ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 29(3); June 2025 DOI: 10.35975/apic.v29i3.2750

ORIGINAL RESEARCH SPINAL ANESTHESIA

Low dose hyperbaric bupivacaine 0.5% with three different doses of dexmedetomidine for spinal anesthesia in transurethral resection of the prostate: A randomized, double-blind trial

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ABSTRACT

Background & Objectives: Transurethral resection of the prostate (TURP) is commonly performed under spinal anesthesia. The advent of bupivacaine replaced cinchocaine, hyperbaric bupivacaine became the favorite, as it offered prolonged effect and maneuverability of the position of the patient. The objective of this research was to assess the efficacy of three distinct concentrations of intrathecal dexmedetomidine in conjunction with 0.5% hyperbaric bupivacaine in TURP.

Methods: This randomized, double-blind study included ninety patients aged 55 to 70 yr admitted for TURP. Patients were divided into three groups; Group A received 1.5 mL hyperbaric bupivacaine 0.5% plus 6 µg dexmedetomidine, Group B received 1.5 mL hyperbaric bupivacaine 0.5% plus 8 µg dexmedetomidine and Group C was administered 1.5 mL hyperbaric bupivacaine 0.5% plus 10 µg dexmedetomidine. The time to onset and duration of sensory and motor block were noted. Postoperatively, morphine was used for analgesia and time to first dose and the total consumption of morphine was noted in each patient. Pain was assessed at NRS scores at 6, 8, and 12 h.

Results: An absence of statistically significant variation was noted at the onset and duration of sensory block and motor block between Groups A and B. Nevertheless, when comparing Group C to Groups A and B, the time to onset was considerably reduced ($P < 0.05$). The duration of first rescue analgesic was significantly prolonged in Groups C and B than in Group A, and in Group C than in Group B ($P < 0.05$). Postoperative total morphine consumption and NRS scores at 6, 8, and 12h were significantly reduced in Groups C and B compared to Group A; and in Group C than Group B ($P < 0.05$).

Conclusions: Combined with hyperbaric bupivacaine, 10 µg of dexmedetomidine significantly prolongs analgesia duration, sensory block, and motor blockade in TURP, as compared to using dexmedetomidine in 6 µg or 8 µg with hyperbaric bupivacaine. This results in a reduction in the requirement of postoperative analgesics, but the incidence of adverse effects is comparable to the lower dosage regimens.

Abbreviations: MAP: mean arterial pressure, NRS: Numeric Rating Scale, PACU: post-anesthesia care unit, SA: spinal anesthesia, TURP: Transurethral resection of the prostate.

Keywords: Dose; Dexmedetomidine; Hyperbaric Bupivacaine; Pain; Spinal Anesthesia; Sensory Block; Transurethral Resection of the Prostate

Citation: Mohamed RM, Abdelbadie M, Anwar AG. Low dose hyperbaric bupivacaine 0.5% with three different doses of dexmedetomidine for spinal anesthesia in transurethral resection of the prostate: A randomized, double-blind trial. Anaesth. pain intensive care 2025;29(3):384-391. **DOI:** 10.35975/apic.v29i3.2750

Received: May 22, 2024; **Revised:** January 26, 2025; **Accepted:** January 26, 2025

1. INTRODUCTION

A widely employed technique involves the administration of patients undergoing transurethral resection of the prostate (TURP) are administered spinal anesthesia.[1] This procedure is typically conducted in elderly patients who frequently suffer from cardiovascular, pulmonary, or hormone-related diseases. Hence, it is imperative to regulate the anesthesia with the intention of minimizing the effect on hemodynamics throughout the procedure.[2] Utilizing lower volumes of local anesthetics in spinal anesthesia facilitates control of the level and accelerates recovery, although this may not always be adequate to anesthetize the area for the duration of the operation.[3]

In order to augment the efficacy of postoperative anesthesia and pain management, opioids or clonidine are administered in conjunction with intrathecal bupivacaine.[4] Clonidine is a well-tolerated adjuvant with local anesthetics without inducing respiratory distress or pruritus, may induce lethargy, hypotension, or a decelerated heart rate.[5]

Since its FDA approval for intravenous sedation in 1999, dexmedetomidine, a more selective alpha-2 adrenoceptor agonist than clonidine, has been put to use for its analgesic, blood pressure-lowering, and analgesic properties.[6] The primary factor responsible for the analgesic effects of dexmedetomidine at the spinal level is its high-fat solubility. This solubility facilitates rapid permeation into the spinal fluid, thereby enhancing its efficacy at the level of the spinal cord.[7]

Previous studies have also examined the possible synergy that may exist between dexmedetomidine and local anesthetics. These investigations have shown that dexmedetomidine has the ability to extend the effectiveness of bupivacaine and comparable local anesthetics, with minimal adverse effects.[8,9] However, these mixtures can occasionally result in excessively high concentrations and lengthy periods of recovery. Therefore, determining the optimal, safe, and effective dosage is vital.

The concurrent administration of dexmedetomidine (3–15 µg) and 10–15 mg of bupivacaine effectively prolonged the duration of local anesthetics while ensuring a negligible occurrence of adverse effects.[8, 10] A definitive agreement concerning the ideal dosage of intrathecal dexmedetomidine remains elusive, notwithstanding the substantial volume of research that has been undertaken in this field. Although higher concentrations improve pain management during and after surgery, they also elevate the risk of compromised hemodynamics.[11,12]

The aim of this study was to evaluate the effectiveness of three different concentrations of dexmedetomidine when combined with 0.5% hyperbaric bupivacaine for TURP.

2. METHODOLOGY

This randomized double-blinded trial was conducted on ninety TURP-admitted patients aged 55 to 70 years old and classified as physical activity I-III by American society of anesthesiologists. The research was conducted utilizing the ethical sanction of the Ethical Committee of Tanta University Hospitals in Egypt. (approval code: 36264PR195/5/23). Written informed consent was obtained from the patient or a representative of their family.

Exclusion criteria were contraindications of SA, drug hypersensitivity, uncontrolled hypertension, previous congestive heart failure and myocardial infarction, cardiac block, and lesions of fixed cardiac output. Additionally, we excluded cases that required an intraoperative switch to general anesthesia.

A complete medical history, clinical examination, and laboratory investigation were performed on every patient. The patients were briefed on the eleven-point NRS (0 = no pain, 10 = severe pain).

Randomization and Blindness

Patients were categorized into three distinct groups using opaque, sequentially numbered envelopes that were sealed and randomly dispersed into three groups by a computer-generated sequence. On the morning of surgery, one of the chief nurses, who did not take part in the study or data collection, manually opened the envelopes and verified the grouping of each patient. Group A: Patients received 6 µg dexmedetomidine combined with 1.5 mL hyperbaric bupivacaine 0.5%, Group B: Patients received 8 µg dexmedetomidine combined with 1.5 mL hyperbaric bupivacaine 0.5%, and Group C: Patients received 10 µg dexmedetomidine combined with 1.5 mL hyperbaric bupivacaine 0.5%. Both outcome assessors and cases were blinded. A dedicated pharmacist, who had no other obligations during the study, devised the study medications. Unaware of the group designation, an additional anesthesiologist evaluated intraoperative and postoperative procedures.

Standard monitors that were employed included non-invasive blood pressure (NIBP), electrocardiography, a temperature probe, and pulse oximetry.

A cannula of 18G diameter was utilized. A preload of 10–20 mL/kg of lactated Ringer's solution was administered. Seated were the individuals who were undergoing spinal anesthesia. Sterile techniques were implemented, which involved the use of povidone iodine as well as surgical drapes. Prior to the procedure, the intervertebral spaces L3/L4 or L4/L5 were identified. Three milliliters of 2% lidocaine were injected into the cutaneous region identified above the intervertebral space using a 22G hypodermic syringe. A 22G pencil-point spinal needle was inserted into the lumbar region. After ten seconds of confirming the

presence of cerebrospinal fluid flow, the intrathecal medication was administered according to the group.

2.1. Observations

We recorded the onset and duration of motor and sensory block, the time required to reach optimal performance, the amount of morphine consumed postoperatively, and the duration of rescue analgesia administration.

Upon introducing a 25 G hypodermic needle through the mid-clavicular line, sensory obstruction is identified by the lack of sensation to a pinprick. Meticulous observation of this threshold was maintained until the peak level of sensory blockade achieved stability. The initiation of the sensory block was determined at the T10 dermatome level as the duration between the end of the intrathecal injection and the disappearance of pinprick sensation.[13] The level apex of sensory blockage is defined as the degree to which the testing procedure achieves sensory blockage following three iterations. The peak sensory level is defined as the duration that elapses from the time intrathecal administration concludes until maximal sensory block is achieved.

In order to assess the motor block, the modified Bromage score[14] was implemented; 0: absence of a motor block, 1: lack of hip flexion, but knee and ankle mobility, 2: lack of hip and knee flexion, but ankle mobility; and 3: hip, knee, and ankle immobility. The onset of motor block is measured from the moment the intrathecal injection was completed until the Bromage 3 score appears. The duration of motor block was the duration from the end of the intrathecal injection till the Bromage 0 score was reinstated.

Heart rate (HR) and mean arterial blood pressure (MAP) were monitored at baseline, 5, 10, 15, 30, 45, and 60 min intraoperatively; at the end of the surgery, in the post-anesthesia care unit (PACU), at 2, 4, 6, 8, 12, 18, and 24 h post-surgery.

NRS scores were assessed at arrival in PACU, then at 2, 4, 6, 8, 12, 18, and 24 hr. When the NRS was four or greater, morphine 1 mg IV was administered as a rescue analgesic; repeated in thirty min. The total quantity of morphine consumed during the initial 24 hours following the procedure was recorded.

Adverse effects such as local anesthetic systemic toxicity (LAST), hypotension, bradycardia, failed blockade, and urinary retention were documented in terms of their incidence. A decrease in systolic blood pressure to less than 90 mmHg or greater than 30% below baseline was categorized as hypotension. Additional intravenous fluids and 5 mg dose of ephedrine were utilized to treat the condition. Bradycardia, which was defined as a 50-beat-per-minute reduction in heart rate, was managed with a 0.5 mg atropine intravenous infusion.

The duration of the sensory block was the primary outcome, whereas the secondary outcomes included the time to achieve maximal sensory block level, duration of the motor block, time to first rescue analgesic, total postoperative morphine consumption, as well as complications.

2.2. Sample Size Calculation

In order to determine the appropriate sample size, G*Power 3.1.9.2 from Universitat Kiel, Germany was utilized. A pilot investigation was initiated, comprising five cases in each group. The findings revealed that Group A experienced duration of the sensory block for 377.4 ± 24.66 hours, Group B for 396.4 ± 23.41 hours, and Group C for 400 ± 24.57 hours. The sample size was determined using 90% study power, a 0.409 effect size, a 95% confidence level, and a 1:1:1 group ratio. Furthermore, to overcome dropout, an additional three cases were appended to each group. As a result, thirty patients were assigned to each group.

2.3. Statistical analysis

The data analysis was conducted using SPSS v27 (IBM, Chicago, IL, USA). To determine whether the data followed a normal distribution, the Shapiro-Wilks test and histograms were utilized. Analyses of variance (ANOVA) (F) and the post hoc test (Tukey) were utilized to examine quantitative parametric data which were expressed as the mean and standard deviation. The researchers utilized a combination of the Mann-Whitney U test and Kruskal-Wallis's test in order to compare the non-parametric quantitative data of the groups presented as the median and interquartile range (IQR). The chi-square test was utilized to assess the qualitative variables, which were expressed as percentages and frequencies. Statistical significance was considered at a two-tailed P value below or equal to 0.05.

3. RESULTS

Upon assessing the eligibility of 109 participants for this trial, 11 patients failed to meet the inclusion criteria, while 8 patients declined to participate. The remaining patients were allocated into three equal groups, with 30 patients in each group, through the use of random assignment. All assigned patients were statistically analyzed and followed up (Figure 1).

Demographic data and duration of surgery were matched among the three groups (Table 1).

There was minimal variation in the time required to attain the maximum level of sensory block among the three groups. The onset timings of sensory block and motor block did not differ significantly between Group A and Group B. In contrast, both Group A and Group

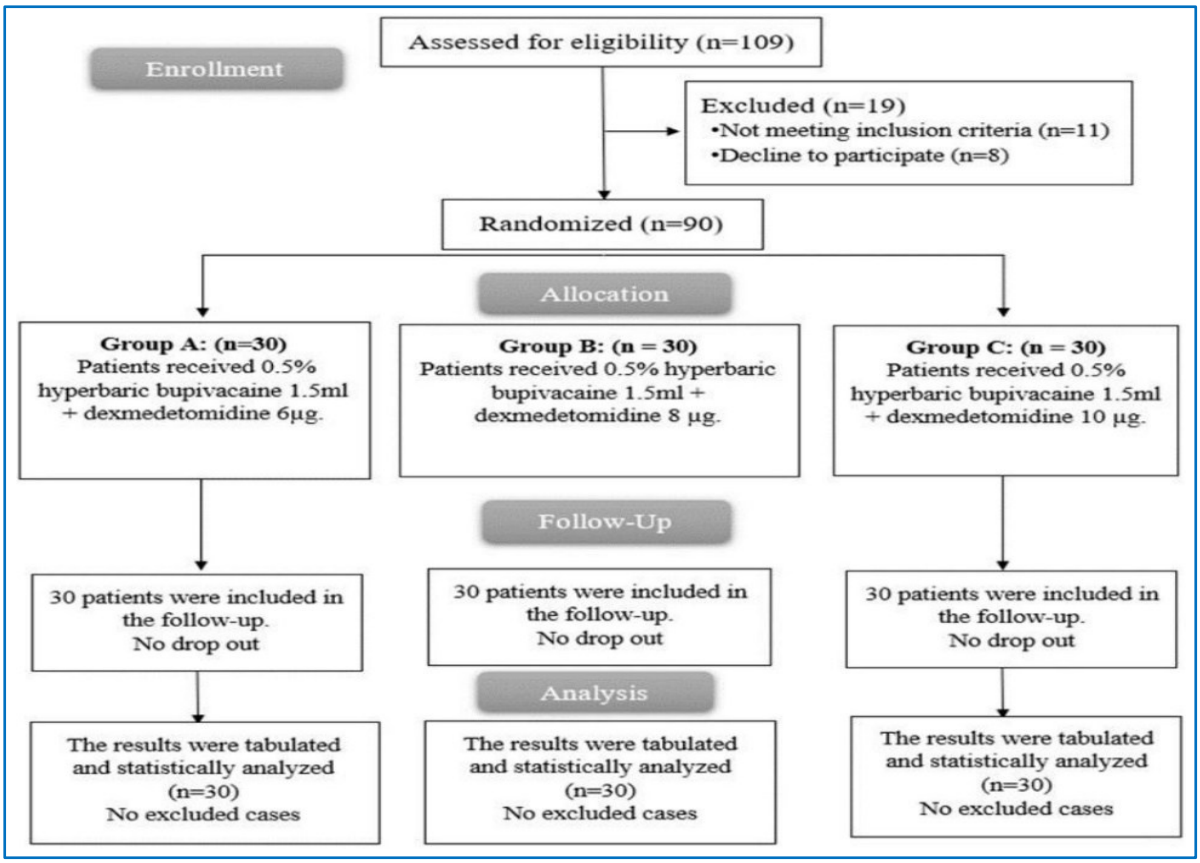

Figure 1: Study follow-up diagram

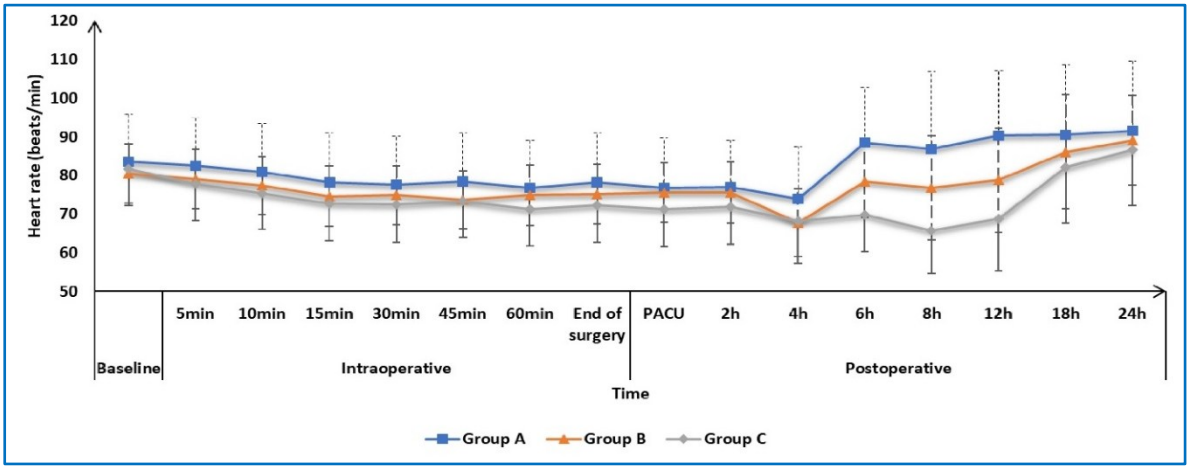

Figure 2: Comparative heart rates at different time intervals in the three groups

B demonstrated significantly longer onset times than Group C ($P < 0.05$). There was no significant difference observed in the duration of motor and sensory blocks between Groups A and B. Nevertheless, Group C exhibited a substantially prolonged duration of blocks compared to both Groups A and B ($P < 0.001$). Both Group C and Group B exhibited considerably longer intervals between the initial analgesic request than Group A ($P < 0.05$), with Group C demonstrating a significantly longer interval than Group B. In comparison to Group A, postoperative total morphine consumption was considerably lower in Groups C and B; in fact, it was even lower in Group C than in Group B ($P < 0.05$) (Table 2).

No statistically significant variations were detected in the intraoperative HR and MAP measurements among the three groups. Regarding postoperative HR and MAP measurements at the PACU at 2, 4, 18, and 24 h, no significant differences were observed between the three groups. However, at 6, 8, and 12 h, these parameters were significantly lower in Group C and Group B compared to Group A ($P < 0.05$) (Figure 2).

At PACU, after 2, 4, 18, and 24 hours, no statistically significant differences were observed in the NRS

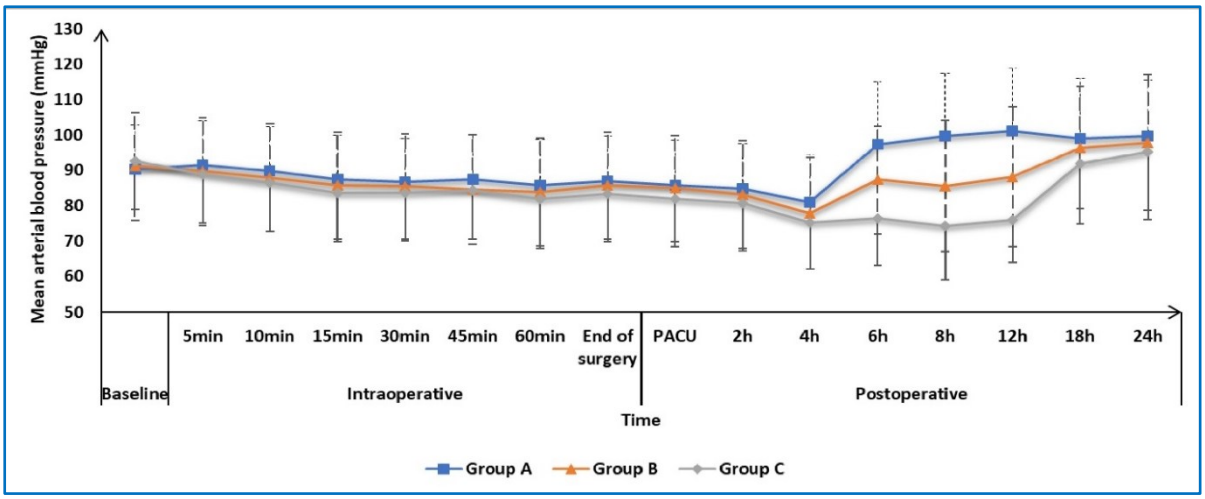

Figure 3: Comparative MAP at different time intervals in the three groups

scores between the three groups. However, at 6, 8, and 12 h, the scores were significantly lower in Groups C and B relative to Group A, and in Group C than in Group B ($P < 0.05$) (Table 3).

Regarding hypotension, bradycardia, and urinary retention, there were no statistically significant variations observed across the three groups. Every patient had an ineffective obstruction and no LAST (Table 4).

4. DISCUSSION

SA is the preferred option for TURP on account of its distinctive advantages. SA not only facilitates unrestricted respiration but also provides relief from postoperative pain, reduces blood loss, and obviates the necessity for airway obstruction via tracheal intubation, which may result in postoperative hemorrhage and wheezing.[15] While regional anesthesia may conceivably provide benefits such as early detection of TURP syndrome in conscious patients, it is not without its limitations, including short duration of anesthesia, patient distress, and discomfort.[9] Rather than technical issues, limitations of regional anesthesia, including SA, are frequently ascribed to inadequate sedation.[16] In addition to alleviating patient anxiety and tension, effective sedatives in SA increases patient and surgeon satisfaction. Nevertheless, overemphasis on sedation may obscure the symptoms of TURP syndrome and induce delirium subsequent to surgical procedures, especially among the elderly.[9]

As a sedative with analgesic properties, dexmedetomidine is an advantageous adjunct to SA for TURP owing to its capacity to compensate for insufficient block height and induce minimal respiratory depression.[6]

Our research proved that higher concentrations of dexmedetomidine were associated with a significant and consistent increase in the duration of sensory and motor blockade, in addition to analgesic effects, according to the results of our study. Significantly, these outcomes were attained while maintaining similar profiles of adverse effects and hemodynamic stability. In particular, an increase in the dosage of dexmedetomidine from 6 µg to 10 µg resulted in a commensurate prolongation of both sensory and motor block, in addition to analgesic effects.

Extending the duration of analgesic administration offers a dual benefit: it mitigates the adverse consequences associated with postoperative discomfort, such as impaired immune function, prolonged hospitalization, delayed wound healing, the potential for neurosensitization, and the development of chronic pain. Furthermore, it promotes the progression of motor obstruction, which may reduce mobility and the probability of developing complications such as deep venous thrombosis, pulmonary embolism, and others that are closely related.[17]

Gupta et al.[13] investigated the dose-response correlation between dexmedetomidine and SA characteristics. Their findings showed that adding 10 µg of dexmedetomidine, the application of 0.5% hyperbaric bupivacaine, as opposed to 2.5 µg or 5 µg, significantly accelerated the onset of sensory and motor blockade. Furthermore, it resulted in an extended duration of sensory and motor impairment, as well as analgesic properties, while retaining a comparable profile of adverse effects.

Yektas et al., Halder et al., and Eid et al. conducted separate studies comparing different doses of intrathecal dexmedetomidine, specifically 2 µg vs. 4 µg, 5 µg vs. 10 µg, and 10 µg vs. 15 µg, respectively.[18-20] In each study, they observed a rise in the sensory block, motor block duration, and analgesic effect that is also dose dependent.

dexmedetomidine exerts its pain-relieving action through a dual mechanism. Firstly, it inhibits neurotransmitter release by targeting presynaptic α2A receptors. Secondly, it hyperpolarizes the postsynaptic

neurons.[21] The motor block prolongation could stem from The inhibiting impact of α2 agonists on the dorsal horn motor neurons of the spinal cord.[22]

It has been suggested that sensitivity to dexmedetomidine may vary depending on the type of nerve fiber, considering that the ED50 for maximal inhibition is 2.5 µg for sensory C fibers and above 10 µg for Aβ motor fibers. This led us to utilize a dosage in this range between 6 µg and 10 µg for this trial. While Eid et al. employed an increased dosage of 15 µg of dexmedetomidine.[20] We chose to exclude it from our dose-response trial design due to the significant increase in sedation scores reported in their study. Additionally, our study's relatively short mean length of surgical procedures contributed to this decision. dexmedetomidine has demonstrated efficacy in managing nociceptive, visceral, and neuropathic pain. Its neurological safety has been established through a follow-up period of up to ten years post-anesthesia.[18,23,24]

In our study, the mean onset of sensory block time was similar among Groups A and B; however, it was significantly earlier in Group C ($P < 0.001$).

These results align with those reported by Halder et al. who employed a comparable definition for the onset time of sensory block and observed a significantly earlier onset with 10 µg than 5 µg of dexmedetomidine.[19] Similarly, Yektas et al. found a substantial rise in the number of sensory segments blocked that depends on dosage when comparing 2 µg and 4 µg of dexmedetomidine.[18] Moreover, Gupta et al. investigated the dose-response correlation between dexmedetomidine and the onset of both sensory and motor block.[13]

The use of dexmedetomidine in conjunction with hyperbaric bupivacaine has been associated with a notable benefit which is a decrease in the need for postoperative analgesia.[8,9,25] We also noted a substantial dose-dependent reduction ($P = 0.001$) in the 24-hour morphine use as the doses of dexmedetomidine were increased.

The primary and clinically notable adverse effect linked with α2 agonists is hemodynamic disturbance; specifically manifesting as hypotension and bradycardia.[26] Most studies did not report any significant rise in the occurrence of hemodynamic adverse events accompanied by the utilization of dexmedetomidine, regardless of the dosage administered.[19,27,28]

We noted a dose-dependent elevation in the incidence of hypotension as well as bradycardia, across groups A, B, and C, respectively. Nevertheless, this rise failed to reach statistical significance.

The potential for further sympatholysis induced by dexmedetomidine may have been constrained in our trial due to the substantial sympatholysis induced by the higher dose and volume of bupivacaine utilized. Our observations are consistent with comparable dose-independent hemodynamic findings reported by other researchers.[19,20] Additionally, side effects such as urinary retention were comparable across all groups.

5. LIMITATIONS

Our study is limited by short follow-up time and the absence of a control group, thus future studies with longer monitoring duration in the presence of a control group in different centers are needed to generalize our findings.

6. CONCLUSIONS

In TURP, 10 µg of dexmedetomidine added to hyperbaric bupivacaine for spinal anesthesia, considerably extends analgesia duration, sensory and motor blockade; and is associated with a reduced need for analgesics postoperatively, while the incidence of adverse effects does not differ significantly when compared to lesser dosages.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Conflict of interest

All authors declare that there was no conflict of interest.

9. Funding

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

RMM: developed the original idea and the protocol, abstracted and analyzed data, wrote the manuscript, and is a guarantor.

MA: contributed to the development of the protocol, abstracted data.

AGA: prepared the manuscript.

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