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Perineural versus Intravenous Dexamethasone for Prolongation of Multiple Nerve Blocks for Pain Relief after Total Knee Arthroplasty

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Abstract

Background: Multiple nerve blocks (MNB) provide excellent time-limited perioperative analgesia following total knee arthroplasty. Both perineural and systemic use of dexamethasone (DXM) as an adjuvant to local anesthetic prolong the duration of single-shot MNB. We hypothesized that preoperative perineural injection of DXM prolongs analgesia after MNB more than the same dose of intravenous (IV) DXM injection due to direct action on the nerves and not only by a systemic action mechanism.

Methods: This is a prospective, randomized, controlled and observer-blinded study. One hundred and nine patients were randomly assigned to one of three groups: Group (Gr) 1-perineural DXM+MNB, Gr 2-systemic IV DXM +MNB, Gr 3-control group, MNB without DXM. Postoperative variables including intensity of pain at rest and during motion, grade of sensory and motor block, opioid consumption, comfort time (the first analgesic request) were the primary end-points of investigation.

Results: Ninety patients completed the study protocol. Very low parameters of intensity of pain at rest and during motion, high grade of sensory and motor block were observed up to 12 hours after MNB performance in all three groups. Patients who received MNB with DXM perineurally or systemically, experienced superior pain relief and had reduced opioid consumption 24 hours post-block compared to the control group without differences between the two "dexamethasone" groups. There were no differences between groups at 36 and 48 hours post-block. Patients in the control group suffered from pain at rest and started treatment by any analgesics significantly earlier than patients from the two “dexamethasone” groups. No difference of comfort time was observed between Gr 1 and Gr 2. In the period between 24 and up to 36 hours the block’s effect (i.e. the effect of local anesthetic with adjuvant dexamethasone) gradually weakened and somewhere at 48 hours post-block, it passed almost completely.

Conclusions: Intravenous 8 mg dexamethasone is equivalent to perineural dexamethasone in prolonging the pain relief duration of an ultrasound guided single-shot multiple nerve block with bupivacaine and adrenaline following total knee arthroplasty.

Keywords: Arthroplasty; Postoperative pain; Comfort time; Opioid consumption; Dexamethasone perineural; Systemic; Intravenous; Ultrasound-guided multiple nerve blocks

Abbreviations: MNB: Multiple Nerve Blocks-block of femoral, popliteal sciatic, obturator (both branches), and lateral femoral cutaneous nerves; DXM: Dexamethasone; IV: Intravenous; PNB: Peripheral Nerve Block; TKA: Total Knee Arthroplasty; LA: Local Anesthetic (bupivacaine 5 mg/mL with adrenaline 5 μg/mL); NRS: Numerical Rating Scale (for intensity of pain measurement); NP scale: Nurses Assessment of Postoperative Pain; DM: Diabetes Mellitus; Gr: Group; PACU: Postanesthesia Care Unit; μg: Micrograms; Kg: Kilograms; m: Meter; mg: Milligrams; mL: Milliliter; dL: Deciliter; hrs: Hours; min: Minutes; Post-op: Postoperative; SE: Standard Error; PONV: Postoperative Nausea and Vomiting; A1C: Hemoglobin A1C, HbA1c, or glycohemoglobin test; h: Height in meters; BW: Body Weight in kg; BMI: Body Mass Index; GA: General Anesthesia; NSAID: Non-Steroidal Anti-Inflammatory Drugs

Introduction

Preoperative peripheral nerve block (PNB) is a modern technique of anesthesia and postoperative (post-op) pain control for total knee arthroplasty (TKA) [1-3].

A preoperative single injection of MNB, i.e. of femoral, popliteal sciatic, both branches of obturator nerve and lateral femoral cutaneous nerve, produces excellent perioperative analgesia and opioid spare effect during the day of surgery and the first post-op day [4]. A significant limitation of this method of analgesia following TKA is its relatively short effect, even after use of a long acting local anesthetic such as bupivacaine with adrenaline (LA) [4]. The use of a perineural catheter for continuous MNB use is unpractical, because three catheters have to be inserted for the blockade of femoral, sciatic and obturator nerves. A lateral femoral cutaneous nerve block plays a role during the operation, but not in the post-op period [5-7]. Other limitations of this method are: the technical challenge of placement and removal of catheters, dislodgment or infection, nerve injury or prolonged motor weakness during the recovery period (resulting in patient falls) [2, 8-12]. The desire for prolonging the action of LA is to avoid the insertion of a perineural catheter. This has led to the search for various additives to the LA solution following a perineural injection [13]. A systemic review with meta-analysis summarized the data of the effectivity and safety of perineural DXM, which is used as an adjuvant to LA for prolongation of the PNB [14-16]. A significant improvement and prolongation of the post-op analgesia was demonstrated [14, 15] without difference between 4 mg and 8 mg of perineural DXM use. Negative results were obtained by Knezevic et al [17], Fredrickson et al [18] and YaDeau et al [19].

The mechanism of action of DXM on peripheral nerves during perineural injection is unknown [14, 15]. The scattered experimental data that has been published is not sufficient to merge them into an integral theory explaining this phenomenon [20-24].

Desmet et al. concluded that for prolonging the analgesic duration of a single-shot interscalene block with ropivacaine, systemic (intravenous) injection of DXM is equivalent to perineural DXM injection [25]. Kawanishi et al. came to the opposite conclusion: perineural DXM but not systemic DXM prolongs the duration of interscalene block [26].

We hypothesized that preoperative (before TKA) perineural injection of DXM prolongs analgesia after MNB more than the same dose of IV DXM injection due to direct action on the nerves and not only by systemic mechanism of action.

Methods

This is a prospective, randomized, controlled and observer-blinded clinical trial; enrollment began after receiving Hillel Yaffe Review Board approval and written informed patient consent. Trial eligibility was as follows: above age 18, physical status of I-III based on American Society of Anesthesiologists criteria [27], and scheduled to undergo elective TKA due to osteoarthritis. A total 121 patients were eligible for the trial.

Exclusion criteria were previous TKA, TKA revision, TKA due to trauma or etiology other than osteoarthritis, systemic glucocorticoid use, skin infection near the block injection site, allergy to local anesthetics, pre-existing peripheral neuropathy of the involved limb, proven opioid dependency [28], coagulopathy (INR>1.4), thrombocytopenia (platelets count <100000), chronic pain syndrome (pain at rest for more than six months, anxiety and/or depression, hyperalgesia, allodynia, chronic treatment with analgesics and more), dementia, lack of orientation to person, place and time, inability to comprehend the Numerical Rating Scale (NRS) [29], and language barrier (the patient does not speak, understand and/or writes in Hebrew, Russian, English, French or Arabic), as well as patients suffering from type I diabetes mellitus (DM), poorly controlled type II DM (hemoglobin A1C ≥ 7%, plasma glucose level of ≥ 131 mg/dL [7.28 mmol/L] [30].

Patients suffering from well controlled type II DM without complications (for example, skin and eyes complications, neuropathy, foot complications, nephropathy, ketoacidosis, stroke, hyperosmolar hyperglycemic nonketonic syndrome and more), which were treated exclusively by oral anti-diabetic drugs were not excluded from the trial.

We chose to include patients with well controlled type II DM because of the Hans et al. study [31]. The authors concluded that after preoperative injection of 10 mg dexamethasone IV, blood glucose levels increased in non-diabetic and type II diabetic patients by the same degree (the computation was performed with respect to baseline). A maximum blood level elevation expressed in percent of baseline in the non-diabetic group was 35 ± 19%, and in well controlled type II DM group was 29 ± 19% [30] without a statistically significant difference between the groups.

Patients were instructed regarding the use of a 0-10 Numerical Rating Scale (NRS) [29]: zero represents 'no pain at all' whereas the upper limit represents 'the worst pain ever possible.'

The author states that the report includes every item in the Consolidated Standards of Reporting Clinical Trials (CONSORT) checklist for a prospective randomized clinical trial. The study was registered prior to patient enrollment. Data collection: February, 2015 to January, 2017. Registry Url: Clinical trial registration number (NIH)-NCT02253784.

Based on the exclusion criteria, 12 patients were excluded from the trial. The inclusion group (109 patients) was randomized into three groups (Figure 1): Group (Gr) 1: MNB with perineural injection of DXM; Gr 2: MNB with systemic (i.e. IV) injection of DXM; Gr 3: (control group) MNB without DXM. Randomization was done using a computer-generated table of random numbers, placing them in a sealed envelope, and then opening the envelope on the morning of surgery.

The patients and the investigators who collected data during the postoperative period (the nursing staff of the Postanesthesia Care Unit (PACU), A.M. after discharge from PACU, the Department of Anesthesiology residents, the nursing staff of both orthopedic departments) were blinded to group assignments throughout the research.

Patients were premedicated with IV fentanyl (0.5 μg/kg) and midazolam (0.03 mg/kg) with option to titrate the fentanyl up to 1.0 μg/kg, midazolam up to 0.05 mg/kg during the procedure. Local anesthesia was used with lidocaine 10 mg/mL before inserting the block needle. A maximum 15 mL of lidocaine was used for MNB.

The same anesthesiologists (A.S. or L.R.) performed all preoperative US-guided MNBs using an ultrasound system (SonoSite S-Nerve, SonoSite, Bothell, WA, USA), S-Nerve Ultrasound system, Sono Site Corp., USA with 6-13 MHz linear array transducer (L25X). A 22-gauge 80 mm Pajunk Sono Tap cannula (Pajunk® Medical Produkte GmbH, Geisingen, Germany) was used for visualization of the target nerves (femoral, popliteal sciatic, obturator) and to inject the local anesthetic around the nerves. A 50 mm 22-gauge needle was used for the lateral femoral cutaneous nerve block.

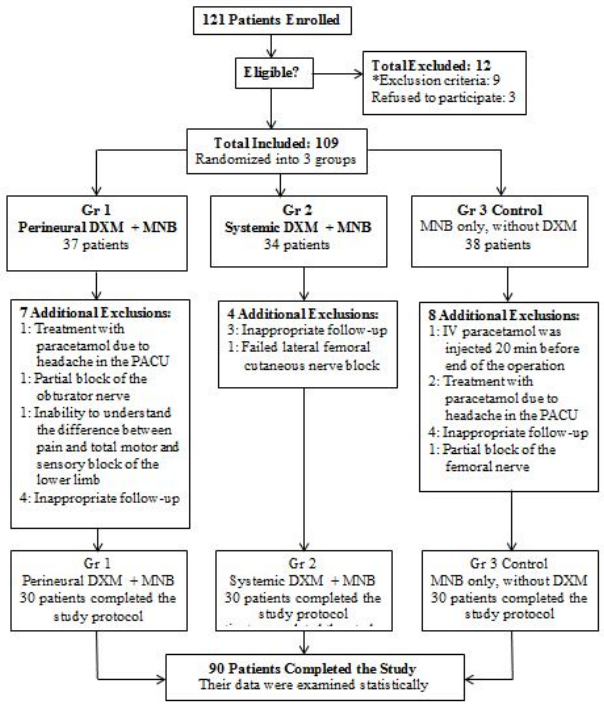


Figure 1: Consolidated Standards of Reporting Clinical Trials (CONSORT) Flow Chart of Included and Excluded Patients. The inclusion criteria were: physical status of I-III based on American Society of Anesthesiologists criteria, and scheduled to undergo elective TKA due to osteoarthritis. *The exclusion criteria were: previous TKA, revision of TKA, TKA due to trauma or etiology other than osteoarthritis, age<18, systemic glucocorticoid use, a skin infection, allergy to local anesthetics, pre-existing peripheral neuropathy, opioid dependence, coagulopathy, chronic pain syndrome, dementia, lack of orientation to person, place and time, inability to comprehend the Numerical Rating Scale for intensity of pain measurement, language barrier, type I diabetes mellitus, poorly controlled type II diabetes mellitus. DXM: Dexamethasone; MNB: Multiple Nerve Blocks (block of femoral, sciatic, obturator, and lateral femoral cutaneous nerves); IV: Intravenous; PACU: Postanesthesia Care Unit.

Standard non-invasive monitoring was used; oxygen was administered via facemask, 5 L/min. Bupivacaine 5 mg/mL with adrenaline 5 μg/mL was used as a LA for MNBs performing in Gr 2 and Gr 3. For patients in Gr 1 a LA/DXM admixture was used, the dose of the DXM in the admixture was 0.2 mg/mL. The total dose of DXM was 8 mg for perineural use. Eight mg DXM IV was injected into all the patients in Gr 2 immediately before beginning the procedure. The volume of LA and/or LA/DXM admixture (for patients in GR 1) was as follows: for the popliteal sciatic nerve block- 15 mL, for the femoral nerve block – 15 mL, for the obturator nerve block- 10 mL (5 mL for each branch, i.e. anterior and posterior branches). The lateral femoral cutaneous nerve in all patients was blocked by an injection of 5 mL of lidocaine 10 mg/mL. A block of the lateral femoral cutaneous nerve is important during the surgery, but less than in the postoperative period, because it does not innervate the knee joint [5-7]. The same volume of LA was used in Gr 2 and Gr 3.

All the US-guided blocks were conducted using previously published techniques [32-38]. The success of the sensory and motor blockade was examined 30 min after completion of the block as described in our previous trial [4]. The sensory function of each blocked nerve was evaluated using pinprick as described by Marhofer et al. [39]. The tip of a 22-G short beveled needle was applied with force adequate to indent the skin but not enough to puncture it. This action produced a painful sensation on the unblocked side and was compared with the similar test in the contralateral (blocked) side.

Gradation of the sensory block was scored as follows: Grade 1-Intact sensation. i.e. absence of sensory block; Grade 2-Dull sensation (analgesia); Grade 3-No sensation (anesthesia). The lateral femoral cutaneous nerve is a sensory nerve only, and the effectivity of the block was examined by evaluation of the sensation in the appropriate area (lateral side of the thigh).

The power of the motor block was examined for each blocked nerve separately:

- Both branches of the sciatic nerve were examined separately 30 min after completion of the popliteal sciatic nerve block. The presence of the tibial nerve block was examined using loss in flexion of the toes and foot. The availability of the common peroneal nerve was observed using presence of foot drop, and the inability to hold the foot up.
- The inability to extend the affected leg with hip passively flexed is a sign of motor blockade of the femoral nerve.
- Adduction ability of the previously abducted lower limb characterizes the obturator nerve block.

Gradation of the motor block was scored as follows: Grade 1-Normal motor function, i.e. absence of motor block; Grade 2- Reduced possibility of flexion/extension movement in the knee joint (paresis); Grade 3- Loss of possibility of flexion/extension movement in the knee joint (paralysis).

Patients were additionally excluded from the study if a failed sensory or motor block was diagnosed (i.e. if normal sensation and/or normal motor function were observed) of one or more nerves.

If a different grade of sensory or motor block was determined about different nerves -for example, Grade 2 sensory block of the femoral nerve and Grade 3 sensory block of the sciatic nerve were diagnosed during evaluation of patient 24 hours after surgery - then the higher grade of block was considered and inserted in the protocol chart (i.e. Grade 3 sensory block in our example).

Eight mg IV ondansetron was injected before general anesthesia induction as prophylaxis for postoperative nausea and vomiting (PONV) [40].

A standardized general anesthesia (GA) protocol was used for all patients: for induction to GA midazolam 0.015 mg/kg, fentanyl 1.5 μg/kg, propofol titration up to effect and atracurium 0.6 mg/kg was injected IV with following tracheal intubation and mechanical ventilation. Maintenance of anesthesia was left to the discretion of the attending anesthesiologist (N_2O/O_2 and isoflurane admixture, fentanyl IV). The anesthetic regiment was changed according to the patient's hemodynamic status. At the beginning of the surgery finger stick blood glucose was measured, as well as two hours after DXM injection (the peak effect of DXM on the elevation of the blood glucose concentration [30, 31]) perineurally or systemically in Gr 1 and Gr 2, respectively. All operations were performed by or under the

supervision of the same experienced orthopedic surgeons (R.S. and M.T.).

Variables assessed and compared statistically between groups before and during surgery:

- Patient characteristics (age, gender, height (h), body weight (BW). Body mass index (BMI) was calculated using the following formula: $BMI=BW/h^2$ (kg/m^2).
- Preoperative level of glucose concentration in blood (mg/dL).
- Preoperative pain at rest and during motion (flexion, extension) was measured using 0 to 10 NRS. Zero represents "no pain at all" whereas the upper limit represents "the worst pain ever possible" [29].
- Block performance time (min).
- Correlation between BMI and block performance time.
- Doses of induction agents: fentanyl (μg/kg), midazolam (mg/kg), propofol (mg/kg).
- Duration of surgery.
- Registration of intraoperative events. If oxygen desaturation, bradycardia, hypotension, or other events persisted for more than 2-3 min, the patient was excluded from the study. The aim of this exclusion was to remove potential temporary intraoperative brain tissue oxygen desaturation which may have influenced mental state [41] and pain intensity estimation during the postoperative period when assessed by NRS.

Variables assessed in PACU:

- Intensity of pain at rest in the PACU was measured using the modified nurses' assessment of postoperative pain scale (NP): 0-no pain or patient asleep; 1-mild pain or discomfort; 2-moderate pain; 3-severe pain; 4-intolerable pain [42].
- Sensory block. Sensory block ratio was calculated by the formula:
- $$Sensory\ block\ ratio = \frac{Nis}{Nanalg + Nanesth}$$

  Nis: Number of patients with intact sensation in group (Grade 1 sensory block);

  Nanalg: Number of patients with analgesia (Grade 2 sensory block);

  Nanesth: Number of patients with anesthesia (Grade 3 sensory block).
- Motor block. Motor block ratio was calculated by the formula:

$$Motor\ block\ ratio = \frac{Nnmf}{Nparesis + Nparalysis}$$

  Nnmf: Number of patients with normal motor function in the group (Grade 1 motor block);

  Nparesis: Number of patients with paresis (Grade 2 motor block);

  Nparalysis: Number of patients with paralysis (Grade 3 motor block).
- Opioids consumption (in mg of morphine IV or IM after conversion). The doses conversion (calculation) of opioids to morphine dosage, used in PACU and during hospitalization of the patients in the orthopedic department 48 hours after surgery was performed by a calculator on internet [43]. This equianalgesic conversion was based on American Society guidelines and critical review papers regarding equianalgesic dosing [43-47].
- Time of stay in PACU (min). The discharge criteria from the PACU were based on the revised Aldrete Scoring System [48].
- The glucose concentration in blood (mg/dL).

Variables assessed 12, 24, 36, 48 hours postoperatively included:

- Intensity of pain at rest and during motion (flexion, extension) (NRS).
- The grades of sensory and motor block were evaluated and compared by the same methods that were used in the PACU (see above evaluation of those parameters in the PACU).
- Opioids consumption (in mg of morphine IV or IM after conversion).
- Glucose concentration in blood (mg/dL).
- Satisfaction with pain relief during postoperative period (this parameter was registered 48 hours after surgery according NRS principle).

An additional variable calculated and compared statistically among groups was 'comfort time', i.e. time in hours after block performance and first time use of any rescue analgesics, such as dipyrone (metamizole), paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (ketorolac, diclofenac), tramadol, opioids (morphine, meperidine, oxycontin).

Our primary end-points were: intensity of pain at rest and during motion, grade of sensory and motor block, opioid consumption, and comfort time. A priori power analysis was calculated for these variables.

Secondary end-points were: correlation between block performance times and BMI, PONV in PACU, PACU time of stay, immediately diagnosed complications of MNB, neurological deficit a month after surgery and MNB (if present, repeated examination should be performed three months after surgery), and satisfaction with pain relief during the postoperative period.

Statistical analysis

A priori power analysis of primary end-points was performed using G* Power 3.0.10 (Heinrich Heine Universität Düsseldorf, Dusseldorf, Germany) with a fixed effect, omnibus, one-way ANOVA for all groups. A total sample size of 66 was considered adequate to achieve an effect size of 0.5 with an α error probability of 0.05 and a power (1-β error probability) of 0.95. After all exclusions, our study included 90 patients. Statistical analysis was performed using IBM® SPSS® Statistics 20 (IBM Corporation, Armonk, NY).

Continuous numerical parameters were analyzed using Shapiro-Wilk test for normality of distribution, followed by the Levene test for homogeneity of variances (if a normal distribution was determined). Parameters with a normal distribution and homogeneous variances were compared by one-way ANOVA followed by Tukey's post-hoc test, if necessary. The Kruskal-Wallis test was used when an abnormal distribution of the continuous variables was detected and/or when variances were not homogenic. The Mann-Whitney post-hoc test was used following the Kruskal-Wallis test, if necessary. Frequency tables and chi-square tests (Pearson or Likelihood ratio) were used to

compare the proportions between the categorical variables among the groups.

The interval "comfort time" was evaluated by construction of Kaplan-Meier curves, followed by the Log Rank (Mantel-Cox) test for comparison of the Kaplan-Meier curves between groups. A value of $P < 0.05$ was considered statistically significant.

Results

From February 2015 to October 2016, 121 patients were found eligible for the trial. Twelve were excluded according to exclusion criteria or refusal to participate. Figure 1 presents the allocation process according to the Consolidated Standards of Reporting Clinical Trials (CONSORT) statement. A total of 109 patients were included and randomized into three groups. Ninety patients completed the study protocol, and their data was analyzed statistically (Figure 1).

Pre and intraoperative variables were compared between groups (Table 1). Correlation between BMI and block performance time was not detected. No patients suffered from PONV in the PACU.

Variables	Gr 1 Perineural DXM	Gr 2 Systemic DXM	Gr 3 Control Without DXM	P ANOVA	P Kruskal Wallis	P Chi-Square
*Age (years)	67.93 ± 1.76	70.00 ± 1.46	66.00 ± 1.24	0.18		
*Height (m)	1.64 ± 0.012	1.64 ± 0.01	1.62 ± 0.02	0.52		
*BW (kg)	83.95 ± 2.60	83.37 ± 3.47	83.47 ± 2.55	0.99		
*BMI kg/m^2	31.16 ± 0.81	31.00 ± 1.22	33.00 ± 1.07	0.59		
§Gender M:F	8:22	10:20	6:24			0.51
+Glucose (mg/dL)	112.54 ± 5.8	106.32 ± 6.52	128.46 ± 7.19		0.052	
+Pain at Rest (NRS)	1.67 ± 0.34	1.50 ± 0.31	1.13 ± 0.24		0.47	
+Pain at motion (NRS)	5.23 ± 0.32	5.2 ± 0.40	4.8 ± 0.33		0.86	
+Block Performing time (min)	23.5 ± 1.29	25.33 ± 1.51	23.83 ± 1.60		0.65	
+Ondansetron (mg/kg)	0.1 ± 0.003	0.1 ± 0.004	0.1 ± 0.003		0.80	
*Time of GA (min)	120.4 ± 3.97	131.1 ± 3.57	126.2 ± 3.74	0.14		
+Time of surgery	93.57 ± 3.90	100.6 ± 3.93	102.67 ± 3.13		0.13	
+Fentanyl (µg/kg)	1.64 ± 0.13	5.05 ± 3.28	1.51 ± 0.90		0.14	
+Propofol (mg/kg)	1.85 ± 0.09	2.23 ± 0.45	1.60 ± 0.15		0.82	

All values are presented as mean ± SE (Standard error).

*Age, height, BW, and BMI were of normal distribution (Shapiro-Wilk test) and homogenous of variances (Levene test). These variables were analyzed using ANOVA test for comparison of means between three groups. P>0.05 means no difference between the groups.

+These variables were of abnormal distribution (Shapiro-Wilk test). Therefore, the Kruskal-Wallis test was used for comparison of continuous variables between three independent groups. The Mann-Whitney post-hoc test was used following the Kruskal-Wallis test, if necessary.

§Chi-Square test was used to compare the proportion of Male: Female between groups. P>0.05 means no difference between groups.

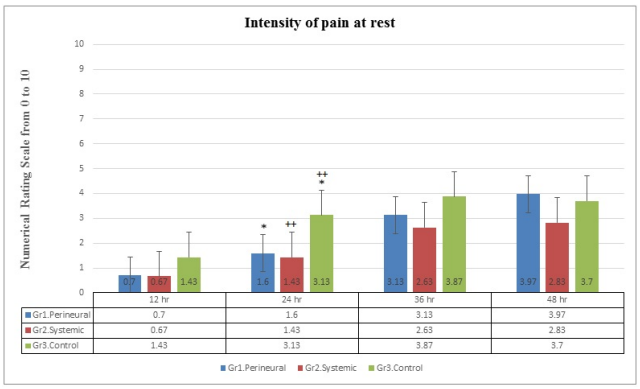
NRS: Numeric Rating Scale 0-10.

Table 1: Pre and Intraoperative Data.

No unexpected serious adverse reactions and/or complications were reported and judged as definitely related to trial treatment. Five patients in Gr 1 and seven in Gr 2 with well treated type II DM [30] were randomized for injection of DXM perineurally or systemically. The differences between preoperative levels of glucose were not statistically significant among groups. No patient in either arm developed new onset diabetes.

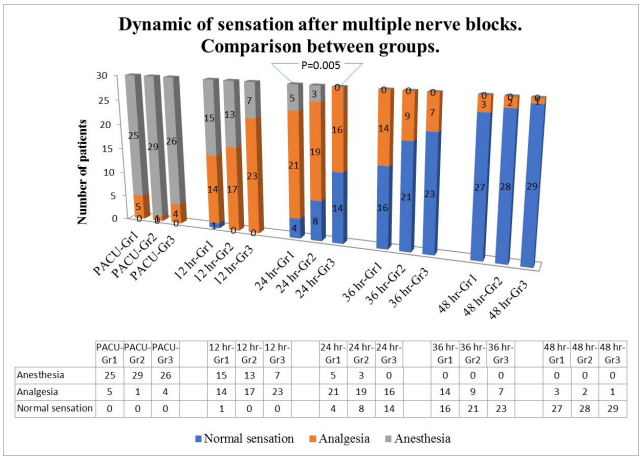
Regarding intensity of pain at rest (Figure 2), the grade of sensory block (Figure 3) and opioid consumption (Figure 4): statistically significant differences between each of the "dexamethasone" groups (Gr 1 and Gr 2) versus the control group (Gr 3) was observed 24 hours after block performance, but without difference between Gr 1 and Gr 2. There were no differences between any of the groups at 36 and 48 hours post-block.

Pain intensity at rest in the PACU (NP scale [42]) was very low (Table 2) in patients of all three groups. Patients in Gr 1 were free from pain. A statistical difference of this parameter was calculated between groups, yet it was of low clinical significance (Table 2). The patients in PACU were not treated with any analgesics. Lack of sensation (i.e. analgesia or anesthesia) and lack of normal motor function (i.e. paresis or paralysis) of the blocked lower limb was observed in all patients in all three groups in PACU (Figures 3 and 5).



	12 hr	24 hr	36 hr	48 hr
Gr1.Perineural	0.7	1.6	3.13	3.97
Gr2.Systemic	0.67	1.43	2.63	2.83
Gr3.Control	1.43	3.13	3.87	3.7

Figure 2: All values are presented as Mean ± SE (Standard Error). Statistically significant difference was discovered 24 hours after blocks performance between each of the DXM groups and the control group, but without difference between Gr 1 and Gr 2. At 12, 36 and 48 hours there was no difference between the groups.



	PACU-Gr1	PACU-Gr2	PACU-Gr3	12 hr-Gr1	12 hr-Gr2	12 hr-Gr3	24 hr-Gr1	24 hr-Gr2	24 hr-Gr3	36 hr-Gr1	36 hr-Gr2	36 hr-Gr3	48 hr-Gr1	48 hr-Gr2	48 hr-Gr3
Anesthesia	25	29	26	15	13	7	5	3	0	0	0	0	0	0	0
Analgesia	5	1	4	14	17	23	21	19	16	14	9	7	3	2	1
Normal sensation	0	0	0	1	0	0	4	8	14	16	21	23	27	28	29

Figure 3: Calculation of the ratio was used for comparison between groups by Chi Square test. *Sensory block ratio=Nis* /(*Nanalg*+*Nanesth*). *Nis*: Number of patients with intact sensation in the group (Grade 1 block); *Nanalg*: Number of patients with analgesia (Grade 2 block); *Nanesth*: Number of patients with anesthesia (Grade 3 block). There was no statistically significant difference between groups regarding the grade of sensory block in PACU, as well as at 12, 36, and 48 hrs after MNB performance. Twenty- four hrs after block performance, there was a significant difference between Gr 1 (perineural injection of dexamethasone) and the control group (Gr 3), but without difference between Gr 1 and Gr 2 (systemic dexamethasone injection).

Blood glucose concentration in the PACU was elevated in all 12 patients with type II DM in Gr 1 and Gr 2 in comparison with preoperative values, as well as in all non-diabetic patients. An elevated level of glucose in the PACU (2-3 hrs after DXM use before or during MNB performance) expressed in per-cent of preoperative values was 16-39%. Additional treatment for decreasing blood glucose concentration was not needed.

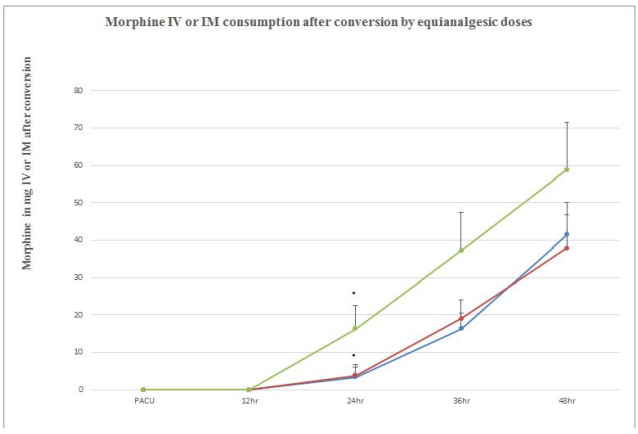
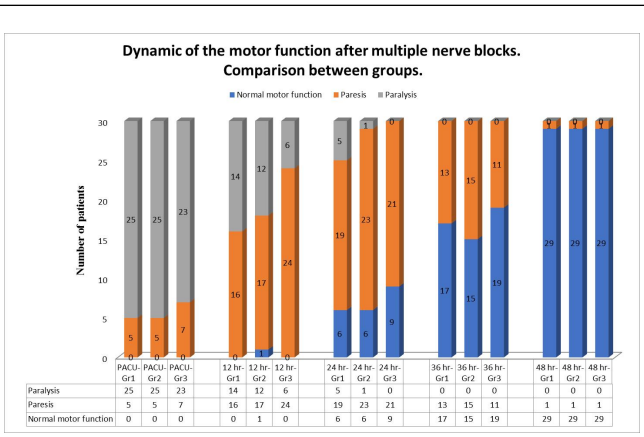


Figure 4: Total doses of opioids were converted to doses of morphine IV or IM by use of equianalgesic dose converter. Statistically significant difference was observed between each of the "dexamethasone" groups and the control group 24 hr after block performance. Patients in control group were treated with higher doses of opioids at this time. Patients in Gr 1 and Gr 2 were treated with a comparable dose of opioids. *Statistically significant difference.



	PACU-Gr1	PACU-Gr2	PACU-Gr3	12 hr-Gr1	12 hr-Gr2	12 hr-Gr3	24 hr-Gr1	24 hr-Gr2	24 hr-Gr3	36 hr-Gr1	36 hr-Gr2	36 hr-Gr3	48 hr-Gr1	48 hr-Gr2	48 hr-Gr3
Paralysis	25	25	23	14	12	6	5	1	0	0	0	0	0	0	0
Paresis	5	5	7	16	17	24	19	23	21	13	15	11	1	1	1
Normal motor function	0	0	0	0	1	0	6	6	9	17	15	19	29	29	29

Figure 5: Calculation of the motor block ratio was used for comparison between groups by Chi-Square test. *Motor block ratio=Nnmf* /(*Nparesis*+*Nparalysis*). *Nnmf*: Number of patients with normal motor function in the group (Grade 1 motor block); *Nparesis*: Number of patients with paresis (Grade 2 motor block); *Nparalysis*: Number of patients with paralysis (Grade 3 motor block). There was no statistically significant difference between groups regarding the grade of motor block in PACU, as well as 12, 24, 36, 48 hr after MNB performance.

Very low parameters of the intensity of pain at rest and during motion (Figures 2 and 6), as well as high grade of sensory and motor block (Figures 3 and 5) were observed after discharge from the PACU and up to 12 hours after performing MNB in all three groups. Patients in Gr 1 and Gr 2 were not treated with opioids, three patients in the control group received opioids: two patients were treated with morphine 10 mg IM total dose, and one was treated with oxycodone 10 mg (4 mg of morphine IV or IM as an equianalgesic dose).

Parameter	Gr 1 Perineural DXM	Gr 2 Systemic DXM	Gr 3 Control Without DXM	P Shapiro-Wilk test	P Kruskal Wallis test	P Mann-Whitney		
						1 *vs.* 2	1 *vs.* 3	2 *vs.* 3
Pain intensity at rest (NP scale) in PACU	0.00 ± 0.00	0.14 ± 0.07	0.53 ± 0.18	0.01	0.01	0.04	0.03	0.15
Time of stay in PACU (min)	55.9 ± 4.24	54.9 ± 5.01	59.4 ± 4.79	Gr 1-0.01 Gr 2-0.00 Gr 3-0.01	0.75			
All values are presented as mean ± SE. Pain intensity in PACU was measured by modified NP scale: 0-no pain or the patient is asleep; 1-mild pain or discomfort; 2-moderate pain; 3-severe pain; 4-intolerable pain. Time of stay in PACU was a parameter of abnormal distribution (Shapiro-Wilk test) in each group (P>0.05 means normal distribution).								

Table 2: PACU Data.

In the 24 and 36 hours post-block, the same manner of differences was observed about the variable "intensity of pain during motion" (Figure 6). The same spread of restoration of motor function after block was observed in all patients in all three groups (Figure 5). A significant increase of the opioid doses was observed in all patients in all three groups between 24 to 36 hours post-block (Figure 4).

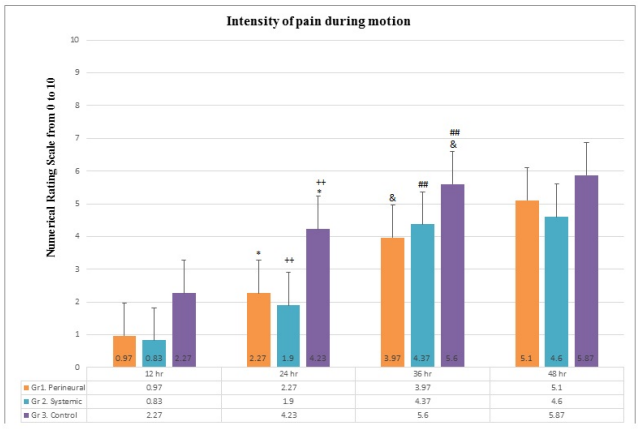


Figure 6: Intensity of pain during motion (flexion and extension). All values are presented as mean ± SE. There was no difference between groups at 12 and 48 hours after block's performance. Differences at 24 and 36 hours after block were statistically significant between each of the "dexamethasone" group and the control group, but not between Gr 1 and Gr 2.

Kaplan-Meier curves [25, 49] were constructed for comfort time presentation (time from end of the block performance and up to first analgesic request), with following comparison between groups. Patients not receiving any analgesics after 48 hours are found on the right (Figure 7).

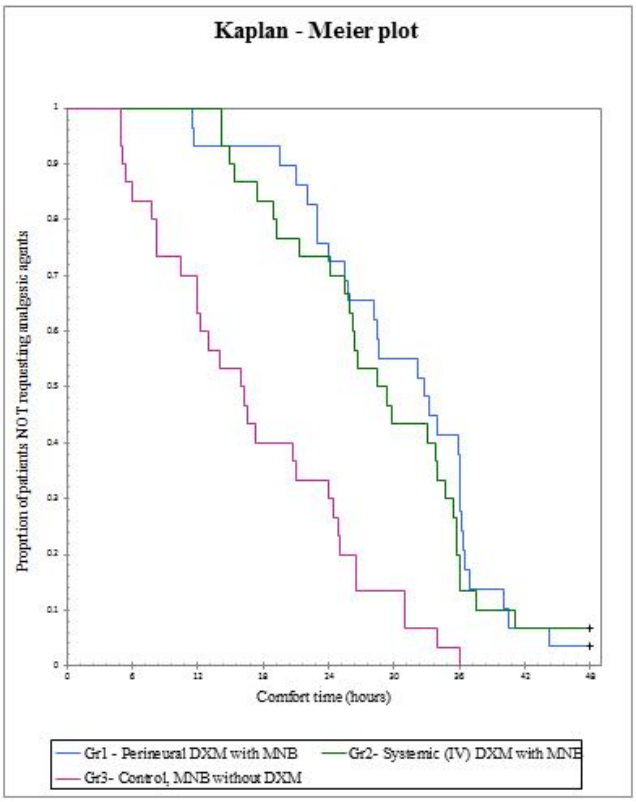


Figure 7: Comfort time. Comfort time: Time to first analgesic request (hours) of any analgesic agent. DXM: Dexamethasone 8 mg as a total dose. An admixture of bupivacaine 5mg/mL, adrenaline 5 µg/mL and dexamethasone 0.2 mg/mL was injected perineurally for block performance in Gr 1, and IV in Gr 2 immediately before start of the procedures. MNB: Multiple Nerve Block (block of femoral, sciatic, obturator and lateral femoral cutaneous nerves). Censored data: three patients: two in Gr 2 and one in Gr 1 that were not treated with any analgesic during 48 hr (an evaluated period).

Log Rank (Mantel-Cox) test was used for comparison of the Kaplan-Meier curves (Table 3). Patients in the control group suffered from pain at rest and started analgesic treatment earlier than patients in the two "dexamethasone" groups: significant differences were obtained between Gr 3 (control group) and each of the "dexamethasone" groups, i.e. Gr 1 and Gr 2 (P<0.0001). No difference was observed between Gr 1 and Gr 2 (P=0.64) as seen in the graph (Figure 7).

	P
Gr1 (Perineural DXM) *vs.* Gr 2 (Systemic DXM)	0.64
Gr1 (Perineural DXM) *vs.* Gr 3 (Control)	< 0.001
Gr 2 (Systemic DXM) *vs.* (Control)	<0.001
Statistically significant difference was observed between each of the "dexamethasone" group and the Control group, but without difference between Gr 1 and Gr 2.	

Table 3: Log rank (Mantel-Cox) test.

There were no observed neurological complications 48 hours post-block and surgery in all patients in all three groups. No differences were observed between the groups regarding satisfaction with pain relief during the first 48 hrs of the post-op period.

Our secondary end-point results are as follows:

- A correlation between BMI in the range of 24-37 kg/m^2 and block performance time was absent.
- Time of stay in the PACU was similar in all three groups.
- Five patients from Gr 1 and seven from Gr 2 suffering from well controlled type II DM were included in the study. In those 12 patients the blood glucose elevation peaked two hours post-block at 16 - 39%, additional treatment was unnecessary.

Discussion

We used a preoperative single-shot MNB as part of the surgical anesthesia and for management of postoperative pain following TKA [4]. A significant limitation of this excellent method of anesthesia and analgesia "is its relatively short effect" [4] usually lasting less than 24 hours, even when a long-acting local anesthetic bupivacaine with adjuvant as adrenaline is applied [4]. The use of additional adjuvants were approbated in clinical practice with the aim of prolonging the duration of the single shot PNB, for example, clonidine [50], opioids [51], midazolam [52], ketamine [53] with little effect. DXM was evaluated and appear to be an effective agent for prolonging the duration of PNB in preclinical [23, 24], and clinical investigations [13-19, 25, 26]. Most of the previous studies were focused on clarifying the effects of DXM as a local anesthetic adjuvant for brachial plexus block [14,16], but even after a systemic review and meta-analysis the authors concluded that "Perineural administration of dexamethasone with LA prolongs brachial plexus block effects with no observed adverse events. The effects of systemic administration of dexamethasone on brachial plexus block must be investigated" [14]. Desmet et al. [25] did not find a difference between an IV or perineural effect of DXM regarding the increase of analgesic duration of a single-shot interscalene block with ropivacaine, but an opposite result was achieved by Kawanishi et al [26]. The results of Kawanishi et al. should be accepted carefully, because this study is underpowered. From the previous trial, it is known that DXM prolongs the duration of bupivacaine used in an interscalene nerve block up to 22 hrs of analgesia [54].

We compared the effect of IV and perineural DXM as an adjuvant to a bupivacaine/adrenaline admixture on six variables (primary end-points of the study) that represent the duration of MNB: intensity of pain at rest and during motion (flexion and extension), sensation, motor function, opioid consumption and comfort time. To the best of our knowledge, this specific issue has not been previously investigated. No statistically significant differences were observed between Gr 1 (perineural DXM) and Gr 2 (systemic DXM) in all primary end-point variables, both immediately after operation in the PACU, and during the 48 hours of the follow up after surgery. Differences were observed between each of the "dexamethasone" groups and Gr 3 (control group) 24 hours after the blocks regarding the intensity of pain at rest and during motion and in opioid consumption. The difference of the comfort time between Gr 3 and two "dexamethasone" groups was observed early; 6 hours post-block (Figure 7). This is a main point of the study, because it proves that adjuvant DXM independently of route of administration prolongs the analgesic property of MNB, that was administered by a bupivacaine/adrenaline admixture over more than 24 hours, but usually no more than 36 hours (Figures 2-7). The same block without DXM produces analgesia that lasts usually less than 24 hours, and there are very few patients who do not need the addition of analgesics within 36 hours (Figures 2-7). The differences between the "dexamethasone" groups and the control group were present 36 hrs after block performance regarding the intensity of pain during motion (Figure 6). Thirty-six hours after block performance all patients in the control group were treated with some analgesics (Figure 7, Kaplan-Meier plot). All primary end-point parameters were nominally low in patients in Gr 1 and Gr 2 versus Gr 3, but a statistically significant difference was observed usually 24 hrs post-blocks (Figures 2,4 and 6), except for comfort time (Figure 7).

DXM when used as a perineural or IV adjuvant to MNB slows the recovery speed of sensory and motor functions of the blocked peripheral nerves. A significant "leap" was observed between 24 and 36 hours post-block (Figures 2 and 3). In the same period of time an increase in intensity of pain at rest and during motion and in opioid consumption was registered (Figures 2, 4-6). Thus, the desired effect of DXM (independently from the route of administration) was observed in the period of 12- 24 hrs and disappeared from 24 to 36 hrs post-block.

The mechanism of action of DXM on the peripheral nerves during perineural injection is unknown [13-15]. The scattered experimental data do not enable their combination into an integral theory explaining this phenomenon [20-24]. The systemic anti-inflammatory action of DXM is well known, and this agent is recommended as a drug commonly used in multimodal pain control methods in knee arthroplasty [55]. Systemic DXM decreases pain during motion, reduces pain and emesis after TKA [56,57]. Consequently, the administration of 8 mg DXM IV immediately before the performance of MNB can be recommended for several reasons: as one of the agents of a multimodal pain control method, for prolongation of MNB, which is the best method for preemptive regional analgesia in comparison with FNB alone [4], as an antiemetic drug [57], etc.

As in our previous studies [4,58,59], a US-guided technique makes it possible to perform PNB fairly quickly in patients with moderate obesity. Appropriate pain relief after MNB immediately after surgery reduces time of stay in the PACU to a minimum.

Persistent nerve palsy during the following two weeks as a complication associated with brachial plexus blocks with local anesthetics and dexamethasone as an adjuvant was recorded in Cummings et al [54], and Parrington et al [60]. Desmet et al. only reported only one patient out of a series of 144 patients who suffered from hypoesthesia in the deltoid region four months after surgery, and cervical disc herniation was diagnosed at the level of C4-C5 (this factor may be an etiology of this neurologic deficit, but not the interscalene block) [25]. In our small series, persistent neurological deficits were not diagnosed after MNB.

Limitations of the Study

Measurement bias

Part of the data on the PNB (sensory and motor function, intensity of pain at rest and during motion) was obtained once every 12 hours post-block and surgery. More frequent registration of these parameters (for example every few hours) can enable more accurate determination of their dynamics.

We used two scales for pain intensity measurement, the modified NP scale [42] in the PACU and the NRS after discharge from PACU [29]. Readers should note this difference in the presented results.

We used a moderate dose of DXM as an adjuvant to LA, 8 mg (approximately 0.1 mg/kg). In the literature, different recommendations are presented regarding DXM doses for perineural use with ropivacaine or bupivacaine for PNB [13-19, 25, 26, 54, 55, 60]. Our results and conclusions should be considered only with reference to 8 mg of DXM. The duration of action of MNB depends on the dose of DXM used systemically or perineurally. A dose related effect is an interesting subject for investigation in the future.

There are no unambiguous recommendations in the medical literature about the safe use of DXM (systemically or perineurally) for prolonging the duration of MNB or other PNB with bupivacaine or ropivacaine in patients with uncontrolled type II DM, insulin dependent DM (type II and type I). While the safety of use of DXM in these patients has not been investigated and generally accepted recommendations in this regard are absent, one should refrain from applying this method in those patients.

General anesthesia was used in all patients in our trial. Fentanyl before induction was used to blunt the hemodynamic response to intubation. We think than this short-acting agent did not influence pain sensation immediately and during 12 hours post-op.

Even a single dose of 8 mg DXM can lead to a number of side effects:

- Perioperative hyperglycemia due to whole body insulin resistance with following alterations in cardiac fatty acid and carbohydrate metabolism [61]. Monitoring of electrocardiography, heart rate, blood pressure, arterial blood gases, blood glucose concentrations, urine analysis (glucose, ketones) is recommended in patients with impaired cardiac function, obesity [62] and DM.
- Gastric ulceration [63].
- Tumor lysis syndrome. A case report of perioperative death after a single dose of DXM causing this syndrome in a three-year-old during tonsillectomy was published [64]. Rapid lysis of lymphocytes with following rapid acute hyperpotassemia, hyperphosphatemia, lactic acidosis and acute renal failure may occur [65].
- Psychiatric effects: mania, psychosis, depression and more [66].

Bartlett and Hartle recommend in an editorial: "all patients receiving dexamethasone should be warned of its potential side-effects. Steroids are powerful agents and should be used with caution." [67].

Conclusions

Eight milligrams intravenous dexamethasone is equivalent to the same dose of perineural dexamethasone in prolonging the pain relief duration of a single injection multiple nerve blocks with bupivacaine 5 mg/mL and adrenaline 5 μ/mL after total knee arthroplasty. The comfort time was prolonged, intensity of pain at rest and during motion in addition to lower opioid consumption was observed during the first 24 hours after block performance in comparison with patients that accepted a multiple nerve block without adjuvant dexamethasone. In the period between 24 and up to 36 hours post-op, the effect of the block (i.e. the effect of local anesthetic with adjuvant dexamethasone) weakens gradually, and sometime within 48 hours post-op, it disappears almost completely. The same blocks that were performed without adjuvant dexamethasone weaken significantly early, during the period of 6 to 12 hrs post-op. Not only the dynamics of purely subjective parameters (intensity of pain at rest and during motion, opioid consumption and comfort time), but also more objective variables, such as time of recovery of sensory and motor function after multiple nerve blocks confirm this conclusion. We recommend taking into account our results when prescribing an analgesic agent after total knee arthroplasty; preoperative use of multiple nerve blocks with or without adjuvant dexamethasone must be taken into account. In moderately obese patients the time of US-guided multiple nerve blocks performance is similar compared to those who are not obese. As an adjuvant to local anesthetic bupivacaine with adrenaline, dexamethasone does not affect the time of stay in the PACU. During 48 hours post-op, there was no neurological complication in our series. We agree with Bartlett and Hartle. When patients agree to a multiple nerve blocks with adjuvant dexamethasone systemically or perineurally, they should be informed about the potential side effects of dexamethasone.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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