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Effect of Intrathecal Fentanyl and Dexmedetomidine On Rebound Pain following Orthopedic Surgery: A prospective Randomized Comparative Study

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ABSTRACT

Background: Rebound pain is a clinically significant newly emerged term that describes acute postsurgical pain occurring after regional anesthesia sensory block regression. Different strategies are adopted to decrease its incidence and severity including the use of intrathecal local anesthetic adjuvants.

Aim of the Work: This study aimed to investigate how adding dexmedetomidine or fentanyl to the local anesthesia (LA) would affect rebound pain following open orthopedic lower limb procedures that are carried out under subarachnoid block.

Patients and Methods: This randomized prospective comparative study involved one hundred-twenty participants scheduled to lower limb orthopedic surgeries under subarachnoid block. According to the intrathecal bupivacaine adjuvant; patients were divided into two equal groups [n = 60 each]: fentanyl group & dexmedetomidine [DEX] group. The severity [rebound pain score [RPS]] and incidence of rebound pain, pain numerical rating scale [NRS], time to the first i.v. meperidine demand, total post-operative 24 hours' meperidine consumption, and adverse events were observed and recorded..

Results: A significantly lower RPS [P = 0.009], a lesser incidence of rebound pain [P = 00.19], a lower NRS scores [P = 0.01], a longer time to the first i.v., meperidine demand [P = 0.002], and a lower total post-operative 24 hours' meperidine consumption [P = 0.005], were observed in the DEX group patients' than those in the fentanyl group. Intra-operative bradycardia occurred more frequently in the DEX group [P =0.031].

Conclusion: Intrathecal dexmedetomidine decreased the severity and incidence of rebound pain, prolonged the time to the first rescue analgesic use, decreased the post-operative 24 hours' meperidine consumption, and was associated with more patients' satisfaction than intrathecal fentanyl in patients subjected to open lower limb orthopedic surgeries.

Keywords: Rebound Pain; Intrathecal Dexmedetomidine; Intrathecal Fentanyl; Spinal Anesthesia; Orthopedic Surgery.

INTRODUCTION

Orthopedic operations rank among the most painful surgical interventions [1]. Lower limb orthopedic surgeries are commonly performed under spinal anesthesia that can provide a reliable, easy, fast, and low-cost block with early postoperative analgesia, reduced opioid consumption, and enhanced recovery [2,3].

Despite these advantages, rebound pain that was reported after fading of the locoregional blocks, after either spinal [4] or single- shot peripheral nerve blocks [5], may reduce or even abolish these analgesic benefits [3].

Rebound pain is a transient acute pain that is characterized by a score ≥ 7 points, of burning or dull nature, and manifesting at rest or during physical activity during the first 12 to 24 h after the worn-off regional anesthesia sensory block [6].

It is a recently recognized common phenomenon and represents the primary cause of patients' low levels of satisfaction with postoperative analgesia [7-9].

Rebound pain has been studied in many trials after peripheral nerve blocks and was documented to occur in an astounding 50% of cases [7,8]. However, a literature search could identify only one study on rebound pain following neuraxial block [4].

In view of the reported high incidence following peripheral nerve blocks and, by extrapolation, a high incidence of rebound pain after neuraxial block is expected.

Multimodal approaches, e.g., preemptive opioids, using intra-articular or intravenous steroidal and nonsteroidal anti-inflammatory drugs before the block wears off, adding local anesthetic [LA] adjuvants to extend the duration of analgesia, and using continuous blocks [as opposed to single- shot blocks], may be used to minimize the incidence of rebound pain [3].

Fentanyl is regarded as the preferred adjuvant for intrathecal LA due to its strength, rapid onset, and reduced likelihood of respiratory depression [10, 11].

Shim SM and others [4] had examined the impact of intrathecal fentanyl on rebound pain in anorectal surgeries and concluded that it has decreased the incidence of rebound pain.

Intrathecal DEX, a selective α2-receptor agonist, exerts antinociceptive benefits as it can prolong the sensory block duration and the time to the first analgesic demand after spinal anesthesia [12].

Many studies had established the analgesic superiority of intrathecal DEX compared to fentanyl as an LA adjuvant [13-15]. So, we hypothesized that intrathecal DEX would reduce the severity and incidence of rebound pain following orthopedic lower limb surgeries more than fentanyl.

To the best of our awareness, there have never been trials that studied the efficacy of intrathecal DEX on postoperative rebound pain, either alone or in comparison to other LA adjuvants.

This research aimed to investigate how adding dexmedetomidine or fentanyl to the LA would affect rebound pain following open orthopedic lower limb procedures that are carried out under subarachnoid block.

PATIENTS AND METHODS

Patients and study population: One hundred and twenty patients subjected to open lower limb orthopedic operations under subarachnoid block were included in the current study.

Ethical considerations: The current prospective randomized double- blinded trial was conducted at Mansoura University hospital during the period from November 2023 to April 2024 following approval of the Institutional Research Board [IRB] of Mansoura Faculty of Medicine [On: 15.08.2022, no.: MS.22.06.2050]. A Pan-African clinical trial registration of the trial's protocol was accomplished on October 18, 2023, with the distinct no. [PACTR202310515862483.]. A written consent was obtained from every patient before being enrolled in the study.

Patients' Criteria:

Inclusion Criteria: Patients of both sexes, 18-65 years, of the American Society of Anesthesiologists [ASA] physical status I-II, subjected to open lower limb orthopedic operations under subarachnoid block, were included in the current study.

Exclusion Criteria: Patients who refused participation, those with allergies to the research drugs, decompensated liver, kidney, or lung disease, any contraindication to spinal anesthesia (e.g., coagulation disorders, elevated intracranial tension, or local skin infection), a history of drug abuse, and patients who received narcotics within at least the last two weeks were excluded.

Randomization and Blindness: A computer-program distributed all participants randomly into two equivalent groups according to random number codes generated and sealed opaque envelopes. Fentanyl group [n =60] and dexmedetomidine [DEX] group [n = 60 each]. The intrathecal bupivacaine adjuvant was masked to both the patients and perioperative care provider. A prefilled 1 mL identical syringe was prepared by a separate nurse anesthetist not participating in the study, who handed it over to the anesthetist who conducted the spinal anesthesia procedure. This syringe contained an equal volume of either fentanyl or dexmedetomidine diluted to 0.5 mL in distilled water.

Methods:

Preoperatively, patients were instructed on how to rate their postoperative pain using the numerical rating scale [NRS], an 11-point numerical scale with 0 denoting no pain and 10 denoting the worst pain ever.

Standard monitoring [electrocardiography (ECG), non-invasive blood pressure (NIBP), and pulse oximetry] were applied, and basal readings were recorded. After that, a co-load Ringer's acetate solution [10 mL/kg] I.V. infusion was started. Subarachnoid block was achieved in the sitting position using aseptic technique at the L2-L4 interspaces via the midline approach using 25- gauge Quincke spinal needle. On observing the cerebrospinal fluid [CSF] freely flowing, intrathecal 15 mg of hyperbaric bupivacaine 0.5% and an adjuvant [20µg fentanyl and 5µg dexmedetomidine in the fentanyl and the DEX group, respectively] were sequentially administered.

The highest sensory level was evaluated using pinprick, and the motor block level was assessed by the Bromage score: I: neither feet nor knees could be moved, II: only feet could be moved, III: only knees could be moved and, IV: knees and feet could be fully flexed.

Up on achieving a sensory level of at least the tenth thoracic dermatome [T10], surgery was allowed to start, and its type and duration were recorded. Failure to attain a sensory level of T10 after ten minutes was considered an unsuccessful block, and patients were excluded and managed as appropriate.

The heart rate [HR] and the mean arterial blood pressure [MAP] were recorded every 5 minutes throughout the first 20 minutes and then every 10 minutes throughout the whole operation , and the incidence of bradycardia [HR was less than 50 beats/minute] and hypotension [MAP decreased by more than 20% from the basal reading] was recorded and managed by I.V. fluid bolus of 250 ml crystalloid solution and incremental doses of I.V. ephedrine 6 mg. Bradycardia was managed by I.V. atropine [0.02 mg/kg]. The occurrence of nausea and/or vomiting and pruritus at any time, intraoperatively or until 24 hours postoperatively, was recorded and managed by I.V. injection of 4 mg ondansetron and 10 mg chlorphenamine maleate for nausea & vomiting and pruritus, respectively.

By the end of the operation, participants were moved to the recovery room under standard monitoring. Assessment of spinal anesthesia sensorial and motor blockade wearing off and duration was recorded.

A standard postoperative analgesic protocol, I.V. paracetamol infusion/8 h and ketorolac tromethamine 30 mg/12 h, was adopted for all patients and was started by the end of the operation.

Resting and dynamic [hip flexion] pain was measured by the NRS at the following time points: 2, 4, 6, 12, and 24 hours postoperatively.

Patients having a NRS from ≥ 4, at any time point after wearing off the spinal anesthesia until 24 h postoperatively, were managed by administration of I.V. meperidine 20 mg, and the time to first I.V. meperidine request and cumulative consumption of I.V. meperidine during the first postoperative 24 hours were recorded. The incidence of rebound pain was measured by a change from mild pain [NRS pain score < 3] when the block was last measured to be working [measured in the recovery room] to severe pain [NRS pain score >7] within 24 h after spinal anesthesia wearing off. Rebound pain score [RPS] was measured using the following formula [16]**:** RPS=HNRS [24] – LoNRS [recovery room]

where: - HNRS [24] is the highest NRS pain score reported in the first 24 hours after wearing off of the spinal anesthesia block. LoNRS [recovery room] is the lowest NRS score in the recovery room. Rebound pain score was taken as a measure of the severity of rebound pain.

Adverse events, such as nausea and or vomiting, pruritus, sedation, bradycardia, and respiratory depression, were noticed, recorded, and managed if any.

A 4-point scale was used to assess sedation level at the 2nd, 4th, 6th, 12th, and 24th postoperative hours**.** 0 = awake and alert, 1 = minimally sedated, responds to speech, 2 = moderately sedated, arousable by tactile stimulation, 3 = deeply sedated, arousable only by painful stimulation.

The patients' satisfaction with the postoperative analgesia was assessed once, at the 24th postoperative hour, through a five-point scale. 1: very unsatisfied, 2: unsatisfied, 3: fair, 4: satisfied, 5: very satisfied.

Sample Size Calculation: Calculating the sample size was accomplished using G*Power software [3.1.9.2], relying on the results from a pilot study that included ten patients in each group taking the rebound pain score [RPS] as the primary outcome. The resultant mean ± SD of the RPS was 7.8 ± 1.133 and 6.9 ± 1.883 for the fentanyl and DEX groups, respectively. 55 participants for each group were needed to achieve 85% power with a type 1 [α] error [0.05] using a two-sided two-sample t-test. A total final sample size of 120 patients was required after adding 10% participants to account for the potential dropouts.

Statistical Analysis: Data were analyzed with SPSS version 20 [IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp]. The Kolmogorov-Smirnov test was used to test the normality of continuous data. Data with normal distribution were presented as mean ± standard deviation and tested with the student's t test. The Mann-Whitney U test was chosen to test the non-normally

distributed data that were presented as median [range]. Testing of the categorical data was achieved using the chi-square test or Fisher exact test. The latter were presented as number [percentage]. A P-value of < 0.05 represents statistical significance.

RESULTS

One hundred and fifty patients were screened for eligibility: among them, five declined participation, and another twenty-five didn't meet the inclusion criteria. So, 30 screened patients were excluded from the current study. The remaining one hundred and twenty patients constituted our two study groups [Figure 1]. Demographics and intraoperative parameters were comparable among the study groups [Table 1].

The highest Numerical Rating Scale [NRS] score, rebound pain score [RPS], and incidence were all higher with the fentanyl group compared to the DEX group [P = 0.01, 0.009, & P = 0.1, respectively] [Table 2]. A significantly longer time to the first i.v. meperidine demand was observed in the dexmedetomidine group in comparison to the fentanyl one [P = 0.002]. A total post-operative 24 hours' significantly lower meperidine consumption was recorded in the dexmedetomidine group than in the fentanyl group [P=0.005] [Table 2].

Regarding the complications, intraoperative bradycardia was the only significant adverse event that had occurred more frequently in the DEX group [P = 0.031]. Others, such as nausea, vomiting, pruritus, respiratory depression, and sedation, showed clinically insignificant differences among both groups [Table 3]. Patients in the DEX group had significantly higher analgesia satisfaction scores compared to those in the fentanyl group [P=0.02] [Table 3].

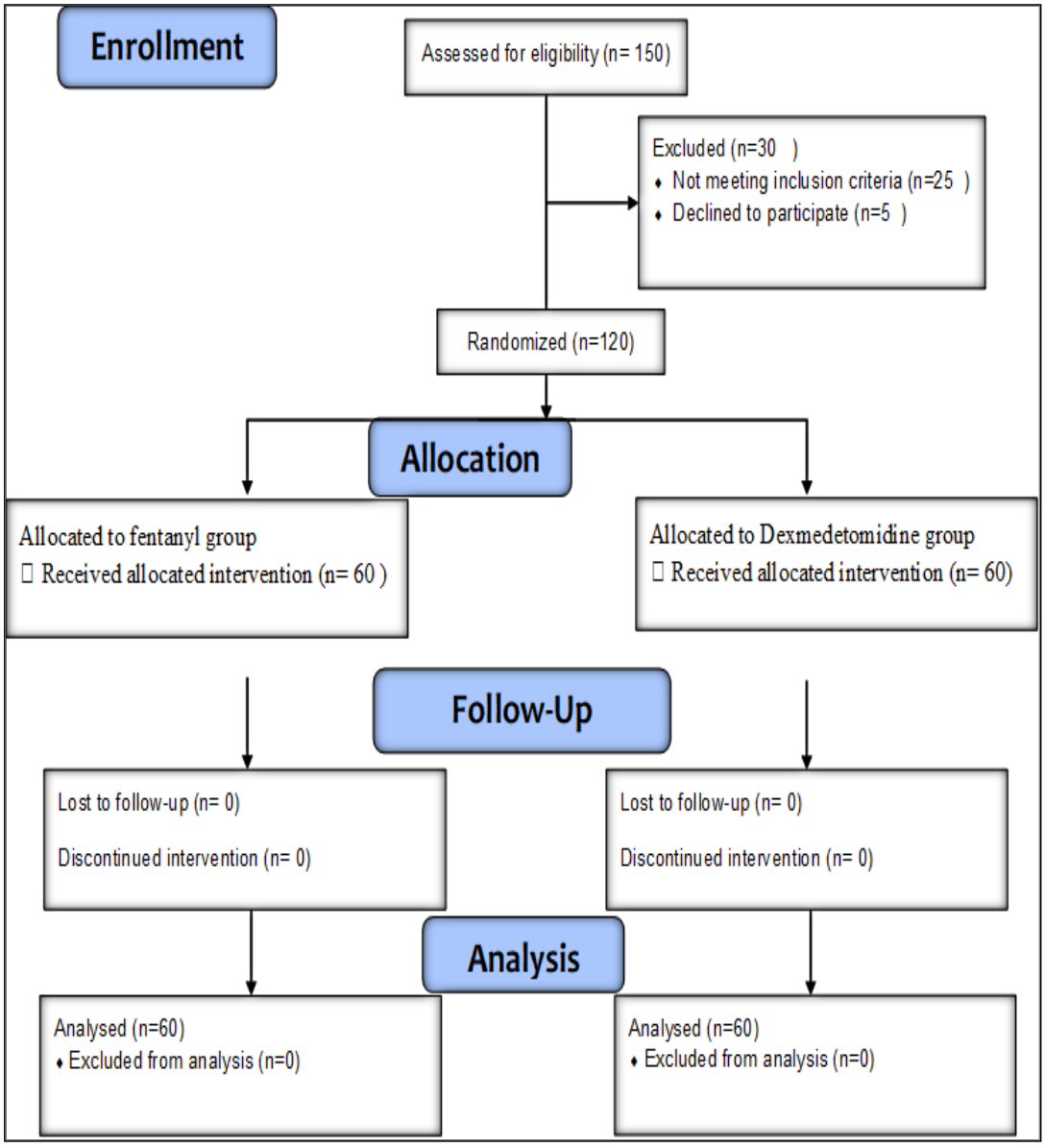

Figure [1]: Study consort flow chart.

Table (1). Patients 'demographics, surgical, and block characteristics

		Fentanyl group [n=60]	DEX group [n=60]	p value
Age [years]		42.42 ± 15.183	40.97 ± 14.806	P = 0.597
Sex	**Male**	29 [48.3%]	32 [53.3%]	
	Female	31 [51.7%]	28 [46.7%]	P = 0.585
ASA	**I**	19 [31.7%]	16 [26.7%]	
	II	41 [68.3%]	44 [73.3%]	P = 0.549
BMI [kg/m^2]		29.70 ± 5.96	27.64 ±5.64	P = 0.054
Type of surgery	**THA**	31 [51. 6%]	29 [48.33%]	p= 0.711
	TKA	19 [30%]	20 [33.3%]	
	HTO	10 [16.6%]	11 [18.3%]	
Duration of surgery[min]		82.20 ± 16.68	84.32 ± 25.72	p= 0.594
Upper sensory level		T4 [T4-T5]	T4 [T4-T6]	p= 0.830

*Data are expressed as mean ± SD or as number and percentage [%] or median [interquartile range]. P is significant when < 0.05. ASA: American society of anesthesiologist. BMI: Body mass index. THA: total hip arthroplasty. TKA: total knee arthroplasty. High tibial osteotomy. T: Thoracic dermatome.

Table (2): The lowest and highest NRS, rebound pain score and incidence, and postoperative time to the first demand and total 24 hours' consumption of meperidine

	Fentanyl group [n = 60]	DEX group [n = 60]	p value
Lowest NRS	0 [0-0]	0 [0-0]	p= 0.594
Highest NRS	8 [6-8]	6 [5-7.5]	p= 0.009*
Rebound pain score [RPS]	8 [6-8]	6 [5-7]	p = 0.007*
Rebound pain incidence	31 [51.7%]	14 [23.3%]	p= 0.001*
Time to first request[min]	181.42 ± 65.12	404.00 ± 63.41	p=0.000*
Cumulative meperidine [mg]	60 [30- 80]	30 [20- 60]	p=0.013*

NRS: Numerical rating scale. Lowest NRS: in the recovery room and highest NRS: during the first 24 hours postoperative.
Data are expressed as median [interquartile range], percentage [%] of patients, or as mean ± SD. P is significant when < 0.05

Table (3): Perioperative complications and patients' satisfaction score

		Fentanyl group [n=60]	DEX group [n=60]	p value
Perioperative complications	**Bradycardia**	9 [15%]	22 [36.7%]	**0.007***
	Nausea & vomiting	5 [8.3%]	4 [6.7%]	0.730
	Pruritis	0 [0%]	0 [0%]	-
	Respiratory depression	0 [0%]	0 [0%]	-
Sedation score	**0**	60[100%]	58 [96.6%]	0.156
	1	0 [0%]	2 [3.3%]	
	2	0 [0%]	0 [0%]	
	3	0 [0%]	0 [0%]	
Satisfaction score	**1**	9 [15%]	6 [10%]	**0.003***
	2	19 [31.7. %]	8 [13.3%]	
	3	8 [13.3%]	4 [6.7%]	
	4	11 [18.3%]	17 [28.3%]	
	5	13 [21.7%]	25 [41.7%]	

*Data are expressed as number and percentages [%] and median [interquartile range]. P is significant when < 0.05.

DISCUSSION

This study has demonstrated that, in comparison with fentanyl, the use of intrathecal dexmedetomidine as a LA adjunct reduced the severity [evidenced by a lower rebound pain score] and incidence of rebound pain and was associated with a longer time till the first call for rescue analgesic, lower 24 postoperative hours' consumption of meperidine, and higher satisfaction scores in patients who were subjected to lower limb orthopedic surgeries under subarachnoid block. However, the group receiving dexmedetomidine experienced intraoperative bradycardia more frequently.

As far as we are aware, this study is unique and may be the first to compare the efficacy of intrathecal fentanyl and DEX on the severity and incidence of rebound pain after subarachnoid block.

Rebound pain is a condition that has recently come to be understood as being significant by patients, anesthetists, and surgeons. Given the high prevalence of rebound pain, it is worthwhile to focus on the preventive or modifying strategies.

A recent bibliometric analysis encouraged research on the perioperative management and results of subjects with fractures[17].

The precise mechanism of rebound pain is not yet clear. Nociceptor activation by surgery leads to the release of inflammatory factors and cytokines.

Regional anesthesia with LA can suppress this. So, one potential mechanism of rebound pain is that the degradation of the LA and termination of the regional blockade can lead to a burst of these mediators and unmasking of that response to the surgery, giving rise to such pain [18]. Therefore, using LA adjuvants that prolong its analgesic effects is a proposed strategy to reduce such pain.

Dexmedetomidine exerts its analgesic effects through different mechanisms. It acts on the α-2 adrenergic receptor located in the locus ceruleus area in the spinal cord posterior horn, inhibiting nociceptive neurotransmission [19], and on the presynaptic membrane, inhibiting norepinephrine release, inducing hyperpolarization, and inhibiting pain signaling to the brain [20]. In addition, it also stimulates spinal interneurons to release acetylcholine that increases synthesis and release of nitric oxide [21]. Recent trials, in accordance with ours, indicated that DEX augmented the analgesic effects, extended analgesia duration, and retarded the rebound pain [22,23].

The current trial has some **limitations: First**, it lacks a control group. However, fentanyl is the most commonly used intrathecal LA adjuvant that has been routinely used for years[10,11]. So, the fentanyl group could be considered as a control group. **Second,** using a dose of 5μg of DEX despite the different studies favoring the analgesic effects of 10μg over that dose. In spite of that, others had used the same dose of DEX with proven analgesic efficacy compared to fentanyl [24,25]. **Third,** we acknowledge that RASS score is a commonly used validated one to assess sedation; however, we have adopted the one in this manuscript for its simplicity.

Recommendations: It is highly recommended to do further study including a control group using intrathecal bupivacaine only. In addition, to use different doses of intrathecal DEX to get the optimal safe dose having the maximal preventive effect on rebound pain occurrence.

Conclusion: Intrathecal dexmedetomidine decreased the severity and incidence of rebound pain, prolonged the time to the first rescue analgesic use, decreased the postoperative 24 hours' meperidine consumption, and was associated with more patients' satisfaction than intrathecal fentanyl in patients subjected to open lower limb orthopaedic surgeries.

Conflict of interest: None

Financial disclosure:

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Authors' contributions

- **Samah Elkenany**; Shared in designing the study, searched the literature, analyzed and interpreted the data, prepared and wrote the manuscript.
- **Moaaz Elsaeed:** shared in study design, ccollected data and shared in revision of first draft and final manuscript.
- **Nabile Abdelmaged**: Developed the study concept, shared in designing the study, supervised the whole work, revise the final manuscript.
- **May Hafez**: Designed the study, searched the literature, helped in writing the manuscript and revision.

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