Original Research Article

Study of Dexmedetomidine as an intrathecal adjuvant to ropivacaine for postoperative analgesia

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Abstract

Background: 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: 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, study done over a period of 12 months.
Results: All demographic details are insignificant. Average duration of surgery was 94.4 min ± 34.4 min. 76% (n= 38) of subjects belonged to ASA grade 1 and 34% (n=12) subjects belonged to ASA grade 2. 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). 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.

Mean values of SBP and DBP were maintained in the study population. 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 min after SAB. The mean Ramsay sedation scale was 2.08 with SD 0.27. Side effects observed were mainly hypotension, nausea and shivering. **Conclusion:** To conclude, 5 microgram dexmedetomidine seems to be an attractive 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. It has excellent quality of postoperative analgesia with minimal side effects.

Key words

Dexmeditomidine, Intrathecal, Adjuvant, Ropivacaine, Post-operative, Analgesia.

Introduction

Quinke in 1891 demonstrated a safe predictable means of performing lumbar puncture [1]. In 1899 August Bier used Quinkes techniques to inject cocaine in order in order to produce operative anesthesia, the first real spinal anesthesia [2]. The first phase in history of spinal anesthesia. In 1905, Heinrich Braun [3] a German surgeon, reported the use of procaine for operative spinal anaesthesia. Means for controlling levels of Anaesthesia by making procaine solutions hyperbaric by adding glucose, was first reported by Barker [4] in 1907 or hypobaric, initially by adding alcohol. Synthesis of Tetracaine in 1931 and its introduction into clinical practice by Sise [5] in 1935, synthesis of Dibucaine and its introduction into clinical practice by Jones [6] in 1930 popularized spinal Anaesthesia. Continuous spinal Anaesthesia was demonstrated by Lemmon [7] in 1940 and Tuohy [8] in 1945. By the mid–1940s spinal Anaesthesia had reached a peak of its popularity, which was soon followed by almost equally widespread avoidance and neglect. The pharmacologic explosion in Anaesthesia between 1945 and 1965 made spinal Anaesthesia appear unnecessarily demanding, inconvenient, and tedious, as well as, at least medico legally, unsafe. Around 1965, spinal anesthesia began a recovery that has persisted and even accelerated over the last 50 years due to its simplicity, minimum skill implementation, optimal operative condition, lowered risk of aspiration, low intra-operative blood loss, continued analgesia in the post-operative period and minimal postoperative morbidity. The endocrine metabolic response to surgery appears to be blunted with spinal anesthesia compared to general anesthesia. In view of the wider application of regional anesthetic procedure in modern anesthesia practice, there is a need for local anesthetic with desirable properties like longer duration of sensory blockade and lesser duration of motor paralysis. Ropivacaine is newer amide type of local anesthetic having a lower potential for cardiac and central nervous system toxicity, shows a greater differentiation between sensory and motor blockade. The ASA "Practice guidelines for acute pain management in the peri-operative setting" 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 and 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–Fentanyl, sufentanyl, morphine (preservative free), α2 agonists-dexmedetomidine, clonidine, Benzodiazepines- midazolam, Neostigmine, ketamine, adrenaline and magnesium sulphate. 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. 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 antinociceptive 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 intraoperatively 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 was ASA grade 1 and 2 patients, age group of 18-60 years, patients giving valid informed consent and those patients scheduled to undergo elective surgery under sub-arachnoid block.

Exclusion criteria was patient refusal, patients with gross spinal abnormality, localized skin sepsis, haemorrhagic 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.

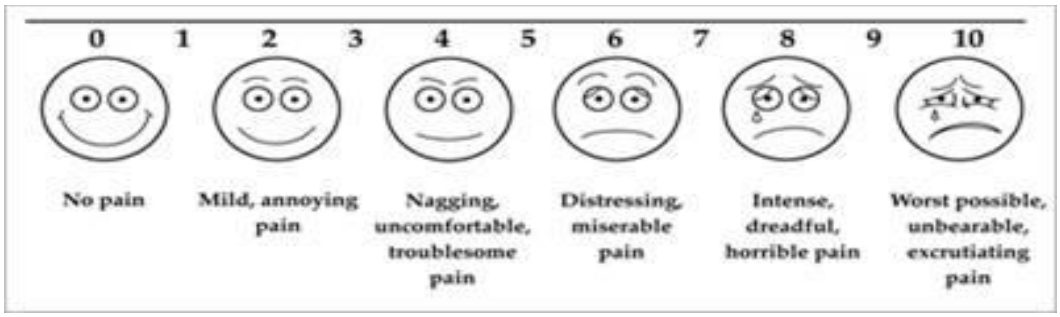
One day before surgery: Details of present study process including potential side effects were explained to all patients and relatives and familiarised with visual analogue scale.

The following laboratory examination were done in selected patients such as Haemoglobin, Urine analysis, Blood sugar, Blood urea, Serum creatinine, Coagulation profile, Blood grouping and Rh typing, ECG for patients over 40 years of age and Chest X ray.

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 were 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. Pain was assessed by visual analogue scale, initially for every 1 hour for 2 hour, every 2 hours for next 8 hours and then every 4hrstill 24 hrs. 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 – 1**).

Figure – 1: VAS scale.



Results

Total of 50 patients entered this open labeled study they were administered 3 ml of ropivacaine and 5 mcg of dexmedetomidine intrathecally by subarachnoid block technique to induce anesthesia in lower abdominal and lower limb surgeries. There was fair distribution of subjects among the age groups and the mean age of study population was 40 years (SD: ±11.5). **Table - 1** shows all demographic details are insignificant.

Table - 2 shows the average duration of surgery was 94.4 min ± 34.4 min. 76% (n= 38) of subjects belonged to ASA grade 1 and 34% (n=12) subjects belonged to ASA grade 2. 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.

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).

Table – 1: Demographic distribution.

Age groups	**No. of subjects**	**%**
20-29 years	15	30%
30-39 years	13	26%
40-49 years	13	26%
50-59 years	9	18%
Sex	**No. of subjects**	**%**
Males	33	66%
Females	17	34%
BMI	**No. of subjects**	%
Underweight: 18.5	2	4%
Healthy: 18.5-24.9	28	56%
Overweight: 25-29.9	20	40%
Obese: 30-34.9	0	0%

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 (**Table – 3**).

Table – 2: Duration of surgery, ASA grading of study population and types of surgeries.

Duration min	**No. of subjects**	**%**
60	11	22
61-90	13	26
91-120	15	30
121-150	10	20
151-180	4	8
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
Level of block		
T2	3	6
T4	17	34
T6	24	48
T8	6	12

Table – 3: Variables in study population,

Study variable	**Mean duration (min)**	**Std. Dev.**
Sensory block onset	4.12	1.69
Motor block onset	10.12	2.89
Study variable		
Time for two segment regression	128.4	15.7
Time for motor recovery	350	50.4
Duration of analgesia	400	58

In our study average mean systolic pressure was 117.7 ± 14.3 mm Hg and diastolic pressure 68.7± 4.6 mmHg. Mean values of SBP and DBP were maintained in the study population. 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 in the study. Sedation in our study was assessed by Ramsay sedation scale. The mean RSS was 2.08 with SD 0.27.

Side effects observed were mainly hypotension, nausea and shivering (**Table – 4**).

Table - 4: Side effects in study.

Side effects	**No. 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 anaesthesia [1]. 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 [1]. Till recently Bupivacaine 0.5% Heavy was the only drug used for spinal anesthesia after the discontinuation of Lidocaine in intrathecal use. Ropivacaine-another amino-amide local anesthetic 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 anesthesia and also 0.2% for infiltration anesthesia. Ropivacaine is in a way a new addition in our Indian field of local anesthetics whose neuronal blocking potential seems to be equal or superior to Bupivacaine [4].

In our study all demographic parameters are insignificant (**Table – 1, 2**). 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 (**Table - 3**).

In study conducted by Shah A, et al. [9] onset of sensory block was 4.8 ± 1.2 sec similar to findings of our study Dhasmana Satish, Singh Vinita, Raman Rajesh, Pal Mahendra [10] conducted a double blind randomized control study of intrathecal ropivacaine 7.5mg with dexmedetomidine 5 mcg versus ropivacaine 7.5 mg 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. [11] 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, Singh Vinita, Raman Rajesh, Pal Mahendra [10] mean time for two segment regression was 133.40 ± 14.20 min. In another study conducted by Alka Shah, Ila Patel, Rachana Gandhi [9] 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 [12]. 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. [11] 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. [13], 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). Dhasmana S [10] 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. [13], 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). Verma R, et al. also observed similar results. The mean systolic pressure in the study was 117.7 ± 14.3 mmHg and diastolic pressure 68.7 ± 4.6 mmHg .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. [14] 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. [15], 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. [16] 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 hemodynamic control. Gupta R [13] conducted a study of Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia and demonstrated a no significant change in haemodynamic parameters. Mahendru V, Tewari A, Katyal S, Grewal A, Singh MR, Katyal R [12] compared dexmedetomidine, clonidine, fentanyl as adjuvants to hyperbaric bupivacaine showed no significant changes in hemodynamic parameters and side effects both were comparable intraoperatively and postoperatively. G. E. Kanazi 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 [10] conducted a double blind randomized control study of intrathecal ropivacaine 7.5mg with dexmedetomidine 5mcg versus ropivacaine 7.5mg 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.

The mean duration of analgesia in our study was 400 min ± 58min (**Table - 3**). In their study Shah A, et al. [9] 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. [11] 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. [13] 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. In a study conducted by Hala E, A Eid, et al. [17] shown significant prolongation of the duration of spinal blockade by intrathecal administration of dexmedetomidine as an adjunct to hyperbaric bupivacaine. Patients in the groups that received dexmedetomidine had reduced postoperative pain scores and a longer analgesic duration than those who received spinal bupivacaine alone. Saravana Babu M, Verma AK, Agarwal A, Tyagi CM, Upadhyay M, Tripathi S [18] conducted a prospective study of ropivacaine with dexmedetomidine versus clonidine by epidural route and concluded that dexmedetomidine is a better neuraxial adjuvant compared to clonidine in providing early blockade and prolonged postoperative analgesia with stable cardiorespiratory parameters. 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 [19] 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 (D' Angelo R, et al.). 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., Nitish Kumar Parmar, et al. [9]. 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. [20], observed in their study that α-2 adrenergic agents also have anti-shivering property.

In our study shivering was noted in only 1 patient (**Table - 4**) 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 nerves, 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 anesthesia was well accepted by surgeons and anesthesiologist. Majority opined that the quality of anesthesia 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 op 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 anesthesia 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.

Conclusion

To conclude, 5 microgram dexmedetomidine seems to be an attractive 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 hemodynamic 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. However, clinical studies to prove its efficacy and safety and varying dosages for supplementation of spinal local anesthetics are recommended.

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