# Combined pre- and post-surgical bupivacaine wound infiltrations decrease opioid requirements after knee ligament reconstruction

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Purpose: To test the efficacy of a combination of selective pre- and post-surgical local anesthetic infiltrations of the knee, compared with standard intra-articular injection at the end of surgery alone, to reduce postoperative opioid requirements following arthroscopic cruciate ligament reconstruction (ACLR).

Methods: In a double-blind, randomized, controlled trial, we studied 23 patients (ASA I or II) scheduled for elective ACLR under general anesthesia. The treatment group ($n = 12$) received infiltrations with bupivacaine 0.25% with epinephrine 1:200 000 presurgically (10 ml into the portals, 10 ml at the medial tibial incision site, 10 ml at the lateral femoral incision site, and 10 ml intra-articularly) and postsurgically (5 ml at the medial tibial incision and 10 ml at the lateral femoral incision). The control group ($n = 11$) received infiltrations with saline 0.9% in the same manner. All patients received a standard intra-articular local anesthetic instillation of the knee (25 ml of bupivacaine 0.25% with epinephrine 1:200 000) at the completion of surgery.

Results: Postoperative opioid requirements were lower in the treatment group (5.8 ± 2.9 mg morphine equivalent) than in the control group (13.7 ± 5.8 mg; $P = 0.008$). Treatment patients were ready for discharge approximately 30 min earlier than control patients ($P = 0.046$). There were no adverse events in the treatment group. In the control group, 2/11 patients vomited and a third experienced transient postoperative diaphoresis, dizziness and pallor.

Conclusion: We conclude that a combination of selective pre- and post-surgical wound infiltration with bupivacaine 0.25% provides superior analgesia compared with a standard post-surgical intra-articular injection alone.

Objectif : Tester l'efficacité d'une combinaison d'infiltrations sélectives du genou, préopératoires et postopératoires, avec un anesthésique local, comparée à l'injection intra-articulaire régulière de fin d'intervention seulement, dans le but de réduire les besoins postopératoires d'opioïdes à la suite de la reconstruction arthroscopique du ligament croisé (RALC).

Méthode : L'étude randomisée, contrôlée et à double insu a porté sur 23 patients (ASA I ou II) pour qui une RALC avait été prévue sous anesthésie générale. Les patients étudiés ($n = 12$) ont reçu des infiltrations préchirurgicales de bupivacaïne à 0,25 % avec de l'épinéphrine à 1:200 000 (10 ml via le portail, 10 ml au site d'incision tibial médian, 10 ml dans l'incision fémorale latérale et 10 ml intra-articulaire) et postchirurgicales (5 ml dans l'incision tibiale médiane et 10 ml dans l'incision fémorale latérale). Les patients témoins ($n = 11$) ont reçu des infiltrations de solution salée à 0,9 %, administrées de la même manière. Tous les patients ont reçu une instillation anesthésique standard locale dans l'articulation du genou (25 ml de bupivacaïne à 0,25 % avec de l'épinéphrine à 1:200 000) à la fin de l'opération.

Résultats : Les patients testés ont demandé moins d'opioïdes postopératoires (5,8 ± 2,9 mg d'équivalent de morphine) que les patients témoins (13,7 ± 5,8 mg; $P = 0{,}008$). Ils ont pu recevoir leur congé 30 min plus tôt que les patients témoins ($P = 0{,}046$). On n'a pas noté d'effets indésirables chez les patients testés. Parmi les patients témoins, 2/11 ont eu des vomissements et un tiers a présenté une diaphorèse postopératoire transitoire, des étourdissements et de la pâleur.

Conclusion : Une combinaison d'infiltrations préchirurgicales et postchirurgicales du site d'incision avec de la bupivacaïne à 0,25 % fournit une analgésie supérieure à la seule injection intra-articulaire postchirurgicale standard.

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ANTERIOR cruciate ligament reconstruction (ACLR) frequently is associated with considerable postoperative pain and it remains a challenge to provide adequate analgesia with minimal side effects. Opioid administration is among the oldest and most commonly used strategies for postoperative analgesia. Unfortunately, pain relief with opioids is often unsatisfactory,[1–3] may cause pain upon intra-articular injection,[4] and can lead to a delay in recovery and hospital discharge due to associated adverse events. Regional nerve blocks, such as femoral nerve blockade, have been employed with some success;[5,6] however, there is an inherent risk of neuropraxia and conflicting data regarding efficacy.[7] Both pre-surgical[8,9] and post-surgical[10] local anesthetic (LA) infiltration have been shown to be effective in reducing postoperative analgesic requirements with minimal side effects. Although pre-emptive injections may decrease postoperative hyperalgesia, this effect may dissipate once the clinically effective block wears off,[11] and therefore may not provide sufficient pain relief into the postoperative period. Post-surgical LA administration, on the other hand, carries the potential to provide longer lasting pain relief but may not offer the benefit of pre-emptive blockade of-post-injury nociceptive processing. Consequently, it was our intention in the present study to optimise analgesia by using a combination of selective pre- and post-surgical infiltrations of the knee, rather than selecting a single period for the LA infiltration.

We hypothesised that a combination of pre- and post-surgical LA infiltrations, selectively infiltrating each site of surgical trauma, would reduce postoperative opioid requirements and allow patients to emerge from general anesthesia with minimal side effects. Here, we report on a technique that is easy to perform, safe, effective, and devoid of major postoperative nausea and vomiting (PONV).

## Patients and methods

### *Study design and patient selection*

We conducted a prospective, randomised, controlled, and double-blind trial at a single centre with approval by the institutional ethics committee on human research. Patients aged 18–65 yr, ASA physical status I or II, and scheduled for elective, outpatient, arthroscopic ACLR under general anesthesia were eligible for the study. Exclusion criteria included inability to provide informed written consent, physical disability other than the assigned surgical procedure, medication use contradictory to this study, allergies to medications used in the study, or history of bleeding tendency. Twenty-four patients were randomised *a priori* in blocks of four to either the treatment or control group. Patients, surgeon, anesthesiologists, nurses, and data collector were blinded to group allocation. All procedures were performed by the same surgeon.

### *Study implementation*

All patients received a standardised general anesthetic. Midazolam (0.1–0.3 $mg \cdot kg^{-1}$) *iv* was optionally administered, followed by propofol (2–3 $mg \cdot kg^{-1}$) for induction. General anesthesia was maintained with isoflurane and nitrous oxide in oxygen, or a continuous propofol infusion. The use of intraoperative opioids was limited to *iv* fentanyl, with a suggested dose not to exceed 2 $\mu g \cdot kg^{-1}$ over the duration of the case.

Before each case, an operating room nurse was provided with an envelope with the randomisation instructions. Syringes containing either 40 ml saline 0.9% or 40 ml bupivacaine 0.25% with epinephrine 1:200 000, were prepared by the nurse for the pre-incisional injections. After induction of general anesthesia, the surgeon administered the local anesthetic to the treatment group as follows: 10 ml evenly distributed intradermally (*id*), subcutaneously (*sc*) and periosteally (*po*) at the anteromedial tibial incision site; 10 ml *id*, *sc* and *po* at the lateral femoral incision site; 10 ml at the three portal sites; and 10 ml intra-articularly (40 ml total volume). Patients in the control group received wound and intra-articular saline (0.9%) prior to the first incision in the same manner.

Hamstring tendon autografts were used in all patients to reconstruct the anterior cruciate ligament. Tendons from the gracilis and semitendinosus muscles were sutured together, guided through a tibial bone tunnel and stapled to the lateral femoral condyle.

At the completion of surgery, patients in the treatment group again received 5 ml bupivacaine around the tibial incision and 10 ml around the lateral femoral incision, while patients in the control group received saline in the same manner. All patients received 25 ml intra-articular bupivacaine post-surgically, in compliance with the institutional standard.

After completion of the procedure, patients were transferred to the postanesthetic care unit (PACU). Postoperative pain was assessed and managed based on the patient's request for analgesia and the nurse's clinical assessment. Pain intensity was assessed using a 10-point verbal rating scale. Patients who reported a score of 5 received *iv* morphine or *iv* fentanyl in the PACU unless they declined. Nurses were also able to administer oral acetaminophen (325 mg) or acetaminophen (300 mg with codeine (30 mg) (one to two tablets every four hours as needed). For home use, patients were prescribed oral acetaminophen (300

TABLE I Patient demographics and surgical data

| | *Control* | *Treatment* |
|---|---|---|
| *n* | 11 | 12 |
| Age (yr) | 30 ± 7 | 33 ± 10 |
| Height (cm) | 169 ± 8 | 179 ± 10 |
| Weight (kg) | 79 ± 12 | 85 ± 13 |
| Duration of surgery (min) | 60 ± 12 | 50 ± 10 |
| Intraoperative fentanyl ($\mu g \cdot kg^{-1}$) | 1.24 ± 0.03 | 1.19 ± 0.04 |
| Intraoperative midazolam ($mg \cdot kg^{-1}$) | 1.0 ± 0.9 | 1.4 ± 1.0 |
| Propofol infusion – no $N_2O$ (No. of patients) | 2 | 1 |
| Gender (M / F) | 7 / 4 | 11 / 1 |

Data are given as mean ± SD where appropriate

TABLE II Secondary variables

| | *Control* | *Treatment* |
|---|---|---|
| Time to readiness for hospital discharge (min) | 206 ± 37 | 169 ± 49 |
| *Adverse events* | | |
| PONV | 2 / 11 | 0 / 12 |
| Other (see text) | 1 / 11 | 0 / 12 |

Data are given as mean ± SD where appropriate
PONV denotes postoperative nausea and vomiting

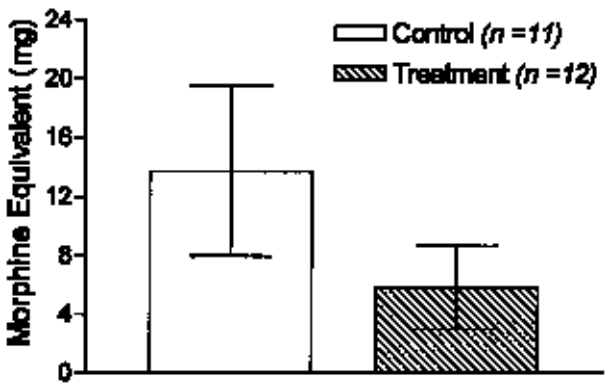


FIGURE Postoperative analgesic requirement within first four hours prior to discharge.
Data are given as mean ± 95% CI. One-tailed t test, $P$=0.008. For morphine equivalent dose conversion, see Appendix.

mg) with codeine (30 mg) (one to two tablets every four hours as needed).

Prior to discharge, patients were requested to complete a record of the time, type, dose and reason for all medication use for 24 hr following surgery. Also included was a four-choice satisfaction questionnaire to assess quality of pain relief and pain management by physician, and a 10-point pain rating scale to assess the intensity of pain experienced 24 hr following the operation. Patients were discharged home according to standard hospital criteria, including clear mentation, stable vital signs, ability to tolerate oral fluids, satisfactory pain control with oral analgesics, ability to ambulate with crutches, and ability to void. Patients were followed up by telephone on the first postoperative day and asked to return the questionnaires and analgesic diaries.

The primary efficacy variable was opioid analgesic requirement in the first four postoperative hours, which was obtained from the patients' chart and expressed as mg morphine equivalent[12–14] (see Appendix). Secondary variables included the incidence of PONV and time to readiness for discharge from hospital, as well as patient satisfaction.

*Statistical analysis*

Results are presented as means ± SD or means ± 95% CI where appropriate. Data from a pilot study were used to project the sample size required to obtain a minimum important difference in postoperative analgesic requirements of greater than 25% at =0.05 and 1–ß=0.8. Parametric (Student's t test), non-parametric (Mann- Whitney U), and categorical (Fisher's exact) tests were used as appropriate. Significance was set at $P$=0.05.

## Results

Patient demographics were comparable between both treatment and control groups (Table I). One of the 24 patients enrolled was excluded following induction of anesthesia because surgery was no longer considered necessary.

Postoperative analgesic requirement was lower in the treatment group (5.8 ± 2.9 mg morphine equivalent) than in the control group (13.7 ± 5.8 mg; $P$ <0.01) (Figure). In the control group, 2 / 11 patients experienced PONV. A third patient underwent a transient period of postoperative diaphoresis, dizziness and pallor. No adverse events were observed in the treatment group. There were no symptoms or signs of LA toxicity in either group. Patients in the treatment group were deemed ready for hospital discharge approximately 30 min earlier than patients in the control group ($P$ <0.05) (see Table II).

Eight patient satisfaction questionnaires were returned per group. In the first 24 hr following discharge, there were no differences in analgesic require-

TABLE III Follow-up diary and questionnaire

| | *Control* | *Treatment* |
|---|---|---|
| Number of questionnaires returned | 8 | 8 |
| *Patient analgesic requirements (mg morphine equivalents)* | | |
| Postoperative opioid requirements up to 24 hr after discharge | 11.8 ± 11.0 | 9.4 ± 11.3 |
| *Pain Rating (10 point scale)* | | |
| 1. What is the worst pain you have experienced in the last 24 hr? | 9.0 ± 1.1 | 7.6 ± 1.6 |
| 2. What pain are you experiencing now, 24 hr after the operation? | 5.3 ± 2.8 | 5.3 ± 2.7 |
| *Patient Satisfaction (four choice questionnaire)** | | |
| 3. How satisfied are you with the way your pain was treated? | 1 | 1 |
| 4. How satisfied are you with the way the doctor treated your pain? | 1 | 1 |

Data are given as mean ± SD or median, where appropriate

*1 represents the highest satisfaction

ments, pain scores, or patient satisfaction between the treatment and the control group (see Table III). Patients in both groups were generally satisfied with their pain management.

## Discussion

We found that in patients undergoing ambulatory ACLR, a combination of selective pre- and post-surgical local infiltrations of the knee with bupivacaine (0.25%) with epinephrine (1:200,000) reduced postoperative analgesic requirements by more than 50% within the first four hours postoperatively, compared with intra-articular instillation at the end of surgery alone. Consistent with previous findings,[15] there was no decrease in postoperative pain in the first 24 hr following discharge.

Despite the popularity of local anesthetic strategies for postarthroscopy analgesia, the data regarding its effectiveness in decreasing postoperative pain is conflicting[16] – whereas some authors have demonstrated a benefit,[15,17–22] others have not.[23–26] Several reasons may account for this. First, most trials have investigated analgesia following diagnostic arthroscopy and meniscectomy, which are considerably less invasive procedures than ACLR. Second, others employed different anesthetic management techniques for each study group, e.g., spinal *vs* general anesthesia.[27] Finally, there is disagreement among authors regarding the optimal time for LA administration. Some have suggested pre-surgical, or 'pre-emptive', injections will provide the most effective postoperative pain relief,[8] whereas others have not found such a benefit when compared to post-surgical injections.[11,28,29] A combination of injections both pre- and post-surgically has been reported by Williams *et al.*;[30] however, the efficacy of this technique remains unclear since this was an observational case series intended to compare postoperative pain following ACL reconstruction to non-ACL knee arthroscopy. Also, there is no mention of patient selection criteria or whether the investigators were blinded during data collection. Thus, our study is the first randomised, double-blind, controlled study that has tested the efficacy of a combination of pre-surgical and post-surgical local anesthetic infiltration in providing pain relief after ACLR.

The total cumulative dose of bupivacaine used in the present study was 200 mg. Higher doses of bupivacaine have been administered into the knee joint at the end of arthroscopic surgery without any signs of CNS or cardiovascular toxicity;[31] however, doses are not recommended to exceed 200 mg.[32] Although serum bupivacaine concentrations were not measured in our trial, the absence of clinical signs of systemic toxicity harmonizes with previous findings that peak serum bupivacaine concentrations remain below toxic concentrations at any given time, particularly following irrigation of the knee.[33,34] Furthermore, the dose of bupivacaine was divided between the beginning and end of the procedure in our trial; thus, a total of 100 mg bupivacaine was injected with 50.3 ± 9.5 min of lapsed time before the second administration.

In summary, the administration of a combination of selective pre- and post-surgical bupivacaine infiltration of the knee reduced analgesic consumption compared with standard intra-articular instillation at the end of surgery alone. In addition to the reduction in analgesic requirement, the time to readiness for discharge was approximately 30 min earlier in the treatment group, which also indicates better pain management in the bupivacaine group as well as a decrease in the incidence of adverse events. The use of this technique allowed patients to recover from general anesthesia with minimal pain and, under the conditions of this trial, to be virtually free from PONV and other opioid-associated adverse events. We conclude that the combination of pre- and post-surgical infiltration provides excellent pain relief well into the postoperative period. We recommend this easy and safe regimen as a standard intervention in the anesthetic management of patients undergoing ambulatory ACLR.

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APPENDIX Morphine equivalency of analgesic agents

| *Agent* | *Dose for equivalent peak effect (mg)* | *Ratio* | *Average duration (min)* | *Ratio* | *Equivalency ratio* |
|---|---|---|---|---|---|
| Morphine *iv* | 10 | 1 | 180 | 1 | 1 |
| Morphine *im* | 10 | 1 | 180 | 1 | 1 |
| Fentanyl *iv* | 0.1 | 0.01 | 30 | 0.17 | 16.6 |
| Acetaminophen with codeine *po* | 1 tablet* | | | | 2.3 |

*One tablet contains 300 mg of acetaminophen and 30 mg of codeine

To obtain a morphine equivalent dose in mg, the total dose of each agent administered over a fixed period is multiplied by the equivalency ratio

Example: For a patient who received a total of 0.3 mg of fentanyl *iv*, 15 mg of morphine *im*, and two tablets of acetaminophen with codeine, the calculated morphine equivalent is 15(1) + 2(2.3) + 0.3(16.6)=24.6 mg

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