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Dexmedetomidine and Morphine as Additives to Intrathecal Levobupivacaine for Infra Umbilical Surgeries: Randomized Clinical Trial

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ABSTRACT

Background: Postoperative pain (POP) management after infra-umbilical surgeries often involves opioids, which can cause side effects like pruritus. The use of dexmedetomidine, an α2-adrenergic agonist, as an adjunct to local anesthetics (LAs) may improve analgesia and reduce opioid use. **Objective**: To compare the efficacy and safety of intrathecal (IT) dexmedetomidine and morphine as additives to levobupivacaine for postoperative analgesia in infra-umbilical surgeries.

Patients and Methods: Ninety adult patients (aged 20-75) scheduled for elective infra-umbilical surgeries were divided into three groups: Group M (200 µg morphine + levobupivacaine), Group D (5 µg dexmedetomidine + levobupivacaine), and Group DM (200 µg morphine + 5 µg dexmedetomidine + levobupivacaine). Spinal anesthesia (SA) was administered, and sensory and motor blocks were evaluated. Postoperative pain, rescue analgesic consumption, and adverse events were monitored.

Results: Insignificant differences were observed in the onset of sensory or motor block between groups. However, the total duration of motor block was significantly increased in Group DM (220.7 ± 18.9 min) compared with Group M (150.2 ± 32.1 min, P = 0.001). Pruritus was more common in Group M (P = 0.04), while insignificant differences were demonstrated for other adverse events comprising nausea, vomiting, hypotension, or bradycardia. Morphine consumption via PCA was lower in Group D (10.5 ± 3.3 mg) and Group DM (10.21 ± 3.3 mg) compared to Group M (11.13 ± 5.2 mg, P < 0.05). There were significant reductions in VAS scores in Groups D and DM up to 36 hours postoperatively.

Conclusion: Adding dexmedetomidine to morphine and levobupivacaine enhances postoperative analgesia, prolongs motor block, and reduces opioid consumption without compromising hemodynamic stability, suggesting its potential as a safer and more effective analgesic option.

Keywords: Dexmedetomidine, Morphine, Levobupivacaine, Spinal Anesthesia, Postoperative Pain.

INTRODUCTION

Postoperative pain (POP) management remains a significant challenge in clinical practice, particularly in procedures involving infra-umbilical surgery [1]. Traditional methods such as systemic analgesics and opioids, although effective, often come with adverse events comprising postoperative nausea and vomiting (PONV), and sedation [2].

Intrathecal (IT) administration of analgesics is an established approach for managing POP. By directly delivering drugs to the cerebrospinal fluid, intrathecal delivery allows for a more localized and potent effect compared to systemic administration. Adjuvants, which include morphine and alpha-2-adrenergic agonists, have been used together with LAs like levobupivacaine to improve analgesia [3].

Opioids have long been the mainstay of POP relief. However, their use is restricted by the risk of dependency, respiratory depression, and other adverse events, which often lead to complications in the postoperative period [4,5]. The search for effective opioid alternatives is crucial to improving patient outcomes and minimizing opioid-related risks [6,7]. Agents like dexmedetomidine, an α2 adrenergic agonist, are being investigated for their ability to provide effective analgesia without the common drawbacks of opioids, making them an attractive alternative in pain management [7].

The spinal cord plays a critical role in modulating pain transmission from the periphery to the brain. Both opioids and non-opioid analgesics influence pain pathways within the spinal cord, affecting neurotransmitter systems such as noradrenaline and serotonin [8,9]. The interaction of such systems in the spinal cord can alter the perception of pain, contributing to the effectiveness of analgesics. Understanding the complex neurophysiological mechanisms of spinal cord modulation is essential for developing better-targeted pain relief strategies, such as combining dexmedetomidine with opioids for enhanced analgesia [10,11].

Spinal anesthesia (SA) is broadly utilized for surgeries below the umbilicus due to its effectiveness in providing sensory and motor block. However, the duration and intensity of pain relief are often limited, particularly postoperatively. Combining intrathecal levobupivacaine with adjuncts like dexmedetomidine or morphine has shown promise in overcoming these limitations. These adjuvants can prolong the analgesic effect, enhance sensory block quality, and reduce the need for systemic analgesics, ultimately leading to better patient comfort and reduced opioid consumption[12-15].

Dexmedetomidine, a selective alpha-2 adrenergic agonist, has gained attention for its potential in postoperative pain management [16]. Compared to

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opioids, dexmedetomidine offers a unique mechanism of action, modulating both the spinal and central nervous systems to provide analgesia and sedation without causing significant respiratory depression [17]. In combination with intrathecal local anesthetics such as levobupivacaine, dexmedetomidine may offer an effective strategy for managing postoperative pain, particularly in patients where opioids are contraindicated or need to be minimized [18-20].

Our rational is to evaluate the effectiveness of dexmedetomidine and morphine as adjuncts to IT levobupivacaine in managing postoperative pain following infra-umbilical surgery.

PATIENTS AND METHODS

This prospective, randomized clinical trial was conducted between January 2022 and April 2024 at Anesthesia and Intensive Care and Pain Management, Faculty of Medicine, Sohag University. The current study included ninety adult cases, aged 20 to 75 years, planned for elective infra-umbilical surgeries under SA with hyperbaric 0.5% levobupivacaine.

Eligibility Criteria

The studied cases were classified as ASA physical status I or II, with key exclusion criteria including ASA physical status III or higher, respiratory diseases, cognitive or psychiatric disorders, and hypertension or other cardiovascular diseases.

Randomization and Grouping

Patients were divided into three groups, 30 each, by using a computer-generated randomization list:

1. Group M: Received 10 mg levobupivacaine plus 200 µg morphine.
2. Group D: Received 10 mg levobupivacaine plus 5 µg dexmedetomidine.
3. Group DM: Received 10 mg levobupivacaine, 200 µg morphine, and 5 µg dexmedetomidine.

Preoperative Management

Data were collected from patients, which included age, weight, height, body mass index (BMI), and type of operation. Upon arrival, all patients were preloaded with ten mL/kg of lactated Ringer's solution via an 18-gauge intravenous (IV) cannula. Standard monitoring, including electrocardiography (ECG), pulse oximetry (SpO_2), and non-invasive blood pressure (BP) (NIBP), was performed throughout the procedure.

Spinal Anesthesia Technique

Under strict aseptic conditions, spinal anesthesia was administered in the right lateral position using a 26-gauge Quincke needle at the L3-L4 or L2-L3 intervertebral space by a midline approach. A total of 3 mL of 0.5% hyperbaric levobupivacaine was injected into all groups.

- Group M received an additional 200 µg of morphine (1 unit from a 40-unit insulin syringe) added to the levobupivacaine syringe.
- Group D received an additional 5 µg of dexmedetomidine (1 unit from a 40-unit insulin syringe) added to the levobupivacaine syringe.
- Group DM received 200 µg morphine and 5 µg dexmedetomidine in addition to the levobupivacaine.

Follow Up and Monitoring

Sensory block assessment was evaluated by noting the time to onset of sensory block and the time for two-segment sensory regression.

Motor block evaluation was evaluated using the modified Bromage scale: Grade zero (no weakness, full power), Grade I (Knee flexion could be done, while the legs could not be raised), Grade II (only foot movements), and Grade III (total paralysis). The onset time, times to achieve Bromage grade III, and overall duration of motor block were reported.

By the start of the operation, assessment of hemodynamic parameters of heart rate (HR), systolic BP (SBP), and diastolic BP (DBP) was conducted at 0, 30, 60, 90, 120, 180, 240, 300, and 360 minutes, and then at 8 hours. Hypotension, (>thirty percent reduction in BP from basal value) was managed with ephedrine and IV crystalloids. Bradycardia was managed by IV atropine injection.

Adverse events which include PONV, pruritus, hypotension, and bradycardia were monitored. Nausea/vomiting was treated with 4 mg IV ondansetron, pruritus with 25 mg IM promethazine (repeatable after 1 hour), and oxygen was given if $SpO_2 < 94\%$.

Postoperative monitoring included time to first rescue analgesic and total doses, with rescue analgesia based on the VAS (zero = no pain, ten = worst pain), administering IV diclofenac, morphine (75 mg) for VAS ≥ 3. The degree of sedation was assessed by utilizing the Four-Point Sedation Scale: Level 1 (alert), Level 2 (drowsy, but gives response to verbal stimulation), Level 3 (drowsy, arousable to physical stimulation), Level 4 (unarousable). Pain was evaluated using the VAS at intervals up to 480 minutes postoperatively.

Ethical approval:

Following approval from the Ethical Committee Faculty of Medicine, Sohag University, written informed consent was obtained from cases before participation. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

Data were analyzed with IBM SPSS (version 25). Continuous data are presented as mean ±SD, and categorical data are presented as frequency and percentage. One-way ANOVA test was utilized for comparisons of continuous data, and the Chi-Squared test was utilized for categorical data. A p-value of < 0.05 was considered statistically significant.

RESULTS

Ninety patients (30 per group) were enrolled. The mean age was 45.11 ± 6.90 years in Group D, 46.45 ± 6.41 years in Group M, and 45.36 ± 8.41 years in Group DM. Most patients were males (70%, 76.7%, and 63.3%, respectively). Insignificant differences were found between groups in age, weight, height, BMI, ASA classification, type of the procedure or surgical duration (Table 1).

Table (1): Patient's demographics and clinical characteristics.

	Group D (n=30)	**Group M (n=30)**	**Group DM (n=30)**	***P* value**
Sex:				
Male	21 (70%)	23 (76.7%)	19 (63.3%)	0.530
Female	9 (30%)	7 (23.3%)	11 (36.7%)	
Age (years)	45.11 ± 6.90	46.45 ± 6.41	45.36 ± 8.41	0.668
Weight (Kg)	75.40 ± 11.14	74.50 ± 7.34	75.23 ± 7.65	0.653
Height (cm)	165.53 ± 4.24	167.10 ± 5.73	165.63 ± 5.14	0.720
BMI (kg/m^2)	25.16 ± 3.63	26.23 ± 3.55	25.10 ± 3.39	0.544
ASA I/II	2/28	1/29	2/28	0.809
Operative procedure:				
Laparotomy	11	11	13	0.638
Appendectomy	11	8	11	0.638
Hysterectomy	8	11	6	0.349
Duration of operation (hr)	2.36 ± 0.64	2.65 ± 0.53	2.56 ± 0.52	0.971

Insignificant differences were observed between groups in onset of sensory and motor blockade, or time to 2-segment sensory regression. The overall duration of motor block differed significantly between groups. Group D had 190.1 ± 56.10 minutes, Group M had 150.2 ± 32.12 minutes, and Group DM had 220.7 ± 18.90 minutes, with Group DM showing the longest duration (Table 2).

Table (2): Spinal characteristics

	Group D (n=30)	**Group M (n=30)**	**Group DM (n=30)**	***P* value**
Onset of sensory block in seconds	60.12±54.12	62.5±32.8	63.6±34.6	0.98
Onset of motor block in seconds	98.01±53.65	95.04±64.30	96.41±54.40	0.76
Two segment sensory regression in min	95.8±43.70	96.5±56.70	95.6±44.21	0.75
Total duration of motor block in min	190.1±56.10	150.2±32.12	220.7±18.90	0.001

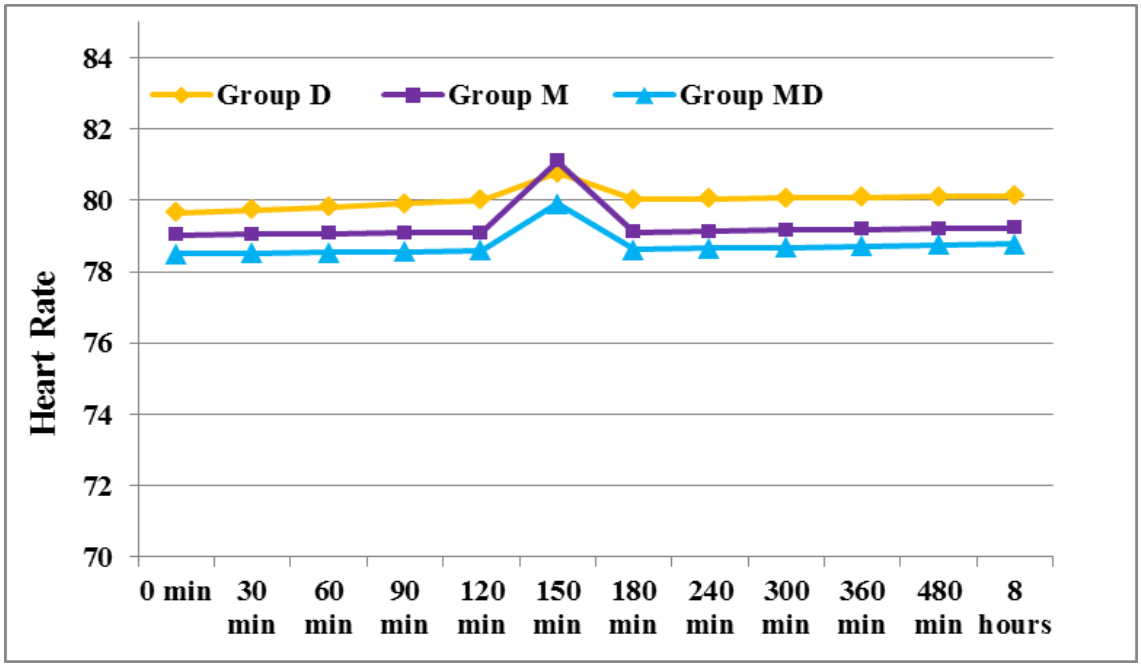

Figure (1): Comparison among groups regarding intra- and postoperative heart rate

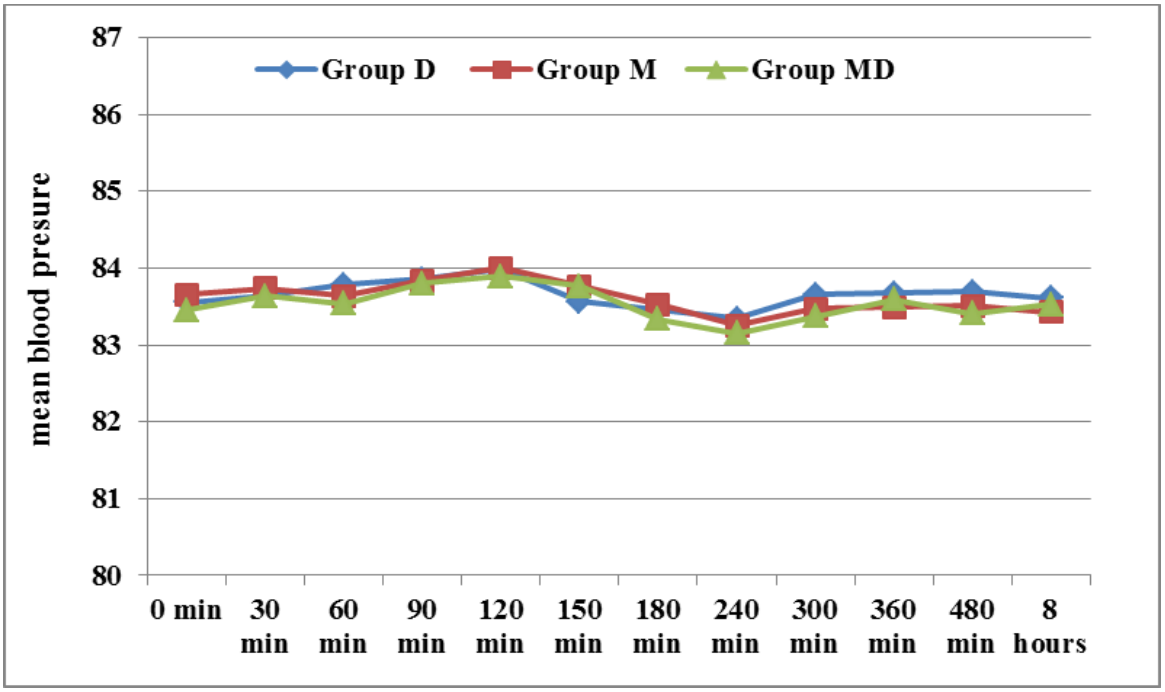

Figure (2): Comparison among groups regarding intra- and postoperative mean arterial pressure (MAP)

Pruritus and hypotension were the only intraoperative adverse effects with a significant difference between groups. Their frequency was increased more in Group DM than in Groups D and M. Insignificant differences were recorded for other adverse effects, comprising PONV, hypotension, or bradycardia (Table 3).

Table (3): Intraoperative comparison among groups regarding side effects

	Group D (n=30)	**Group M (n=30)**	**Group DM (n=30)**	**P value**
Bradycardia	12	13	15	0.32
Hypotension	16	10	20	0.03
Nausea	4	5	6	0.43
Vomiting	6	4	5	0.21
Pruritus	0	15	17	0.04

Total morphine consumption via PCA was significantly reduced in Group D and Group DM compared to Group M. Insignificant difference in PCA morphine consumption was recorded between Group D and Group DM (Table 4).

Table (4): Time of first request of rescue analgesia in the initial 48 hours after surgery.

	Group D (n=30)	group M (n=30)	group DM (n=30)	P1	P2	P3
Time of first rescue analgesia (hr)	10.5 ± 3.3	11.13 ± 5.21	10.21 ± 3.32	0.001	0.481	0.002

P1; Comparison between group D and group M, P2; Comparison between group D and group DM, P3; Comparison between group M and group DM.

Mean VAS scores were significantly diminished in Groups D and DM compared to group M up to 36 hours postoperatively. Scores in Groups D and DM were lower during the first 12 hours ($P \leq 0.001$) and from 18 to 36 hours ($P < 0.01$). Insignificant differences were recorded at 48 hours. Insignificant difference in postoperative pain levels was observed between Group D and Group DM (Figure 3).

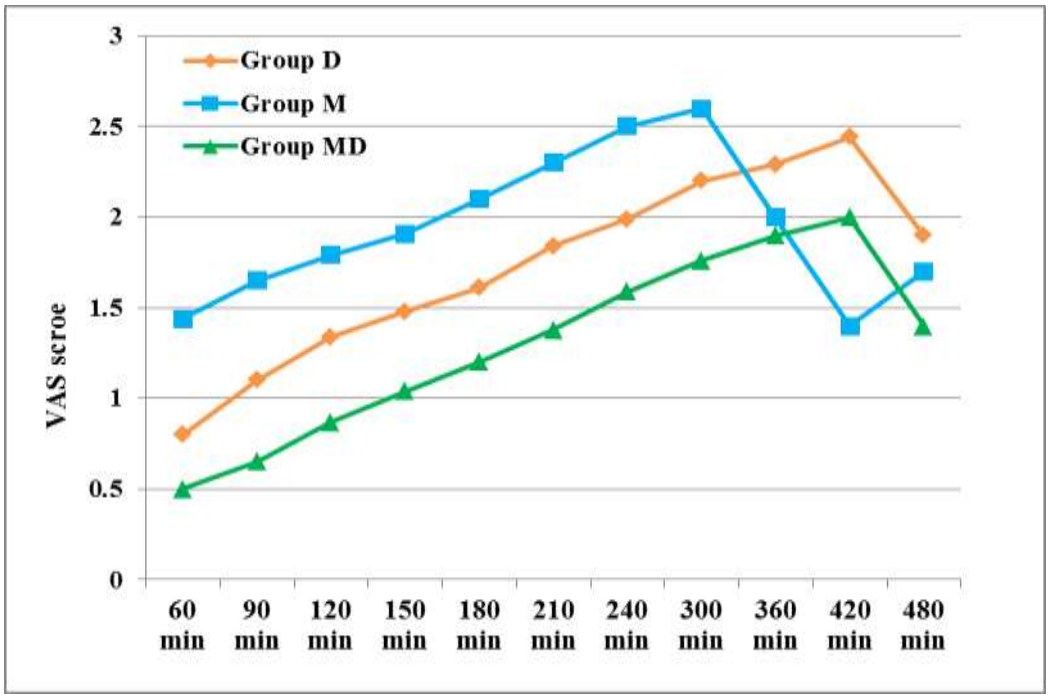

Figure (3): Comparison among groups regarding postoperative visual analogue score

Table (5) shows that insignificant differences were demonstrated for other adverse events comprising nausea, vomiting, pruritus, or bradycardia.

Table (5): Comparison among groups regarding postoperative adverse events

	Group D (n=30)	Group M (n=30)	Group DM (n=30)	P value
Nausea	8 (26.7%)	7 (23.3%)	6 (20.0%)	0.83
Vomiting	8 (26.7%)	6 (20.0%)	7 (23.3%)	0.83
Pruritus	0 (0.0%)	7 (23.3%)	6 (20.0%)	0.02
Hypotension	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Bradycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Respiratory depression	0 (0.0%)	0 (0.0%)	0 (0.0%)	–

There were insignificant differences in postoperative sedation scores among the three groups (Table 6).

Table (6): Comparison among groups regarding sedation score

	Group D (n=30)	Group M (n=30)	Group DM (n=30)	P value
Score 1	30 (100.0%)	27 (90.0%)	28 (93.3%)	0.23
Score 2	0 (0.0%)	3 (10.0%)	2 (6.7%)	0.23

DISCUSSION

Spinal anesthesia with levobupivacaine is commonly used for infra-umbilical surgeries, but its limited duration of postoperative analgesia is a drawback. To extend subarachnoid block analgesia, various intrathecal adjuvants have been tested. The addition of 3–15 μg dexmedetomidine enhances anesthesia, analgesia, and hemodynamic stability in a dose-dependent manner, as demonstrated in multiple studies [21,22]. While no consensus exists on the optimal intrathecal morphine dose, it is generally considered to be 100–250 μg, with 200 μg used in this study based on its analgesic ceiling effect [23,24].

The current study evaluated the postoperative analgesic efficiency of IT dexmedetomidine compared to IT morphine and their combination with levobupivacaine in cases undergoing lower abdominal surgeries. Our results demonstrate that the addition of five μg of dexmedetomidine to 200 μg of morphine, alongside spinal levobupivacaine, significantly increased analgesic effects and motor block compared with 200 μg of IT morphine alone. Additionally, both the dexmedetomidine and combination groups exhibited significantly decreased VAS scores compared with the morphine-only group up to 300 minutes postoperatively. Importantly, all groups remained hemodynamically stable, and no patients experienced respiratory depression.

Intrathecal dexmedetomidine has been widely studied for its analgesic properties, particularly in comparison to other α2-adrenergic agonists such as clonidine. **Kurhekar *et al.*** [20] **and Qi *et al.*** [21] revealed that intrathecal dexmedetomidine, at doses ranging from 2.5 μg to 10 μg, produced a significant prolongation in sensory and motor block compared with clonidine, with an added benefit of reduced postoperative analgesic consumption. Our study supports these findings, demonstrating that the addition of 2.5 μg of dexmedetomidine, when combined with 200 μg of morphine and levobupivacaine, causes a significantly extended the analgesic duration.

The analgesic effect of intrathecal morphine is well-documented, especially in providing long-lasting pain relief following surgeries. However, the use of morphine is not without its challenges, particularly opioid-related adverse events such as itching, PONV, and respiratory depression. In the current study, itching was recorded in 7 cases in the morphine-only group, which aligns with previous study confirming that pruritus is a common adverse event of morphine [22]. In contrast, dexmedetomidine offers an advantage over morphine by not inducing pruritus, which is a significant benefit, particularly for patients who are prone to opioid-related side effects. Previous studies comparing intrathecal morphine with intrathecal dexmedetomidine have generally shown similar or improved analgesic outcomes with dexmedetomidine. For instance, **Gupta *et al.*** [23]**,** displayed that five μg of IT dexmedetomidine increased the duration of sensory and motor block compared to 200 μg of morphine, without significant differences in adverse events like hypotension or bradycardia [17]. The current results corroborate this, with the combination of 2.5 μg dexmedetomidine and 200 μg morphine showing enhanced analgesia while decreasing the need for rescue analgesics.

A critical point in postoperative analgesia is the reduction in opioid consumption. The addition of dexmedetomidine was recorded in several studies to significantly decrease postoperative opioid requirements. For example, **Eid *et al.*** [24] reported that intrathecal dexmedetomidine (5 μg) combined with bupivacaine reduced total analgesic consumption postoperatively compared to bupivacaine alone. Our study similarly found that the addition of dexmedetomidine resulted in delayed first request for analgesia, a longer duration of analgesia, and decreased rescue analgesia consumption. These results are consistent with other report that suggests dexmedetomidine enhances the analgesic effects of both opioids and local anesthetics, reducing the need for additional analgesics [25].

One of the advantages of intrathecal dexmedetomidine is its ability to maintain hemodynamic stability, a key consideration in spinal anesthesia. Although dexmedetomidine can cause hypotension and bradycardia due to its α2-adrenergic activity, studies have shown that these effects are generally minimal at lower doses (2.5 to 5 μg). Also, **Qi *et al.*** [21], displayed that insignificant changes in HR or MAP were observed among cases receiving intrathecal dexmedetomidine, further supporting the safety of this drug in spinal anesthesia. Our study found similar results, with insignificant differences in HR or MAP between the groups, suggesting that the dose of 2.5 μg of dexmedetomidine used in combination with morphine and levobupivacaine is safe and does not induce significant hemodynamic changes during both the intraoperative and postoperative periods.

Interestingly, studies using higher doses of intrathecal dexmedetomidine (5 μg or more) have demonstrated even faster onset times and longer duration of motor and sensory blocks [24]. While higher doses may provide more rapid analgesia, our study's use of a lower dose (2.5 μg) provides important insights into how lower doses of dexmedetomidine can still deliver efficient analgesia, while minimizing the potential for adverse effects, which include excessive sedation or bradycardia. This finding is particularly relevant for clinical practice, where the safety profile of spinal anesthetics is a priority. The fact that even lower doses of dexmedetomidine result in substantial analgesic benefits, as evidenced by the significantly prolonged analgesia and delayed time to first analgesic need, indicates that dexmedetomidine's effects are dose-dependent.

The combination of intrathecal dexmedetomidine with morphine and local anesthetics appears to produce an additive or synergistic action, which enhances the overall analgesic experience. The mechanisms of action behind this synergism are multifactorial, with dexmedetomidine inhibiting nociceptive neurotransmission via α2-adrenergic receptors in the spinal cord, while morphine and local anesthetics like levobupivacaine exert their analgesic effects through opioid and sodium channel blockade, respectively [13]. Our study supports this, demonstrating that the combination of dexmedetomidine with morphine and levobupivacaine results in prolonged analgesia, reduced need for rescue analgesics, and a longer duration of motor block. This synergistic interaction between the drugs is consistent with other study that have shown improved analgesic outcomes when dexmedetomidine is added to morphine and local anesthetics, particularly in the context of spinal anesthesia [26].

In our study, pruritus was the only adverse effect with a significant difference between groups, being more common in morphine group compared to dexmedetomidine and combination group. This aligns with previous study, which have reported a higher incidence of itching with intrathecal morphine [22]. The absence of pruritus in the dexmedetomidine and combination groups may be secondary to the lack of opioid-related adverse events. Insignificant differences were observed in other adverse effects, comprising PONV, hypotension, or bradycardia. This came in disagreement with preceding studies, which showed insignificant hemodynamic changes with dexmedetomidine [12,17].

The study's small sample size limits its broader application, and much research with longer follow-up is needed to evaluate the long-term effects on pain and opioid consumption. Much research has to be conducted with a special focus on determining the optimum dexmedetomidine dose and exploring its combination with other analgesics across various patient populations.

CONCLUSION

Our study shows that adding five μg of IT dexmedetomidine to 200 μg morphine and levobupivacaine provides enhanced postoperative analgesia compared to morphine alone. This combination significantly prolonged sensory and motor block duration and delayed the time to first analgesic request, without affecting hemodynamic stability. Hence, we suggest that intrathecal dexmedetomidine can be an efficient and safer option for postoperative pain management, potentially reducing opioid consumption.

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