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Dexamethasone as a bupivacaine adjuvant for ultrasound-guided interscalene brachial plexus block: a prospective randomized study

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Abstract

Background: Finding adjuvants to local anesthetic used in interscalene block that could efficiently extend the analgesia duration has recently been the focus of researchers. The aim of the work was to determine whether the addition of perineural dexamethasone to bupivacaine in-ultrasound guided interscalene block would prolong the duration of sensory analgesia in patients undergoing shoulder surgery.

Results: This prospective, randomized, double-blinded study comprised 50 patients. They were randomly subdivided into 2 groups: group C [control] and group D [dexamethasone]. We noted a significant difference regarding the timing for the first rescue analgesia being shorter in group C than in group D with a *P* value < 0.001. Regarding postoperative analgesia, higher Ketolac consumption was noticed in group C than in group D. Patients from both groups showed excellent analgesic effects with VAS score less than 2 points up to 6 h postoperative then patients in group C had a higher VAS score compared to group D, and the difference was statistically significant (*P* value < 0.05). We also noticed an increase in the heart rate and mean arterial blood pressure in group C than in group D at 12 h and 24 h postoperatively.

Conclusion: We concluded that the addition of 8 mg of perineural dexamethasone to 30 ml of 0.5% bupivacaine showed improvement in the postoperative analgesia in shoulder surgery without obvious complications.

Keywords: Bupivacaine, Interscalene block, Perineural dexamethasone, Ultrasound-guided regional anesthesia

Background

Inadequate management of postoperative pain remains a major problem after many surgeries. Optimal postoperative pain management demands a thorough understanding of the pain pathophysiology, invasiveness of the surgical procedure, and patient factors associated with increased pain, such as anxiety and depression. The use of multimodal perioperative pain management provides a rational basis for enhanced postoperative pain control, decreased adverse effects, and improved patient satisfaction **(Lovich-Sapola et al.** 2015**)**.

In particular, handling postoperative pain after shoulder surgery remains a challenge to both anesthesiologists and orthopedic surgeons. In an attempt to improve analgesia, interscalene brachial plexus block can be used either as an adjunct to general anesthesia or as the primary anesthetic (Chun et al. 2016).

Several drugs have been studied as adjuvants for regional anesthesia such as epinephrine, clonidine, opioids, and ketamine. They have been evaluated for their effects on anesthesia and analgesia, but the results have conflicted

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depending on the drug used and the choice of local anesthetic (Vieira et al. 2010).

Because of the limited efficacy or questionable toxicity of the previously studied drugs, some investigators evaluated glucocorticoids as adjuvants for regional anesthesia. Known for their anti-inflammatory, analgesic, immunosuppressive, and antiemetic properties, they exert their action by inhibiting phospholipase A_2, in addition to changes in cell function induced by glucocorticoid receptor activation. Furthermore, the literature suggests that a single perioperative dose of glucocorticoid is safe (Albrecht et al. 2015).

Whether dexamethasone would prolong regional anesthesia is a subject of much discussion. Steroids induce a degree of vasoconstriction, acting like epinephrine by decreasing local anesthetic absorption. Another hypothesis is that dexamethasone may act locally on nociceptive C-fibers to increase the activity of inhibitory potassium channels, thus decreasing their activity (Chun et al. 2016).

In this study, we have hypothesized that perineural dexamethasone added to bupivacaine in ultrasound-guided interscalene brachial plexus block would prolong the duration of sensory analgesia and delay the need for postoperative rescue analgesia.

Methods

All procedures performed in this study involving human participants were in accordance with the Ethical Standards of the Institutional Research Committee, and with the 1964 Helsinki Declaration and its later amendments, as well as comparable ethical standards. The work was approved by the Ethics Committee of the University Hospital (code number: FMASU M D 82/ 2018), and it was carried out at the Orthopedics Department from April 2018 to March 2020. Written informed consent was sought and obtained from all participants.

The study included grade I and grade II patients according to the American Society of Anesthesiology Physical Status Classification System (ASA-PS) of either sex from 18 to 65 years of age, with a body mass index (BMI) ranging from 25 to 35, who were scheduled for shoulder surgical procedures, for which an ultrasound-guided interscalene block was planned. The exclusion criteria included patient refusal, age below 18 or above 65, pregnant and lactating women, diabetic patients, allergy to any of the used drugs, recent (less than 6 months) use of glucocorticoids for at least 2 weeks, chronic pain requiring daily use of opioid medication, and contraindications to interscalene block (included severe chronic obstructive pulmonary disease, infection, coagulopathy, contralateral diaphragmatic paralysis, neuropathy of the surgical limb).

Randomization was carried out using sequentially numbered, opaque, sealed envelopes containing computer-generated random allocations in a ratio of 1:1. Fifty patients were subdivided into 2 groups: the control group (C group) where 25 patients were given ultrasound-guided interscalene block after induction of general anesthesia with 30 ml 0.5% bupivacaine (Markyrene®; Sigmatec Pharmaceuticals Industries Co., Egypt) mixed with 2 ml 0.9% saline and the dexamethasone group (D group) where 25 patients were given ultrasound-guided interscalene block after induction of general anesthesia with 30 ml 0.5% bupivacaine mixed with 8 mg dexamethasone (2 ml) (dexamethasone sodium phosphate 8 mg/2 ml; Egyptian International Pharmaceutical Industries Co., 10th of Ramadan City, Egypt). Two patients in the C group and 3 patients in the D group had failed block and were excluded. (We considered block failed under general anesthesia in the following conditions: (1) the patient's heart rate and mean arterial blood pressure were elevated with skin incision after exclusion of other causes for tachycardia, (2) use of intravenous (IV) opioid analgesics ≥ 100 μg fentanyl after skin incision, and (3) postoperatively, the patients were moving the limb freely and no loss of sensation).

Routine preoperative anesthetic review was done for every patient including routine history taking, clinical examination, and laboratory investigations (complete blood picture, kidney function tests, liver function tests, prothrombin time partial thromboplastin time, and random blood sugar).

Patients were educated about the visual analog scale (VAS) scored from 0 to 10 (where 0 = no pain and 10 = worst imaginable pain). All the patients' body weights were recorded in their files. All patients fasted according to standard rules. On arrival to the operating room, an intravenous access was established in the contralateral upper limb to the side of surgery, and all patients were pre-medicated with 2 mg of IV midazolam.

Monitoring included electrocardiography (ECG), non-invasive blood pressure (NIBP), arterial oxygen saturation (SaO_2), and end-tidal carbon dioxide ($EtCO_2$).

The patients took general anesthesia, and the block was mainly administered for analgesia intra- and postoperatively. Anesthesia was induced with 2 μg/kg fentanyl and 2–3 mg/kg propofol. Endotracheal intubation was facilitated by 0.5 mg/kg atracurium. Anesthesia was maintained by 1–1.5 MAC isoflurane in 50% oxygen/air mixture and 0.1 mg/kg atracurium every 20 min, ventilation parameters that maintain normocapnia (CO_2 between 35 and 40 mmHg) [volume control mode, tidal volume 6–10 ml/kg, RR 12–14 b/min, peak respiratory pressure < 40 mmHg], and fluids as crystalloids used by a fluid chart for the deficit and maintenance as needed

in each operation. Atropine and ephedrine were present on the table as emergency drugs in case of bradycardia and hypotension, respectively.

All blocks were performed by attending anesthesiologists skilled in the interscalene approach. Interscalene block had been performed by the following steps: the area of injection was prepped with Betadine, and sterile technique was observed using sterile gloves, sterile ultrasound probe cover, sterile drape, cap, and face mask.

Marking external landmarks including the clavicle, interscalene groove, and lateral border of the clavicular sternocleidomastoid (SCM) muscle was done, using 50-mm-long insulated needles (*Stimuplex® A - B. Braun; Melsungen, Germany*). The ultrasound technique consisted of an "in-plane" posterior approach at the level of the cricoid cartilage; visualizing the great vessels, SCM, and scalene muscles was considered; scanning caudally, until the brachial plexus nerve roots/trunks were identified as hypoechoic structures between the anterior and middle scalene muscles. If difficult to locate, going straight to the supraclavicular approach was considered and then scanning upwards ("trace-back method"). The "stoplight sign" is a frequently cited name for the typical sonographic appearance of 3 root structures arranged vertically in the interscalene groove. The 3 structures are from cephalad to caudal: the C5 root, the C6 upper fascicle, and the C6 lower fascicle (Franco and Williams 2016). Local anesthetic was injected, and needle position readjusted to ensure appropriate spread.

Skin incision was carried out 15 min after the block was given. Vital data such as heart rate (HR), mean blood pressure (MBP), and O_2 saturation were assessed at skin incision and all through the surgery.

At the end of the surgery, a reversal of the muscle relaxant was carried out using neostigmine (0.04 mg/kg) and atropine (0.01 mg/kg). After extubation, all patients were transmitted to the post-anesthesia care unit (PACU).

Postoperative analgesia was according to our hospital's protocol; we gave an initial dose of pethidine 50 mg intravenously as the first rescue analgesia taken only once when the patient demands or when his VAS score was above or equal to 3. This was followed by Ketolac 30 mg per dose intravenously on patient demand or when the VAS score is above or equal 3 with a maximum dose of 90 mg per day.

All patients were followed up and assessed at baseline, skin incision, all through surgery, at PACU, and 1 h, 2 h, 6 h, 12 h, and 24 h postoperatively for vital signs (HR, MBP, SPO_2), blood glucose and cortisol level postoperatively; VAS score; first rescue analgesia; and total pethidine and ketorolac consumption in 24 h.

Sample size justification

The sample size was calculated using the PASS® version 11 program, setting the type 1 error (α) at 0.05 with a power of 80%. The results from a previous study (Lee et al. (Lee et al. 2016)) reported that the duration of the sensory block was extended in the dexamethasone group (715.1 ± 286.3) compared to the control group (433.2 ± 152.7) with a 281.9-min difference. Calculation based on detecting a 180-min difference between the two study groups produced a minimal sample size of 25 cases per group. Effect size equals 0.72.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using the IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. Descriptive statistics were done for quantitative data as mean ± SD (standard deviation) for quantitative normally distributed data, Median (1st–3rd IQ) for quantitative non-normally distributed data, while it was done for qualitative data as number and percentage. Inferential analyses were done for quantitative variables using the Shapiro-Wilk test for normality testing, independent t test in cases of normally distributed data, and Mann-Whitney in cases of non-normally distributed data. In qualitative data, inferential analyses for independent variables were done using the chi-square test for differences between proportions and Fisher's exact test for variables with small expected numbers. The level of significance was taken at P value < 0.050 which was significant; otherwise, it is non-significant.

Results

There was no statistical difference between the C group and the D group regarding age, sex, ASA score, and BMI. There was also no statistical difference with regard to the type and duration of surgery (Table 1). As for HR, there were highly significant statistical differences between the control (C group) and the D groups at 12 h and 24 h postoperatively with P values of 0.041 and 0.031, respectively (Fig. 1; Table 2).

As for MAP, there were highly significant statistical differences between the control C group and the D group at 12 h and 24 h postoperatively with P values of 0.025 and 0.010, respectively (Fig. 2; Table 2). Oxygen saturation showed no statistical difference between the two groups (Fig. 3; Table 2).

We noticed a highly significant statistical difference between the two groups of the study concerning the VAS scores starting at the fourth hour and remaining throughout during the sixth, twelfth, and twenty-fourth hours with P values 0.033, 0.005, and < 0.001, respectively (Table 3). Furthermore, there was a statistical

Table 1 Comparison between the C group and D group according to demographics, surgery type, and duration

Variables		Group D (*N* = 22)	Group C (*N* = 23)	*P* value
Age (years), median (1st–3rd IQ)		52.0 (42.0–61.0)	45.0 (32.0–57.0)	[d]0.375
Sex (*n* (%))	**Male**	13 (59.1%)	14 (60.9%)	[b]0.903
	Female	9 (40.9%)	9 (39.1%)	
BMI (kg/m^2), Median (1st–3rd IQ)		28.1 (27.6–29.7)	27.7 (26.0–30.9)	[d]0.447
ASA (*n* (%))	**I**	10 (45.5%)	16 (69.6%)	[b]0.102
	II	12 (54.5%)	7 (30.4%)	
Operation type (*n* (%))	**Arthroscopic rotator cuff tear repair**	9 (40.9%)	6 (26.1%)	[c]0.366
	Arthroscopic capsular release	6 (27.3%)	4 (17.4%)	
	Bankart repair for anterior shoulder dislocation	4 (18.2%)	4 (17.4%)	
	Arthroscopic subacromial decompression	3 (13.6%)	6 (26.1%)	
	AC joint dislocation stabilization	0 (0.0%)	3 (13.0%)	
Operation duration (h), mean ± SD		1.8 ± 0.4	1.7 ± 0.4	[a]0.307

[a]Independent *t* test
[b]Chi-square test
[c]Fisher's exact test
[d]Mann-Whitney test

difference between the two groups concerning the timing of the first rescue analgesia being longer in the D group (Table 3). There was no statistical difference between the total pethidine consumption in both groups, but on the other hand, higher Ketolac consumption was noticed in the control group (C group) than in the dexamethasone group (D group) that was statistically significant (Table 3). In group C, the patient's request for the pethidine dose was earlier in time than in group D, noting that the pethidine dose is a single dose that was not repeated, followed by Ketolac doses on patient request; as such, the number of Ketolac doses requested in total 24 h was more in group C than in group D.

As for blood glucose level and cortisol level as markers of metabolic stress response to surgery, we found that there was a significant increase in mean postoperative blood glucose and cortisol values in both groups compared with baseline values but with no statistical difference between the two groups (Figs. 4 and 5; Table 4).

There was no difference between the two groups concerning postoperative complications, except for nausea and vomiting that were significantly higher in the control group, when compared to the dexamethasone group (Table 5).

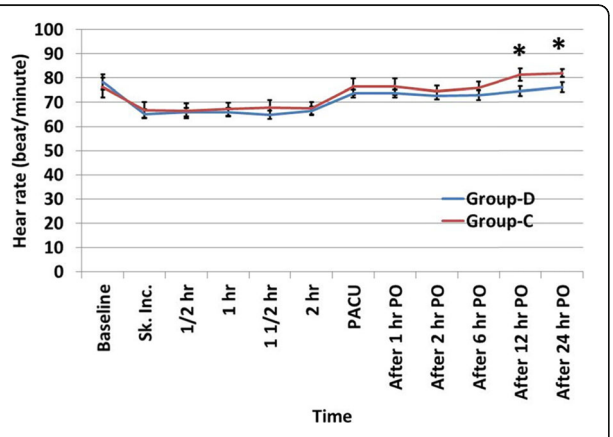

Fig. 1 Comparison between the C group and D group according to heart rate (beats/min) (*significant)

Discussion

Several drugs have been evaluated as adjuvants for single-injection regional block such as epinephrine, clonidine, opioids, ketamine, and dexmedetomidine. Because of their limited efficacy or questionable toxicity, many investigators evaluated glucocorticoids and the perineural addition of dexamethasone as an adjuvant to have become common in clinical practice **(Marhofer et al.** 2019**)**.

Dexamethasone is a synthetic corticosteroid with a known anti-inflammatory, analgesic, immunosuppressive, and antiemetic properties. The mechanism of action as an adjuvant to local anesthetics is unclear. It may produce some vasoconstriction, so that it acts like epinephrine by reducing local anesthetic absorption. Alternatively, it has been suggested that it directly affects nerve conduction along with anti-inflammatory effects. In addition, the efficacy of dexamethasone administered perineurally or systemically in combination with a local anesthetic to peripheral nerve block was recently evaluated in several trials, systematic reviews, and meta-analyses with varying results **(Pehora et al.** 2017**)**.

Our results demonstrate that perineural dexamethasone significantly prolonged the analgesic effect of plain bupivacaine when used as a single injection in

Table 2 Comparison between the C group and D group according to HR, MAP, and SpO_2

Time	Group D (*N* = 22)	Group C (*N* = 23)	*P* value	Effect of group D relative to group C	
				Mean ± SE	95% CI
Heart rate (beats/min), mean ± SD					
Baseline	78.3 ± 14.0	76.1 ± 19.4	^0.661	2.2 ± 5.1	− 8.0–12.4
Sk. Inc.	65.2 ± 8.8	66.8 ± 15.6	^0.677	− 1.6 ± 3.8	− 9.3–6.1
1/2 h	65.9 ± 8.5	66.5 ± 15.2	^0.869	− 0.6 ± 3.7	− 8.1–6.8
1 h	65.9 ± 7.8	67.2 ± 13.4	^0.703	− 1.3 ± 3.3	− 7.9–5.4
1 1/2 h	64.8 ± 8.1	67.8 ± 14.5	^0.391	− 3.1 ± 3.5	− 10.2–4.1
2 h	66.4 ± 8.3	67.5 ± 12.2	^0.724	− 1.1 ± 3.1	− 7.4–5.2
PACU	73.6 ± 7.7	76.5 ± 16.3	^0.456	− 2.9 ± 3.8	− 10.6–4.8
After 1 h PO	73.6 ± 7.7	76.5 ± 16.3	^0.456	− 2.9 ± 3.8	− 10.6–4.8
After 2 h PO	72.7 ± 7.8	74.6 ± 10.5	^0.501	− 1.9 ± 2.8	− 7.5–3.7
After 6 h PO	73.0 ± 9.7	75.8 ± 12.5	^0.403	− 2.8 ± 3.3	− 9.6–3.9
After 12 h PO	74.5 ± 9.1	91.3 ± 12.0	**^0.041***	− 6.7 ± 3.2	− 13.1–0.3
After 24 h PO	76.1 ± 9.2	82.0 ± 8.2	**^0.031***	− 5.8 ± 2.6	− 11.1–0.6
Mean blood pressure (mmHg), mean ± SD					
Baseline	102.5 ± 13.	95.1 ± 11.3	^0.053	7.4 ± 3.7	− 0.1–14.9
Sk. Inc.	88.9 ± 9.4	81.1 ± 16.3	^0.057	7.8 ± 4.0	− 0.3–15.8
1/2 h	88.9 ± 9.4	81.1 ± 16.3	^0.057	7.8 ± 4.0	− 0.3–15.8
1 h	88.9 ± 9.4	81.1 ± 16.3	^0.057	7.8 ± 4.0	− 0.3–15.8
1 1/2 h	88.9 ± 9.4	81.1 ± 16.3	^0.057	7.8 ± 4.0	− 0.3–15.8
2 h	88.9 ± 9.4	81.1 ± 16.3	^0.057	7.8 ± 4.0	− 0.3–15.8
PACU	88.9 ± 9.4	81.1 ± 16.3	^0.057	7.8 ± 4.0	− 0.3–15.8
After 1 h PO	96.5 ± 8.3	96.3 ± 9.9	^0.956	0.2 ± 2.7	− 5.3–5.6
After 2 h PO	95.9 ± 8.2	95.1 ± 8.6	^0.758	0.8 ± 2.5	− 4.3–5.8
After 6 h PO	96.3 ± 5.8	95.0 ± 8.6	^0.566	1.3 ± 2.2	− 3.2–5.7
After 12 h PO	95.9 ± 8.8	101.9 ± 8.8	**^0.025***	− 6.0 ± 2.6	− 11.3–0.8
After 24 h PO	95.6 ± 9.7	102.8 ± 8.4	**^0.010***	− 7.2 ± 2.7	− 12.7–1.8
Oxygen saturation (SpO_2%), mean ± SD					
Baseline	98.9 ± 0.9	98.8 ± 1.0	^0.766	0.1 ± 0.3	− 0.5–0.6
Sk. Inc.	99.3 ± 0.7	98.8 ± 1.0	^0.073	0.5 ± 0.3	0.0–1.0
1/2 h	99.3 ± 0.7	98.8 ± 1.0	^0.073	0.5 ± 0.3	0.0–1.0
1 h	99.3 ± 0.7	98.8 ± 1.0	^0.073	0.5 ± 0.3	0.0–1.0
1 1/2 h	99.3 ± 0.7	98.8 ± 1.0	^0.073	0.5 ± 0.3	0.0–1.0
2 h	99.3 ± 0.7	98.8 ± 1.0	^0.073	0.5 ± 0.3	0.0–1.0
PACU	99.2 ± 0.7	99.0 ± 0.9	^0.331	0.2 ± 0.2	− 0.2–0.7
After 1 h PO	99.2 ± 0.7	99.0 ± 0.9	^0.331	0.2 ± 0.2	− 0.2–0.7
After 2 h PO	99.2 ± 0.7	98.9 ± 0.9	^0.212	0.3 ± 0.2	− 0.2–0.8
After 6 h PO	99.2 ± 0.7	98.7 ± 0.9	^0.052	0.5 ± 0.2	0.0–1.0
After 12 h PO	99.2 ± 0.7	98.8 ± 0.8	^0.074	0.4 ± 0.2	0.0–0.8
After 24 h PO	99.2 ± 0.7	98.8 ± 0.8	^0.051	0.4 ± 0.2	0.0–0.9

^Independent *t* test
*Significant

interscalene block for patients undergoing shoulder surgery. They generally correlate well with other published trials, but direct comparisons are difficult because of the variety of local anesthetic mixtures used, different blocks studied, and different methods of evaluating block duration.

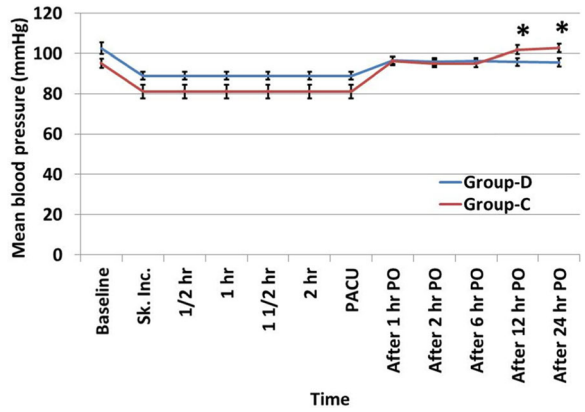

Fig. 2 Comparison between the C group and D group according to mean arterial blood pressure (*significant)

As regards hemodynamics, they were stable all through surgery and postoperatively in the two groups. We noticed an increase in the HR and MAP in the C group higher than in the D group at 12 h and 24 h postoperatively: 91.3 ± 12.0 versus 74.5 ± 9.1 beats/min at 12 h and 82.0 ± 8.2 versus 76.1 ± 9.2 beats/min at 24 h for the HR and 101.9 ± 8.8 versus 95.9 ± 8.8 at 12 h and 102.8 ± 8.4 versus 95.6 ± 9.7 at 24 h for the MAP.

Patients from both groups showed excellent analgesic effects with VAS score less than 2 points up to 6 h postoperative ($P > 0.05$). Patients in the C group had higher VAS scores [2.0 (1.0–2.0), 2.0 (2.0–3.0), 5.0 (4.0–5.0)] compared to the D group [1.0 (1.0–2.0), 2.0 (1.0–2.0), 2.0 (2.0–2.0)] at 6 h, 12 h, and 24 h, respectively [represented by median and interquartile range], and the difference was statistically significant ($P < 0.05$).

Similar to our results were those found by Jadon et al. (Jadon et al. 2015) who performed a study on 112 patients undergoing arthroscopic shoulder surgery under interscalene block. Patients in the ropivacaine group received 30 ml of 0.5% ropivacaine plus 2 ml normal saline, and the dexamethasone-ropivacaine group received 0.5% ropivacaine 30 ml plus 8 mg dexamethasone. They found that VAS scores in the first 4 h were comparable; however, VAS scores were significantly higher in the ropivacaine group at the end of 8 h, 12 h, 16 h, 20 h, and 24 h. Patients in the dexamethasone-ropivacaine group showed excellent pain control up to 24 h and had significantly lower VAS scores (2.5–3.3) compared to the ropivacaine group (4.2–5.06) ($P < 0.05$).

Also, there was a significant difference between the two groups regarding the timing for the first rescue analgesia being shorter in the C group than in the D group (11.4 ± 1.5 h versus 19.2 ± 2.4 h). As for postoperative analgesic consumption, higher Ketolac consumption was recorded in the C group than in the D group, but there was no difference in pethidine consumption between the 2 groups. Similarly, Tandoc and colleagues (Tandoc et al. 2011) evaluated 90 patients undergoing shoulder surgery using interscalene block with 0.5% bupivacaine (40 ml) and divided them into 3 groups: control patients, with no additive, and two dexamethasone groups, to whom 4 mg and 8 mg dexamethasone were added. The duration of analgesia was significantly prolonged in both dexamethasone groups (21.6 h and 25.2 h, respectively) compared with the control group (13.3 h). Postoperative analgesic consumption for the first 48 h was significantly lower in both dexamethasone groups compared to the control group

Furthermore, Cummings and co-workers (Cummings III et al. 2011) conducted a large double-blinded trial utilizing single-injection interscalene block in shoulder surgeries where 218 patients were randomly allocated to four groups: mixing 30 ml of either 0.5% ropivacaine or 0.5% bupivacaine with dexamethasone 8 mg and compared with a placebo group. They concluded that dexamethasone significantly prolonged the duration of analgesia of both ropivacaine 1.9-fold and bupivacaine 1.5-fold. The effect of dexamethasone was significantly stronger with ropivacaine than with bupivacaine.

In contrary to our study, Jæger et al. (Jæger et al. 2016), performed a paired, blinded, randomized trial, including healthy men. All subjects received bilateral blocks of the saphenous nerve with ropivacaine 0.5%, 20 ml mixed with dexamethasone 2 mg in one leg and saline in the other. They found that block duration was not statistically significantly longer in the leg receiving dexamethasone when assessed by temperature discrimination and concluded that perineural administration of dexamethasone 2 mg showed a modest and inconsistent effect of questionable nature on block duration. Their results could be attributed to the smaller dose of dexamethasone added to ropivacaine. Also, Noori and his

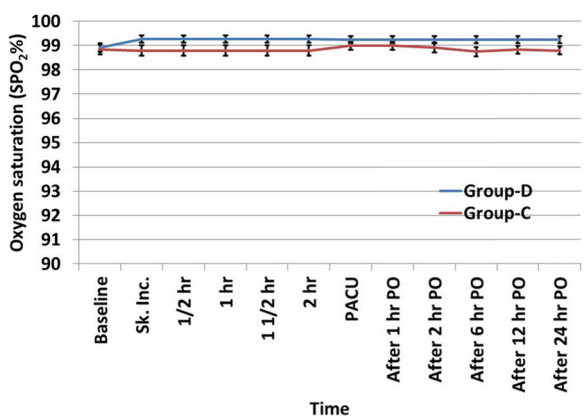

Fig. 3 Comparison between the C group and D group according to SPO_2

Table 3 Comparison between group C and group D according to VAS score and analgesia

Time	Group D (*N* = 22)	Group C (*N* = 23)	*P* value	Effect of group D relative to group C	
				Mean ± SE	95% CI
Pain perception (VAS-10), median (1st–3rd IQ)					
PACU	1.0 (1.0–2.0)	2.0 (1.0–2.0)	¤0.064	Not applicable	
After 1 h PO	1.0 (1.0–2.0)	2.0 (1.0–2.0)	¤0.064		
After 2 h PO	1.0 (1.0–2.0)	2.0 (1.0–2.0)	¤0.056		
After 6 h PO	1.0 (1.0–2.0)	2.0 (1.0–2.0)	**¤0.033***		
After 12 h PO	2.0 (1.0–2.0)	2.0 (2.0–3.0)	**¤0.005***		
After 24 h PO	2.0 (2.0–2.0)	5.0 (4.0–5.0)	**¤< 0.001***		
Analgesia					
First time (h), mean ± SD	19.2 ± 2.4	11.4 ± 1.5	**^< 0.001***	7.8 ± 0.6	6.6–9.0
Pethidine (mg), median (1st–3rd IQ)	50.0 (50.0–50.0)	50.0 (50.0–50.0)	¤0.999	Not applicable	
Ketolac (mg), median (1st–3rd IQ)	0.0 (0.0–30.0)	60.0 (60.0–60.0)	**¤< 0.001***		

*Significant
^Independent *t* test
¤Mann-Whitney test
§Fisher's exact test

colleagues **(Noori et al.** 2020), tested the addition of 8 mg dexamethasone to popliteal nerve blocks by evaluating 49 patients undergoing foot and ankle surgery, and their result was that there was no statistically significant difference in analgesia duration between the 2 groups.

On the assessment of blood glucose level and cortisol level as markers of metabolic stress response to surgery, we found that there was a significant increase in mean postoperative blood glucose and cortisol values in both groups compared with baseline values but no statistical difference between the two groups, which shows no extra effect from administering perineural dexamethasone on elevating blood glucose and cortisol level. Similarly, Chun et al. (Chun et al. 2016) analyzed 99 patients in the two groups; the first group of patients received interscalene block using ropivacaine 5 mg/ml with normal saline as a control, while in the second group, patients received interscalene block using ropivacaine 5 mg/ml with dexamethasone 5 mg. They compared the blood glucose level in both groups and found that glucose level was elevated in both groups with no significant difference between the two groups.

Despite the safety concerns surrounding the "off-label" use of perineural adjuvants, no trial has reported neurotoxicity due to dexamethasone. However, sample sizes to date are insufficient to detect rare adverse events, and the majority of the studies did not follow patients for weeks after surgery. Enormous sample sizes would be needed to prove safety with rare adverse effects. Reassuringly, though, animal studies demonstrate no long-term changes in the nerve structure or function after local steroid administration (Johansson et al. 1990). Toxicity to corticosteroids could be due to the particulate nature or vehicle used in different steroid preparations (Benzon

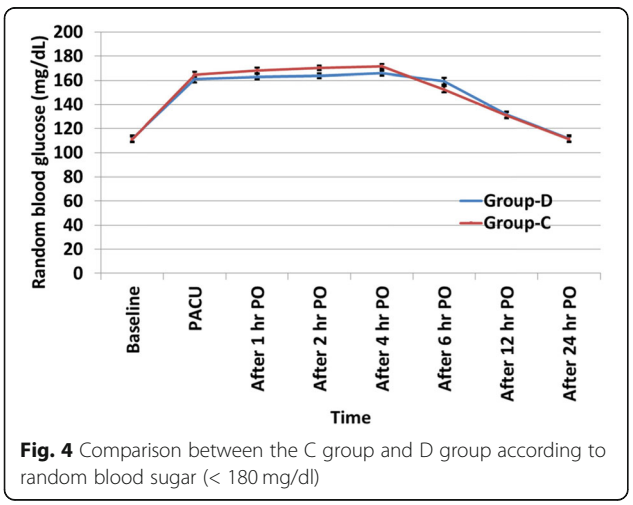

Fig. 4 Comparison between the C group and D group according to random blood sugar (< 180 mg/dl)

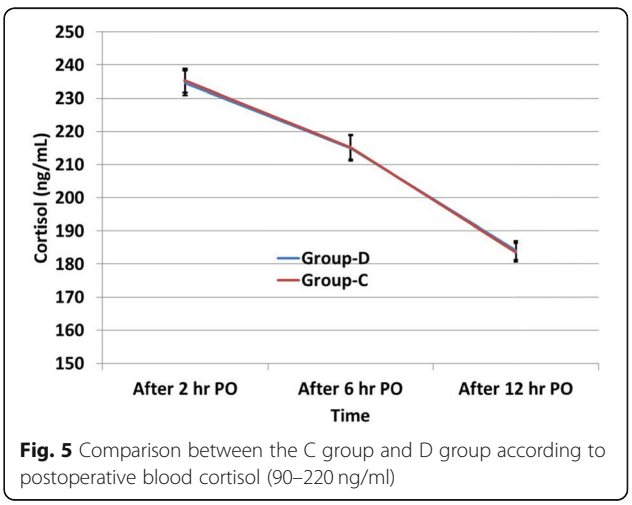

Fig. 5 Comparison between the C group and D group according to postoperative blood cortisol (90–220 ng/ml)

Table 4 Comparison between group C and group D according to RBS and cortisol level

Time	Group D (*N* = 22)	Group C (*N* = 23)	*P* value	Effect of group D relative to group C	
				Mean ± SE	95% CI
Random blood glucose (mg/dl), mean ± SD					
Baseline	111.6 ± 12.	111.1 ± 12.	^0.888	0.5 ± 3.6	− 6.7–7.7
PACU	160.9 ± 12.	164.3 ± 13.	^0.374	− 3.4 ± 3.8	− 11.2–4.3
After 1 h PO	163.0 ± 10.	168.0 ± 10.	^0.109	− 5.1 ± 3.1	− 11.4–1.2
After 2 h PO	163.6 ± 8.5	170.2 ± 8.7	^0.170	− 3.6 ± 2.6	− 8.8–1.6
After 4 h PO	165.9 ± 8.7	171.5 ± 9.6	^0.558	− 1.6 ± 2.7	− 7.1–3.9
After 6 h PO	159.3 ± 12.	152.6 ± 12.	^0.087	6.7 ± 3.8	− 1.0–14.4
After 12 h PO	131.6 ± 12.	131.1 ± 12.	^0.888	0.5 ± 3.6	− 6.7–7.7
After 24 h PO	111.6 ± 12.	111.1 ± 12.	^0.888	0.5 ± 3.6	− 6.7–7.7
Cortisol (ng/ml), mean ± SD					
After 2 h PO	234.5 ± 17.	235.2 ± 17.	^0.897	− 0.7 ± 5.2	− 11.1–9.8
After 6 h PO	215.0 ± 17.	215.2 ± 17.	^0.967	− 0.2 ± 5.3	− 10.9–10.
After 12 h PO	184.1 ± 13.	183.5 ± 13.	^0.880	0.6 ± 4.0	− 7.5–8.7

CI confidence interval
^Independent *t* test

et al. 2007), neither of which applies to the formulation of dexamethasone (dexamethasone sodium phosphate) we used. Additionally, steroids have been used safely in the epidural space for the treatment of radicular pain arising from nerve root irritation (Price et al. 2005), and dexamethasone specifically has been studied as an adjuvant to epidural local anesthetics (Khafagy et al. 2010). The neurological risk, if any, of dexamethasone thus appears to be small.

Concerning the side effects in the current study, there were no dexamethasone-specific adverse effects; however, we noticed that postoperative nausea and vomiting were more common within the C group (7 out of 23 patients), when compared to the D group (1out of 22 patients), which can be attributed to the antiemetic effect of dexamethasone on the D group. Similarly, Kim et al. (Kim et al. 2012) allocated 60 patients into three groups, and the block was done using 10 ml of 0.5% levobupivacaine with different additives: group I, 1 ml of normal saline; group II, 5 mg of dexamethasone; and group III, 1:400,000 epinephrine was added. They found that the addition of dexamethasone to levobupivacaine in interscalene block showed improvement of postoperative analgesia for arthroscopic shoulder surgery without complications such as neurological disabilities and lessened postoperative nausea and vomiting.

As regards the interscalene block side effects, Horner syndrome was the most common and was observed in 5 patients out of 23 (21.7%) in the C group and 4 patients out of 22 (18.2%) in the D group. Phrenic nerve affection in the form of diaphragmatic paresis was observed in 2 patients out of 23 (8.7%) in the C group and in 3 patients out of 22 patients (13.6%) in the D group, which was ipsilateral without breathing difficulty. There were no pneumothorax cases found.

Jadon et al. (Jadon et al. 2015) also observed Horner syndrome in 11/50 (20.5%) in the dexamethasone-

Table 5 Comparing complications in the two groups

	Group D (*N* = 22)	Group C (*N* = 23)	*P* value	Effect of group D relative to group C	
				Mean ± SE	95% CI
Complications (*n* (%))				**RR (95% CI)**	
Allergy to bupivacaine (ester)	0 (0.0%)	1 (4.5%)	§0.999	Could not be calculated	
Horner (presented by ptosis)	4 (18.2%)	5 (21.7%)	§0.999	0.84 (0.26–2.72)	
Limb paresthesia (probability of hematoma/intraneural injection)	1 (4.5%)	1 (4.3%)	§0.999	1.05 (0.07–15.70)	
Shortness of breath after extubation (probability of phrenic *n* affection)	3 (13.6%)	2 (8.7%)	§0.665	1.57 (0.29–8.51)	
Nausea/vomiting	1 (4.5%)	7 (30.4%)	**§0.047***	0.15 (0.02–1.12)	
Skin allergy	1 (4.3%)	0 (0.0%)	§0.999	Could not be calculated	

*Significant
§Fisher's exact test

ropivacaine group and 15/50 (23.5%) in the ropivacaine-only group, but diaphragmatic paresis was observed in 10 out of 50 patients (20%) in the dexamethasone group and in 8 out of 50 patients (16%) in the ropivacaine-only group. The low rate of occurrence in our study could be due to the fact that we only used 30 ml instead of the large volumes reported in their study.

There were some studies that compared dexamethasone with other adjuvant drugs such as Vermeylen et al. (Vermeylen et al. 2016), who compared clonidine with dexamethasone as an adjuvant to 0.75% ropivacaine in sciatic popliteal nerve block, and their study included a total of 72 patients and concluded that perineural clonidine (limited to 100 μg) also prolonged block duration but to a lesser extent than 5 mg of dexamethasone. Also, Albrechet et al. (Albrecht et al. 2019) did a metanalysis comparing dexamethasone with dexmedetomidine as an adjuvant in supraclavicular nerve block, and their study included fifty trials and concluded that there is low-quality evidence that both adjuvants similarly prolong sensory/motor block. However, dexamethasone could be considered superior as it improves the duration of analgesia by a statistically significant increase, equivalent to 2.5 h more than dexmedetomidine, without the risks of hypotension or sedation.

There is an ongoing debate that "intravenous" dexamethasone may be used as an alternative to perineural dexamethasone with a peripheral nerve block. Single-dose intravenous dexamethasone could lead to complications such as hyperglycemia, postoperative infection, delayed wound healing, and avascular necrosis of bone (Polderman et al. 2018).

Rosenfeld et al. (Rosenfeld et al. 2016) who used perineural and intravenous dexamethasone in interscalene block found that both routes were associated with the prolonged sensory block when compared with placebo, but no difference was noticed in the duration of the sensory block between both routes. On the other hand, Kawanishi et al. (Kawanishi et al. 2014) who tested both routes as an adjuvant to ropivacaine in interscalene block found that perineural and not intravenous dexamethasone was associated with the prolonged sensory block when compared with placebo. Furthermore, Marhofer and his colleagues (Marhofer et al. 2019) found that neither perineural nor intravenous (IV) dexamethasone 4 mg had a beneficial effect in prolonging sensory block with ropivacaine after ulnar nerve block in 24 volunteers, not patients.

The main strength of this study is that it is a prospective blinded randomized control study; however, there are several limitations. The main limitation is our small sample size, and secondly, the exclusion of diabetic patients, higher morbidity patients as ASA III and IV, and patients above 65 despite the high prevalence of multimorbidity and aging among Egyptians.

Conclusion

The main conclusion is that 30 ml 0.5% bupivacaine mixed with 8 mg dexamethasone significantly prolongs the analgesic effect of plain bupivacaine used as a single injection ultrasound-guided interscalene block for patients undergoing shoulder surgery. The current controversy in the literature reinforces the need for future research into the effects of perineural dexamethasone on nervous tissue, axonal transmission, and neural blood flow and the extent of its systemic distribution.

Abbreviations

ASA: PS American Society Of Anesthesiologists Physical State; BMI: Body mass index; CO2: Carbon dioxide; ECG : Electrocardiogram; $EtCO_2$: End-tidal carbon dioxide; HR: Heart rate; IV: Intravenous; MAC: Minimum alveolar concentration; MAP: Mean arterial blood pressure; NIBP: Non-invasive blood pressure; PACU: Postoperative anesthesia care unit; Sao2: Arterial oxygen saturation; SCM: Sternocleidomastoid; SD: Standard deviation; SPO2: Oxygen saturation; SPSS: Statistical Package for Social Science; USA: United States of America; VAS: Visual analog score; VRS: Verbal response score

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Authors' contributions

MA designed the study, revised the literature, followed the patients, and critically reviewed the manuscript. AM designed the study, analyzed the data, and wrote and critically revised the manuscript. HM and RH revised the literature, followed the patients, collected the data, performed the analysis, and wrote the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Approval from the research ethics committee of the Faculty of Medicine, Ain-Shams University, was obtained (code number: FMASU M D 82/ 2018), and a written informed consent was obtained from all patients.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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