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RANDOMIZED TRIAL

Patients Cannot Reliably Distinguish the Iliac Crest Bone Graft Donor Site From the Contralateral Side After Lumbar Spine Fusion

A Patient-blinded Randomized Controlled Trial

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Study Design. A multicenter, randomized, intrapatient controlled trial.

Objective. This study investigated whether lumbar fusion patients blinded to the harvest site (A) can identify the iliac crest used for bone harvesting and (B) whether this iliac crest is more painful than the contralateral side.

Summary of Background Data. Spinal fusion with iliac crest autograft is a frequently performed surgical procedure. A widely reported disadvantage of the harvesting procedure is potential donor site morbidity. This has driven the development of many bone graft substitutes. However, more recently the incidence and severity of donor site pain is debated, especially in lumbar fusion surgery.

Methods. Ninety-two nontraumatic adult patients underwent a posterolateral (thoraco)lumbar fusion. Iliac crest bone graft was harvested unilaterally through the primary midline incision. At 6 weeks, 3 months, 6 months, and 1 year follow-up, patients were asked to identify the donor site and to rate pain in their back, left iliac crest and right iliac crest on a Visual Analogue Scale (VAS).

Results. Ninety patients, 44 males and 46 females with a mean age of 54 years, were analyzed. The left/right distribution of the iliac crest donor site was 50/50 and 89% of the patients underwent a lumbar fusion below L3. Only 24% patients identified the harvest site correctly. Moreover, the VAS pain scores for the donor site and contralateral iliac crest did not differ and were at each timepoint lower than the scores for back pain.

Conclusion. This study showed that, during the first year after lumbar fusion surgery via a single midline incision approach, patients could not reliably identify the iliac crest used for bone graft harvesting and this iliac crest was not more painful than the untouched contralateral iliac crest. Therefore, donor site pain should not be the main reason to use bone graft alternatives for lumbar spinal fusion.

Key words: autograft, bone graft harvesting, donor site pain, iliac crest bone graft, lumbar fusion, randomized controlled trial, spinal fusion.

Level of Evidence: 2

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The device is FDA-approved or approved by corresponding national agency for this indication.

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Spinal fusion is a surgical procedure that frequently involves a bone grafting procedure to establish a permanent bony fusion between vertebral segments. It is most commonly performed in the lumbar spine, followed by the cervical spine. Over the last decades, the number and costs of spinal fusion as treatment for various spinal conditions increased significantly.[1–3] With more than 500,000 procedures performed annually in the United States,[4] spinal fusion is likely the largest single indication for bone grafting.

Autologous bone graft is considered to be the gold standard to promote a bony fusion[5,6] and the iliac crest is the most common harvest site due to its easy access and adequate bone stock. However, potential donor site morbidity is generally considered a serious disadvantage of the harvesting procedure, with donor site pain being the most

commonly reported problem.[7–14] This has driven the development and popularity of many bone graft substitutes like allografts, bone morphogenetic proteins, and synthetic bone grafts, with a global market value of more than US$2.5 billion.[15–18]

Interestingly, some recent studies have debated the incidence and severity of donor site pain. Especially in lumbar fusion surgery, where the pain related to the primary surgical site may interfere with perceived iliac crest pain and a less traumatic harvesting technique avoiding separate incisions can be used.[19–23] However, most of these studies are limited by their retrospective design, nonblinded assessment of subjective outcomes or small sample size, which contributes to the controversy about donor site morbidity in this specific group.

We investigated the relevance of pain attributed to the donor site after instrumented posterolateral lumbar fusion in a prospective cohort of patients blinded to the bone graft harvest site. These data are collected as part of a multicenter, blinded, randomized, intrapatient controlled trial to investigate the noninferiority of a ceramic bone graft substitute compared with autograft. The current study investigated (A) whether patients can identify the iliac crest that is used for bone harvesting and (B) whether this iliac crest is more painful than the contralateral side.

MATERIALS AND METHODS

Study Design

The study involves a cohort of 92 adult patients who underwent an open, instrumented, posterolateral fusion between T10 and S1, as part of a multicenter, randomized, intrapatient controlled trial on safety and efficacy of AttraX Putty (NuVasive Inc, San Diego, CA; ClinicalTrials.gov Identifier NCT01982045). One side of the fusion trajectory was grafted with the ceramic bone graft substitute; the contralateral side was grafted with autologous bone from the iliac crest combined with local decompressive bone (autograft). Unilateral iliac crest bone graft harvesting was done through the same midline incision as used for the primary fusion surgery. Allocation of the graft type (left *vs.* right), and therefore the iliac crest bone graft harvest site, was based on computerized simple randomization. So each patient was blinded to both the allocation of the graft types and the iliac crest donor site. Radiological and clinical assessments were performed preoperatively and at 6 weeks, 3 months, 6 months, and 1 year after surgery.

Patients

Patients between 18 and 80 years of age were enrolled and treated in four Dutch hospitals between November 2013 and July 2016. Indications for fusion surgery were deformity, structural instability and/or expected instability (for example as a result of decompression for spinal stenosis). Exclusion criteria included recent traumatic spinal fracture, primary or metastatic spinal tumor, active local or systemic infection, any previous surgical attempt for spinal fusion or previous autologous bone grafting procedures that comprised the quality and amount of iliac crest bone graft.

Surgical Technique

All patients underwent a standard single or multilevel, instrumented, posterolateral fusion, with or without an additional interbody fusion device filled with local bone, at any of the segments between T10 and S1 via a posterior midline approach. The allocation side of the bone graft substitute was disclosed peroperatively after placement of all spinal implants, by opening a sealed envelope.

Iliac crest bone graft was harvested through the primary midline skin incision if possible, from the posterior iliac crest at the same side as placement of the autograft was allocated. Typically, a separate fascia incision was made and cancellous bone was harvested through a unicortical window using osteotomes and surgical spoons or gouges. The use of hemostatic sponges was according to the surgeon's preference. For the autograft side, a total of 10 cc autograft per fusion level, comprising of at least 50% iliac crest bone, was intended. The volume was assessed by gentle pressure of the graft in a 20 cc syringe.

After placement of both grafts around the posterior instrumentation and in the decorticated lateral gutters, the wound was closed in layers according to the surgeon's preference. No local anesthetics in the wound were used.

Outcome Measures

Patients received a set of patient reported outcome measures (PROMs) preoperatively and at 6 weeks, 3 months, 6 months, and 1 year after surgery. Pain in the lower back, left iliac crest area and right iliac crest area was measured using a continuous Visual Analogue Scale (VAS) ranging from 0 (''no pain at all'') to 100 (''intolerable pain''). In addition, patients were asked to identify the iliac crest used for bone graft harvesting (''left'' or ''right'') at all postoperative timepoints.

Statistical Methods

Data were processed in Research Online for Researchers (Julius Center, University Medical Center Utrecht) and analyzed using SPSS Statistics Version 22 (IBM). Baseline characteristics, surgical details, and the identified harvest site were summarized using descriptive statistics.

To investigate whether patients could identify the iliac crest used for bone graft harvesting during the first year after surgery, their responses at each timepoint were summarized into three categories: ''consistently correct'' (harvest site identified correctly at each follow-up), ''consistently incorrect'' (contralateral iliac crest identified as harvest site at each follow-up) and ''no idea/alternating responses'' (no idea or alternating responses between follow-up visits). These categories were analyzed with descriptive statistics.

The VAS pain scores were analyzed using mixed effects models, to take into account the correlation of repeated measurements within patients. Postoperative pain scores for the iliac crest donor site were compared with the pain scores

for the contralateral iliac crest. Fixed effects were timepoint (in weeks), preoperative iliac crest pain score and iliac crest side. In addition, the relation between donor site pain and amount of bone graft harvested was assessed with timepoint, preoperative iliac crest pain score and amount of bone graft harvested as fixed effects. In both models, a random intercept per patient and a first-order autoregressive correlation structure (AR(1)) were used to account for the correlation of measurements within patients over time. A third mixed model with a random intercept per patient was built to assess the relation between iliac crest pain and back pain, by subsequently adding the variables timepoint and back pain as fixed effects and calculating the R^2. The robustness of the mixed models was verified by a log transformation of iliac crest pain scores to correct for the right-skewed distribution. Statistical significance was set at $P < 0.05$ and a minimal clinically important difference (MCID) value of 15 mm for the VAS was adopted.[24]

Patients who completed less than two postoperative questionnaires were excluded from all analyses. Missing values were handled by pairwise deletion of cases, except for the mixed models. Normally distributed data are presented as mean and standard deviation (SD), whereas non-normally distributed data are presented as median and range or interquartile range (IQR).

Ethical Considerations

This investigator-initiated study was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht and the Institutional Review Board of each participating hospital. All study procedures were performed in accordance with the World Medical Association Declaration of Helsinki (version October 2008) and the Medical Research Involving Human Subjects Act (WMO). Written informed consent was obtained from each individual patient included in the study.

Source of Funding

The Department of Orthopaedic Surgery of the University Medical Center Utrecht received a restricted academic research grant from NuVasive Inc. to partially fund this investigator-initiated study.

RESULTS

Patient Characteristics

In 92 of the 100 patients operated on, the iliac crest bone graft was harvested through the primary midline incision and they were blinded to the donor site. The remaining eight patients were excluded as a separate incision was used. Two other patients were excluded, because they completed the PROMs at only one postoperative timepoint (Figure 1).

Baseline characteristics and surgical details of the 90 patients included in this study are presented in Table 1. There were 44 males and 46 females with a mean age of 54.4 ± 12.1 years (range 27–79). The majority of the patients underwent a single level (67%) or two-level

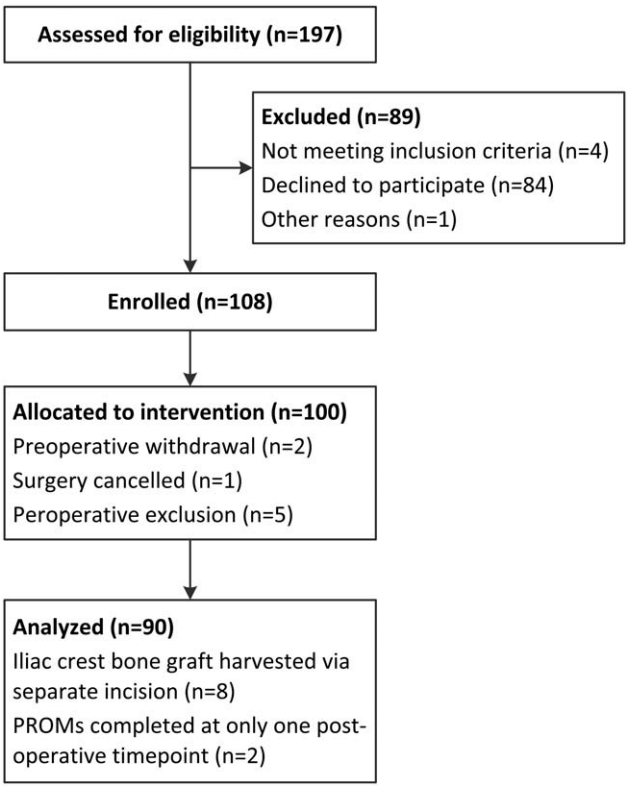

Figure 1. CONSORT flow diagram showing the flow of patients through each stage of the study.

TABLE 1. Baseline Characteristics and Surgical Details

Number of Patients	90	
Age, mean ± SD (range), *years*	54.4 ± 12.1 (27–79)	
Sex, n (%)		
Male	44 (49%)	
Female	46 (51%)	
Smokers, n (%)	31 (34%)	
Number of segments fused, median (range)	1 (1–8)	
Spinal region fused, n (%)		
Thoracolumbar	5 (6%)	
Lumbar	85 (94%)	
Decompression, n (%)	87 (97%)	
Interbody device, n (%)	57 (63%)	
Level and type of interbody device, n	PLIF	TLIF
L3–L4	6	4
L4–L5	18	6
L5–S1	25	6
Donor site, n (%)		
Left iliac crest	45 (50%)	
Right iliac crest	45 (50%)	
Obtained iliac crest bone graft, median (range), *cc*	6 (5–40)	

n indicates number of patients; PLIF, posterior lumbar interbody fusion; SD, standard deviation; TLIF, transforaminal lumbar interbody fusion.

(20%) fusion. All fusions involved the lower lumbar area (L3 or more caudally), whereas 89% underwent a low lumbar fusion between L3 and S1. Additional posterior lumbar interbody fusion and transforaminal lumbar interbody fusion procedures were performed in 49% and 14% of the patients respectively. The left/right distribution of the iliac crest donor site was 50/50. The amount of obtained iliac crest bone graft ranged from 5 to 40 cc, with a median of 6 cc. A total of 73 patients (81%) completed all PROMs. Two patients dropped out after 3 and 6 months of follow-up respectively. The remaining 15 patients completed follow-up, but had one or more missing values.

Harvesting Procedure

Iliac crest bone graft harvesting was uneventful in all patients and there were no deviations from the assigned iliac crest based on bone quality. One patient was unblinded after 3 months because of concerns about pain in the iliac crest area. The pain was indeed on the donor site and no further treatment was required.

To gain some insight in the extra surgical time required for harvesting, this was recorded in the last 36 patients. The median time to obtain median 5 (5–40) cc bone graft was 7.5 (5–25) minutes.

Donor Site Identification

To the question ''Is bone graft harvested from your left or right iliac crest?'', 46 patients (51%) consistently reported the same iliac crest site at each follow-up (Figure 2). Of these patients, only 22 (48%) identified the harvest site correctly (consistently correct); the other 24 (52%) patients identified the nonoperated iliac crest (consistently incorrect). The remaining 44 (49%) patients had no idea which iliac crest was used for bone graft harvesting or their responses alternated between follow-up visits. Looking at the iliac crest reported most frequently by these patients, 20 (45%) guessed the harvest site correctly.

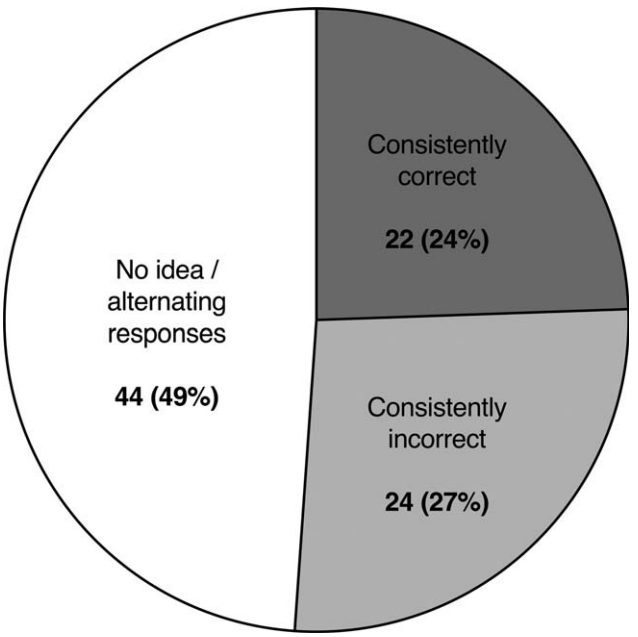

Figure 2. Number and percentage of patients that identified the iliac crest used for bone graft harvesting at each follow-up correctly (*consistently correct*), incorrectly (*consistently incorrect*), or had no idea/alternating responses between follow-up visits (*no idea/alternating responses*).

Post-hoc subgroup analyses using Mann–Whitney *U* tests showed no difference in number of segments fused ($P = 0.444$) or amount of iliac crest bone graft harvested ($P = 0.471$) between the 22 patients that identified the harvest site correctly and the other 68 patients.

VAS Pain Scores

The results of the VAS pain scores are summarized in the Tukey boxplots in Figure 3, each representing at least 84 patients. Although the pain scores varied widely, the VAS for back pain was higher than the iliac crest pain scores at all timepoints measured. The highest scores for both back pain and iliac crest pain were observed preoperatively. Postoperatively, the median VAS for iliac crest pain ranged between 8 and 18 mm (IQR 1–41), whereas the median VAS for back pain ranged between 28 and 35 mm (IQR 8–61). Based on a MCID of 15 mm, no relevant changes in pain scores over time were observed, except for a mean decrease of 28 mm (SD 32) in the VAS for back pain at 6 weeks follow-up compared with the preoperative score.

The mixed model for iliac crest pain, corrected for preoperative pain scores, showed no difference between the VAS pain scores for the donor site compared with the contralateral iliac crest (estimated difference 0.57 mm, 95% confidence interval −3.57 to 4.71, $P = 0.787$). In addition, there was no effect of time after surgery ($P = 0.807$) and no relation between the VAS for donor site pain and the amount of bone graft harvested ($P = 0.574$). There was a strong relation between iliac crest pain and back pain ($P < 0.0005$). Analysis of the estimates of covariance parameters showed that 34% of the variance in iliac crest pain can be explained by back pain.

DISCUSSION

Despite numerous articles that highlight the morbidity of iliac crest bone graft harvesting, there is actually controversy regarding the true morbidity of this procedure in spinal surgery. Especially in lumbar fusion surgery, where donor site pain might be overestimated due to the close proximity of the primary surgical site. The incidence and severity of iliac crest donor site pain reported in the literature varies widely, probably explained by poor (unblinded) study designs, as well as different study populations and surgical techniques.

In this current prospective, patient-blinded, randomized, controlled trial, the perceived pain during the first year after instrumented posterolateral fusion of the lumbar spine via a single midline incision approach could not be related to the actual donor site. Half of the patients had no idea from which iliac crest the bone graft was harvested and of the other half, only 48% identified the donor site correctly. In

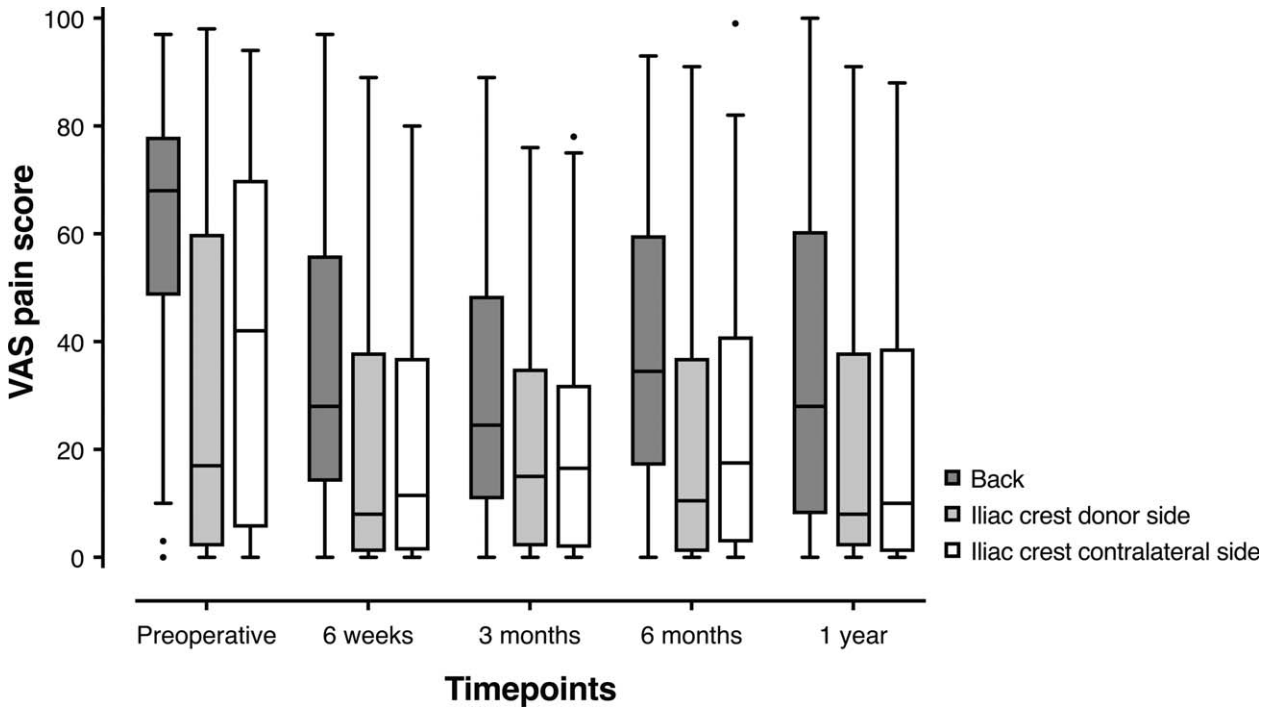

Figure 3. VAS scores (0–100) for back pain (*back)*, pain at the iliac crest used for bone graft harvesting (*iliac crest donor side*) and pain at the contralateral iliac crest (*iliac crest contralateral side*) at each timepoint. The Tukey boxplots illustrate the median, interquartile range (IQR), 1.5 IQR (whiskers) and outliers (dots).

other words, the correct identification of the donor site followed a perfect random distribution. Moreover, the patient reported VAS pain scores for the donor site and untouched contralateral iliac crest did not differ and were at each timepoint lower than the scores for back pain. Remarkably, the highest iliac crest pain scores were observed preoperatively. These findings are actually in line with some recently published studies, which underlined the difficulty to distinguish iliac crest pain from other potential sources of back pain after lumbar fusion surgery.[7,13,19–21,25] In a similar, patient-blinded, randomized study with 32 patients and 12 months follow-up, also no difference in iliac crest VAS pain scores was identified and highest pain scores were measured preoperatively.[25] Delawi *et al*[19] found that pain attributed to the donor site at mean 7.3 (range 2.3–11.6) years follow-up was significantly lower in patients who underwent a high lumbar fusion compared with low fusions, suggesting an interference from the primary surgical site or residual back pain. By investigating the incidence of iliac crest pain in patients with and without unilateral iliac crest harvesting for lumbar spinal fusion, Howard *et al*[20] demonstrated that iliac crest pain is a poor marker for donor site morbidity.

Bone graft harvesting from the iliac crest, whether or not via a separate incision, is an invasive procedure, inherent to donor site morbidity. Especially the harvest of large structural grafts via a separate incision may be problematic. However, the vast majority of iliac bone graft is used for lumbar spinal fusion surgery and can often be obtained via the primary skin incision. As shown in the current study including 90 patients, this iliac crest bone graft harvesting technique does not lead to clinically relevant pain that can be attributed to the actual donor site. This knowledge is important since the presumed donor site pain is the main reason for many surgeons to use expensive commercially available bone graft alternatives. We believe that, until alternatives have demonstrated clear superiority over autologous bone graft, the added value of these materials in lumbar fusion surgery is limited to specific cases where the quality or quantity of the autologous bone graft is limited or to shorten the surgical procedure. The knowledge from this study may also help to manage patient's expectations.

Strengths of this study include the prospective and blinded design with multiple measurements including at baseline, as well as the relatively large sample size. Blinding is known to reduce the risk of bias, especially in trials with subjective outcome measures like pain scores.[26,27] In addition, pain in both iliac crests and the back were measured separately. However, there are also limitations. First of all, this study was a priori powered to determine noninferiority of a bone graft substitute and not to detect differences between iliac crest pain scores. However, as the 95% confidence interval around the estimated difference in iliac crest pain is much narrower than the MCID of 15 mm on the VAS, it is unlikely that we missed a clinically relevant effect. Second, the exact locations of perceived pain in the iliac crest/hip region and lower back region were not assessed. In addition, the type of pain (*e.g.*, sharp, aching, or tingling) and interference with functioning in the direct postoperative

phase and daily activities were not measured. Pain sensation may also be influenced by satisfaction with treatment.[11] Regarding donor site identification, patients were not asked for the level of confidence in their responses. To account for guessing, the corresponding question was repeated at each follow-up and responses were summarized into three categories. Finally, the bone graft harvesting procedure was not standardized, although all surgeons applied a comparable cortical window technique without heat necrosis.

In conclusion, patients surgically treated for lumbar spine fusion could not reliably identify the iliac crest used for bone graft harvesting and this iliac crest was not more painful than the untouched contralateral iliac crest. Therefore, donor site pain should not be the main reason to use bone graft alternatives for lumbar spinal fusion surgery.

➢ Key Points

- ❑ We investigated the relevance of iliac crest donor site pain after instrumented posterolateral lumbar fusion in a prospective cohort of 90 adult patients blinded to the bone graft harvest site.
- ❑ Iliac crest bone graft was harvested unilaterally through the midline incision and each patient served as its own control.
- ❑ During the first year after surgery, only 24% of the patients were able to identify the iliac crest used for bone graft harvesting correctly at each follow-up.
- ❑ The VAS pain scores for the donor site and contralateral iliac crest did not differ and were lower than the scores for back pain.

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