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Intra-articular morphine or neostigmine does not assure better pain relief

Research Article

Saule Svediene*, Audrius Andrijauskas, Juozas Ivaskevicius

Clinic of Anesthesiology and Intensive Care,
Vilnius University, Lithuania

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Abstract: Background and Objectives: Choice of optimal postoperative analgesia technique remains challenging. Our double - blind randomized prospective clinical study compares efficacy of end-of- surgery intra-articular application of morphine or neostigmine after anterior crutiate ligament repair. Methods: 60 adult ASA I - II patients were randomized into 3 groups: intra-articular morphine 6 mg, neostigmine 0.5 mg, placebo. All received femoral nerve block and spinal anesthesia. Numeric rating scale used for pain assessment at rest and motion during 48 postoperative hours, and 0-10 scale for evaluation of overall patient satisfaction. Adjunct analgesics were recorded.

Results: The only significant difference between protocol groups was better pain relief at motion at the end of trial in neostigmine 0.5 mg group than in placebo ($p=0.018$). Consumption of adjuncts wasn't different on day of surgery, postoperative Day 1 and Day 2 respectively - diclofenac ($p=0.85$, $p=0.41$, $p=0.9$) and tramadol ($p=0.62$, $p=0.72$, $p=1$). Patient satisfaction was similar ($p=0.59$) among groups. Conclusions: Intra-articular neostigmine provided similar pain control at motion as morphine during the trial, but it was better than placebo on the 2nd postoperative day. Similar pain control at rest, adjunct consumption and patient satisfaction recorded throughout the whole observation period in all groups.

Keywords: *Postoperative pain management • Single-shot femoral nerve block • Intra-articular morphine and neostigmine*

1. Introduction

Majority of patients report moderate to severe pain following arthroscopic anterior crutiate ligament (ACL) repair surgery [1]. Numerous methods and their combinations for perioperative pain management were put into test during the last decade. Regional techniques are usually preferred for inpatient ACL repair surgery [2]. Conventional spinal anesthesia is frequently replaced by the nerve blocks, and especially by a single-shot femoral nerve block (SFNB) [3,4]. Intra-articular injection of local anesthetic is expected to provide a better postoperative pain control, but the related reports are scarce and controversial [5]. Intra-articular injection of bupivacaine with 10 mg of morphine was reported to provide a significant reduction in systemic opiate consumption [6,7]. However, reports of associated low levels of morphine and morphine-6-glucuronide in plasma suggest that analgesic effect of intra-articular opiates is dose-dependent, and mainly related to systemic action [8,9]. The similar use of intra-articular neostigmine is even less investigated, but it was reported to be effective in other settings [10,11]. A combination of spinal anesthesia, SFNB and intra-articular injection of morphine or neostigmine seems a clinically justified combination, but the choice between morphine and neostigmine remains inconclusive [12].

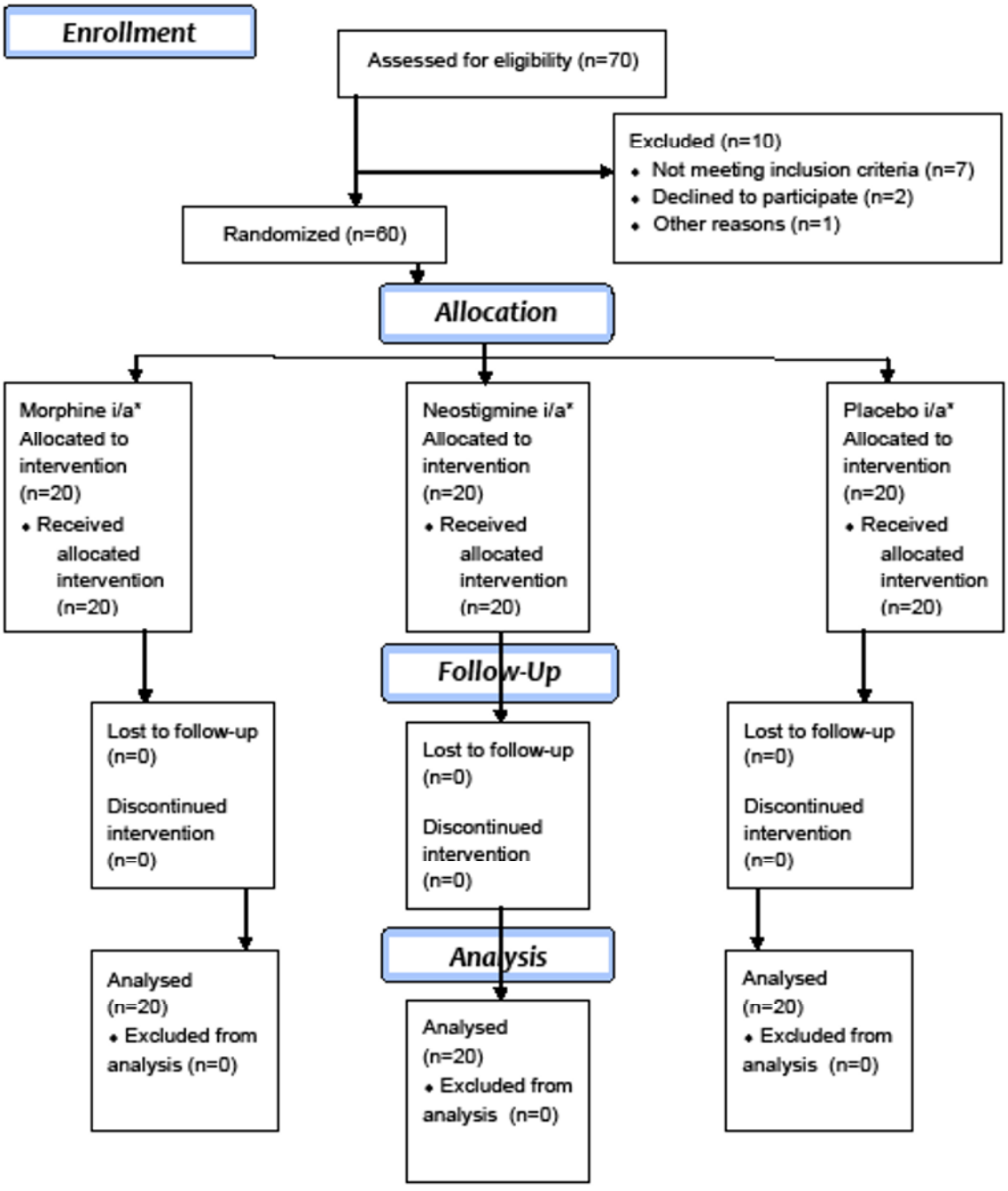
The primary objective was to compare the efficacy of end-surgery intra-articular injection of morphine, neostigmine, or placebo on the pain management at motion (with activity) after arthroscopic ACL reconstruction performed under spinal anesthesia followed by SFNB. The secondary purpose was to compare the postoperative pain management at rest, also consumption of the adjunct analgesics and overall patient satisfaction.

* *E-mail: saulyte71@yahoo.com*

2. Materials and methods

Approval was granted from Lithuanian Ethics Committee. Patients with a contraindication to regional anesthetic technique (local skin infection, congenital or acquired coagulation disorders, known allergy to any of the study agents, pre-existing femoral neuropathy) were excluded. 2 patients declined to participate. Written informed consent was received from 60 adult ASA physical state class I–II patients with body mass index ≤ 30 kg/m^2 scheduled for arthroscopic ACL reconstruction and they were prospectively enrolled in this study. All patients were eligible for spinal anesthesia followed by SFNB and intra-articular morphine or neostigmine. Subjects were randomized into 3 groups: (I) SFNB+M (morphine), *n=20*; (II) SFNB+N (neostigmine), *n=20*; (III) SFNB+P (placebo), *n=20* (Figure 1). The

Figure 1. Flow-chart of patient enrollment in the study of efficacy of intra-articular analgesia with morphine or neostigmine after anterior crutiate ligament repair surgery (*i/a: intra-articular injection).



simple randomization method was used to assign treatment groups. There were printed 60 envelopes with assigned treatment groups using allocation ratio 1:1:1. These envelopes were mixed and then assigned to patients in consequent order. The unblinded operating room nurse assisting with the procedure was responsible for preparation of the study medication for each subject appropriately in such manner that participants and those administering the medication remained blinded to group assignment. The study was conducted between September 2007 and July 2009.

2.1. Intraoperative period

Before induction of anesthesia all patients were premedicated with 0.1 mg of iv fentanyl and 10 mg of iv diazepam. All groups received an ultrasound-controlled single-shot femoral nerve block which was accomplished after skin disinfection of the inguinal region of the involved limb. An insulated stimulating needle 50 mm 21-gauge ("Contiplex", BBraun) was inserted at a 40° in a cephalic direction. Quadriceps contraction and patellar elevation via nerve stimulation with a minimum current of between 0.6 and 0.3 mA were used to confirm exact location of the femoral nerve. The bolus of 20 ml of 0.5% bupivacaine (100 mg) with epinephrine (1:200.000) was injected. The spinal anesthesia was induced in a sitting position for all subjects immediately after the completion of the femoral block procedure. After skin disinfection and sterile draping of the procedure site the lumbar block was performed in L_{3-4} interspace. A 27-gauge needle type Quincke ("Spinocan", BBraun) with 15^0 cephalad angulation was advanced until the specific click was felt. After the free flow of cerebro-spinal fluid was observed the 0.5% isobaric bupivacaine was injected aiming to obtain a sensory block to Th8. Patients were then returned to supine position and given to breathe the mixture of air and oxygen (3 L/min) via facial mask. At the end of the operation (10 min. before tourniquet's release) the surgeon injected into the articular cavity 6 mg of morphine (I group) with 10 ml 0.9% normal saline, 0.5 mg of neostigmine (II group) with 10 ml 0.9% normal saline or placebo (III group) – 10 ml 0.9% normal saline sole. Continuous observation of pulse oximetry data was applied, and basic hemodynamic parameters (ECG, non-invasive arterial blood pressure) were evaluated every 5 min in the operating theatre, and also every 6 hrs during the 48 hrs postoperative period.

2.2. Postoperative rescue pain management

The numeric rating pain scores (NRS) [0–10] were evaluated every 6 hours by the nursing staff asking unified questions. The following adjuncts were administered on as needed basis: intramuscular diclofenac 75 mg was given when NRS was 1–3, and/or iv tramadol 50 mg– when NRS ≥ 4.

2.3. Data Collection

Study personnel who collected data was blinded to the group allocation of subjects. Postoperative motor block of the operated leg was evaluated by the Bromage scale [1–4]. Pain intensity data at rest and especially at motion (treading down) was collected at three timepoints during 48 hours after induction of anesthesia: first checkpoint referred to as Day 0 was at the time when motor block reached Bromage scale 2 (just able to flex knees with free movement of feet). The next checkpoint referred to as Day 1 was at 24 hrs following induction of anesthesia; the last checkpoint referred to as Day 2 was at 48 hrs following induction of anesthesia: patient was asked about the most painful score at rest and at motion during last 24 hours. Consumption of NSAIDs and opiates was registered at the same time. The patient satisfaction was evaluated at the end of the trial by asking subjects to provide the overall evaluation in a scale from 0 to 10. The adverse events included hypotension (with or without nausea/vomiting), postoperative bladder catheterization and postdural puncture headache. Postoperative hospital length of stay was also reported.

2.4. Statistical Analysis

We have not performed the prospective power calculation while planning our research as no reference data on this specific method were available. Descriptive summaries are presented as frequencies and percentages for categorical data (sex and ASA) and as means and standard deviations for continuous variables (age and other). The analysis of variance *One Way ANOVA* and nonparametric *Kruskal-Wallis test* have been applied in the investigation of difference between the groups. For the comparing groups in pairs *Wilcoxon-Mann-Whitney test* for two independent samples was used. Percentages between the groups were compared with *Fisher's exact* or *Chi-square test*. A value of $p \leq 0.05$ was considered significant in all tests.

3. Results

Baseline characteristics of the subjects was similar considering sex (p=0.65) and ASA physical state class (p=0.64); the similitude of age, BMI, surgery duration, motor block duration and hospital stay is shown in Table 1.

Table 1. Demographics

	I (n=20)	II (n=20)	III (n=20)	P(ANOVA)
Age, year	30.50±9.50	29.05±7.94	30.50±7.90	0.82
BMI*, kg/m^2	25.15±3.15	25.50±2.87	24.90±3.28	0.83
Surgery duration, min	66.55±15.95	76.50±18.14	71.00±22.40	0.26
Motor blockade duration, h	6.84±2.23	6.17±1.99	5.62±1.17	0.12
Hospital stay, day	3.65±0.75	3.30±0.80	3.70±0.73	0.23**

Data are reported as mean ± SD, standard deviation.
**BMI: body mass index.*
***Kruskal-Wallis test was used, because normality assumption was not valid in this case.*

Table 2. Pain intensity, VAS [0–10]

	I (n=20)	II (n=20)	III (n=20)	P(ANOVA)	P(Kruskal-Wallis)
Day of operation	4.85±1.42	4.9±1.45	5.05±1.96	0.92	0.96
1st day in rest	0.7±1.08	0.45±0.76	0.75±0.91		0.59*
1st day at motion	3.4±2.01	3.65±2.06	3.9±2.02	0.74	0.76
2nd day in rest	0.45±0.69	0.15±0.37	0.4±0.68		0.29*
2nd day at motion	1.95±1.19	1.45±1.36	2.3±1.17	0.103	0.05

Data are presented as mean ± SD, standard deviation.
** Kruskal-Wallis test sole was used, because normality assumption was not valid in this case.*

3.1. Postoperative pain

3.1.1. Pain at rest (NRS)

There was no significant difference between the mean values of NRS in all groups on Day 0 (*Kruskal-Wallis* p=0.96) and Day 1 (Kruskal-Wallis p=0.59) (Table 2). The comparison of pairs also did not provide significant differences on Day 1 between groups I and II (*Mann-Whitney* p=0.79), I and III (*Mann-Whitney* p=0.93), also II and III (*Mann-Whitney* p=0.8). Similarly, there was no significant difference between the mean values of NRS in all groups on Day 2 (*Kruskal-Wallis* p=0.29), and among the paired groups I and II (*Mann-Whitney* p=0.12), I and III (*Mann-Whitney* p=0.77), also II and III (*Mann-Whitney* p=0.22).

3.1.2. Pain at motion (NRS)

There was no significant difference between the mean values of NRS in all groups on Day 1 (*Kruskal-Wallis* p=0.76), and Day 2 (*Kruskal-Wallis* p=0.05), but the comparison of pairs revealed that pain at motion on Day 2 was significantly better in group II than in group III (*Mann-Whitney* p=0.018) (Figure 2). Meanwhile, differences were not significant between paired groups I and II, also I and III (*Mann-Whitney* p=0.11, p=0.34, accordingly).

3.2. Adjunctive pain management

Consumption of Diclofenac was not significantly different between groups on Day 0 (*Chi-square* p=0.85), on Day 1 (*Chi-square* p=0.41) and on Day 2 (*Chi-square* p=0.9). Consumption of Tramadol was also similar on Day 0 (*Fisher's exact* p=0.62), on Day 1 (*Fisher's exact* p=0.72) and on Day 2 (p=1).

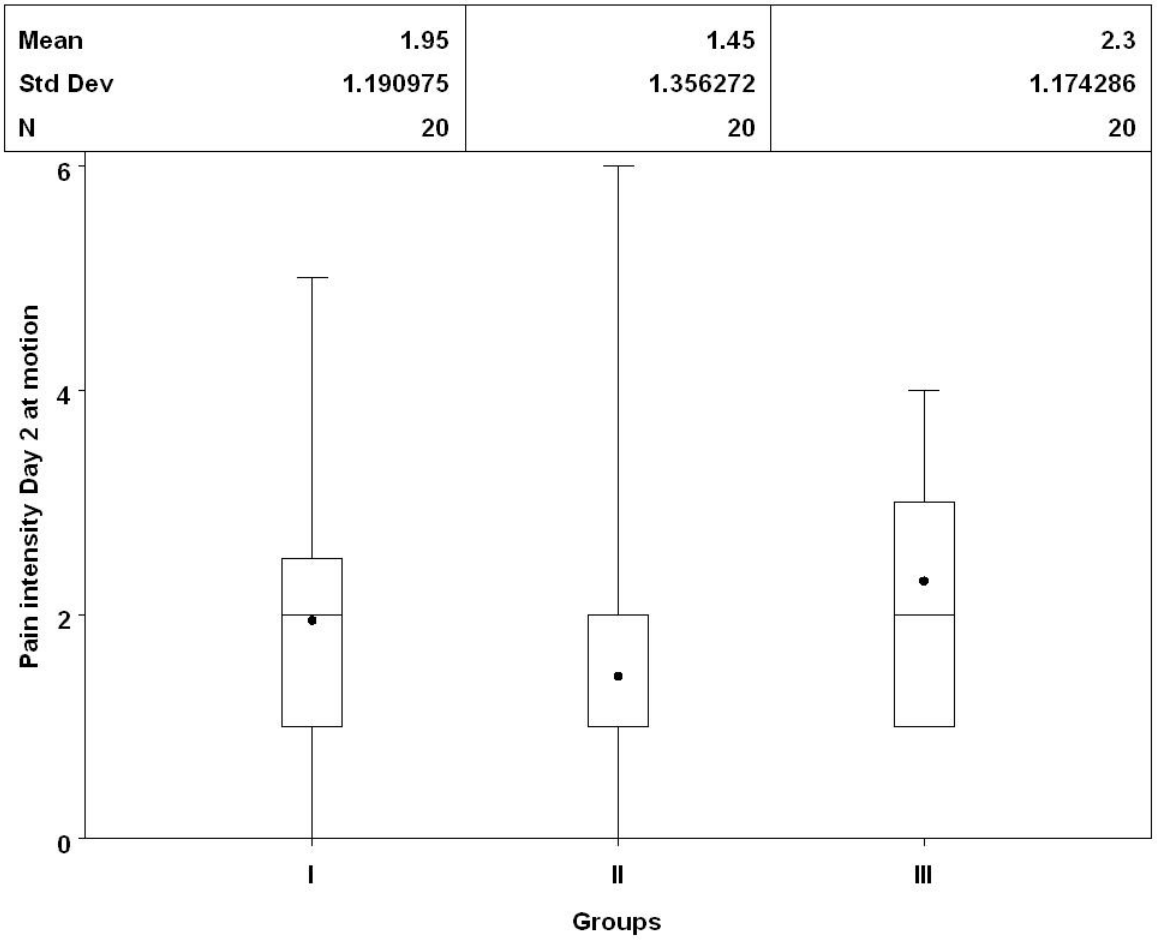
3.3. Patient satisfaction at the end of trial

There was no significant difference between the mean values of patient satisfaction in protocol groups I, II and III (*Kruskal-Wallis* p=0.59; *Mann-Witney* p=0.32).

3.4. Complications

The complications were mostly related to the spinal anesthesia technique (urine retention 5%; postdural puncture headache 8.33%; hypotension 13.33%; and backache 6.67%). Also, 11.67% of patients had fever and 1.67% of patients – the paresthesias in femoral nerve area (after single-shot femoral nerve block). However, any complications related to the usage of intra-articular medicament were observed.

Figure 2. Pain intensity [0–10] at motion on Day 2 was significantly better in group II than in group III (Mann-Whitney p=0.018).



4. Discussion

In contrast to conventional practice, in our trial the intra-articular morphine or neostigmine were diluted in normal saline rather than mixed with bupivacaine solution. We expected that intra-articular morphine (group I) will be associated with a better pain control after the ACL repair surgery during the whole trial (48 postoperative hours). But we didn't observe its significant analgesic effectiveness. However, our study revealed that the difference only was observed on Day 2. It was associated with the primary endpoint (pain at motion), and it was observed between two groups, since only intra-articular neostigmine (group II) has demonstrated advantage over placebo (group III). Several mechanisms may explain this peripheral cholinergic antinociception. That may be related to hyperpoliarization of neurons, reduction in the release of pronociceptive neurotransmitters, or activation of the nitric oxide-cyclic guanosine monophosphate pathway by elevating endogenous acetylcholine [13]. A possible explanation why there were no differences on Day 1 is the residual analgesic effect of SFNB since the allowed force of treading down was similar in all groups at the time of evaluation.

Numerous reports in literature do not show significant advantages of intra-articular morphine (1-5 mg) alone or in combination with bupivacaine over bupivacaine alone [10,14]. Moreover, the qualitative systematic review of well controlled trials compared postoperative pain intensity and reported no additive analgesic effect of intra-articular morphine comparing to saline [12]. Our study is probably the first to compare in a placebo controlled manner the efficacy of end-surgery injection of intra-articular morphine and nesotigmine without local anesthetics in addition to spinal anesthesia combined with SFNB. The rather similar study by McCarty and colleagues also did not find support for intra-articular injection of morphine (5 mg) after arthroscopic ACL reconstruction in addition to general anesthesia combined with SFNB [15]. We used a bigger dose of morphine (6 mg) aiming for a more pronounced analgesic effect.

According to literature reports, the adverse systemic reactions of intra-articular morphine and neostigmine is a reasonable concern [6,9,11,16]. However, we did not observe the side effects such as nausea, bradycardia, miosis, pruritus, hypersalivation or confusion. The deficiency of our study is that we did not evaluate the systemic action of morphine or neostigmine by measuring their levels in circulation.

The peripheral nerves such as sciatic and obturator may probably contribute to the postoperative pain [17]. That may be the cause of the need for rescue analgesics despite the end-of-surgery intra-articular injection of morphine or neostigmine. Thus, in our trial there was a need for adjunct analgesics to contest with mild-to--moderate pain during 48 hrs after ACL reconstruction in all groups.

The main shortcoming of our study can be associated with the fact that different surgical teams have operated the subjects. Thus, although the surgical methodology was the same, differences in surgical stress could be present.

5. Conclusions

Intra-articular neostigmine (0.5 mg) provided similar pain control at motion as morphine (6 mg) during 48 hrs after ACL reconstruction, but neostigmine (0.5 mg) was better than placebo on the 2nd postoperative day. Similar pain control at rest, adjunct consumption and patient satisfaction was recorded during 48 hrs after ACL reconstruction in all groups.

6. Acknowledgement

Conflict of interest: there is no conflict of interest among the authors.

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