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The Effect of Intravenous Dexamethasone on Prolonging Analgesia After Supraclavicular Brachial Plexus Block: A Randomised Controlled Study

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Supraklavicüler Brakial Pleksus Sonrası Analjezinin Uzatılmasında İntavenöz Dekzametazonun Etkisi: Randomize Kontrollü Çalışma

ABSTRACT

Objective: *Duration of analgesia provided by brachial plexus block can be prolonged by simultaneous administration of intravenous dexamethasone.*
Methods: *Thirty adult patients undergoing upper limb surgery receiving supraclavicular brachial plexus block (SBPB) with 30 mL 0.5% ropivacaine were randomly allocated to receive 10 mg dexamethasone (Group RD) or normal saline (Group R) intravenously just before the block. The primary outcome was duration of analgesia. Secondary outcomes included duration of sensory and motor block, pain scores, time to readiness to discharge, quality of sleep, patient satisfaction and postoperative analgesic requirement.*
Results: *Demographic data was comparable in both groups. The mean duration of analgesia was 19.00±3.07 hrs in Group RD as compared to 9.47±1.82 hrs in Group R (p<0.001). Mean duration of sensory block was 16.93±2.84 hrs in Group RD versus 7.77±1.92 hrs in Group R (p<0.001) while mean duration of motor block was 9.40±2.96 hrs and 4.77±1.10 hrs in Groups RD and R respectively (p<0.001). Pain scores of patients in Group R were significantly higher from 9th to 24th hour postoperatively. The number of patients requiring additional analgesia was almost 2-fold more numerous in Group R (80%) as compared to Group RD (40%) (p=0.021). The PADSS score, rise in blood sugar, sleep quality and patient satisfaction were similar in both groups.*
Conclusion: *The administration of single dose of 10 mg intravenous dexamethasone prior to SBPB with ropivacaine is an easy, simple, safe, and effective method to increase the duration of analgesia.*

Keywords: *Dexamethasone, brachial plexus block, ropivacaine, postoperative pain relief*

ÖZ

Amaç: *Brakiyal pleksus bloğunun sağladığı analjezi süresi, eşzamanlı intravenöz deksametazon uygulamasıyla uzatılabilir.*
Yöntem: *Üst ekstremite ameliyatı geçiren 30 mL %0.5 ropivakain ile supraklavikular brakiyal pleksus bloğu (SBPB) uygulanan 30 yetişkin hasta, bloktan hemen önce intravenöz olarak 10 mg deksametazon (Grup RD) veya normal salin (Grup R) almak için rastgele ayrıldı. Primer sonuç analjezi süresiydi. Sekonder sonuçlar arasında duyusal ve motor blok süresi, ağrı skorları, taburcu edilmeye hazır olma zamanı, uyku kalitesi, hasta memnuniyeti ve postoperatif analjezik gereksinimi vardı.*
Bulgular: *Demografik veriler her iki grupta benzerdi. Grup RD'de ortalama analjezi süresi 19.00±3.07 saat, Grup R'de 9.47±1.82 saat idi (p<0.001). Ortalama duyu bloğu süresi Grup RD'de 16.93±2.84 saat, Grup R'de 7.77±1.92 saat (p<0.001) iken, ortalama motor blok süresi Grup RD ve Grup R'de sırasıyla 9.40±2.96 saat ve 4.77±1.10 saat idi (p<0.001). Grup R'deki hastaların ağrı skorları postoperatif 9.-24. saatlerde anlamlı derecede yüksekti. Ek analjezi gerektiren hasta sayısı Grup R'de (%80) Grup RD'ye (%40) kıyasla yaklaşık iki kat idi (p=0.021). Her iki grupta da PADSS skoru, kan şekeri artışı, uyku kalitesi ve hasta memnuniyeti benzerdi.*
Sonuç: *Robivakain ile SBPB'den önce tek doz intravenöz 10 mg deksametazon uygulanması, analjezi süresini uzatmak için kolay, basit, güvenli ve etkili bir yöntemdir.*

Anahtar kelimeler: *Deksametazon, brakiyal pleksus bloğu, ropivakain, postoperative ağrı kesici*

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INTRODUCTION

Use of regional anesthesia provides excellent analgesia and is widely accepted for postoperative pain relief [1]. In the upper limb, brachial plexus block (BPB) is used as an adjunct to general anesthesia (GA) or as a sole anesthetic. However, the duration of analgesia is limited by the duration of pharmacological effectiveness of the local anesthetic (LA) and may be prolonged by placement of indwelling perineural catheters or by adding adjuvant drugs. Indwelling catheterization techniques are effective, providing analgesia for several days but their utility is limited by technical challenges with proper placement, secondary failure rates, difficulties during removal of the catheter and infection [2].

Various drugs have been used to prolong analgesia from nerve blocks. These cause local vasoconstriction and limit systemic uptake, have a direct effect on peripheral nerves or have systemic anti-inflammatory effects. Steroids have powerful anti-inflammatory and analgesic properties. Dexamethasone appears to be effective in preclinical [3] and clinical [4-7] studies. Steroids induce vasoconstriction and may reduce LA absorption into the systemic circulation [8]. Also, dexamethasone may decrease activation of nociceptive C-fibres by acting via glucocorticoid receptors to increase the activity of inhibitory potassium channels on the C fibres [9-11].

Cummings et al. [8] observed a 1.9-, and 1.5-fold increase in the duration of interscalene block when dexamethasone was added to ropivacaine and bupivacaine, respectively. Desmet and Abdullah [1,12] found intravenous dexamethasone to be equivalent to perineural dexamethasone in prolonging the analgesia of BPB. Current understanding of the mechanism of action and potential side effects of perineural dexamethasone remains incomplete and presently dexamethasone is not approved for perineural administration by various regulatory bodies worldwide. Thus there may be definite advantages in administration of single dose intravenous dexamethasone prior to regional nerve blockade. The study was conducted to assess the effect of intravenous dexamethasone on prolonging the duration of analgesia of supraclavicular BPB with ropivacaine following upper limb surgery.

MATERIAL and METHODS

Ethical approval was provided by the institutional ethics committee. This double-blind randomized prospective trial was conducted from March 2015 to March 2016 on 30 adult patients of either sex, aged 18-65 years, American Society of Anesthesiologists (ASA) physical status I/II, undergoing upper limb surgical procedures under GA. Patients with brachial plexus neuropathy, bronchopulmonary disease, coagulopathy, intolerance to study medications, diabetes mellitus and obesity, those using systemic glucocorticoids, and opioid medications routinely, and pregnant patients were excluded from the study. The study protocol was explained to all patients and their written informed consent was obtained.

On the morning of surgery patients were randomly allocated to Group R (Ropivacaine) or Group RD (Ropivacaine-Dexamethasone) by block randomization using randomly mixed block sizes. On the day of surgery patients were taken to the operation theatre and standard monitoring comprising of electrocardiography, pulse oximetry and noninvasive blood pressure was instituted. Intravenous access was secured and a venous blood sample was sent for the measurement of blood sugar. All patients were given 1 mg intravenous midazolam 5 minutes prior to supraclavicular BPB (SBPB). Patients in Group RD received 10 mg dexamethasone in 2.5 mL solution intravenously and patients in Group R received 2.5 mL normal saline (NS). All study drugs were prepared by an independent investigator not involved in the study protocol. SBPB was performed with 30 mL 0.5% ropivacaine using a nerve stimulator by a standard technique described by the New York School of Regional Anesthesia (NYSORA) [13]. General anesthesia was administered after SBPB. Intraoperatively, intravenous fentanyl at a dose of 2 μg kg^{-1} was given at induction and 0.5 μg kg^{-1} at every hour. If another surgical incision was made concurrently at any other site, eg. for harvesting a bone graft, that case was to be excluded from statistical analysis.

The duration of analgesia was recorded as the time interval between completion of SBPB and first analgesic request. Duration of sensory block was defined as the time from completion of SBPB to complete resolution of sensory block which was assessed

using a 3-point scale as 0 = Normal sensation, 1=Loss of sensation at pinprick test (analgesia), and 2=Loss of tactile sensation (anesthesia) [14]. Duration of motor block was the time elapsed from the completion of SBPB to recovery of full muscle power. Motor Block Score (MBS) was 1=Unable to move fingers, 2=Able to move fingers but weaker than other arm and 3=Equal strength in both hands [1]. Sensory and motor blocks were evaluated on arrival into the post-anesthesia care unit (PACU) and subsequently at every 60 min until complete resolution. Pain was evaluated using a 4-point Verbal Rating Score (VRS) as 1-No pain, 2-Mild pain, 3-Moderate pain and 4-Severe pain [1] on arrival in PACU and subsequently at every 60 min for 24 hours. Intravenous 1 g paracetamol was administered for VRS≥2. If the patient still complained of pain, intravenous 75 mg diclofenac was administered. For further analgesia, intravenous 50 mg tramadol was administered if necessary. A patient who was asleep was assumed to be pain free (VRS 1). Postoperative nausea and vomiting (PONV), antiemetic requirement and timing and dosage of analgesics administered within 24 hours were recorded. Time taken to achieve a Post-Anaesthetic Discharge Scoring System (PADSS) score of ≥9 was also noted. PADSS assesses vital signs, ambulation, pain, nausea and/or vomiting and bleeding on surgical site [15]. The time required to attain a score of ≥9 was noted. At discharge from PACU, blood glucose levels were assessed. On the morning after surgery, the quality of sleep was assessed using a 2 point scale as 1=No sleep disturbance because of pain and 2=Sleep disturbance because of pain [1]. Patient satisfaction concerning the procedure was assessed using a 2-point scale as 1=Satisfied, I would want the same anesthesia/analgesia method for the next surgery, and 2=Unsatisfied, I would want a different anesthesia/analgesia method for the next surgery [1]. The sample size was calculated on the basis of a previous study by Desmet et al. [1] who found that the duration of analgesia provided by intravenous dexamethasone was equivalent to that provided by perineural administration of dexamethasone. The median duration of analgesia was 1405 (1015-1710) min in perineural dexamethasone group and 1275 (1095-2035) min in intravenous dexamethasone group (p=0.6254). In another study, Dar et al. [16] compared the duration analgesia between perineural dexamethasone and NS groups and established that the mean duration of analgesia for dexamethasone patients of 12.3±0.4 hours was more than 1.5 times than that of NS group (7.5±0.55 hours). Taking these values as a reference, the minimum required sample size with 5% level of statistical significance and 80% power was found to be 0.616 (less than 1 patient). Even if the statistical power of the study is increased to 95%, the same sample size persists (1.01). If the level of significance was decreased to 1% and the power was 95%, the sample size was 1.9. It was thus evident that any sample size of greater than 1 patient per group was expected to provide results similar to other researchers. We included 15 patients for each group. Secondary outcome variables included duration of sensory and motor block, pain scores, PONV, time to discharge readiness, quality of sleep, patient satisfaction and the requirement for postoperative analgesics within the first 24 hours. The quantitative variables were expressed as mean±SD and compared between groups using unpaired t-test. Qualitative variables were expressed as frequencies/percentages and compared using chi-square/Fisher's exact test. A p-value of <0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS) version 17.0 was used for statistical analysis.

RESULTS

Demographic data was comparable in both groups (Table I). There was no failed block in either group. The mean duration of analgesia was significantly longer in Group RD (19.00 ± 3.07 hrs) as compared to Group R (9.47±1.82 hrs) (p<0.001) as were sensory block [16.93±2.84 hrs versus 7.77±1.92 hrs (p<0.001)] and motor block [9.40±2.96 hrs versus 4.77±1.10 hrs (p<0.001)] (Table II). The mean postoperative VRS in both groups is depicted in Figure 1. Assuming common differences between groups: the overall repeated measures test result showed that mean pain

Table I. Patient Characteristics

Patient Characteristics	Group R (n=15)	Group RD n=(15)	P
Age (years) (mean±SD)	36.73±14.30	32.33±10.43	0.344
Gender (M:F)	12:3	12:3	1.00
Weight (kg) (n) (mean±SD)	62.20±6.87	60.60±9.99	0.613
Height (cm) (mean±SD)	163.07±6.79	159.47±6.38	0.146
BMI (kg m^{-2}) (mean±SD)	23.44±2.63	23.77±3.11	0.754
Duration of surgery (mins) (mean± SD)	109.67±45.65	119.0±60.54	0.637

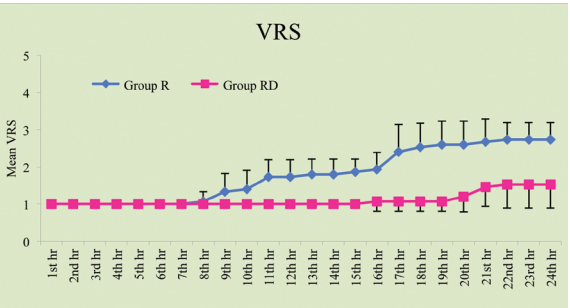

Figure 1. Postoperative VRS scores: There was a significant rise in pain scores from the 9th to 24th hour in patients in Group R as compared to Group RD.

Table II. Comparison of Duration of Supraclavicular Brachial Plexus Block Between Groups

Parameter	Group R (n=15)	Group RD n=(15)	p
Duration of Analgesia (hrs)	9.47±1.82	19.00±3.07	<0.001
Duration of Sensory Block (hrs)	7.77±1.92	16.93±2.84	<0.001
Duration of Motor Block (hrs)	4.77±1.10	9.40±2.96	<0.001

Descriptive statistics were given as mean±SD

Table III. Comparison of individual analgesics between groups

	Group R (n=15)		Group RD (n=15)		
Analgesics	Frequency	%	Frequency	%	p
Paracetamol	12	80%	6	40 %	0.060
Diclofenac	7	46.66%	1	6.66%	0.035
Tramadol	1	6.66%	0	-	1.000

Table IV. Comparison of other variables between groups

	Group R (n=15)	Group RD n=(15)	p
Number of patients requiring additional analgesia	12	6	0.025
PADSS on arrival in PACU	7.2±0.68	7.27±0.70	0.793
PADSS after 30 mins	9.13±0.35	9.13±0.35	1.00
Rise in blood sugar levels (mg dL^{-1})	14.80±3.62	15.0±2.72	0.866
Quality of sleep (mean±SD)	1.00±0.00	1.00±0.00	-
Patient Satisfaction Score (mean±SD)	1.00±0.00	1.00±0.00	-

Descriptive statistics were given as mean± SD or frequency

levels differed between the two groups by -0.67 units, which was statistically significant with an F (1,23)=34.21 (p<0.001). There was a slightly less statistically significant result for both groups, pain levels were higher at later postoperative hours (e.g. on average 1.13 at the 24th hour compared to baseline =postoperative 1. hour), with F (23,23)=2.24 (p=0.0294).

The frequency of analgesic requirement was higher in Group R as compared to Group RD (p=0.021). Paracetamol requirement was similar (p=0.060) but 7 of 12 patients from Group R and 1 of the 6 patients from Group RD had pain despite paracetamol treatment and received diclofenac. Diclofenac requirement was higher in Group R (p=0.035). One patient in Group R had pain after diclofenac and required tramadol. No patient in Group RD received tramadol (Table III).

The mean PADSS on arrival in PACU was 7.2±0.68 in Group R and 7.27±0.70 in Group RD (p=0.793) and all patients in both groups attained a PADSS of >9 within 30 minutes (Table IV). No patient had PONV or required antiemetics. While there was a significant rise in blood sugar after surgery from preoperative values in both groups (p<0.001), there was no significant intergroup difference in the rise in blood sugar levels (p=0.866) (Table IV). Quality of sleep and patient satisfaction were good in patients in both groups (Table IV).

DISCUSSION

The mean duration of analgesia in Group R was 9.47±1.82 hrs versus 19.00±3.07 hrs in Group RD indicating a 2-fold increase in the duration of analgesia in patients receiving intravenous dexamethasone. The duration of sensory and motor block was also significantly higher in patients receiving intravenous dexamethasone. Desmet et al. [1] compared perineural and intravenous administration of 10 mg dexamethasone and found that the duration of analgesia was 1275 min (IQR 1095-2035) in the intravenous dexamethasone group vs 1405 min (IQR 1015-1710) in the perineural group after interscalene BPB suggesting that the analgesic effect was independent of the route of administration. Faraj Abdallah et al. [12] obtained a mean duration of analgesia of about 25 hrs (17.6-23.6) in patients receiving 8 mg intravenous dexamethasone with supraclavicular block versus 13.2 hrs in those receiving placebo. There was no notable difference in duration of analgesia between intravenous and perineural groups. Similarly, Hong et al. [17] reported that intravenous dexamethasone 0.5 mg kg^{-1} in combination with caudal block augmented the intensity and duration of postoperative analgesia without any adverse effects

in children undergoing orchidopexy. Results of a study by Kawanishi et al. [18] seemed to suggest that intravenous dexamethasone had no significant effect on duration of analgesia (14.0 hrs vs 11.2 hrs in placebo group) following interscalene BPB with ropivacaine while perineural administration led to a significantly increased duration of analgesia (18.0 hrs). However, the dose of intravenous dexamethasone used was 4 mg and the statistical power of the study was insufficient.

De Olieveira GS et al. [19] in 2011 conducted a systematic analysis of 24 randomized controlled trials evaluating effects of single dose systemic dexamethasone on postoperative pain and opioid consumption. The studies used three dosage groups: low (<0.1 mg kg^{-1}), intermediate (0.11-0.2 mg kg^{-1}) and high (0.21 mg kg^{-1}). A meta-analysis that included clinical trials with 2,751 subjects suggested that the mean (95% CI) combined effects were found to be in favour of dexamethasone over placebo for pain at rest and with movement. Opioid consumption was decreased to a similar extent with intermediate and high dose dexamethasone, but not with low dose dexamethasone. Also, analgesic effectiveness and opioid use was similar in high and intermediate dose dexamethasone groups. In our study we used an intermediate dose of 10 mg intravenous dexamethasone.

There are numerous reports in the literature regarding the efficacy of perineural administration of dexamethasone in prolonging the duration of analgesia by various LA's [5-8,16]. Tandoc MN et al. [20] randomly assigned 90 patients to receive no additive (Group C), low dose (4 mg) dexamethasone (Group L) or high dose (8 mg) dexamethasone (Group H) in interscalene block with 0.5% bupivacaine. The duration of analgesia was significantly prolonged in Groups L and H compared with Group C as was the duration of motor block suggesting that lower doses may suffice for perineural usage whereas intravenous efficacy requires intermediate to high dose dexamethasone. In another meta-analysis, Zorrilla-Vaca A [21] reported that perineural dexamethasone at a dose of 4-5 mg was universally more effective to prolong analgesia as compared with intravenous dexamethasone but there was no significant difference between intravenous and perineural dexamethasone when using ≥8 mg dexamethasone. This suggests the presence of a local interaction between dexamethasone and the nerve as systemic absorption alone cannot explain the superior quality of peripheral nerve blocks.

Postoperative pain has different components-nociceptive, inflammatory, and neuropathic which form different possible targets for any analgesic strategy [1]. The precise mechanism of action of dexamethasone when added to LA's remains unknown [1]. Steroids have a powerful anti-inflammatory action and systemic administration suppresses tissue levels of bradykinin and neuropeptide release from nerve endings [22]. Other mediators of inflammatory hyperalgesia, like prostaglandins, tumour necrosis factor-a, interleukin-17b, and interleukin-6 are also inhibited. The clinical effects of dexamethasone may be related to changes in the transcription of DNA to proteins and continue for some time after the drug is cleared from plasma [17]. As the plasma elimination half-life of dexamethasone is only about 6 hours, there must be some ongoing drug effect for a period of time after drug clearance from the plasma [17]. Yilmaz et al. [23] found no effect of dexamethasone on the compound action potential of A and C fibres in the isolated sciatic rat nerves and hypothesized that a direct effect of dexamethasone on the nerve seems unlikely and the anti-inflammatory properties of dexamethasone are probably responsible for prolonged analgesia after regional nerve block. In 2014, S Choi et al. [24] conducted a systematic review on effects of perineural dexamethasone on the duration of BPB in which 9 trials were included with 393 patients receiving dexamethasone (4-10 mg) and found that dexamethasone prolonged the analgesic duration of long-acting LA's from 730 min to 1306 min [mean difference 576 min, 95% confidence interval (CI) 522-631] and for intermediate LA's from 168 to 343 min (mean 175, 95% CI 73-277). They found that prolongation of motor and sensory block was similar. If dexamethasone acts by specific inhibition of nociceptive C-fibre transmission, motor function should be spared. Thus dexamethasone probably has some direct effect on nerve transmission that is yet to be defined. In our study too, the mean duration of motor block in Group R was 4.77±1.10 hrs while in Group RD it was 9.40±2.96 hrs, suggesting that intravenous dexamethasone does prolong motor block significantly.

Although the efficacy of perineural dexamethasone as an adjuvant to LA's is proven, the drug is not approved for perineural administration by various regulatory authorities all over the world [25]. No clinical trials have reported an increased incidence of adverse effects after perineural dexamaethasone but they may have been underpowered to truly detect an increase in the incidence of serious side effects. So far no safety trial on use of perineural dexamethasone has been performed and extrapolation of in vitro to in vivo evidence regarding possible neurotoxicity of dexamethasone should be done cautiously [1]. Few recent studies suggesting that perineural and intravenous dexamethasone similarly and significantly prolong postoperative analgesia after regional nerve block suggest that the analgesic effect of perineural dexamethasone is due to its systemic absorption and anti-inflammatory effect [1,12,17,26,27].

Many previous studies have demonstrated that a perioperative single-dose of dexamethasone is not associated with a significant increase in the incidence of adverse effects in either pediatric or adult patients [28]. In the present study no patient had nausea or vomiting and there was no significant difference in time taken to attain readiness to discharge. All patients in both groups were satisfied with the anesthesia technique and had a good quality of sleep on the night of surgery. There was an overall satisfaction score of 85-98% in the study by Desmet et al. [1] but patients in their control group reported a high incidence of sleep disturbance in the first night after surgery. Faraj Abdallah [12] also found that patients receiving dexamethasone reported a higher satisfaction as compared to the control group. Steroid-induced hyperglycaemia has been noted after high-dose intravenous regimens but does not seem to be a problem in clinical practice [29]. Desmet et al. [1] observed a significant increase in postoperative blood glucose levels in patients receiving dexamethasone, the rise being higher in the intravenous dexamethasone group (5.1 mg dL^{-1} vs 3.8 mg dL^{-1}). Pasternak et al. [28] suggested that a single dose of 10mg intravenous dexamethasone led to a significant rise in blood sugar levels in the dexamethasone group. However surgical stress leads to hyperglycemia and postoperative rises in blood glucose that cannot be attributed solely to dexamethasone. In our study there was a significant rise in blood glucose in both groups but the rise was similar in both groups.

In a meta-analysis in 2017, Chong et al. [30] concluded that the duration of action of 3.77 hours of perineural over intravenous dexamethasone questions the justification of use of the perineural over the intravenous route routinely and perineural administration should be restricted to patients where such a prolongation is of significant clinical utility. In 2018, Heesen et al. [31] reported that there is only low quality evidence suggesting a significantly longer duration of analgesia with perineural dexamethasone. Recently in 2019, Hewson D [32] suggested that intravenous dexamethasone has good analgesic and antiemetic properties and should be used during anesthesia, with or without peripheral nerve block.

There are some limitations in our study. In order to save operation theatre time, all patients were given GA after performance of BPB so the onset time of the BPB could not be determined. Also BPB was performed without ultrasound guidance. However, the block was successful in all patients and we assume that our study results would not have been different with use of ultrasound. All patients received intraoperative opioids but the duration of action of fentanyl was shorter than the anticipated duration of analgesia and it is unlikely that it affected our results.

CONCLUSION

A single dose of 10 mg intravenous dexamethasone with SBPB with ropivacaine reduced the intensity of postoperative pain and prolonged analgesia after upper limb surgery without any adverse effects. The low cost of dexamethasone, antiemetic action and high safety profile make this an easy, simple and effective intervention for routine use and it may be preferred over perineural dexamethasone in settings where prolonged analgesia after peripheral nerve block is required.

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