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Buprenorphine Added to Bupivacaine Prolongs Femoral Nerve Block Duration and Improves Analgesia in Patients Undergoing Primary Total Knee Arthroplasty—A Randomised Prospective Double-Blind Study

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ABSTRACT

The aim of the study was to determine whether the addition the long-acting opioid buprenorphine as an adjuvant to the local anaesthetic agent would improve quality and prolong duration of femoral nerve blockade in post-operative analgesia following primary total knee arthroplasty. The study involved 48 patients. The femoral nerve was anaesthetised with a 0.25% solution of bupivacaine with adrenaline or with the addition of 0.3 mg of buprenorphine. The duration of the sensory block and analgesic effect was assessed according to NRS scale at 12, 24, 36, 48, 60 and 72 hours post-surgery. Patients who received buprenorphine as an adjuvant to the local anaesthetic had significantly longer sensory blockade and lower NRS-rated pain intensity with the difference reaching statistical significance at 12 hours post-surgery.

One of the surgical method of treatment for patients with knee arthrosis is total knee arthroplasty (TKA), which is one of the most common orthopaedic surgery procedures world-wide[1]. Arthroplasty procedures in general, and knee arthroplasty in particular, are associated with severe to very severe post-operative pain. Among the many strategies for controlling post-operative pain, regional analgesia techniques are the most popular ones [2]. Practicable techniques of regional analgesia include central blocks in the form of continuous epidural and subarachnoid anaesthesia as well as blocks of nerve plexuses or individual peripheral nerves [2,3]. Besides good control of acute post-operative pain, regional analgesia techniques are associated with less adverse effects compared to systemic opioids [2,4,5].

A single administration of a long-acting regional anaesthetic into the femoral nerve region reduces pain in TKA patients for about 24–36 hours [6–8]. Prolongation of this effect without an accompanying increase in the risk of adverse effects would allow for even more effective post-operative analgesia [9,10]. To this end, the quest is on for pharmacologically active agents referred to as adjuvants. The most popular add-on agents used in peripheral nerve blockades include the opioids: fentanyl, sufentanyl, morphine and pethidine, but the effects have been equivocal [10]. More recently, there has been an interest in buprenorphine and its unique pharmacological properties, and clinicians have been encouraged to test this compound in regional anaesthesia [10,11]. Buprenorphine is the longest acting opioid with clinical analgesic effect of about 8 hours after single parenteral dose. The unique effect of buprenorphine is blocking Na + voltage gated sodium channels of nerve fibers, similarly to local anaesthetics [12].

The primary objective of the study was to evaluate the effect of buprenorphine as an adjuvant on the duration and quality of isolated femoral nerve block with a 0.25% solution of bupivacaine and adrenaline in the treatment of post-operative pain in TKA patients. The secondary outcomes were the influence of buprenorphine on the morphine consumption, progress of rehabilitation and duration of hospital stay.

In this study we wanted to verify hypothesis that buprenorphine prolongs femoral nerve blockade performed with long-acting local anaesthetic agent and improves its efficacy.

Materials and Methods

Sample Size Calculation

Before the start of the study the sample size calculation was performed. For predicted time of blockade of about 36 hours and difference of duration of the block of 6 hours as the results of our previous clinical observations the study needed 44 patients. We added 10% of calculated size (4 patients) for unpredictable situations which make pain assessment impossible.

Randomisation

Before the operation the anaesthesiological nurse being a member of the research team via coin toss assigned patients to particular group keeping the result of the randomisation secret (concealment of

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allocation). Next according to the draw she prepared a solution of the local anaesthetic with the addition of buprenorphine or without it. Anaesthesiologists who performed the blockade of the femoral nerve (2 doctors participated in anaesthetizing peripheral nerves), and next evaluated its effectiveness and length of sensory blockade did not know from which group the patient was derived (double blinding). After the end of the research, results of the randomisation were declassified and collected data were analyzed.

Forty-eight adult patients undergoing primary total knee arthroplasty were enrolled to the randomised prospective study. The inclusion criteria involved: age > 18 years and recognized primary arthrosis of knee joint confirmed clinically and radiologically. The exclusion criteria were: corticosteroid therapy and known systemic conditions (diabetes, rheumatoid arthritis, and systemic lupus erythematosus) that could interfere with peripheral nerve function and perception of pain by the patients. The patients had been informed about the aim of the study and had provided written informed consent. Operative risk was assessed according to the ASA (American Society of Anaesthesiology) physical status classification. Following pre-medication with 7.5 mg oral midazolam (Dormicum, Roche), surgical anaesthesia for the procedure was achieved by subarachnoid administration of a hyperbaric solution of 0.5% bupivacaine (Marcaine Spinal Heavy 0.5%, Astra-Zeneca Inc.).

Knee arthroplasty (TKA—total knee arthroplasty) was performed with implant Triathlon Total Knee Replacement System (Stryker ®, USA). The system needs tibial and femoral components fixation with bone cement. Between two components the plastic element for providing distance and friction reduction is inserted. All surgeries were done with the use of pneumatic torniquet at femoral level after exsanguination of the extremity with elastic gum tape. The tourniquet was inflated to a pressure of 150 mmHg above systolic blood pressure and deflated after implant insertion and obtaining stability of the joint. After obtaining surgical haemostasis the autotransfusion drain was left. After stratified wound closure the autologic blood collection system for autotransfusion HandyVac ATS (Unomedical, A/S, DK) was initiated. Operation wound was closed with sterile closure. The time of surgery was assessed from the time of leg exsanguination to the skin closure. Autologic blood transfusion was started according to the volume of collected blood, but not later than 6 hours after the start of ATS system. In the neccessity the leucoreduced Red Blood Cells Concentrate was given. All patients had thromboprophylaxis with LMWH (low molecular weight heparins) according to AAOS guideline. All patients got antibiotic prophylaxis with cefazolin (Kefzol) 1.0 g and amikacin (Amikin) 0.5 g 30 minutes before start of surgery.

Femoral nerve anaesthesia was performed immediately on completion of the surgery, with the patient still under subarachnoid anaesthesia, the aim being to minimise pain during needle movements and to prolong the nerve blockade for as long as possible. After the skin of the inguinal area had been carefully disinfected, the femoral nerve was identified just below the inguinal ligament under ultrasound guidance (Sonosite M-Turbo, Sonosite Inc. USA) and using a peripheral nerve stimulator (Stimuplex HNS 12, BBraun, Germany). The long axis of the ultrasound probe was positioned along the inguinal ligament [13]. A sterile stimulator needle (Stimuplex A, 21Gx4", 0.80 × 100mm, BBraun, Germany) was introduced in the plane of the long axis of the probe laterally at an angle of approximately 30° from the skin. After the nerve was visualized and a motor response was obtained from the femoral quadriceps muscle (pulse intensity 0.5 mA) and following a negative aspiration test, a 0.25% bupivacaine solution with adrenaline 1:200000 (Marcaine-Adrenaline 0.5%, Astra-Zeneca Inc.) was administered at a dose of 0.5/mL/kg body weight with an addition of 0.3 mg buprenorphine (Bunondol, Polfa Warszawa, Poland) in group I patients or without the buprenorphine adjuvant in group II patients. After the surgery, patients stayed at the Department of Orthopaedics and analgesics were administered "on demand" to control pain.

The analgesic quality of the nerve block was evaluated at 12, 24, 36, 48 and 60 and 72 hours after the completion of the TKA procedure. The analgesic effect was assessed with a numerical rating scale (NRS) for pain, where 0 corresponded to no pain, and 10 corresponded to unbearable pain. Patients' subjective sensations during the period of hospitalization were also assessed. The consumption of opioid analgesics (morphine) on individual post-operative days was recorded. Data were also collected on progress in rehabilitation and duration of the hospital stay.

Statistical Design

The raw data were subjected to a statistical analysis in Statistica 10.0. (Statsoft Inc, Tulsa, IL, USA). Each analysis involved testing for normality of distribution with the Shapiro–Wilk W test. For normally distributed variables, means and standard deviations were calculated and comparisons employed Student's t test. When a variable was not normally distributed, parameters calculated comprised the median, 25th and 75th percentile, and maximum and minimum, and the Mann–Whitney U test was used for comparisons. A P-value of <0.05 was established as the level of statistical significance in all calculations.

Results

As a result of the randomisation, study subjects were divided in 2 groups with various numbers: group I—28 patients and group II—20 patients. These two groups were not significantly different with regard to demographic data (Table 1). The post-operative pain scores are presented in Table 2 and Fig. 1. Group I (femoral nerve block with buprenorphine) had lower mean NRS scores (possible range 0–10 points) at all time points. The difference in means was statistically significant ($P = 0.013$) at 12 hours post-surgery. The mean score was lower in group I at 12, 36, 48, 60 and 72 hours post-surgery. Buprenorphine also significantly prolonged the analgesic effect of the femoral nerve block (48.07 ± 5.0 hours vs. 43.6 ±7.16 hours, $P = 0.014$). Morphine consumption on each post-operative day as well as overall morphine consumption during hospitalization were lower in group I, but the differences were not statistically significant (total morphine dose 11.43 ± 10.79 vs. 17 ± 13.80, $P = 0.188$) (Table 3). Patient satisfaction and comfort of bed confinement did not differ between the groups. There were also no significant differences in the progress of rehabilitation and duration of hospital stay. Patients from group I started exercises at 2.18 ± 0.61 day and walking at 3.57 ± 1.79 day after operation (P = 0.92), so did the patients from group II (2.20 ± 0.89, 4.05 ± 0.89, P = 0.3). Duration of stay in orthopaedic division since operation to discharge from the hospital was respectively 10.68 ± 2.67 and 10.3 ± 2.32 days (P = 0.61). The femoral nerve block was not associated with any immediate or distant complications.

Discussion

The aim of the study was determination the effect of buprenorphine added to the solution of bupivacaine with adrenaline on the

Table 1
Demographic Characteristics of Patients.

	Group I $n = 28$	Group II $n = 20$	P
Gender (female:male)	22:6	12:8	ns
ASA physical status			
II	27 (96.43%)	20 (100%)	ns
III	1 (3.57%)	0 (0%)	ns
Age (years) median, (range)	72 (54–84)	71 (57–82)	ns
Body weight (kg) median, (range)	85 (50–110)	86.5 (59–106)	ns
Time of surgery (minutes) median, (range)	95 (60–165)	97.5 (60–125)	ns

ns—statistically not significant.