Intravenous versus intrathecal dexmedetomidine as an additive to hyperbaric bupivacaine in spinal anesthesia for hip arthroplasty. A randomized controlled trial

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**ABSTRACT**

**Background:** This study aimed to assess the safety and efficacy of intravenous (IV) versus intrathecal (IT) dexmedetomidine as an additive to hyperbaric bupivacaine in spinal anesthesia in adult patients undergoing hip arthroplasty.

**Methods:** This randomized, controlled, triple-blinded trial enrolled 90 patients aged 18–65 years, American Society of Anesthesiologists physical status I–II who were scheduled for hip arthroplasty under spinal anesthesia. The study subjects were randomly assigned into three groups. The control group (group C) received IT hyperbaric bupivacaine (0.5%, 12.5 mg) plus 1 ml of normal saline. The IT group received IT hyperbaric bupivacaine (0.5%, 12.5 mg) plus 5 µg of dexmedetomidine diluted in 1 ml of normal saline. The IV group received hyperbaric bupivacaine (0.5%, 12.5 mg) plus 0.5 µg/kg of dexmedetomidine diluted in 20 ml of normal saline administered slowly IV. A modified Bromage scale was used to assess motor blocks. We used the Numerical Pain rating scale (NRS) for pain assessment. We used morphine for post-operative analgesia.

**Results:** Groups IT and IV had significantly lower total morphine consumption and higher time to the first analgesic request than group C. Durations to two-segment regression and motor block regression to Bromage 1 were significantly higher in groups IT and IV than in group C. Motor block regression to Bromage 1 showed a significant difference between the IT and IV groups with a more delayed motor recovery in the IT group.

**Conclusion:** Both IT and IV dexmedetomidine extend the effect of the sensorimotor impact of subarachnoid anesthesia, but IT dexmedetomidine was superior to IV dexmedetomidine in adult patients undergoing hip arthroplasty.

**1. Introduction**

Hip arthroplasty (HA) has been considered one of the most successful surgical operations since its introduction in the 1960s and is identified as the “surgery of the century” [1]. Each year, more than one million operations are done globally, with this figure expected to increase over the next years [2].

Hip arthroplasty is accompanied by moderate-to-severe postoperative pain. Good control of pain facilitates early rehabilitation after surgery [3].

Spinal anesthesia is often used in patients undergoing HA with the potential advantage of better pain control and less deep vein thrombosis in the early postoperative period. Additionally, it has an essential role in postoperative analgesia that enhances patients’ postoperative outcomes [4,5].

Numerous adjuvants, including fentanyl, morphine, and clonidine, have been used to extend the effect of spinal anesthesia [6].

By binding to two adrenoreceptors in the locus ceruleus, dexmedetomidine works as an analgesic, sedative, and anxiolytic. These effects may occur as a consequence of systemic absorption, vascular redistribution to higher centres, or cephalad migration in the cerebrospinal fluid after intrathecal dexmedetomidine injection [7]. When given intravenously (IV) or intrathecally, dexmedetomidine has been shown to prolong spinal anesthesia and enhance postoperative analgesia [8,9].

Dexmedetomidine is a highly lipophilic medication that is quickly absorbed into the cerebrospinal fluid and functions as an analgesic by connecting the spinal cord alpha-2-adrenergic receptor. It extends to sensory and motor paralysis induced by local anaesthetics, regardless of the route of administration (epidural, caudal, or spinal) [10].

The increase of sensory block of the local anaesthetic during spinal anesthesia and peripheral nerve block was also seen for intravenous dexmedetomidine, although...
the mechanism remains unclear [11]. This mechanism is believed to be mediated via dexmedetomidine’s supraspinal, direct analgesic, and/or vasoconstricting effects [12].

This study aimed to compare the efficacy and safety of intravenous versus intrathecal dexmedetomidine as an additive to hyperbaric bupivacaine in spinal anesthesia for adult patients undergoing hip arthroplasty.

2. Methods

2.1. Ethical considerations

The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Suez Canal University, Egypt (2449). We obtained written informed consent from all patients. The trial was registered at ClinicalTrials.gov (NCT04374318).

2.2. Study design, setting, and date

This prospective, randomized, controlled, triple-blinded trial was conducted at Suez Canal University, Egypt, from June 2020 to June 2021.

2.3. Eligibility criteria

This study included 90 patients aged 18–65 years, American Society of Anesthesiologists (ASA) physical status I–II who were scheduled for hip arthroplasty under spinal anesthesia. Patients with coagulopathy, infection at the lumbar region, usage of beta-blockers and/or calcium channel blockers, hypersensitivity to bupivacaine or dexmedetomidine, or any other spinal anesthetic contraindications were excluded.

2.4. Sample size

At 95% level of confidence and 80% power of the study, 19 patients per group will be sufficient to detect a difference of 56 ± 61 minutes between both groups using the following equation. [13]

\[
\text{where } n = \text{sample size}, Z_{\alpha/2} = 1.96 \text{(The critical value that divides the central 95% of the Z distribution from the 5% in the tail)}, Z_{\beta} = 0.84 \text{(The critical value that separates the lower 20% of the Z distribution from the upper 80%)}, \sigma = \text{the estimate of the pooled standard deviation}, \mu_1 = \text{mean in the study group} = 302 \text{ minutes}, \mu_2 = \text{mean in the control group} = 246 \text{ minutes}. \text{ We concluded 30 patients in each group} [14].
\]

2.5. Randomization and blindness

Patients were randomly assigned by computer-generated random sequence to three equal groups. Group C (Control group) received 12.5 mg hyperbaric bupivacaine 0.5% in combination with 1 ml normal saline intrathecal, in addition to 20 ml normal saline administered slowly IV; Group IT (Intrathecal dexmedetomidine) received 12.5 mg hyperbaric bupivacaine 0.5% in combination with 5 µg dexmedetomidine diluted in 1 ml normal saline intrathecal in addition to 20 ml normal saline administered slowly IV. Group IV (IV dexmedetomidine) received 12.5 mg hyperbaric bupivacaine 0.5% with 1 ml of normal saline intrathecal and 0.5 µg/kg dexmedetomidine diluted in 20 ml administered slowly IV.

Patients and anesthesiologists, and outcome assessors were blinded to group allocation. Drug preparation was done by a pharmacist who did not participate in other steps of the trial.

2.6. Anesthetic management

Patients were seen preoperatively for a comprehensive review of their medical history, clinical examination, and laboratory investigations. Each patient was taught how to utilize the numerical rating pain scale (NRS) until they were proficient.

Baseline vital signs were recorded in the holding area [heart rate, blood pressure, respiratory rate, and oxygen saturation by pulse oximetry (SpO2)]. An 18-G intravenous cannula was placed, and no premedication was received by patients. All patients received saline 0.9% (10 ml/kg) during 30 minutes. Spinal anesthesia was administered with a 25-G Quincke spinal needle after infiltration of the skin with 2% lidocaine 3 ml at the L3-L4 level, a midline approach in the sitting position. Time zero was established as the injection time of the spinal anesthesia (T0). The patient’s intravenous drug regimen was started depending on the assigned group. A nasal cannula at a rate of (2–4 l/min) was used to deliver oxygen.

2.7. Outcome parameters

The primary outcome was to assess the motor block regression to Bromage 1 of intrathecal (IT) dexmedetomidine as an additive to hyperbaric bupivacaine in spinal anesthesia versus intravenous (IV) in adult patients undergoing hip arthroplasty.

Unaware of the study, an investigator has assessed each patient’s sensory level bilaterally at the midclavicular line using an ice bag from T4 level and going downward. The onset of sensory blockade, the onset of motor blockade, the duration of two-segment regression, the duration of sensory regression for 51 segment, the duration of motor block regression to Bromage 1 and the time of first request for analgesia were calculated using the spinal injection time as the starting point. The degree of sensory and motor block was assessed every 2 minutes after spinal block injection, until achieving the maximum sensory level of block and Bromage 3.
A modified Bromage scale was used to assess motor blocks. Bromage 0: The patient is mobile in the hip, knee, and ankle; Bromage 1: The patient is immobile in the hip but mobile in the knee and ankle; Bromage 2: The patient is immobile in the hip and knee but mobile in the ankle; and Bromage 3: The patient is immobile in the hip, knee, and ankle. The time required to achieve Bromage 3 motor block was determined before surgery, and the time required to regress to Bromage 1 was determined after surgery.

Heart rate (HR) and mean arterial pressure (MAP) were measured at baseline, 2, 5, 10, 15, 30, 45, and 60 minutes intraoperatively and at the end of surgery. Hypotension was defined as a decrease of more than 20% in MAP from baseline or a decrease in a MAP under 65 mmHg. Hypotension was treated with an IV bolus of 6 mg ephedrine and a crystalloid bolus of 250 ml fluid over 10 min. Both were repeated if the hypotension persisted. Bradycardia was defined as a decline in HR of more than 20% from baseline or HR below 60 beats per minute; it was treated with an IV bolus of 0.5 mg atropine.

Assessment of pain was performed using NRS at PACU, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 18 h, and 24 h. Intravenous paracetamol 1 gm was given every 6 hours. When the NRS score was 4 or more, patients were administered morphine 0.1 mg/kg IV to achieve an NRS score of less than 4. The timing of the initial request and the total morphine consumption were recorded for 24 hours postoperatively.

### 2.8. Statistical analysis

SPSS (version 21.0; Inc., Chicago, IL, USA) was used to analyze the collected data. Shapiro–Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by ANOVA (F) test with post hoc test (Tukey). Quantitative non-parametric data were presented as the median and interquartile range (IQR) and were analyzed using the Kruskal–Wallis test and Mann Whitney-test to compare each group. Qualitative variables were presented as numbers and percentages were analyzed utilizing the Chi-square test. Statistical significance was defined as a two-tailed P value of less than 0.05.

### 3. Results

In this study, 108 patients were assessed for eligibility, 14 patients did not meet inclusion criteria and four patients declined to participate. The remaining 90 patients were randomly allocated into three groups (30 patients each). All of them were followed up and statistically analyzed (Figure 1).

Demographic data and surgical duration were not significantly different between the three groups (Table 1).

The duration of motor block regression to Bromage 1 was significantly higher in the IT and IV groups than in the control group (P < 0.001 and 0.017), respectively. Furthermore, the motor block regression to Bromage 1 had a significant difference (P < 0.001) between the IT and IV groups with a more delayed motor recovery in the IT group (Table 2).

The duration of two-segment regression and the duration of sensory regression for S1 were significantly higher in the IT and IV groups than in the control group (P < 0.001 and <0.001), respectively. Furthermore, there was no significant difference between IT and IV groups concerning two-segment sensory regression and the sensory regression to S1 (Table 2).

The onset of sensory blockade was significantly lower in the IT and IV groups than in the control group (P < 0.001 and 0.001), respectively, and significantly lower in the IT group than in the IV group (P < 0.001). Also, the onset of motor blockade was significantly lower in IT and IV groups than in the control group (P < 0.001 and 0.035), respectively, and significantly lower in the IT group than in the IV group (P < 0.001).

The time to the first request of analgesia was significantly higher in the IT and IV groups than in the control group (P < 0.001 and <0.001), respectively, and significantly higher in the IT group than in the IV group (P = 0.045) (Table 2).

The total morphine consumption was lower in IT and IV groups than in the control group (P < 0.001 and <0.001), respectively, and significantly lower in the IT group than in the IV group (P < 0.001) (Table 2).

MAP was significantly different between the three groups from 5 min to the end decreased in both group IT and group IV in comparison with group C and was significantly increased in group IT than in group IV (Figure 2).

HR at 5 min to 60 min was significantly decreased in both group IT and group IV compared to group C and was significantly increased in group IT compared with group IV. HR at 10 min and the end was significantly decreased in group IV than in both group C and group IT and were insignificantly different between group C and group IT (Figure 3).

At all times, NRS was significantly different between the IT, IV and control groups (P < 0.001) except at PACU and at 6 h when NRS was insignificantly different among the three groups. NRS at 1 h, 2 h, and 18 h
was significantly decreased in both group IT and group IV than in group C and was significantly increased in group IT than in group IV ($P = 0.026$) (Table 3).

### 4. Discussion

Hip arthroplasty is accompanied by moderate-to-severe postoperative pain. Good control of pain facilitates early rehabilitation after surgery [3]. This study aimed to assess the safety and efficacy of intravenous (IV) versus intrathecal (IT) dexmedetomidine as an additive to hyperbaric bupivacaine in spinal anesthesia in adult patients undergoing hip arthroplasty.

In this study, the motor blockade was significantly extended in all patients who received dexmedetomidine, but intrathecal dexmedetomidine provided more prolonged motor block and delayed motor recovery than for the intravenous dexmedetomidine, other investigations have shown a similar prolongation [15,16].

The duration of sensory block for patients who received dexmedetomidine either intravenous or intrathecal was significantly prolonged than for the
Table 2. Blockade and analgesia characteristics among the three studied groups.

|                          | Group C Control group (n = 30) | Group IT Intrathecal group (n = 30) | Group IV Intravenous Group (n = 30) |
|--------------------------|---------------------------------|-------------------------------------|------------------------------------|
| The onset of sensory blockade (min) *,**,** | 7.80 ± 2.59                      | 3.70 ± 1.47                         | 5.73 ± 2.05                        |
| The onset of motor blockade (min) *,**,** | 10.90 ± 2.80                     | 7.07 ± 1.74                         | 9.43 ± 2.06                        |
| Duration to two segment regression (min) *,** | 68.33 ± 17.97                    | 127.83 ± 45.46                      | 106.67 ± 45.59                    |
| Duration for sensory regression to S1 segment (min) *,** | 158.00 ± 27.66                   | 249.00 ± 59.01                      | 236.83 ± 4.43                     |
| Duration for motor block regression to Bromage 1 (min) *,**,** | 140.17 ± 29.23                   | 230.17 ± 58.93                      | 164.17 ± 45.32                    |
| Time to first request of analgesia (min) *,**,** | 262.63 ± 29.82                   | 376.17 ± 69.55                      | 345.50 ± 54.29                    |
| Total morphine consumption (mg) *,**,** | 17.63 ± 6.47                     | 5.33 ± 1.92                         | 9.43 ± 2.80                       |

Data are presented as mean ± SD
* Significant compared to the C and IT groups as P value < 0.05
** Significant compared to the C and IV groups as P value < 0.05
*** Significant compared to the IT and IV groups as P value < 0.05

Figure 2. Mean arterial blood pressure among the three studied groups.

control group, which is consistent with previous results [14,17,18]. Similar results were found for the onset of the sensory block.

More specifically, this study showed that the mean time required for two-segment regression of sensory blockade was significantly extended for intravenous and intrathecal dexametomidine than for the control group. This is similar to other findings from previous research [17–19].

When compared to the intravenous method, the intrathecal route significantly extends the analgesia duration. In another study, Hamed and Talaat [16] compared IV dexametomidine 0.5 μg/kg immediately after spinal anesthesia and intrathecal dexametomidine 3 μg, they found that the duration of sensory block in group IT was much longer. Our findings are in line with those of this research.

Harsoor et al. investigated 50 patients underwent lower limb and infraumbilical surgeries with a bolus dose of IV dexametomidine 0.5 μg/kg followed by an infusion of IV dexametomidine 0.5 μg/kg/h and found that intravenous dexametomidine during spinal anesthesia shortens the onset of the sensory block and prolongs its duration compared to the control group [19]. Also, Magdy et al. [14] investigated 105 pregnancies for caesarean section and compared IT dexametomidine 5 μg with IV dexametomidine 0.5 μg/kg/h and found that intrathecal and infusion of dexametomidine accelerates the onset of sensory block and prolongs the regression to S1 segment [20]. While in contrast, Sharma et al. [21] showed that the onset of sensory between IV dexametomidine, IT dexametomidine and control groups was comparable, and this can be explained by the lower intrathecal dose of dexametomidine they used (3 μg) in their intrathecal group and by their slow intravenous dose titrated over 15 minutes and given very early.

Additionally, the onset of the motor block was shown to be different in each of the three groups, whereas it was comparable in prior trials [15,16,20]. In Kumar et al. study [22], the addition of intrathecal dexametomidine led to faster onset of sensory and motor block, extended duration of sensory and motor block, and provided a sufficient intraoperative and
postoperative sedation while reducing the requirement for rescue analgesia. All of these characteristics are advantageous for surgery performed under spinal anesthesia.

A meta-analysis by Niu et al. [8], who had studied 8 trials including 412 patients receiving IT or IV dexmedetomidine, showed that dexmedetomidine had prolonged subarachnoid anesthesia and improved postoperative analgesia. The meta-analysis [8] showed that dexmedetomidine is more necessary in subarachnoid anesthesia to utilize atropine to reverse bradycardia. The data set examined showed a significant level of heterogeneity due to many dosages of bupivacaine and dexmedetomidine used for various kinds of surgical operations. There was no standardized route of administration, and the criteria for motor recovery and sensory were not similar.

Dexmedetomidine could depress the cardiovascular system causing bradycardia and hypotension [23,24]. In this study, we found the same results. Abdallah et al. discovered that in patients receiving intravenous dexmedetomidine, the incidence of transient reversible bradycardia was increased 3.7 times when the first loading dose was promptly provided [17]. Also, Reddy et al. [25] and Kaya et al. [26] examined the effect of single-dose dexmedetomidine 0.5 μg/kg IV versus placebo and observed an increase in the incidence of bradycardia and hypotension with dexmedetomidine, but it was statistically insignificant. In follow-up visits, neither patient had any neurological impairment.

As found in a meta-analysis performed by Abdallah et al. [17], there was no significant hypotension difference. The incidence recorded was 14%, 17%, 23%, and 27%, respectively, with 0.25, 0.5, 1, and 2 μg/kg of IV infusion.

In disagreement with earlier research that examined the impact of intravenous and intrathecal dexmedetomide, our study is different in terms of methodology and dexmedetomidine doses used [15,17,18]. The strengths of our study were being triple-blind and the presence of a control group. The limitations of the study were a single-center study and a relatively small sample size.

Table 3. Numerical rating pain scale among the three groups.

| Group C | PACU | 1 h t. | 2 h t. | 4 h t. | 6 h | 8 h t. | 12 h t. | 18 h t. | 24 h t. |
|---------|------|-------|-------|-------|-----|-------|-------|-------|-------|
| Control group (n = 30) | Median | 1.0 | 4.5 | 4.0 | 4.0 | 5.0 | 4.0 | 4.0 | 4.0 |
| IQR | 1–2 | 3–5 | 3–5 | 3–5 | 3–6 | 3–6 | 3–5 | 3–5 | 2–5 |
| Group IT Intrathecal group (n = 30) | Median | 1.0 | 1.0 | 1.0 | 2.0 | 4.0 | 2.0 | 3.0 | 3.0 |
| IQR | 0–2 | 1–2 | 0–2 | 1–3 | 2–6 | 0–3 | 2–4 | 2–4 | 1–3 |
| Group IV Intravenous Group (n = 30) | Median | 1.0 | 1.0 | 1.5 | 3.5 | 3.0 | 1.0 | 4.0 | 3.0 |
| IQR | 0–1 | 1–2 | 1–2 | 2–5 | 3–5 | 0–2 | 5–3 | 2–4 | 2–5 |

Data are presented as the median and interquartile range (IQR).

† Significant compared to the C, IT or IV group as P value < 0.05
* Significant compared to the C and IT groups as P value < 0.05
** Significant compared to the C and IV groups as P value < 0.05
*** Significant compared to the IT and IV groups as P value < 0.05

Figure 3. Heart rate among the three studied groups.
5. Conclusion

Both IV and IT dexmedetomidine are safe and effective in extending the sensorimotor impact of subarachnoid anesthesia, but IT dexmedetomidine was superior to IV dexmedetomidine in adult patients undergoing hip arthroplasty.

5.1. Recommendation

Although both intrathecal and intravenous dexmedetomidine can improve sensory and motor block, the intrathecal method takes longer to regain motor function. We advise against using intrathecal dexmedetomidine since we can use the intravenous route to avoid delayed motor recovery, especially when early ambulation is a key component of surgery success, as it is in hip arthroplasty.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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