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Dexmedetomidine vs hyaluronidase addition to fluoroscopy-guided caudal analgesia with steroid in lumbosacral spine surgery. A comparative double blinded study

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ABSTRACT

Background: Caudal analgesia is a safe technique that can be performed under fluoroscopy in lumbosacral spine surgeries. Studies have raised evidence supporting the use of epidural dexamethasone in such surgeries. Adding second adjuvant like dexmedetomidine or hyaluronidase to dexamethazone has not been investigated before.

Methods: Sixty patients scheduled for lumbosacral spine surgery were randomized and allocated in 3 groups. All patients received 30ml of caudal mixture after insertion of caudal catheter.

Group A received 0.125% bupivacaine with 8 mg dexamethasone.

Group B received 50 µg dexmedetomidine in addition to the mixture given to group A.

Group C received 1500 IU hyaluronidase in addition to the mixture given to group A.

Results: Mean time to the first analgesic dose in group B was 589.5 min and in group C was 565.5 min, which is longer than mean time in group A (492 min), $p = 0.021$. Number of patients who needed intraoperative top-up doses of fentanyl was 5 (25%) in group B and 10 (50%) in group C versus 13 (65%) in group A, $p = 0.038$. Total pethidine dose in 24 hours was 50.75 ± 10 mg in group B and 55.25 ± 8 mg in group C versus 64.25 ± 22 mg in group A, $p = 0.021$. Post hoc analysis and pairwise comparisons were conducted to determine which intervention groups had significant differences.

Conclusion: Dexmedetomidine and hyaluronidase addition to caudal bupivacaine and dexamethasone increased duration of analgesia after lumbosacral spine surgery, but dexmedetomidine was superior to hyaluronidase.

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Hundreds of thousands of patients are having spine surgeries every year [1,2]. These surgeries produce severe postoperative pain, leading to negative effects on patients' recovery. Preemptive analgesia for such surgeries can be implemented to provide perioperative effective pain control and prevent central nervous system plasticity [3].

Acute pain after spine surgery is usually controlled by intravenous opioids. Utilizing a combination of different analgesic modalities achieves better pain relief, spares opioids and decreases their side adverse effects. Caudal epidural can be incorporated as a part of multimodal analgesia for lumbosacral spine surgeries [4]. It is a simple and safe technique that can be easily performed under fluoroscopy in prone position. Injection site is far away from the operative site, which decreases the risk of CSF leakage or infection [4,5].

However, the analgesic effect of single-shot caudal block can last only for short time even with long acting local anesthetics [6]. Adding nonopioid adjuvants like steroid (dexamethasone, betamethasone), alpha-2 agonists (clonidine, dexmedetomidine) or hyaluronidase improves both quality and duration of analgesia [7].

Dexamethasone has specific anti-inflammatory effect in spine surgeries. Thus, it helps acute postoperative pain relief. Moreover, dexamethasone decreases the incidence of postsurgical chronic pain syndrome, decreases epidural fibrosis and prevents tissue scarring [8].

Dexmedetomidine is a sympatholytic selective α2 agonist. Alpha-2 receptors are found in postsynaptic dorsal horn neurons. Activation of these receptors has an analgesic effect mediated by depressing neurotransmitters of C fibers [9].

Hyaluronidase increases tissue permeability and improves other drug delivery to nerve roots, leading to more effective analgesia in chronic low back pain and post-laminectomy syndrome [10].

Combination of mentioned adjuvants may produce synergetic or additive effect. Furthermore, this technique might be a part of postoperative opioid sparing strategies after lumbosacral spine surgeries.

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1. Objective

We investigated the effect of adding dexmedetomidine or hyaluronidase to caudal mixture of bupivacaine and dexamethasone on the time to first analgesic dose after lumbosacral spine surgeries.

2. Methodology

This study was a randomized prospective double-blinded comparative study. It was performed at Ain Shams University Hospitals after approval of the research ethical committee FMASU R15/2020 and registration in Clinical trials.gov; NCT04411329. The study was reported according to the Consolidating Standards of Reporting Trials (CONSORT) 2010 Statement [11].

After obtaining an informed consent, patients included in the study were 18–65 years old, classified as ASA I and II, scheduled for lumbar spine surgery through posterior approach from L2- S1 with or without instrumentation. Exclusion criteria were patients with traumatic lumbar surgery, multiple level fixation, complicated spinal canal stenosis, revision surgery, patients with allergy to local anesthetics or to any drug used in the study and patients with coagulation abnormalities.

Time to the first rescue analgesia was recorded as our primary outcome. Total postoperative pethidine dose in 24 hours and visual analogue scale (VAS) score in the first 24 hours were the secondary outcomes. VAS was explained to the patients during the preoperative visit. VAS is a 10 cm line with zero at one end indicating no pain and 10 cm at the other end indicating the worst imaginable pain.

Standard monitors were applied before anesthesia induction. Wide bore venous access was inserted. Patients received 2 mg/kg propofol, 1 µg/kg fentanyl and 0.6 mg/kg rocuronium bromide. Anesthesia was maintained with rocuronium bromide 0.15 mg/kg increments and sevoflurane 2%–2.5% as clinically judged. Also, granisetron 1 mg and pantoprazole 40 mg was given intravenously.

Patients were placed in the prone position. After proper sterilization, lateral view of the sacral canal was identified by fluoroscopy. An 18-gauge Tuohy-type needle was inserted in the sacral hiatus. After negative aspiration, 2 ml of contrast (Omnipaque 240; GE Healthcare, Little Chalfont, UK) was injected to ensure accurate positioning of the needle (Figure 1(a)). C arm was rotated to show Christmas tree appearance in the antero-posterior view (Figure 1(b)). A catheter was inserted through the needle into the epidural space and advanced for 4 cm. After negative aspiration, 20 ml of the investigated mixture was injected. The epidural catheter was secured to the skin and skin incision started 30 minutes after injection The anesthetist and the surgeon were blinded to the type of mixture used. The injected solutions were prepared by an anesthetist not involved in the study. Another 10 ml of the same mixture was injected at the end of surgery as a top up dose before removing the catheter.

Sixty patients were enrolled in the study from June 2020 to May 2021. They were allocated randomly by a sealed envelope technique after computer-generated randomization into three groups (A, B and C).

Group A (dexamethasone group): patients received 0.125% bupivacaine with 8 mg dexamethasone.

Group B (dexamethasone + dexmedetomidine): patients had 50 µg dexmedetomidine added to the mixture given to group A.

Group C (dexamethasone + hyaluronidase): patients had 1500 IU hyaluronidase added to the mixture given to group A.

During the operation, adjustment of sevoflurane concentration and fentanyl incremental doses (0.5 µg/kg) was given according to hemodynamic measurements. Inadequate analgesia was defined as an increase in blood pressure and heart rate more than 20% from baseline at skin incision.

If heart rate decreased to 45 beats/min, atropine sulfate 0.01 mg/kg was given intravenously. In case of decrease in blood pressure greater than 20% from

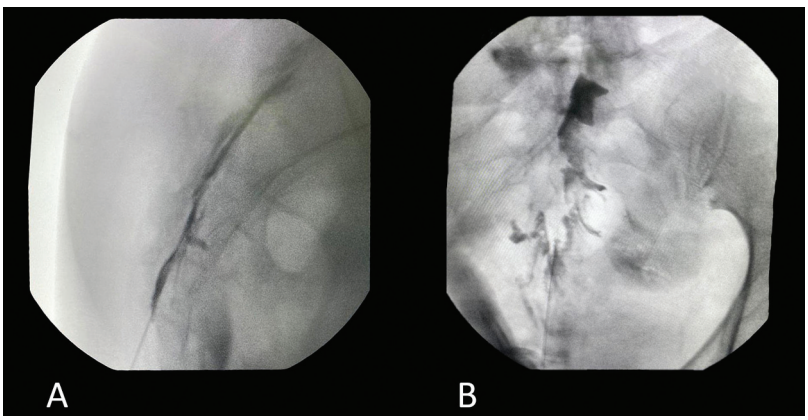

Figure 1. (a) Caudal epidural injection of dye to confirm the position of the tip of needle (lateral view). (b) Antero-posterior view showing christmas tree appearance.

baseline, patient was infused by 500 ml ringer lactate, and if blood pressure was not responding, administration of increments of 3 mg ephedrine was given intravenously.

Patients received 1 gm acetaminophen and 8 mg lornoxicam intravenously during the surgery. Acetaminophen was continued every 8 hours and lornoxicam was given every 12 hours postoperatively. Rescue analgesia was in the form of intravenous pethidine 0.5 mg/kg given if VAS was >3.

Intraoperative hemodynamic parameters were recorded by observer not included in the study at baseline (before caudal injection) then intraoperatively every 15 minutes. Need for intraoperative top-up doses of fentanyl was documented. VAS score was recorded at patient's full recovery (0 h) and then every 2 hours for 12 hours then every 6 hours till 24 hours by acute pain service team.

Time to first analgesic request and the total dose of postoperative pethidine in the first 24 hours was also documented. Side effects and complications were reported.

2.1. Sample size

We calculated the sample size based on the results of the study of Hasan et al [12]. This study showed that the mean time for the first rescue analgesia was about 3 hours more when dexmedetomidine was added to dexamethasone as a combination of adjuvants with bupivacaine in comparison to dexamethasone or dexmedetomidine alone in pediatric patients undergoing hypospadias repair. Accordingly, we calculated that the minimum proper sample size was 12 patients in each group to be able to reject the null hypothesis with 80% power at $\alpha = 0.05$ level using one-way analysis of variance test. Sample size calculation was done using G*Power software version 3.1.2 for MS Windows, Franz Faul, Kiel University, Germany. We intended to recruit at least 20 per group to account for random errors and dropped out patients.

3. Statistical analysis

The data were collected, revised, coded and entered to the Statistical Package for Social Science (Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, New York: IBM Corporation). Qualitative variables were presented as number and percentages and compared between groups using Chi-square test, while quantitative data were presented as mean and standard deviations and compared between the three groups using one-way ANOVA test followed by post hoc analysis using LSD test, while nonparametric data were presented as median with interquartile range and compared between the three groups using Kruskal-Wallis test followed by post hoc analysis using Mann-Whitney test. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the p value was considered significant at the level of <0.05.

Kaplan-Meier survival analysis was conducted to compare for the time to the first analgesic dose in the three different intervention groups, and a log rank test was conducted to determine if there were significant differences in the time-to-event outcome (first analgesic dose) for the 3 types of intervention. Pairwise log rank comparisons were conducted to determine which intervention groups had different time-to-event distributions. A Bonferroni correction was made with statistical significance accepted at a p value <0.0167.

4. Results

Initially, 70 patients were recruited to participate in this study. During the enrollment stage, 5 patients were excluded; 3 of them refused to participate and 2 patients did not meet our inclusion criteria. Then 5 more patients were excluded during the allocation and follow-up stages due to different reasons either lost to follow-up, occurrence of dural tear, failure to insert the needle or thread the catheter or intraoperative blood loss >1000 ml. Finally, 60 patients completed the study protocol divided equally among the 3 groups. Figure 2 represents the flow diagram showing patients' progress through the study.

Table 1 shows that there were no significant differences in patient characteristics between the 3 groups. The intraoperative hemodynamics were also comparable between the 3 groups except for the heart rate as patients in group B had lower values, as shown in Table 2. There were significant differences between the 3 groups regarding the number of patients who needed intraoperative incremental doses of fentanyl, and the total pethidine dose in the first 24 hours after surgery as shown in Table 2.

Table 3 shows the post hoc analysis and pairwise comparisons between groups. Bonferroni correction showed no significant difference between the 3 groups regarding need for intraoperative fentanyl in spite of the difference detected by Chi-square test. Further study with larger sample size is required to investigate this particular point.

Table 4 represents the VAS score, which revealed significant differences between the 3 groups at the immediate postoperative time and then at 2, 4, 6 and 8 hours.

Kaplan-Meier survival analysis was conducted to compare for the time to the first analgesic dose in the three different intervention groups (Figure 3). Patients in group A had a mean time to the first analgesic dose of 492 ± 24.06 min (mean ±SE), which is shorter than those for groups B and C. The mean

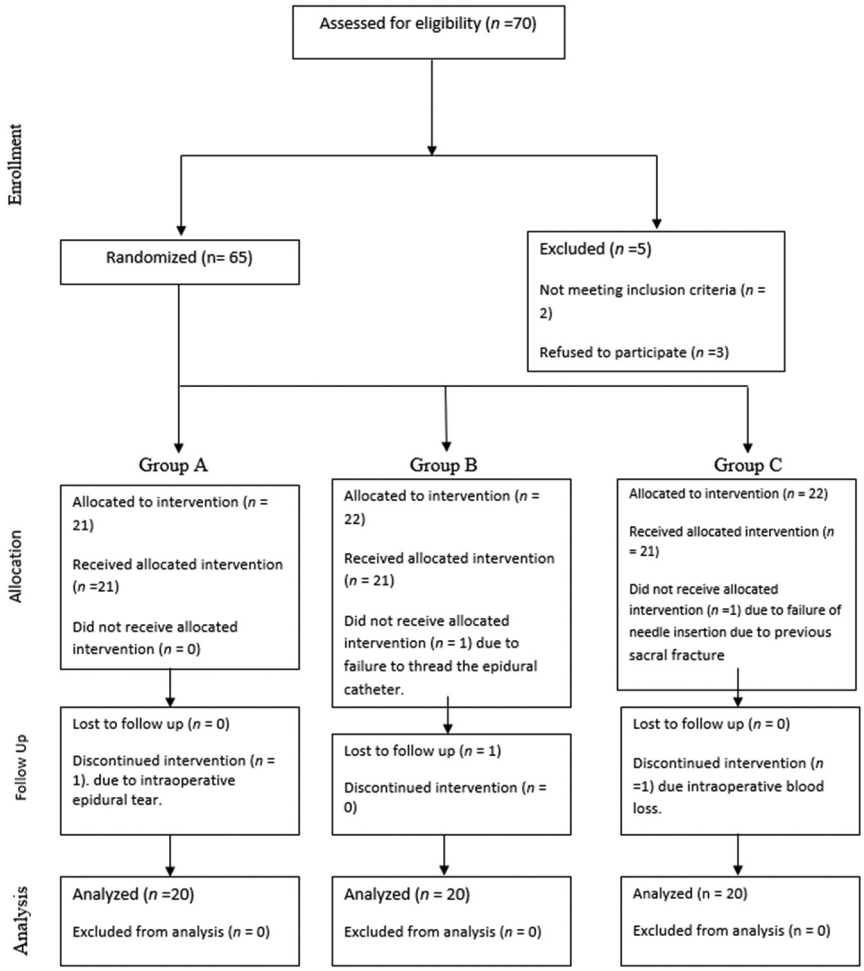

Figure 2. Flow consort chart.

Table 1. Demographic data of the patients and duration of surgery in the 3 groups.

Variable		Group A N = 20	Group B N = 20	Group C N = 20	*p* value
Sex	Females	7 (35%)	8 (40%)	6 (30%)	0.803*
	Males	13 (65%)	12 (60%)	14 (70%)	
Age (years)	Mean±SD	51.3 ± 10.74	52.8 ± 10.13	50.8 ± 10.13	0.817°
Weight (kg)	Mean±SD	81.65 ± 10.40	81.7 ± 10.21	84.05 ± 10.25	0.703°
Height (cm)	Mean±SD	170.3 ± 6.49	170.81 ± 7.28	170.55 ± 6.75	0.974°
ASA I	Number (%)	10 (50%)	12 (60%)	11 (55%)	0.810*
ASAII		10 (50%)	8 (40%)	9 (45%	
Duration of surgery (min)	Mean±SD	121.54 ± 33.17	121.94 ± 36.97	124.35 ± 30.48	0.966°

*p*value >0.05: Nonsignificant, *p*value <0.05: Significant t, °One-Way ANOVA test,*Chi-square test.

Table 2. Intraoperative haemodynamic parameters, need of intraoperative fentanyl and total dose of pethidine in 24 hours in the 3 groups.

Variable		Group A = 20	Group B N = 20	Group C N = 20	*p*- value
Mean blood pressure baseline (mmHg)	Mean±SD	95.20 ± 8.68	95.45 ± 8.38	95.15 ± 9.28	0.993°
Mean blood pressure intraoperative (mmHg)	Mean±SD	79.75 ± 6.61	76.55 ± 8.31	81.15 ± 6.45	0.125°
Hear rate base line (beat/min)	Mean±SD	82.02 ± 5.08	80.10 ± 7.34	82.40 ± 6.10	0.466°
Heart rate intraoperative (beat/min)	Mean±SD	75.95 ± 6.49	73.81 ± 4.68	79.85 ± 7.86	0.017°
Need for intraoperative fentanyl (number of patients)	frequency	13 (65%)	5(25%)	10(50%)	0.038*
Total postoperative dose of pethidine in 24 hours (mg)	Mean±SD	64.25 ± 22	50.75 ± 10	55.25 ± 8.	0.021°

p value >0.05: Nonsignificant, *p* value <0.05: Significant, °One-Way ANOVA test, *Chi-square test.

Table 3. Post hoc analysis.

Post hoc analysis			
	Group A vs B	Group A vs C	Group B vs C
Heart rate (beat/min)	0.003	0.06	0.005
Number of patients who needed increments of Intraoperative fentanyl (no %)	0.025	0.523	0.191
Analgesic dose of pethidine in the first 24 hours (mg)	0.006	0.064	0.349
First rescue analgesic time (min)	0.011	0.06	0.547

A Bonferroni correction was made with statistical significance accepted at a p value<0.0167.

Table 4. Comparison between the 3 groups regarding the VAS score at the different times of assessment.

		Group A N = 20	Group B N = 20	Group C N = 20	p value*
VAS score at 0	Median (range)	0 (0–2)	0 (0–0)	0 (0–1)	0.07
VAS score at 2	Median (range)	1 (0–2)	0 (0–1)	0 (0–2)	0.015
VAS score at 4	Median (range)	2 (1–4)	0 (0–2)	1 (0–3)	0.010
VAS score at 6	Median (range)	2 (1–4)	1 (1–2)	2 (1–6)	0.015
VAS score at 8	Median (range)	2 (1–5)	1 (1–3)	2 (1–6)	0.026
VAS score at 10	Median (range)	3 (1–6)	3 (1–5)	3 (2–6)	0.122
VAS score at 12	Median (range)	3 (2–6)	3 (2–5)	4 (2–5)	0.549
VAS score at 18	Median (range)	3 (1–6)	2 (1–4)	3 (2–6)	0.058
VAS score at 24	Median (range)	4 (2–7)	4 (2–7)	4 (1–7)	0.393

p value >0.05: Nonsignificant, p value <0.05: Significant, *Kruskal-Wallis test.

time to the first analgesic dose in groups B and C were 589.5 ± 27.96 and 565.5 ± 31.48 min, respectively (Table 5 and 6).

A pairwise log rank test was conducted to determine if there were differences in the distributions for the 3 types of intervention as shown in the table [6].

Table 5. The mean times in minutes for the first analgesic dose in the 3 groups and their confidence intervals.

	Mean			
			95% confidence interval	
Intervention	Estimate	Std. error	Lower bound	Upper bound
Group A	492	24.06	444.8	539.2
Group B	589.5	27.96	534.7	644.3
Group C	565.5	31.48	503.8	627.2
Overall	549	16.78	516.1	581.8

Results showed that there was a statistically significant difference between group B and group A, $p = 0.027$. However, the difference between C and A ($p = 0.098$) was statistically insignificant.

No significant differences were observed in the incidences of vomiting, nausea and pruritus among the three groups. In our study, only one patient in group B had bradycardia, which was treated with atropine 0.7 mg.

5. Discussion

To our knowledge, this is the first study that investigates the role of combining dexmedetomidine or hyaluronidase with caudal steroid (dexamethasone) for prolonging the effect of bupivacaine after lumbosacral spine surgeries.

Patients undergoing spine surgeries experience moderate to severe postoperative pain. Preventive analgesia is a recent concept, which includes preemptive, intraoperative and postoperative pain control [4]. Preventive analgesia can be achieved by combining regional anaesthesia with other analgesic modalities. Preemptive analgesia decreases the incidence of development of central sensitization due to prolonged triggering of peripheral pain receptors. Central sensitization leads to permanent pain perception, even after cessation of the painful stimulus [4].

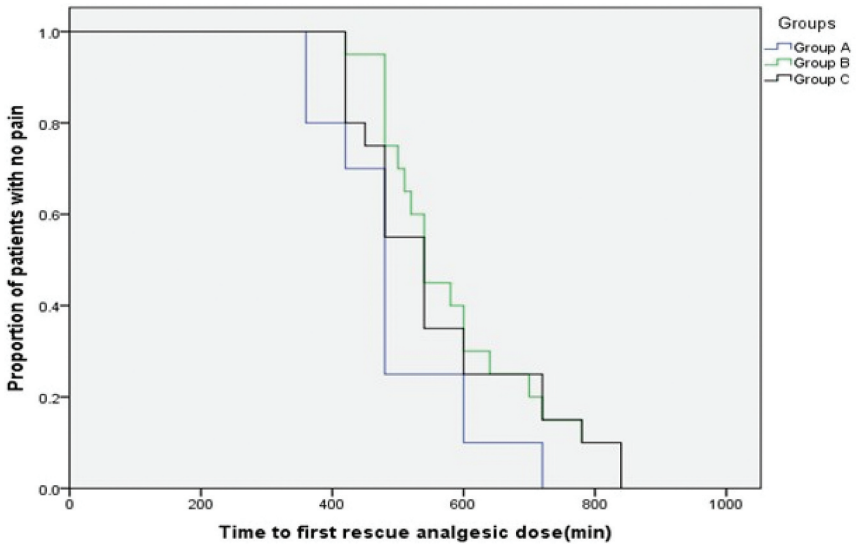

Figure 3. Kaplan-Meier survival plot representing the time of first analgesic dose in the three groups.

Table 6. Log rank test of time to first analgesic dose in minutes.

	Overall comparison		Pairwise comparisons						
	Chi-Square	*p* value	Intervention	Group A		Group B		Group C	
				Chi-square	*p* value	Chi-square	*p* value.	Chi-square	*p* value
Log Rank test	7.72	0.021	Group A			4.9	0.027	2.7	0.098
			Group B	4.9	0.027			0.114	0.736
			Group C	2.7	0.098	0.114	0.736		

p value >0.05: Nonsignificant, *p* value <0.05: Significant.

Caudal analgesia is one of the regional blocks that can be applied easily in spine surgeries. The presence of patients in the prone position before skin incision and the availability of C arm in the operating room increases the success rate of caudal injection under fluoroscopy in such patients. We thought that inserting caudal catheter in spine surgery is better than inserting an epidural catheter to be away from the site of surgery. Also, injecting a second dose at the end of the surgery rather than the loading dose before surgery might be more effective as the presence of blood in the epidural space might interfere with the action of injected drugs. Furthermore, the presence of a suction drain might cause inadequate retention of the drugs in the epidural space.

Dexamethasone is a nonopioid adjuvant that has been widely used during spine operations through the last 20 years. Therefore, dexamethasone through various routes, intravenous, epidural or topical, became a consistent part of our anesthetic protocol for spine surgeries. Our clinical practice is supported by the strong evidence inferred from many studies. Previous systematic reviews and meta-analyses confirmed that epidural steroids produce good short-term pain relief and shorten hospital stay after lumbar spine surgeries [13–15].

In addition, Kalappa et al advocated that mixing 8 mg dexamethasone with caudal ropivacaine improved quality of analgesia after lumbosacral spine surgeries without increase of blood sugar or delayed wound healing [16]. So we chose group A in the present study to be an active treatment control group in which 8 mg dexamethasone was mixed with low-dose bupivacaine.

Pain-relieving effect of epidural dexmedetomidine as a sole adjuvant has been searched in different surgeries: orthopedic, abdominal and spine surgeries [17–20]. A study done in our university hospitals in 2019 by Alansary et al [21] showed that addition of 50 µg dexmedetomidine to epidural bupivacaine provided better postoperative pain control than addition of 50 µg fentanyl in lumbar disc operations.

As mentioned, studies demonstrated that dexamethasone and dexmedetomidine can prolong duration of epidural analgesia after spine surgeries when used as sole agents [16,20]. The mechanism by which each drug increase the duration of local anesthetics is not completely known but different actions of these drugs have been documented. However, the effect of mixing both drugs has not been investigated.

In our study, dexmedetomidine was added to dexamethasone in group B. Patients reported lower VAS score than group A at 0, 2, 4, 6, 8 hours. Furthermore, time of first rescue analgesia was significantly prolonged in group B (589.5 min) in comparison to group A (492 min) who received dexamethasone only. Our results go with the results of Hassan et al's study [12]. Authors compared the effect of combined dexamethasone (0.1 mg/kg) and dexmedetomidine (1 µg/kg) to the effect of each drug as a sole agent in pediatric patients undergoing hypospadias surgery. The authors concluded that the combination of both adjuvants remarkably prolonged the duration of analgesia. Similar results were found in the study of Zhang et al, as mixing dexamethasone and dexmedetomidine significantly prolonged the time to first rescue analgesia after intercostal nerve block for thoracoscopic pneumonectomy [22].

Postoperative pain severity VAS score in the present study revealed significant differences between the 3 groups at the immediate postoperative time, and then at 2, 4, 6 and 8 hours, our results are in line with the previous studies [12,22].

Using dexmedetomidine in group B decreased the heart rate significantly in comparison to group A and C, but the mean blood pressure did not show significant difference between the groups. Haemodynamic parameters in the 3 groups were within accepted clinical ranges. Only one patient in group B had bradycardia, which was treated with 0.7 mg atropine. This can be explained by low dose of dexmedetomidine used in the study. Effect of higher doses of dexmedetomidine needs further studies.

In the present study, the need of intraoperative fentanyl was less in group B. Moreover, the total dose of pethidine in the first 24 hours significantly decreased in group B (50.75 ± 10 mg) in comparison to group A (64.25 ± 22 mg). Similar results were found in the study of Zhang [22], which showed that total postoperative fentanyl consumption was significantly lower in combined dexamethasone and dexmedetomidine group (106.0 ± 84.0 µg) compared with dexamethasone group (243.0 ± 175.2 µg) or dexmedetomidine group (237.0 ± 98.7 µg).

Hyaluronidase is effective as an adjuvant to local anesthesia in different regional blocks such as supraclavicular and peribulbar blocks. Hyaluronidase increases tissue permeability and facilitates other drug delivery to nerve roots [10]. Studies have confirmed the positive analgesic effect of epidural addition of hyaluronidase to steroids in the management of chronic pain due to central spinal stenosis, nerve root radiculopathy or failed back syndrome The presence of epidural septa or adhesions may eliminate the continuity of this space. Fibrosis might occur in the absence of previous back surgery due to aging, previous epidural catheter insertion or repeated aseptic inflammation after disc rupture [23–25]. However, the effect of adding hyaluronidase to epidural steroids on the early acute postoperative pain after spine surgery has not been investigated yet.

We hypothesized that addition of hyaluronidase to dexamethasone (group C) can augment dexamethasone delivery to nerve roots and result in longer postoperative analgesia. Although the difference was statistically insignificant, the mean time to first rescue analgesic dose in group C was longer by 73.5 min than in group A. Also the number of patients in group C who needed intraoperative fentanyl was less than those in group A. In addition, total postoperative pethidine consumption was lower in comparison to group A. However, the difference regarding fentanyl and pethidine requirements did not reach a significant level. Further study with larger sample size is recommended.

6. Conclusion

In this study, we demonstrated that dexmedetomidine was superior to hyaluronidase when added to dexamethasone as dual adjuvant combination to caudal bupivacaine for prolongation of postoperative analgesia time.

7. Limitation

(1) Postoperative sedation was not accessed despite being one of the common side effects of dexmedetomidine.
(2) Time of first mobilization was not studied as neurosurgeons had different protocols in this regards.
(3) Long-term effects of hyaluronidase and dexamethasone mixture in the prevention of post-surgical chronic back pain due to fibrosis was not done.

Authors' contributions

SW provided the idea of the research, did the analysis and interpretation of the data and drafted the manuscript. MA contributed to the acquisition of data and data interpretation and revised the manuscript. WN provided the acquisition of data and analysis of data and drafted the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

Please contact corresponding author for data requests.

Disclosure statement

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

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Ethics approval and consent to participate

The study was approved by the ethical committee of the Ain Shams University (file reference no FMASU R15/2020). A written consent for all patients was taken.

Trial registration

At ClinicalTrials.gov: NCT04411329

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