Evaluation of The Efficacy of Bupivacaine Soaked in Gelfoam® at the Iliac Crest Bone Graft Site

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Summary: Gamli M, Dalgic A, Ornek D, Horasanli E, Kilci O, Un C, Dikmen B – Evaluation of The Efficacy of Bupivacaine Soaked in Gelfoam® at the Iliac Crest Bone Graft Site.

Background and objective: A substantial number of patients report pain after graft harvest from the anterior iliac crest. This study examined the efficacy of local application of bupivacaine soaked in a Gelfoam® at the bone donor site in controlling postoperative pain and parenteral opioid use.

Method: We performed a prospective, double-blind, randomized, placebo-controlled study comparing intraoperative infiltration of 20 mililiters of bupivacaine (treatment, group B) versus saline (placebo), with Gelfoam® soaked into the iliac crest harvest site for patients undergoing elective cervical spinal surgery. Postoperative administration of dihydromorphinone hydrochloride (post anesthesia care unit and patient-controlled analgesia) was standardized. A pain score based on a 10-point visual analog scale (VAS). was used to assess the severity of pain associated with donor site. Pain scores and narcotic use/frequency were recorded at the twenty-four and forty-eighth hour after the operation. Physicians, patients, nursing staff, and statisticians were blinded to the treatment.

Results: The groups were similar in baseline age, gender, and comorbidities. There was no significant difference between groups in VAS scores. Narcotic dosage, were significantly less in the Group B at 24 and 48 hours ($p < 0.05$).

Conclusion: This study has demonstrated that bupivacaine soaked in gelfoam at the iliac bone graft harvest site reduced postoperative parenteral opioid usage.

Keywords: Bupivacaine; Bone Transplantation; Diskectomy; Gelatin Sponge, Absorbable.

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INTRODUCTION

Iliac crest is the most common donor site for bone grafts regarding spinal arthrodesis procedures due to easy access to large quantities of both cortical and cancellous (trabecular) bone. Although iliac crest grafting remains the gold standard in spinal reconstructive surgery due to its osteoinductive, osteoconductive, and nonimmunogenic properties, donor site morbidity associated with iliac bone graft (ICBG) harvesting is a significant postoperative concern both for patient and surgeon[1-4]. Pain on the donor side is sometimes so severe that it could mask the pain at the operative region, and thus may increase the demand for postoperative analgesia [1-6]. A subgroup of these patients report severe pain and experience significant functional loss as a result of graft site pain [2,6]. Many approaches and techniques have been proposed to minimize the morbidity associated with iliac crest bone graft harvest. These include surgical approaches and techniques, preventive infiltration continuously with local anesthetics and opioids, and preventive systemic use of medications [3,4].

We hypothesize that bupivacaine soaked in gelfoam will decrease the pain and opioid use at the ICBG harvest site. The purpose of this study was to evaluate whether bupivacaine soaked in gelfoam at the ICBG harvest site reduces postoperative pain and parenteral opioid use.

METHOD

A single-center, prospective, double-blind, randomized, placebo-controlled trial conducted to evaluate the bupivacaine infiltration of anterior iliac crest donor sites (treatment) against saline infiltration (placebo control) in elective cervical spinal fusion surgery. Patients were enrolled in the study after ethic committee approval and informed consent was obtained, between August 2006 and August 2007 in the 'Ankara Numune Training and Research Hospital' in Ankara (Turkey) at neurosurgery's operation rooms.

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Participants in this study were identified by the spine surgeon. Inclusion criteria entailed patients between 18 and 85 years of age who failed conservative treatment (physical therapy, trigger point injections, epidural injections, drug regimens consisting of NSAIDs, muscle relaxants, and pain-specific medication) for their symptoms associated with either cervical pathology, and willingness to participate in the study, and patients who were scheduled for a one level anterior cervical discectomy with the use of autograft were candidates for the study.

Exclusion criteria considered individuals who underwent surgical intervention in the past six months, previous iliac crest bone harvesting, history of tumor and spondyloarthropathies (rheumatoid arthritis, seronegative arthritis), history of adverse reaction to local anesthetic, opioid addiction, pregnancy, acute mental illness, uncontrolled major depression and any other psychiatric disorders, who had lumber disk pathology and two or more cervical spinal fusion and inability to understand the informed consent and demands of the study.

A standardized anesthesia protocol was used. Induction was done with propofol at 2-3 $mg.kg^{-1}$ and fentanyl at 3 $\mu g.kg^{-1}$ intravenous infusion. Muscle relaxation for tracheal intubation was obtained with vecuronium bromide 0.1 $mg.kg^{-1}$ and bolus doses were done when needed. Anesthesia was maintained with one minimum alveolar concentration (MAC) sevoflurane in oxygen with 50% nitrous oxide. At the end of the procedure, reversal of residual neuromuscular blockade was permitted using appropriate doses of neostigmine and atropine. Once spontaneous respiration resumed, patients were extubated and taken to the postanesthesia care unit (PACU).

On enrollment in the study, the participants were coded to optimize blindness and facilitate randomization by means of a computer-based number generator. Randomization attempted to entail a 1:1 design. Randomization and allocation to group type were concealed and not made public to the individual enrolling the patients, the treating physician, or the nursing staff until the end of study.

Drugs were prepared by the pharmacy, labeled by study identification number only, and were administered by the surgeon who remained blinded to the syringe contents. Patients, nurses, research assistants, and the statistician were also blinded to the treatment allocation.

The design consisted of a control group (Group S; n = 8) and a treatment group (Group B; n = 11). In Group S; patients received a piece of Gelfoam® soaked with 20 mililiters of physiologic saline at ICBG harvesting site. In Group B they received the same Gelfoam® soaked with 20 mililiters 0.25% bupivacaine packed into the bone defect.

In the PACU patients were connected to a patient controlled analgesia (PCA) pump containing dihydromorphinone hydrochloride 0.2 $mg.mL^{-1}$. Initial settings were for administration of a loading dose of 0.4 mg, a lockout interval of 10 minutes, and PCA dose 0.2 mg. If analgesia was inadequate after 1 hour, the bolus dose was increased to 0.4 mg by the PCA team, all of which was blinded to the treatment arm.

With regard to opioid usage, the total amount of delivered (in milligrams) analgesic was recorded for the 24 and 48 hour postoperative period. Furthermore, a pain score based on a 10-point visual analog scale (VAS; range 0-10) was used at the same time intervals (24, 48) to assess for the pain associated with the spinal incision, iliac crest-related pain, and overall pain. A VAS score of 1 was defined as no pain, and a score of 10 was defined as the worst pain imagined by the patient. Assessment of pain outcomes was conducted subjectively by the patients. The amounts of used opioid were recorded by a consistent assessor and validated by the observations from the nursing staff, all blinded to the type of intervention each group received. In addition, evaluation of the iliac crest also served to detect the presence of infection and nerve-related injury at all time points (24, 48 hours after surgery).

The main endpoint of this study was a pain score (VAS) evaluation. Secondary endpoint was postoperative opioid consumption through PCA. All data were collected and recorded using a Microsoft Excel spreadsheet. SPSS version 11.5 software was used to conduct statistical analyses. Based on a previous study [4], we calculated a simple size that would allow a type I error $\alpha = 0.05$ with a type II error of $\beta = 0.05$ and power of % 95. The enrollment of 10 patients in each group was required. Results are presented as mean (SD). Frequency and descriptive analyses were conducted of all data sets. Testing for normality of distribution and appropriate parametric and nonparametric analyses were performed. Statistical analysis was performed using Student's *t* test for parametric data and the chi-square test for nonparametric data. A p value of 0.05 was considered significant.

RESULTS

Twenty-four patients were asked to participate, and five patients declined. Patient demographic data are presented in Table I. There was no significant difference between the groups considering age, weight, gender, anesthesia and surgery duration.

There was no difference between groups for VAS scores ($p > 0.05$) (Table II). There was significant difference in the dose of dihydromorphinone hydrochloride administered during titration or in the average intake of dihydromorphinone hydrochloride. Patients in Group B needed a smaller amount of dihydromorphinone hydrochloride ($p < 0.05$) (Table II).

Table I – Demographic Data According to Study Group

	Group S (n = 8)	Group B (n = 11)	p value
Males	3	5	0.373
Females	5	6	0.373
Age (yr)	39.6 (13.3)	40.1 (12.2)	0.673
Weight (kg)	89.8 (21.7)	87.2 (17.4)	0.320

The values are given as the mean (SD). The difference was significant at $p < 0.05$; Group S: Control Group; Group B: Bupivacaine Group.

Table II – Differences with Regard to VAS, and Amount of Pain Medication Delivered

	Group S (n = 8)	Group B (n = 8)	p value
VAS score at donor site	4.17 ± 1.3	3.98 ± 0.1	0.962
dihydromorphinone hydrochloride dosage first 24 hr (mg)	11.2 ± 0.43	5.9± 0.30	0.065*
dihydromorphinone hydrochloride dosage cumulative 48hr (mg)	16.0 ± 2.3	7.5 ± 2.2	0.025*
dihydromorphinone hydrochloride demand first 24 hr	109.6 ±2.31	55.8 ± 8.2	0.007*
dihydromorphinone hydrochloride demand cumulative 48 hr	135.1 ±12.7	63.5 ± 8.6	0.012*

The values are given as the mean (SD).
*($p < 0.05$); Group S: Control Group; Group B: Bupivacaine Group.

Furthermore, no indications of ICBG site infection, nerve injury, or other graft-site related complications were noted on postoperative examination.

DISCUSSION

The results of this study suggest that there is benefit in treatment with bupivacaine soaked in a Gelfoam® at the bone donor site during elective spinal fusion surgery to reduce postoperative dihydromorphinone consumption. No significant differences were detected with regard to VAS at any time points. The bupivacaine helped decrease opioid usage.

Several authors have proposed methods to reduce graft site pain. Wang et al. [7] found that reconstruction of the graft site with a resorbable mesh seemed to reduce pain in a retrospective case series. Singh et al. [1] found that continuous infusion of 0.5% bupivacaine at the ICBG harvest site reduced postoperative parenteral narcotic usage by 50% and decreased overall pain scores. In a double-blind, randomized, controlled trial of local bupivacaine injection into the iliac crest site performed by Cowan et al. [8], the authors used six postoperative injections of bupivacaine into the iliac crest of patients undergoing anterior cervical fusions. They observed that the patients receiving bupivacaine (n = 14) reported lower hip pain scores than the control group (n = 8). In addition, bupivacaine infiltration decreased mean morphine intake for the first 24 hours after surgery (treatment, 32 mg; placebo, 44 mg), and decreased hospital stay by one day (treatment, 3.6 days; placebo, 4.5 days). However, the disadvantages of repeated injection of a local anesthetic with obvious discomfort to the patient were an increased demand on the staff and increased chance of infection. Gundes et al. [9] conducted a randomized, controlled trial evaluating 45 patients alocated into three groups that were given a regional application of bupivacaine, morphine-bupivacaine or saline. The authors were interested in determining the effects of the local anesthetic infiltration into the ICBG site as a method of treating long-term pain and dysesthesia. The authors concluded that the infiltration of bupivacaine provided satisfactory anesthesia in the perioperative period and that the addition of morphine significantly reduced the analgesic requirements after surgery as compared to bupivacaine alone. Our findings were similar to those found in their studies. In ours, we it was observed a statistically significant decrease in opioid usage in patients treated with bupivacaine soaked in a Gelfoam® at the bone donor site. However, we did not find any statistically significant difference between groups in VAS scores.

Absorbable gelatin sponges are available in multiple formulations (sheds, powder, foam) of bovine, porcine or equine origin. Except for thrombin-soaked formulations, their hemostatic effect appears to be a physical effect rather than a 'surface effect'. Compared with collagen-based products, gelatin sponges reportedly form a better-quality clot. They are widely used in spine surgery and, as they do not swell, can be left in the canal [9]. We have not found out about the pharmacokinetics of local anesthetic added to Gelfoam®; however, the effects of the pharmacokinetics of a local anesthetic added to Gelfoam® may evaluate a different study.

During orthopedic surgery of the limb, Estebe et al. [4] performed a prospective, double-blind controlled study to evaluate the pharmacokinetic and pharmacodynamic effect of infiltration of the ICBG site with 20 mL of bupivacaine (100 mg), ropivacaine (150 mg) or control saline group (n = 10 each group). They concluded that pain at the ICBG site was reduced during the first 12 hours postoperatively in local anesthetic groups, compared to the control group. But they found no difference between the three groups in the average intake of PCA morphine.

Wai et al. [3] evaluated the efficacy of intraoperative infiltration of morphine into the anterior or posterior iliac crest harvest site for reduction of postoperative pain in elective lumbar or cervical spinal fusion surgery. They concluded there was no significant benefit from morphine infiltration to iliac crest harvest site in elective spinal surgeries. On the other hand, Gundes et al. [10] concluded that the infiltration of bupivacaine and morphine into the ICGB site significantly reduced the analgesic requirements after surgery.

Differences in the findings may be due to method of drug application or differences in surgery. One of the missing aspects of this study was that we did not compare the local anesthetic Gelfoam® implantation with infiltration or infusion.

Future studies can evaluate these groups. In addition, pharmacokinetic and pharmacodynamic studies can be performed in this practice-oriented drug absorption and compare levels of maximum activity.

Typically, protocols are enabled in the hospital that limits the speed at which patients are discharged. The reduced opioid requirements and pain relief afforded by the local anesthetic at the ICBG site can decrease hospitalization [1]. Opioid-related medical problems - such as respiratory complications - may be reduced as a result of adjunctive local anesthesia lowering opioid doses required, potentially decreasing medical costs associated with hospitalization, apnea monitoring, and intensive care unit stays [11]. Opioids also have a profound effect on cognitive ability. Administering smaller dosages of opioids in the geriatric population may theoretically decrease the incidence of mental status changes and may improve their rehabilitation [12]. Local anesthetic usage at the ICBG site can decrease these complications; however, this will require further prospective studies.

A risk for infection is present any time a foreign object is placed into the surgical site. In this study, no patient was noted to develop postoperative wound complications. This is most likely be explained by the use of antibiotics.

In conclusion, the local application of bupivacaine soaked in a Gelfoam® at the bone donor site helped decrease opioid usage postoperatively.

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