-operative analgesia for 6-8 hours with reasonably stable hemodynamics and negligible pharmacological intervention to prop up the hemodynamics. This aspect is very important because the most serious complication of spinal anaesthesia in the immediate post-operative period is hypotension.

In our study, most of the patients were calm and composed during both operative and post-operative period and this can be explained by the pharmacological properties attributed to dexmedetomidine.

Conclusions

To conclude, 5 microgram dexmedetomidine is alternative as an adjuvant to spinal ropivacaine in surgical procedures, especially those requiring long time. This combination (ropivacaine and dexmedetomidine) provides very good quality of haemodynamic stability. This dose have an effect on sedation level, HR and MAP which does not however require any therapeutic intervention and hence can be advocated as an adjuvant to ropivacaine in spinal anesthesia. It has excellent quality of postoperative analgesia with minimal side effects.

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