Effects of Intrathecal Dexmedetomidine as an Adjuvant to Hyperbaric Bupivacaine for Spinal Anaesthesia in Adults Undergoing Elective Infra-umbilical Surgery

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ABSTRACT

Introduction: Various adjuvants to local anaesthetic are used to improve quality and duration of spinal anaesthesia. Dexmedetomidine, a novel alpha-2 adrenergic agonist, has been proposed to augment local anaesthetic effects. This study aims to investigate effects of intrathecal Dexmedetomidine on duration of analgesia and duration of sensory block during spinal anaesthesia.

Methods: In this randomized double-blind study 38 patients were allocated into each of two groups. Otherwise healthy patients (18 to 75 years) scheduled for inguinal hernia repair or vaginal hysterectomy were included. For spinal anaesthesia, Group A received 2.5 ml hyperbaric Bupivacaine 0.5%, whereas Group B received five micrograms intrathecal Dexmedetomidine in addition. Characteristics of sensory and motor blocks, duration of analgesia, analgesic requirements, and side effects were studied for 24 hours. Student's t-test for quantitative variables and Chi- squared test for qualitative variables were used for statistical analysis.

Results: Duration of analgesia was prolonged in Group B (326 min ±91) as compared to 217 min ±98 in Group A (P value <0.05). Sensory and motor block durations were significantly prolonged in Group B. Time taken to reach significant peak sensory block level was earlier in Group B. Significant reductions in incidence of visceral pain, shivering and analgesic requirements were observed in Dexmedetomidine group, without increased need of medications for altered hemodynamic parameters.

Conclusions: Dexmedetomidine as an intrathecal adjuvant to hyperbaric Bupivacaine in spinal anaesthesia prolongs duration of analgesia and sensory block with minimal adverse effects.

Keywords: *Bupivacaine; Dexmedetomidine; intrathecal adjuvant; spinal anaesthesia.*

INTRODUCTION

Spinal anaesthesia offers excellent surgical anaesthesia but doesn't provide prolonged analgesia, especially when sole local anaesthetic is used. Analgesic effects of intrathecal Opioids, the most commonly used spinal adjuvants, are associated with side effects including sedation, pruritus, nausea-vomiting, urinary retention and respiratory depression.[1,2]

Attempts aimed at a search for an ideal intrathecal adjuvant, which improves quality of surgical anaesthesia, prolongs analgesia and lacks adverse effects, is still unending. Studies show promising results with Dexmedetomidine, a selective alpha-2 adrenoceptor agonist, on improving analgesia and without the adverse effects of Opioids.[3,4] Effects of Dexmedetomidine as an

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adjuvant to spinal anaesthesia in our surgical population have not been studied.

Main objective of this study was to investigate duration of sensory block and analgesic effects of intrathecal Dexmedetomidine when added to hyperbaric Bupivacaine in spinal anaesthesia. The secondary objectives included block characteristics and side effects.

METHODS

This is a randomized, double-blind, parallel-arm interventional study conducted from February 15, 2017 to August 15, 2017. Ethical approval was obtained from the Institutional Review Committee before start of the study. Informed written consent from each 76 participants was obtained during pre-anaesthetic checkup, done a day prior to surgery, when Verbal Analogue Score (VAS; '0' = no pain and '10' = worst imaginable pain) for grading the intensity of postoperative pain was explained. No sedative, analgesic, or antiemetic premedication were prescribed.

Adults of American Society of Anesthesiologists' physical status 1 and 2, from both gender, of 18 to 75 years of age, who speak Nepalese language well and scheduled to undergo inguinal hernia repair or vaginal hysterectomy with or without pelvic floor repair were included. Patients with the following conditions were excluded: history of spine surgery, heart block, cardiac conduction defects, coagulopathy, diabetes mellitus, neurological disease, mental disturbance, illicit drug abuse, body weight >100 kg, height <150 cm, pregnancy, infection focus at back, hypersensitivity to local anaesthetics or Dexmedetomidine, ingestion of analgesics or any other study drugs within 24 hours, patients receiving any of anti-arrhythmic, beta-blocker, alpha-adrenergic antagonists, angiotension converting enzyme inhibitors/blockers or anti-coagulant.

Microsoft Office Excel 2007 was used to generate the random allocation sequence which was concealed in sequentially numbered sealed opaque envelops. Principal investigator was responsible to generate the random number allocation sequence and these envelops were opened only at the time of intervention. The test injectate was prepared under a sterile technique by an investigator who was not involved in further patient management. The investigators responsible for assigning the intervention, providing the care and assessing the study outcomes intra- and post-operatively were blinded to which intervention arm the patient belonged to. The participants were also unaware of the group they belonged to.

Sample size calculation is based on the formula

$n_1 = 2(Z_{alpha/2} + Z_{beta})^2 . SD^2/D^2$

Where,

n_1 = number in each group

$Z_{alpha/2}$ = 1.96 at the desired significance level of 5%

Z_{beta} = 1.28 at the desired power of 90%

SD = standard deviation

D = size of difference of clinical importance

A sample size of 33 in each group is sufficient to detect a mean difference (D) of 73 minutes of sensory block duration, standard deviation (SD) of 91 and on the assumption that measurements taken are randomly distributed.[5] The number has been increased to 38 per group (total 76) to allow for predicted block failure and drop-out from intervention of 15%.

In the operating room baseline systolic blood pressure (SBP), heart rate (HR), respiratory rate, and oxygen saturation (SPO_2) were recorded in a calm supine position while the routine monitors like non-invasive blood pressure, pulse-oximetry, and electrocardiography were being established. Peripheral line was secured with an 18 G intravenous cannula and a bolus of 10 ml/kg Ringer Lactate solution was infused.

Lumbar puncture was performed in a sitting patient under aseptic conditions at L3-L4 intervertebral space. A 27 G pencil-point spinal needle was passed through a 20 G introducer needle using midline approach after infiltrating the overlying skin with two ml of 2% Lignocaine. The identical dose of 0.5% hyperbaric Bupivacaine (Bupican™ Heavy: Bupivacaine Hydrochloride Dextrose Injection – Claris Injectables Ltd, Ahmedabad, India) 12.5 mg (2.5 ml) was injected into the intrathecal space over 30 seconds in both groups. In addition, using a separate syringe, Group A received 0.5 ml 0.9% normal saline whereas Group B received five micrograms Dexmedetomidine (Xamdex™: Dexmedetomidine Hydrochloride 100 mcg/ml, Themis Medicare Ltd, Abbott-Manufacturer, Uttarakhand, India) freshly prepared in 0.5 ml 0.9 % normal saline via intrathecal route. Time of completion of spinal injection was considered the '0' time and all times were calculated from this point onwards. Patients were made to lay supine immediately in a flat operating table after the intervention. HR, SBP, respiratory rate and SPO_2 were monitored continuously and recorded every five minutes throughout the operating period or for one hour whichever lasted longer and every 15 minutes for the next two hours and according to the nursing protocol thereafter.

Level of sensory block was assessed every two minutes, along the bilateral mid-clavicular lines by

testing for a loss of cold sensation to a spirited cotton swab, till the occurrence of peak sensory block level. The one with higher level was considered for recording if a discrepancy in sensory block level was observed between two sides. Peak sensory block level was defined as the same highest level of sensory block recorded on more than three consecutive readings; and the time taken to reach the first such reading was defined as time to reach peak sensory block. Time to reach Thoracic – 10 (T-10) sensory block was also recorded and when surgical proceedings were allowed. Failure to attain a bilateral T-10 sensory block within 15 minutes was defined as a block failure and these patients were excluded from further analysis. Sensory block level was further assessed every hour till the time for sensory block regression to Sacral – 1 (S-1), and at the 24th post-operative hour. Duration of sensory block was defined as the duration extending till sensory block regression to S-1.

Motor block of lower limbs was assessed every two minutes till T-10 sensory block was reached according to a modified Bromage Scale (Bromage 0, the patient is able to move the hip, knee and ankle; Bromage 1, the patient is unable to move the hip but is able to move the knee and ankle; Bromage 2, the patient is unable to move the hip and knee but able to move the ankle; Bromage 3, the patient is unable to move the hip, knee and ankle).[6] Motor block was also assessed at the completion of surgery, hourly till motor block regressed to Bromage 0 and at the 24th post-operative hour. Maximum motor block was defined as the highest Bromage Scale attained at time of T-10 sensory block or at the end of surgery. Duration of motor block was defined as the duration till motor regression to Bromage 0. Level of sedation was assessed at 15, 30, 45, and 60 minutes using Ramsay sedation score (1 = anxious or restless or both, 2 = cooperative, oriented and tranquil, 3 = responding to commands only, 4 = brisk response to loud auditory stimulus, 5 = sluggish response to loud auditory stimulus, and 6 = no response to loud auditory stimulus).[7]

During the study period, hypotension was defined as a fall in SBP of more than 30% from the baseline, or SBP less than 90 mmHg and was treated with 200 ml of Ringer's Lactate and intravenous Ephedrine nine mg in increments. Bradycardia (HR <50 beats per minute) was treated with intravenous Atropine 0.5 mg. Respiratory depression (respiratory rate <8 breaths per minute) was treated with Oxygen supplementation and respiratory support if needed. Time of occurrence, management and outcome of side effects like hypotension, bradycardia, respiratory depression, nausea, vomiting, shivering and pruritus were recorded. Fluid infused till the time to reach peak sensory block, total intra-operative fluid, amount of blood loss and a need for sedative, analgesic, Ephedrine, Atropine and any other medication were recorded.

Duration of analgesia was defined as the time extending from time '0' to time of first analgesic request by the patient for the wound site pain. Pain (Verbal Analogue) Scores were recorded at the time to first analgesic request; and at such a score of four or more, either intramuscular Diclofenac 75 mg or intravenous Paracetamol one gram was administered. Pain Scores were also recorded at the 6th and 24th hours. Frequency of analgesics needed, time to first oral fluid intake, time to first self-void and the need for in/out urinary bladder catheterization for urinary retention, as per the surgeons' decision, were recorded at the 24th hour when the study period ended.

Statistical package for social science evaluation version 20 (SPSS Inc; Chicago, IL) was used for statistical analysis. Data was expressed as mean, standard deviation and standard error of mean or numbers. Student's t-test (two-tailed) was used to compare mean differences between groups for duration of analgesia, duration of sensory block and other quantitative variables. For the sedation levels and VAS scores at different time intervals, analysis of variance was utilized. For categorical measurements Chi-square test and Fisher's exact test as appropriate were used. The level of significance used was $P<0.05$.

RESULTS

In Group A, one participant had block failure and two withdrew consent immediately after the intervention demanding for sedation. Whereas in Group B, one patient withdrew consent for the similar reasons and violation of study protocol occurred in one due to administration of analgesics without the patient's request for such. So, all together 35 patients in Group A and 36 in Group B completed the study protocol to be included in analysis (Figure 1).

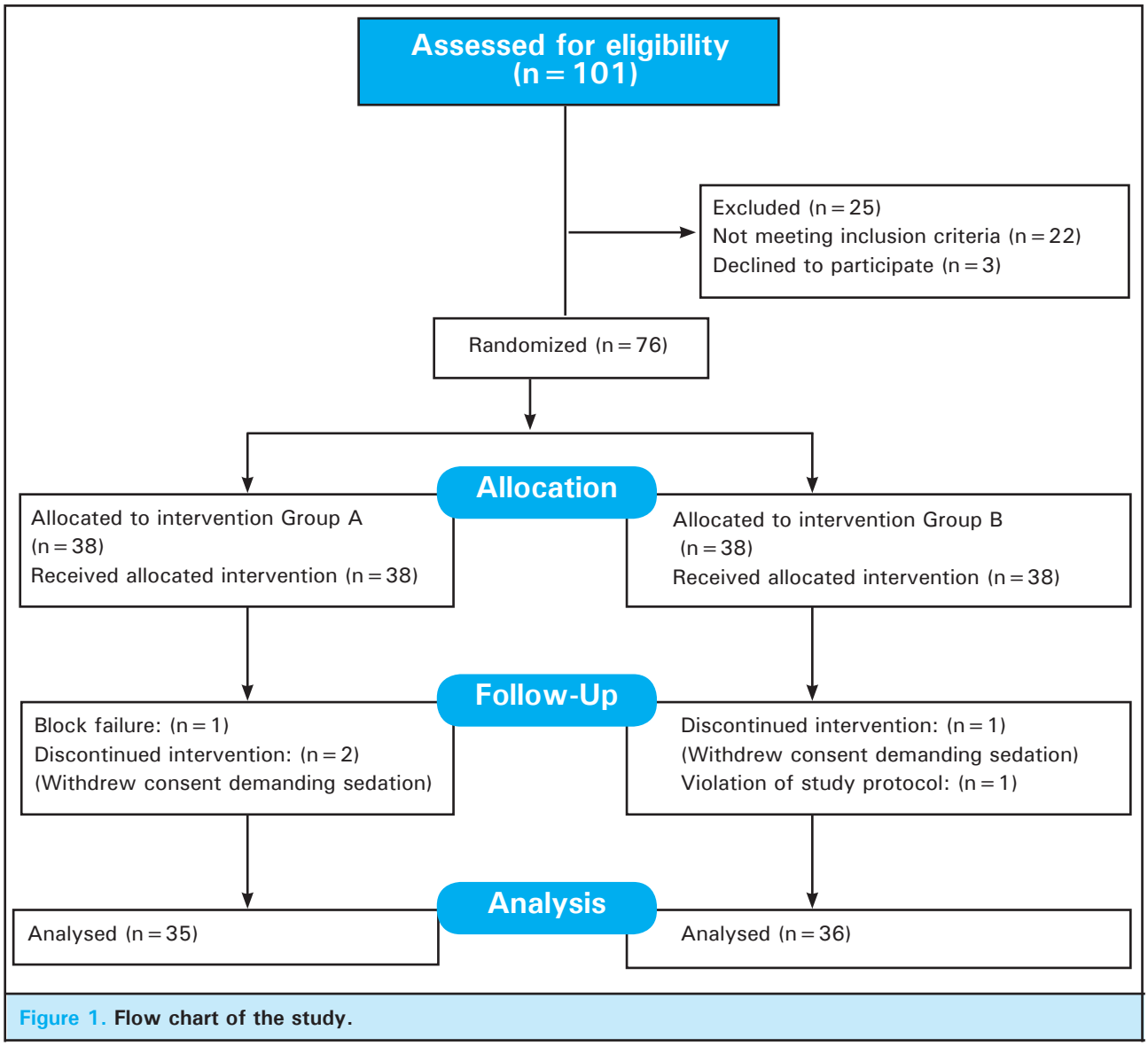

Figure 1. **Flow chart of the study.**

The duration of post-operative analgesia was significantly prolonged in Group B; and, frequency of analgesic requirement in post-operative period was significantly reduced (Table 1).

The onset of sensory block indicated by times to reach T-10 and peak sensory blocks appeared earlier in the Group B. Peak sensory block was significantly higher and duration of sensory and motor blocks were both significantly prolonged in Group B when compared to Group A (Table 2).

Table 1. **Analgesia characteristics.**

	Group A (n = 35)	Group B (n = 36)	SED	P value
Duration of post-operative analgesia (min)	217.80(±98.77) (16.69)	326.22(±91.87) (15.31)	22.63	0.0001
Frequency of postoperative analgesic requirement mean (SD)	4.06 (±1.53)	2.42 (±0.87)	0.295	0.0001

values are mean (± standard deviation) standard error of mean, SED = standard error of difference

Table 2. Characteristics of sensory and motor block.

Block characteristic	Group A (n = 35)	Group B (n = 36)	SED	P value
Time to reach T-10 sensory block (min)	7.77(±3.02) (0.511)	5.22(±1.69) (0.282)	0.579	0.0001
Time to reach peak sensory block (min)	15.60(±3.782) (0.639)	12.14(±3.26) (0.544)	0.837	0.0001
Peak sensory block level*	T-6 (1.48) T-9 to T-2	T-4 (0.93) T-7 to T-3	0.293	0.004
Duration of sensory block (min)	378.86(±106.70) (18.037)	497.33(±121.51) (20.252)	27.17	0.0001
Maximum motor block	Bromage 3 (±0.04)	Bromage 3 (±0.00)	0.039	0.239
Duration of motor block (min)	334.29(±97.92) (16.55)	433.06(±129.61) (21.602)	27.321	0.001

*values are means (± standard deviation) standard error of mean, *values are median and range, SED=standard error of difference*

General characteristics of patients, type and duration of surgery, and amount of fluid infused were similar in both the groups (Table 3).

Table 3. Characteristic of patients and surgery.

Characteristics	Group A (n = 35)	Group B (n = 36)	SED	P Value
Age (yrs)	46.03(±16.78) 2.83	47.8 (±15.94) 2.657	3.884	0.649
Gender = Male : Female (number)	25:10	30:6		0.267
Weight (kg)	61.23(±10.11) 1.70	57.50(±8.54) 1.425	2.220	0.098
Height (cm)	161.97(±8.91) 1.50	161.53(±7.08) 1.18	1.908	0.817
Surgery = hernia repair: vaginal hysterectomy (number)	25:10	30:6		0.267
Duration of surgery (min)	75.77(±110.08) 18.60	56.58(±33.41) 5.56	19.194	0.321
Fluid infused till peak sensory block level (ml)	605.71(±172.25) 29.11	568.06(±194.25) 32.37	43.618	0.391
Total intraoperative fluid (ml)	1184.43(±257.10) 43.45	1110.42(±310.37)51.73	67.742	0.278
Intraoperative blood loss (ml)	25.14(±33.22) 5.61	40.69(±83.97) 13.99	15.238	0.308

values are means ± standard deviation, standard error of mean, SED=standard error of difference

Need of Fentanyl for intraoperative visceral pain and Pethidine for shivering were significantly higher in Group

A (Table 4). Comparison of side effects and need for administration of medications during the study period are shown in Table 4.

Table 4. Adverse effects and need for medications.

	Group A (n = 35)	Group B (n = 36)	P value
Hypotension	3	8	0.189
Bradycardia	1	3	0.614
Nausea/vomiting	5/1	0	0.011
Visceral pain	10	3	0.027
Need of intraoperative Fentanyl	10	3	0.027
Shivering: total / spontaneous resolution / pethidine need	11 / 3 / 8	4 / 3 / 1	0.043
Need for Ephedrine	3	8	0.189
Need for Atropine	1	3	0.614
Need for Midazolam	8	1	0.012
Need for antiemetic	2	0	0.55

values are numbers, P value calculated using Chi-square test (Fisher's exact test)

Sedation scores, post-operative pain (VAS) scores and post-operative features are shown in Table 5, Table 6 and Table 7 respectively.

Table 5. Sedation scores.

Time	Group A	Group B	P value
15 minutes	1.74 (±0.44) (0.075) 1-2	1.89 (±0.39) (0.066) 1-3	0.149
30 minutes	2.20 (±0.58) (0.099) 1-4	2.22 (±0.42) (0.070) 2-3	0.854
45 minutes	2.40 (±0.73) (0.124) 1-4	2.39 (±0.54) (0.092) 2-4	0.943
60 minutes	2.31 (±0.58) (0.098) 1-4	2.39 (±0.49) (0.082)2-3	0.562

values are means (±standard deviation) standard error of mean and range, P value calculated using analysis of variance

Table 6. Post-operative pain (VAS) scores.

Time	Group A (n = 35)	Group B (n = 36)	P value
At first analgesic request	6.11(±1.71) (0.289)1-4	5.83(±1.57) (0.263)3-8	0.474
Six hours	3.51(±1.56) (0.264)0-6	3.31(±1.84) (0.308)0-8	0.609
24 hours	3.11(±1.47) (0.249)1-6	2.50(±1.23) (0.205)0-6	0.060

values are means (±standard deviation) standard error of mean and range, P value calculated using analysis of variance

Table 7. Postoperative recovery features.

	Group A (n = 35)	Group B (n = 36)	SED	"P"
Time to spontaneous void (min)	351.77 (±89.03) 18.98	444.39 (±156.74) 32.68	38.239	0.020
Urinary retention*	7	6		0.385
Time to break nil per orum (min)	341.06 (±112.34) 19.26	356.64 (±107.23) 17.87	26.444	0.555

*values are means (±standard deviation) standard error of mean, SED=standard error of difference, *numbers*

DISCUSSION

Whether a single-shot spinal anaesthesia with Dexmedetomidine as an intrathecal adjuvant can be efficient in prolonging a pain-free period was aimed to be investigated in this study. Administration of Dexmedetomidine five micrograms added to 2.5 ml of 0.5% hyperbaric Bupivacaine via intrathecal route produced a rapid onset of sensory block; prolonged the durations of effective analgesia, sensory and motor blocks; decreased the need for intra-operative analgesics; decreased the incidence of shivering; and reduced post-operative analgesic requirement.

The exact mechanism by which intrathecal Dexmedetomidine prolongs the motor and sensory blocks produced by local anaesthetics is not well known; but, site of action is definitely spinal cord rather than systemic absorption. It may be an additive or synergistic effect secondary to a mechanism different from action of local anaesthetics. The local anaesthetics block sodium channels, whereas the analgesic action of intrathecal alpha-2 adrenoceptor agonists is thought to result from their binding to pre-synaptic C-fibres and

post-synaptic dorsal horn nucleus in the spinal cord.[8] Depression of release of transmitters from C-fibres and hyperpolarization of dorsal horn neurons responsible for anti-nociceptive effects, against both somatic and visceral pain, might be related to lipophilicity of these agents.[9] Prolongation of motor block might be caused by direct impairment of excitatory amino acids release from the spinal interneurons or from binding to motor neurons in the dorsal horn.[10] In our study, the rapid onset of sensory block in the Dexmedetomidine group confers with the finding in a study done by Al-Mustafa who showed that Dexmedetomidine produced an earlier onset of sensory block.[4] Also, Ogan and Esmaoglu on their respective studies found an earlier and significantly higher peak sensory block level in the Dexmedetomidine group compared to control groups, resembling our results.[11,12] However, Dexmedetomidine when co-administered with Bupivacaine intrathecally, didn't show a further increase in motor block in our study, presumably because the blockade produced by Bupivacaine is nearly maximum.

Duration of sensory and motor block were both prolonged significantly in the Dexmedetomidine group in our study. Gupta R et al concluded that addition of five micrograms Dexmedetomidine to spinal anaesthetic significantly slowed the regression of sensory block.[13] Al-Mustafa also found that intrathecal Dexmedetomidine resulted in a significant prolongation of sensory and motor block duration in a dose-dependent manner.[4] As little as 2.5 micrograms of Dexmedetomidine when added to 2.5 mg hyperbaric Bupivacaine in spinal anaesthesia was shown by Ogan to prolong sensory and motor block duration significantly, although the participants in this study were parturients.[11]

As regards the duration of analgesia, perhaps the most important patient outcome in the clinical context was significantly prolonged in the Dexmedetomidine group. In agreement with our results, different studies have also shown a significant prolongation of duration of effective postoperative analgesia by intrathecal Dexmedetomidine compared to control groups.[3,4,13] In addition, Gupta R et al showed that intrathecal Dexmedetomidine decreased the analgesic consumption by 64% at 24 hours, which bears similarity to our finding of significantly reduced need for post-operative analgesics.[13]

Number of participants receiving Fentanyl for treating their intraoperative visceral pain was significantly higher in the Bupivacaine only group in our study. Use of a relatively lower dose of Bupivacaine could have been a factor.[14] Even though the study was not adequately powered, this finding might reflect that intrathecal Dexmedetomidine improves quality of intraoperative anaesthesia by reducing visceral pain during surgeries associated with mesenteric traction.[10] This is further supported by the findings that incidence of nausea and need for sedatives were significantly higher in the Bupivacaine only group. As the amount of fluid infused, surgical blood loss and incidence of hypotension in both the groups did not differ; the higher incidence of intra-operative nausea in the Bupivacaine only group can be attributed to visceral pain, apart from the exaggerated propulsive gastrointestinal activity due to a shift in autonomic balance toward a relative increase in parasympathetic tone.[14,15] Sedation scales, although, were comparable probably because the Bupivacaine group received Fentanyl, Pethidine and Midazolam more frequently.

Delayed recovery from sensory and motor blocks by Dexmedetomidine would most appropriately explain the delayed time to spontaneous void in Group B. However, the incidence of urinary retention was comparable between the groups. Higher need of Fentanyl and Pethidine to treat shivering could also have contributed to urinary retention in the Bupivacaine only group.[16] The overall incidence of urinary retention in our study however is consistent with previous findings that spinal anaesthesia being itself as one of the most important risk factors in its causation.[17] Although shivering was not our primary end point, there was evidence that with Dexmedetomidine its incidence was decreased. The mechanism is not well explained, but may be due to its potential to decrease shivering threshold as when used in intravenous infusion.[18]

Kanazi et al showed an insignificant effect of Dexmedetomidine on mean blood pressure when added to intrathecal Bupivacaine.[3] Al-Mustafa and colleagues, using five and ten micrograms Dexmedetomidine found a dose-dependent, but still insignificant, decrement in mean blood pressure.[4] These findings compare with our study where incidence of hypotension and bradycardia was not significant, probably because we used a small dose of intrathecal Dexmedetomidine.

A large number of patients were excluded because they were receiving anti-hypertensive medications. Given the increasing use of these agents in routine clinical practice, this may represent a significant limitation to the application of intrathecal Dexmedetomidine, and a further randomized, controlled trial including patients taking anti-hypertensives may be warranted. Similarly, the study included only healthy adults and the effects in diabetics and older patients are not known. Also, associated costs and patient's satisfaction towards the intervention were not studied. In our study, there was one block failure. The failure to establish spinal blockade was not related to the learning curve and a possibility of failure with spinal anaesthesia has long been recognized.[19]

Our findings provide an evidence base for rational decision making to ensure the prolonged pain-free period with the use of intrathecal Dexmedetomidine in appropriate surgical patients. Post-operative pain control with a single-shot spinal anaesthesia is not time-consuming; technical skills are not as demanding; and, professional surveillance of patients is not that complicated. This technique requiring no complex gadgets and no need for intensive monitoring would be extremely beneficial for the surgical patients and the medical institutions, especially in our part of the world where resource still remain a major issue. The lack of adverse effects such as hemodynamic disturbances, excessive sedation, respiratory depression, nausea/vomiting and pruritus could be additional advantages. Future researches on intrathecal Dexmedetomidine will be appropriate to clarify its dose response behavior; potential to reduce local anaesthetic dose requirement; and application in elder and sick Nepalese surgical population.

CONCLUSIONS

The addition of intrathecal Dexmedetomidine to hyperbaric Bupivacaine for spinal anaesthesia produces a rapid onset of sensory block, prolongs the sensory and motor blocks and the duration of post-operative analgesia, reduces the frequency of analgesic requirement together with stable hemodynamic parameters, and minimal side effects. Dexmedetomidine appears to be an attractive adjuvant to spinal Bupivacaine especially in surgical procedures that are of long duration and are associated with visceral pain.

ACKNOWLEDGEMENTS

We would like to acknowledge our heartfelt thanks to Prof Dr. Babu Raja Shrestha from the Department of Anaesthesia and Intensive Care, Kathmandu Medical College for his regular encouragement. We also would like to recognize Institutional Review Committee-Kathmandu Medical College for the inputs during designing of the study.

Conflict of Interest: None.

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