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Article

The Efficacy of Intrathecal Dexmedetomidine vs. Fentanyl on Post-Operative Pain: A Retrospective Study

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Abstract: *Background and aims:* For many surgical procedures, spinal anesthesia is a reliable and efficient anesthetic approach. Numerous drugs have been reported to be administered to intrathecal local anesthetics as adjuvants to increase the efficacy of spinal anesthesia. There is little evidence of the effect of intrathecal dexmedetomidine on pain scores and the consumption of analgesia postoperatively. *Methods:* After obtaining ethical approval, demographical and clinical data of patients who underwent surgical procedures under spinal anesthesia with intrathecal dexmedetomidine or fentanyl was collected and analyzed. *Results:* In this study with 96 patients, intrathecal dexmedetomidine (group D) resulted in significantly lower post-operative pain scores compared to intrathecal fentanyl (group F) ($p=0.000$). Across various surgical types, including Orthopedic, General, Urology, and Obs/Gyne procedures, group D consistently displayed reduced pain scores ($p<0.001$). The number of patients who needed post-operative analgesia was significantly higher in group (F) than in group (D) (40 vs 23, $p=0.002$). *Conclusion:* Compared to fentanyl, intrathecal dexmedetomidine as an adjuvant to local anesthesia was found to lower post-operative pain scores and decrease the need for post-operative analgesia.

Keywords: dexmedetomidine; fentanyl; spinal anesthesia; post-operative pain; VAS score

1. Introduction

Spinal anesthesia is a safe and effective technique of anesthesia for various surgeries with the benefits of a quick onset of action, affordability, and ease of administration, as well as a low rate of side effects and a brief stay in the post-anesthesia care unit [1,2]. On the other hand, these benefits can be outweighed by the short duration of action and a higher chance of delay in motor power recovery associated with some drugs used in spinal anesthesia which can result in delaying ambulation and lengthening hospital stay [3,4]. It has been found that numerous medications can be added to intrathecal local anesthetics as adjuvants to boost the effectiveness of spinal anesthesia [5]. These medications include α_2 adrenergic agonists (clonidine and dexmedetomidine), opioids

(morphine, sufentanil, and fentanyl), neostigmine, magnesium sulfate, midazolam, and ketamine [5]. Some of these adjuvant medications such as clonidine and opioids have negative side effects including pruritus, micturition problems, bradycardia, sedation, hypotension, and respiratory depression. Fentanyl, one of the most widely used neuraxial opioids, has a faster onset and lesser duration of action than morphine during intrathecal or epidural administration [6].

Dexmedetomidine is an adrenoreceptor agonist that selectively targets α_2 -receptors [7]. Dexmedetomidine exerts its analgesic effects by downregulating the α_2 -receptor-mediated nociceptive process in the brain (locus coeruleus) and the spinal cord [8–11]. Uncertainty surrounds the method by which dexmedetomidine extends the local anesthetic's sensory and motor block [12]. Directly preventing the release of pro-nociceptive transmitters such substance P and glutamate may be possible through binding to the α_2 -receptors [13]. Dexmedetomidine is superior to clonidine (α_2 adrenergic agonists) as dexmedetomidine possesses higher specificity to α_2 -receptors than clonidine [14]. The α_2/α_1 activity of dexmedetomidine is 1620:1 while the α_2/α_1 activity of clonidine is only 200:1 [14]. This improvement in specificity to α_2 -receptors makes dexmedetomidine a more potent and effective sedative and analgesic when compared to clonidine [15]. Moreover, dexmedetomidine was associated with a significant drop in the rate of adverse drug reactions including cardiovascular ones [15,16].

Many uses of dexmedetomidine have been reported including sedation of intubated patients in the Intensive Care Units (ICUs) and during surgical procedures performed under local anesthesia as well [17]. Furthermore, dexmedetomidine has been also used with local anesthetic in performing different types of nerve block procedures [18].

Several studies have measured the effect of intrathecal dexmedetomidine on the duration of the spinal sensory block [6,19,20]. Furthermore, it was found that the use of intrathecal dexmedetomidine was associated with a lower risk of experiencing nausea and vomiting, bradycardia, and hypotension during cesarian sections [21]. There is little evidence of the effect of intrathecal dexmedetomidine on pain scores and the consumption of analgesia postoperatively. One study has demonstrated that intrathecal administration of dexmedetomidine lowers post-operative pain scores and consecutively analgesic consumption [22]. Furthermore, the reduction of analgesic consumption including opioids provided by intravenous dexmedetomidine administration may result in a reduction of gastrointestinal adverse events and a decrease in the hospital stay duration [23].

The aim of this study is to provide more knowledge regarding the impact of adding intrathecal dexmedetomidine in spinal anesthesia in improving post-operative pain and reducing the need for post-operative analgesic consumption in comparison with the usually used intrathecal fentanyl.

2. Materials and Methods

Design, Setting, and Participants

This is a retrospective cohort study conducted on patients undergoing spinal anesthesia for different surgical procedures at Princess Basma Teaching Hospital, Irbid, Jordan, a teaching hospital affiliated with Yarmouk University, Irbid, Jordan between 2021 and 2022.

Clinical data collected from electronic medical records included age, sex, height, weight, American Society of Anesthesiologists (ASA) score, type of surgical procedure, duration of the procedure, medication used in anaesthesia, post-operative Visual Analogue Scale (VAS) score, and the used post-operative analgesia.

Based on five classes, the ASA score is a subjective evaluation of a patient's general health used for pre-operative assessment for patients undergoing different surgeries and anesthesia techniques [24].

Visual Analogue Scale (VAS) is a psychometric measuring tool that consists of a 10 cm line with two end points that stand for 0 (no pain) and 10 (pain as severe as it can be) created to record the characteristics of symptoms severity in patients [25].

The study population was divided into two groups based on the medications used for their spinal anesthesia. The first group (Fentanyl group) consisted of patients who received an average

dose of 10 mg Bupivacaine 5% and 25mcg Fentanyl intrathecally. The second group (Dexmedetomidine group) received an average dose of 10 mg Bupivacaine 5% and 8 mcg Dexmedetomidine intrathecally.

Patients who had allergies to bupivacaine or any anaesthetic medications, hepatic, or renal impairment, and patients with neurological or psychiatric conditions were all excluded.

This study was approved by the Institutional Review Board (IRB) of Yarmouk University, Irbid, Jordan; IRB Reference: IRB/2023/17. The IRB follows the guidelines of Good Clinical Practice (GCP) and the Declaration of Helsinki.

Statistical Analysis

Continuous variables were assessed for normality using histograms, Quantile-Quantile plots in addition to Kolmogorov–Smirnov and the Shapiro–Wilk tests. The mean with standard deviation were calculated for the normally distributed continuous variables. Median with Interquartile range (IQR) was used to describe non-normal continuous variables whereas frequencies and percentages were used to describe categorical variables.

The Man-Whitney test was used to compare means for continuous variables when the data was not normally distributed, and categorical variables were compared between the two groups using chi-square test.

All data analyses were conducted using Stata version 17 software (StataCorp. 2021. Stata: Release 17. Statistical Software. College Station, TX: StataCorp LLC.). The statistical significance was set at a 2-sided P<0.05.

3. Results

Demographics and clinical characteristics

A total of 96 patients were involved in this study. The mean age of the study population was 51.74-year-old, and the median was 55.5-year-old (Table 1). The number of males (n=48, 51.06%) involved in this study was higher than females (n=46, 48.94%). The mean BMI was 28.96 kg/m2 and the median was 27.05 kg/m2. The number of patients who were overweight (n=52, 55.32%) was higher than those who had normal BMI (n=21, 22.34%) or were obese (n=21, 22.34%). Most of patients involved in this study had ASA score of 2 (n=52, 55.32%), and 1 (n=30, 30.91%). The median duration of surgery among all study participants was 60 minutes. Of the 96 total participants, 63 patients received post-operative analgesia. Finally, the median VAS score for all patients was 3.

Table 1. Demographics and clinical characteristics of the study population.

	Total	Group (F)	Group (D)	p-value
Median Age	55.5 (66-36)	46 (61-35)	59 (67-40)	0.0395
Gender				0.004
Male	48 (51.06)	18 (36.73)	30 (66.67)	
Female	46 (48.94)	31 (63.27)	15 (33.33)	
BMI by category				0.607
Normal	21 (22.34)	9 (18.37)	12 (26.67)	
Overweight	52 (55.32)	23 (51.11)	29 (59.18)	
Obese	21 (22.34)	10 (22.22)	11 (22.45)	
ASA				0.011
1	30 (31.91)	16 (32.65)	14 (31.11)	
2	52 (55.32)	32 (65.31)	20 (44.44)	
3	10 (10.64)	9 (20)	1 (2.04)	
4	2 (2.13)	0 (0)	2 (4.44)	
Type of Surgery				

Orthopedic	24 (25)	12 (24.49)	12 (25.53)	0.906
General	24 (25)	13 (26.53)	11 (23.4)	0.906
Obs/Gyne	24 (25)	12 (24.49)	12 (25.53)	0.724
Urology	24 (25)	12 (24.49)	12 (25.53)	0.906
Median Duration of Surgery (Mins)	75 (120-55)	67.5 (120-45)	85 (120-60)	0.0943
Use of post operative analgesia	63 (67.02)	40 (81.63)	23 (51.11)	0.002
Median VAS score	3 (1-4)	4 (4-6)	1 (0-2)	0.000

The differences between dexmedetomidine and fentanyl groups

As demonstrated in (Table 1), 47 patients received intrathecal dexmedetomidine (group D) and 49 patients received intrathecal fentanyl (group F). The median age for group (D) (59-year-old) was significantly higher than group (F) (46-year-old) ($p=0.0395$). The number of males in group (D) ($n=30$, 66.67%) was higher than in group (F) ($n=18$, 36.73%). On the other hand, the number of females was higher in group (F) ($n=31$, 63.27%) when compared to group (D) ($n=15$, 33.33%). The distribution of gender was statistically significant between the two groups ($p=0.004$).

The number of patients with normal BMI in group (D) ($n=12$, 26.67%) was higher than in group (F) ($n=9$, 18.37%). Moreover, patients with overweight BMI were higher in group (D) ($n=29$, 59.18%) compared to group (F) ($n=23$, 51.11%). Likewise, the number of patients who were obese was slightly higher in group (D) ($n=11$, 22.45%) when compared to group (F) ($n=10$, 22.22%). The distribution of the BMI category was not statistically significant between the two groups ($p=0.607$).

The distribution of the ASA score between the two groups was statistically significant ($p=0.011$). Moreover, the median duration of surgeries was statistically insignificant between groups (F) and (D) ($p=0.0943$).

The effect of dexmedetomidine and fentanyl on post-operative pain scores and use of analgesia

As illustrated in (Table 1), the median VAS score was significantly higher in patients of group (F) when compared to those in group (D) (4 vs 1, $p=0.000$). In our study, we compared Visual Analog Scale (VAS) scores across various surgical procedures, categorizing the data into group (F) and group (D) as demonstrated in (Table 2). The results revealed significant differences in VAS scores for all surgical types—Orthopedic, General, Urology, and Obs/Gyne. In orthopedic surgery, group (D) exhibited a notably lower median VAS score (1.5) compared to group (F) (6.5), with a statistically significant p -value of 0.0004. Similarly, in general surgery, group (D) displayed a significantly lower VAS score (1) compared to group (F) (4), with a p -value of 0.0000. In Urology and Obs/Gyne surgeries, group (D) also demonstrated statistically lower VAS scores, 0 and 2, respectively, compared to group (F), 2.5 and 5, with p -values of 0.0001.

Table 2. VAS score comparison between types of surgery.

	Total	Control	Intervention	<i>p-value</i>
Orthopedic	4.5 (1.5-6.5)	6.5 (5-7)	1.5 (0.5-3)	0.0004
General	3 (1-4)	4 (4-4)	1 (0.5-1)	0.0000
Urology	1 (0-2.5)	2.5 (2-3.5)	0 (0)	0.0001
Obs/Gyne	4 (2-5)	5 (4-7)	2 (0-2)	0.0001

The number of patients who needed post-operative analgesia was significantly higher in group (F) ($n=40$, 81.63%) than in group (D) ($n=23$, 51.11%) ($p=0.002$). Type of analgesia needed post-operatively varied between individuals based on physicians' judgment as illustrated in (Figure 1A,B). In group (F), pethidine was the most commonly used analgesic ($n=24$) followed by morphine ($n=15$), paracetamol ($n=12$), Diclofenac Sodium ($n=8$), Dexketoprofen ($n=4$), Tramadol ($n=2$), and ketorolac

(n=1). On the other hand, in group (D), Paracetamol was the most commonly used analgesic (n=21, %), followed by Ketorolac (n=10), and pethidine (n=2).

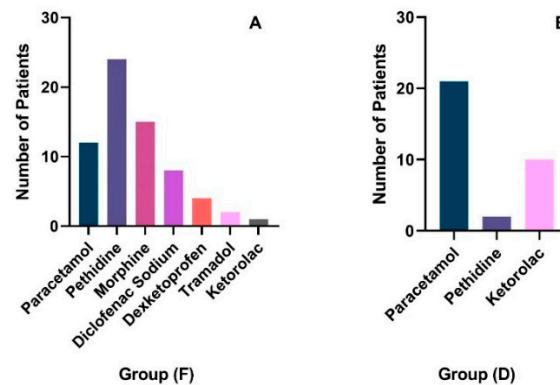


Figure 1. Medications used post-operatively in groups (F) and (D).

4. Discussion

This study involved 96 patients, with a slight male majority (51.06%). The average age was approximately 51 years, and the median Body Mass Index (BMI) was 28.96 kg/m². Most participants were overweight (55.32%) and had an ASA score of 2. The average surgery duration was 60 minutes, and 63 patients received post-operative analgesia. The median VAS score for pain was 3.

The study compared two groups: 47 patients received dexmedetomidine (Group D) and 49 received fentanyl (Group F). Group D had a higher median age (59 years) and a larger proportion of males (66.67%) compared to Group F. The distribution of BMI and ASA scores differed significantly between the groups, but the surgery duration did not.

Group D reported significantly lower VAS scores, indicating less pain, across all types of surgeries (Orthopedic, General, Urology, and Obs/Gyne) compared to Group F. The need for post-operative analgesia was also significantly lower in Group D (51.11%) than in Group F (81.63%). The types of analgesics used varied, with Paracetamol being the most common in Group D, whereas Pethidine was more common in Group F.

In different studies, Dexmedetomidine demonstrated analgesic effects belonging to α_2 -receptors binding activity when it was initially used in the clinical settings in the Intensive Care Unit (ICU) as a short-term intravenous sedative medication [26]. Moreover, the application of dexmedetomidine as a systemic analgesic adjuvant has been examined, mostly in the acute perioperative context [27–29]. Despite that the half-life elimination time of systemic dexmedetomidine was short (2–3 hours), its analgesic effect was noticed to last for 24 hours [28,29]. This extended analgesic-sparing impact was related to dexmedetomidine's sedative, anxiolytic, and thymoanaleptic characteristics. Furthermore, it was found that systematic dexmedetomidine extended the duration of action of local anesthesia's sensory block during peripheral nerve block and spinal anesthesia [30,31]. To sum up everything that has been stated so far, it is clearly observed that systematic dexmedetomidine is an effective sedative and analgesic that can be used during various procedures (under general or local anesthesia).

Coombs and colleagues were the first to notice the analgesic characteristics of intrathecal α_2 -receptors agonists [32]. Several researchers found that spinal α_2 -receptors agonists exert analgesic effects by decreasing the secretion of substance P and C-fiber transmitters [33–35]. Furthermore, hyperpolarization of post-synaptic neurons of the dorsal horn of the spinal cord may play a role in the effect of these medications [33–35]. The analgesic effect of these medications was noticed to be directly correlated with the binding affinity to α_2 -receptors in the spinal cord [36]. After that, several studies have investigated the effect of spinal administration of dexmedetomidine (high binding affinity to α_2 -receptors) in upper abdominal and thoracic surgeries [22,37,38].

This was a retrospective cohort study designed to compare the effect of spinal dexmedetomidine and bupivacaine vs fentanyl and bupivacaine on postoperative pain scores and analgesic need. We have found that despite the significantly higher age in patients who received intrathecal dexmedetomidine,

postoperative pain scores and need of analgesia were significantly lower compared to those who received intrathecal fentanyl. This study compared the Visual Analog Scale (VAS) scores across various surgical procedures. The findings of the present study collectively suggest that dexmedetomidine significantly improved post-operative pain management across various surgical specialties, highlighting its effectiveness in reducing patients' pain levels.

In one study investigated the effect of intravenous vs spinal dexmedetomidine in knee arthroscopy, it was found that intrathecal dexmedetomidine significantly prolonged the duration of action of spinal chloro-procaine when the surgery lasted more than 40 minutes compared to intravenous dexmedetomidine [19].

Recently, a systematic review and meta-analysis was conducted to compare spinal dexmedetomidine and fentanyl as adjuvants to local anesthesia [6]. From 9 studies, a total of 639 patients were included in this systematic review. This meta-analysis showed that patients who received intrathecal dexmedetomidine had a significantly longer duration of sensory block and motor block. Also, those patients had a significantly longer duration of pain-free periods.

Liu et al conducted a trial to evaluate the effect of spinal dexmedetomidine and morphine on daily morphine consumption in patients with cancer [39]. All patients entered two phases of the trial (phase M and phase D+M). In phase M, intrathecal morphine was administered, while in phase M+D, intrathecal morphine and dexmedetomidine were administered. A monitoring period of 7-day duration was done for all patients in each phase. Half of the patients were in phase M and the other half were in phase M+D for one week, then patients in both phases were cross-overed. Both phases showed a considerable reduction in pain frequency and intensity compared to baseline. Moreover, the intrathecal morphine and dexmedetomidine phase show a marked reduction in daily consumption of morphine and bolus injections compare to the intrathecal morphine phase.

In a recent randomized clinical trial conducted by Li et al, the analgesic effect of intrathecal dexmedetomidine (5 µg) or sufentanil (5 µg) vs normal saline (0.9%) was compared [40]. All patients received epidural ropivacaine (0.1%) and sufentanil (0.2 µg/mL). It was found that the analgesia was significantly higher in patients who received spinal dexmedetomidine or sufentanil when compared to those who received normal saline.

This study was strengthened by the fact that it compared intrathecal dexmedetomidine compared to fentanyl (opioid analgesic) instead of normal saline. One of the limitations is that data regarding the side effects of patients in both groups was incomplete or missing so we could compare the effect of dexmedetomidine on the incidence of adverse effects.

5. Conclusions

This study was designed to compare the effect of intrathecal dexmedetomidine vs fentanyl as adjuvant to bupivacaine on post-operative pain scores and analgesic need. Patients who received intrathecal dexmedetomidine had significantly lower the post-operative pain scores and analgesic need compared to those who received intrathecal fentanyl.

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