International Surgery Journal
Chandra GP et al. Int Surg J. 2017 Dec;4(12):3833-3838
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20175099

Original Research Article

Comparison of effect of intrathecal dexmedetomidine and clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing surgery for fracture femur and tibia

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Received: 13 October 2017
Accepted: 16 October 2017

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ABSTRACT

Background: Spinal anaesthesia with bupivacaine is administered routinely for lower abdominal and lower limb surgeries. The ensuing nerve block is sufficient to ensure patient's wellbeing, while motor block facilitates the surgeon's work. Post-operative pain relief can be achieved by various methods namely systemic opioid and non-opioid peripheral nerve blocks and local wound infiltration, each with their own merits and demerits. the present study was undertaken to compare the effect of intrathecal dexmedetomidine and clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing surgery for fracture femur and tibia.
Methods: 80 patients between 20-60 years, undergoing elective surgery for closed fracture shaft of femur and tibia with ASA physical status of 1 and 2 were included in the study. All the subjects were randomly allocated to one of the two groups (Group C and Group D) by a computer-generated randomization chart. Group C received 2.5ml of 0.5% hyperbaric bupivacaine with 50mcg clonidine and group D received 2.5ml of 0.5% hyperbaric bupivacaine with 5mcg dexmedetomidine.
Results: 30 of the 40 patients in group C were of ASA I and 10 were ASA II, while in group D, 25 were ASA I and 15 were ASA II. A significant difference was found in the onset time for sensory and motor block, receding time for sensory and motor block and the need of the first rescue analgesia between the two groups, showing that Dexmedetomidine was more potent than clonidine.
Conclusions: Dexmedetomidine is a potent, highly selective and specific α2-adrenoreceptor agonist that has both sedative and analgesic effects and is also a valuable adjuvant when regional anaesthesia is incorporated.

Keywords: Bupivacaine, Clonidine, Dexmedetomidine, Femur and tibia fracture

INTRODUCTION

Surgery represents a form of premeditated injury to the body. The physical process of incision, traction and cutting tissues stimulate free nerve endings and specific nociceptors, leading to post-operative pain. This acute pain has adverse effects on patient's morale as well as various physiological functions of the body.

Good post-operative analgesia is an integral part of perioperative care. Ever since spinal anaesthesia was first used as an anaesthetic during surgery in 1898, it is a preferred method of anaesthesia for surgeries on lower

half of the body. This is due to its efficacy, rapidity, minimal side effects on mental status, reduction of blood loss and protection against thrombo-embolic episodes. It also reduces the risk of vomiting and pulmonary aspiration in patients with full stomach along with that it is useful in patients with chronic airway diseases. Spinal anaesthesia with bupivacaine is administered routinely for lower abdominal and lower limb surgeries. The ensuing nerve block is sufficient to ensure patient's wellbeing, while motor block facilitates the surgeon's work. It also provides effective pain relief in the initial post-operative period. Additional analgesia is needed after the effect of spinal anaesthesia wears off.

Improved pain management for blunt trauma to the lower extremity has effectively led to the improvement of the post-operative outcome, lesser morbidity, shortening the hospital stay not to mention lesser anxiety of surgery and increased comfort to the patient.[1] Therefore, effective pain management is essential to facilitate proper rehabilitation and acceleration of the return to functional capability.[2] Post-operative pain relief can be achieved by various methods namely systemic opioid and non-opioid peripheral nerve blocks and local wound infiltration, each with their own merits and demerits.

In patients receiving spinal anaesthesia, with local anaesthetic agents like bupivacaine, addition of another intrathecal drug as adjuvant prolongs the analgesia. For this, a number of adjuvants have been added to spinal local anaesthetics e.g. opioids like morphine, buprenorphine, pethidine, hydromorphone, fentanyl, sufentany and tramadol.[1,3] Other classes of drugs such as epinephrine, midazolam, neostigmine, ketamine, magnesium and clonidine have been added to the intrathecal local anaesthetics to prolong the analgesic effect and to reduce the incidence of adverse events.[4-7]

These opioids produce satisfactory analgesia for 24hours postoperatively, but are frequently associated with side effects like respiratory depression, itching, nausea, vomiting and urinary retention.[8-12] Other adjuvants like ketamine, neostigmine has been tried but none has become established in regular clinical practice. Various studies have shown that intrathecal clonidine produces prolongation of spinal anaesthesia and reduces the need of post-operative analgesic requirement and there is now adequate evidence that clonidine given intrathecally produces antinociceptive effects without any neurotoxicity and may be useful in the treatment of somatic pain. The α2-adrenergic agonist Clonidine has a variety of different actions, including the ability to potentiate the effects of local anesthetics. However, unlike spinal opioids, clonidine does not produce pruritus or respiratory depression. It also prolongs the sensory blockade and reduces the amount or concentration of local anaesthetic required to produce postoperative analgesia. The rationale behind intrathecal administration of clonidine is to achieve a high drug concentration in the vicinity of α-2 adrenoreceptors in the spinal cord and it works by blocking the conduction of C and Aδ fibres, increases potassium conductance in isolated neurons in vitro and intensifies conduction block of local anaesthetics.

Dexmedetomidine is an S-enantiomer of medetomidine with a higher specificity for α2-adrenoreceptor (α2: α1, 1620: 1) compared to clonidine (α2:α1, 220 : 1). It was first introduced into practical use as intravenous sedative after the approval of U.S. Food and Drug Administration in 1999. Since then it has been investigated as the anxiolytic, sympatholytic, and analgesic properties related to α2-adrenoceptor binding, and it is now being used as a co-analgesic drug. As adjuvant, neuraxial administration is the appropriate route to dexmedetomidine, because the analgesic effect of α2-agonists mostly occurs at spinal level, and dexmedetomidine's high lipophilicity facilitates rapid absorption into the cerebrospinal fluid and binding to the spinal cord α2-adrenoreceptor. Intrathecally-administered dexmedetomidine has been shown to exert potent antinociceptive effects in animals. To date, a few studies have reported on the effects of intrathecal dexmedetomidine combined with local anesthetics in humans.

Hence, we have undertaken the present study to compare the effect of intrathecal dexmedetomidine and clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing surgery for fracture femur and tibia.

METHODS

This randomized double blind controlled study was conducted by the department of anesthesia at Medicity medical college and hospital from June 2014 to Feb 2017. 80 patients between 20-60 years, undergoing elective surgery for closed fracture shaft of femur and tibia with ASA physical status of 1 and 2 were included in the study.

Patients who were allergic to the drugs being used, with uncontrolled hypertension or on therapy with beta blockers and ACE inhibitors were excluded from the study. Patients with polytrauma and head injury were also excluded from the study.

After obtaining the clearance from the Institutional Ethical Committee, all the patients were, and their relatives were informed of the nature of the study and informed consent was obtained from all of them. All the subjects were randomly allocated to one of the two groups (Group C and Group D) by a computer-generated randomization chart.

The 40 patients in the Group C received 2.5ml of 0.5% hyperbaric bupivacaine with 50mcg clonidine and those in group D received 2.5ml of 0.5% hyperbaric bupivacaine with 5mcg dexmedetomidine. Preoperative evaluation was carried out in all patients with detailed

clinical history, physical examination, evidence of spinal deformities or any neurological disease and mental status of the patient. Vital parameters were noted, and systemic examination was performed along with general and spine examination. Other routine investigations such as complete haemogram, Blood urea nitrogen and serum creatinine, Random blood sugar level, Chest X-ray and ECG, if age > 40years was done.

All patients received pre-operative sedation with Injection butorphanol 1mg + Injection promethazine 12.5mg IM 1hr before surgery. Preoperatively adequate starvation (NBM status) was confirmed and baseline heart rate, blood pressure was noted, and pre-operative VAS score was noted. A peripheral venous access was secured on the dorsum of the nondominant hand with 20G cannula and preloading with lactated ringer (200ml) solution 15 minutes prior to subarachnoid block. Subarachnoid block was given in sitting position with midline approach with aseptic precautions using 25G spinal needle. After confirming the clear and free flow of cerebrospinal fluid, the study drug i.e 2.5 ml Bupivacaine 0.5% (Hyperbaric)+50 mcg Clonidine (Group C), 2.5 ml Bupivacaine 0.5% (Hyperbaric)) +5 mcg Dexmedetomidine (Group D) was given intrathecally.

Patients were immediately placed in supine position with a pillow supporting the head and shoulders. Oxygen face mask was applied with flow rate of 5L/min the level of sensory block was checked by pinprick method using a blunt 26G half inch needle caudal to cephalad direction every 5 minutes after the procedure of subarachnoid block was complete and time taken to achieve this was noted.

Vital parameters like heart rate and arterial blood pressure were noted every 5 minutes for 30 minutes and thereafter every 15 minutes for next 30 minutes then every 30 minutes till the end of surgery. At the end of surgery, no prophylactic pain relief was given, and patients were transferred to post anaesthesia care unit and monitoring was continued for vital parameters. Level of sensory block, motor level and visual analogue score (VAS) was noted every hour for next 4 hours and thereafter till the patient demanded rescue analgesia.

Data are expressed as mean±SD. For comparison between the groups, the Chi-square test and independent two sample 't'-test for unpaired samples were used. A value < 0.05 was considered to be significant.

RESULTS

Out of the 80 patients included in the study, 40 each were randomly allocated to one of the two groups (Group C and Group D). 30 of the 40 patients in group C were of ASA I and 10 were ASA II, while in group D, 25 were ASA I and 15 were ASA II. However, using Pearson chi square test, it was observed that there is no significant difference between the two groups with respect to ASA grading (Table: 1).

Table 1: ASA grading.

Group	Total no. of patients	ASA I	ASA-II	P-value
Clonidine	40	30	10	0.227
Dex	40	25	15	

The mean onset time for sensory block in the case of Group C was 8.63±3.75mins in comparison to 6.13±2.40 mins in group D showing high significance. A significant difference was found between the two groups in the onset of motor time which was 12.88±4.51 mins in Group C and 8.25±3.11 in Group D. Similar was the significant difference in the receding time for sensory and motor block which was 4.35±0.975 mins and 3.8±0.723 for Group C and 5.2±0.791 and 4.65±0.834 for Group D respectively. The need for analgesic was required by 4.88±1.36 hrs in group C and 7.13±1.8 hrs in group D, which was also highly significant (Table: 2).

Table 2: Comparison (in mins) for sensory and motor block.

Parameter	Group	Mean± SD	P value
Onset time for sensory block (in mins)	Group C	8.63±3.75	0.001
	Group D	6.13±2.40	
Onset time for motor block (in mins)	Group C	12.88±4.51	0.00
	Group D	8.25±3.11	
Receding time for sensory block (in mins)	Group C	4.35±0.975	0.00
	Group D	5.2±0.791	
Receding time for motor block (in mins)	Group C	3.8±0.723	0.00
	Group D	4.65±0.834	
Need of first rescue analgesia (in hrs)	Group C	4.88±1.36	0.00
	Group D	7.13±1.8	

Table 3: Fall in parameters below critical level.

Parameter	Group	No. of patients (%)	P value
Fall in systolic blood pressure below critical level (<85 mm Hg)	Group C	9 (22.5%)	0.793
	Group D	10(25%)	
Fall in diastolic blood pressure below critical level (<50 mm Hg)	Group C	14 (35%)	0.816
	Group D	15(37.5%)	
Fall in pulse rate below critical level (<50bpm)	Group C	2 (5%)	0.556
	Group D	1(2.5%)	

In group C, 9 patients (22.5%) had a fall in the systolic pressure below 85 mm Hg in group C and 10 (25%) IN Group D, although these values had no significant difference. Similarly, the fall in diastolic pressure (<50 mm Hg) was seen in 14 (35%) patients in Group C and 15 (37.5%) patients in Group D and there was no significant difference among these levels also. A fall in pulse rate of <50 bpm was seen in 2 patients in Group C and 1 patient in group D, with no significant difference (Table: 3).

DISCUSSION

Spinal anaesthesia was a popular, simple and reliable anaesthetic technique for lower limb orthopedic surgeries. It has been used widely in clinical practice of anaesthesia because of rapid onset, high reliability and low cost. It produces excellent operating conditions and has high success rate. Though it provides effective analgesia in the initial postoperative period, patients need supplementation of potent opioid analgesics systemically for pain relief. Systemic opioids have been associated with respiratory depression, nausea, vomiting, itching, and urinary retention.[11] Hence, attempts were made to increase duration of analgesia produced by subarachnoid block by adding various agents intrathecally, like opioids e.g. morphine, buprenorphine, hydromorphone, fentanyl, and non-opioids e.g. ketamine, neostigmine, midazolam but none of them have been accepted in clinical practice due to their side effect or non-availability.[3]

Clonidine, is an α-2 adrenergic agonist that produces analgesia in humans mediated by α-2 adrenoreceptors, located postsynaptic ally in the dorsal horn of spinal cord. Administered intrathecally, it has shown good results, as it prolongs the duration of intrathecally administered local anaesthetics and has potent antinociceptive properties.[12,13] Although such prolongation of the effects of local anaesthetics has also been reported for oral and IV administration the intrathecal route was more effective in prolonging bupivacaine spinal anaesthesia.[12,14-17] Clonidine achieves a high drug concentration in the vicinity of α-2 adrenoreceptors in the spinal cord. It blocks the conduction of C and Aδ fibers, increases potassium conductance in isolated neurons in vitro and intensifies conduction block of local anaesthetics. Clinical trials provide evidence that less clonidine was needed intrathecally than orally or epidurally to produce nearly same analgesic effect with fewer side effects like hypotension.[17,18] So, in present study intrathecal clonidine was chosen as an adjuvant.

Dexmedetomidine, a highly selective α2 adrenoceptor agonist, with sedative and analgesic properties has been approved by Food and Drug Administration (FDA) to be used as a short-term sedative for mechanically ventilated intensive care unit (ICU) patients.[19] Dexmedetomidine given though IV has been found to reduce the anaesthetic requirements during the general anaesthesia.[20] This analgesic is known to act at both the spinal and supraspinal levels.[21] Though still under evaluation as an ideal neuraxial adjuvant, Dexmedetomidine provides stable hemodynamic conditions, excellent quality of intraoperative and prolonged postoperative analgesia with minimal side effects.[22-24] Kanazi et al., demonstrated a significant prolongation in the duration of sensory and motor block with dexmedetomidine used as intrathecal additive for 0.5% heavy bupivacaine.[22]

This study was done using clonidine and dexmedetomidine as an adjuvant to intrathecal bupivacaine. We compared intrathecal injection of Inj. Clonidine 50ug + 2.5ml(12.5mg) of 0.5% hyperbaric Bupivacaine (group C) and Inj. Dexmedetomidine 5ug + 2.5ml(12.5mg) of 0.5% hyperbaric Bupivacaine (group D) in patients with fracture of shaft of tibia or femur.

In the present study, it was found that, time for onset of sensory block upto T10 level was 8.63±3.75 mins in Group C and 6.13±2.40 mins in Group D, showing that adding dexmedetomidine to bupivacaine decreased the time of onset of sensory block upto T10 level. These findings were similar to astudy done by Singh et al who found that the onset of sensory block up to T8 level was faster for dexmedetomidine group although the difference between the groups was not significant.[24] Similar was the case in another study by Halder et al who reported that the median height of sensory blockade was similar in both the groups.[25]

median height of sensory blockade though similar in both the groups, group D10 shows slightly higher block levels in few patients but the comparison is clinically and statistically insignificant.[2] Similarly, Gupta et al., found that addition of 5 μg dexmedetomidine to intrathecal ropivacaine produced one segment higher sensory block than placebo group though the results were clinically insignificant.[25] However, the findings of present study was different from the study done by Kanazi et al who found that the onset of sensory block upto T10 level was faster for clonidine group (7.6 ± 4.4 mins) as compared to dexmedetomidine group (8.6±3.7 mins), but the difference found was not significant.[22]

In motor parameters, mean time for onset of motor block (Bromage 3) was 12.88 ± 4.51 mins for Group C and 8.25 ± 3.11 mins in Group D. There is decrease in onset time of motor block after adding dexmedetomidine as compared to clonidine as measured by Bromage scale.[26] Difference was significant ($p<0.05$) when both groups were compared. These results were in concordance to the studies by Singh et al and Halder et al, while Kanazi et al found that the onset of motor block was faster for clonidine group (11.7 ± 5.9 mins) as compared to dexmedetomidine group.[22,24,25]

The mean duration of receding time of sensory block upto L5 S1 level was 4.35 ± 0.975 hrs and 5.2 ± 0.791hrs for Group C and Group D respectively, showing an increased duration of sensory block in dexmedetomidine

group as compared to clonidine group. The difference between the groups was significant (P<0.05). These findings are concordance to studies done by Kanazi et al and Singh R et al who concluded that dexmedetomidine produced significantly longer duration of sensory block as compared to clonidine.[22,24] Similar was the case with mean duration of receding time of motor block upto Bromage 0 level, with significant difference between the two groups.

It was found that Dexmedetomidine significantly increased the interval from spinal anaesthesia to the first request for supplemental analgesia (Paracetamol 1gm i.v and Diclofenac 75mg im) when compared to Clonidine. The mean duration at which the patient demanded rescue analgesia was 4.88±1.36 hrs for Group C and 7.13±1.8 hrs for Group D. The difference was statistically significant (p<0.05) when both groups were compared. Similar results were observed by Singh et al in their study.[24] In other studies, it was observed that addition of various doses of clonidine to bupivacaine intrathecally significantly prolongs duration of analgesia of bupivacaine,[16,27,28] while others reported that addition of dexmedetomidine to bupivacaine significantly prolongs the duration sensory and motor block and post-operative analgesia.[23,25,29-31]

CONCLUSION

Dexmedetomidine is a potent, highly selective and specific α2-adrenoreceptor agonist that has both sedative and analgesic effects. Use of Injection dexmedetomidine 5ug in combination with 2.5ml (12.5mg) of 0.5% hyperbaric bupivacaine as compared to Injection clonidine 50ug with 2.5ml of 0.5% hyperbaric bupivacaine intrathecally resulted in faster onset of sensory and motor block, prolongation of sensory and motor block, prolongation of post-operative analgesia and manageable haemodynamic alterations. Dexmedetomidine seems to be valuable adjuvant when regional anaesthesia is incorporated but further studies are still needed to establish the safe dose to be used and there should be a favorable risk/benefit ratio for its use in regional anaesthesia.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Chandra GP, Krishna SS, Singh P. Comparison of effect of intrathecal dexmedetomidine and clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing surgery for fracture femur and tibia. Int Surg J 2017;4:3833-8.