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Efficacy and Safety of a Novel Moldable, Resorbable, and Degradable Sealant of Bone Surfaces for Hemostasis After Bone Graft Harvesting From the Iliac Crest

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Study Design. A prospective, controlled, open, randomized multicenter study.

Objective. The study's objective was to demonstrate equivalence of a novel, moldable, resorbable, and degradable synthetic polymer (Bone Seal) compared with a collagen fleece (Lyostypt) in efficacy and safety for topical hemostasis after iliac crest bone graft harvesting.

Summary of Background Data. Harvesting corticocancellous bone from the iliac crest is a well established procedure in orthopedic and particularly in spine surgery. It is associated with significant morbidity at the donor site where hematoma formation may cause impaired wound healing and infections in up to 10% of cases.

Methods. A total of 112 patients were included in the safety analysis. Safety was determined by a compound wound healing score and the incidence of adverse clinical effects. One hundred and eight patients were studied for equivalence in efficacy using a compound bleeding score. The handling properties and the application to the bone surface of either device were measured with two additional compound scores.

Results. The mean bleeding scores in the final analysis was 4.5 ± 1.3 for the Bone Seal group and 4.2 ± 1.3 for the collagen fleece group. Bone Seal was better applicable to the bleeding bone surfaces than the collagen fleece, even though its handling was more complicated. Wound healing and the incidences of adverse clinical events were comparable in either study group.

Conclusions. Bone Seal is an effective and safe hemostatic material for sealing bleeding bone surfaces after iliac crest bone graft harvesting. By virtue of its hemostatic efficacy, Bone Seal is preventive for wound healing disorders.

Key words: hemostasis, bone graft, biomaterial, clinical safety, topical hemostat. **Spine 2005;30:1911–1917**

Autologous bone graft harvesting is frequently part of elective and emergency orthopaedic surgery. Local blood loss and/or hematoma formation can cause significant additional morbidity through wound healing disorders and deep infection.[1–6] Incidence and size of postoperative hematomas are increased in patients undergoing simultaneous anticoagulation for the prevention or treatment of thromboembolism.[7,8] The risk of wound healing disorders, osteitis, deep infection, and wound dehiscence is particularly high in immuno-compromised patients. It is also increased in patients whose osteotomy site is subjected to early physiologic (e.g., sternotomy) or pathologic loading (e.g., sternotomy in patients with concomitant chronic obstructive lung disease).[9,10] Blood loss and hematoma formation can be minimized by surgical technique, minimally invasive approaches, reducing mean arterial pressure, careful layered wound closure avoiding cavities, local external compression, electrocautery, laser beam coagulation, blood-saving methods (cell saver, autologous retransfusion sets), or topical hemostatic agents.

For topical hemostasis, bone wax (Bone Wax, Ethicon, Norderstedt, Germany) and various other topical hemostatic agents (powdered oxidized cellulose in polyethylene glycol wax,[11] oxidized regenerated cellulose, gelatin paste, microfibrillar collagen, gelatin sponge soaked in thrombin[12–14]) are currently being used. Bone wax is made of purified beeswax and effects hemostasis by mechanical occlusion of the bone surface. It is not resorbable, causes foreign body reactions, and has been associated with pulmonary wax emboli.[15–18] Complete osseous regeneration of the harvesting site occurs after application of resorbable hemostatic substances but not after application of bone wax.[19] A polyorthoester (Alzamer, Alza Corp., Palo Alto, CA) has hemostatic properties similar to bone wax and may be resorbed

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more than 1 year after application, but similarly to bone wax, it also induces a foreign body reaction.[20] Other topical hemostatic materials are carriers of thrombogenic substances that have been shown to have a good hemostatic effect but are associated with the transmission of infectious viruses or proteins and adverse immunization.[21–24] Partially deacetylated chitin (chitosan) and a wax-like β-tricalciumphosphate augmented with transforming growth factor-β1 have been studied for their hemostatic efficacy in rabbits only. The sealing ability of the chitosan hydrogel to puncture sites of the carotid artery and the lung was stronger than that of fibrin glue.[25] β-Tricalciumphosphate augmented with transforming growth factor-β1 promoted the osseous regeneration of circular calvarial defects better than β-tricalciumphosphate alone but impaired new bone formation as compared with controls.[26] In conclusion, there is a demand for an effective, resorbable, and medically safe material to provide local hemostasis after osteotomies for bone graft harvesting, reconstructive, and cardiovascular surgery.

The present study has been conducted to demonstrate the safety and equivalence in the clinical efficacy of a novel, moldable, resorbable, and degradable sealant of bone surfaces (Bone Seal) to that of a documented, clinically safe, and effective collagen fleece (Lyostypt, B. Braun, Melsungen, Germany).[27,28]

■ Materials and Methods

A set of 112 consecutive patients (113 cases) who met the inclusion criteria and did not comply with the exclusion criteria (Table 1) were prospectively randomized at seven major orthopaedic and trauma surgery centers to receive either Bone Seal or a standard collagen fleece (Lyostypt, B. Braun, Melsungen, Germany) in order to achieve hemostasis at the iliac crest after autologous bone graft harvesting. Four patients (one of the Bone Seal group, three of the collagen fleece group) were excluded because of missing data leaving 108 patients in the intention-to-treat set. One patient underwent bilateral bone graft harvesting leaving 109 cases for efficacy analysis. All 112 patients (113 cases) were included into the safety analysis to detect any adverse clinical event. An adverse event was defined as any untoward medical occurrence in a patient observed in the course of the clinical trial. All adverse clinical events were documented, diagnosed, treated, and followed-up, irrespective of being rated as related or unrelated to the investigational product. Adverse events were looked for by standard blood biochemistry tests, hematological tests, perioperative monitoring of blood pressure and pulse rate, and clinical examination during the follow-up period.

To achieve a homogenous distribution, the randomization was stratified according the following criteria: study center, arterial hypertension (no arterial hypertension or treated arterial hypertension), and absence or presence of obesity [(Broca index >1.2; body mass in kg/(height in cm minus 100)]. The stratification criteria "obesity" and "treated hypertension" were evenly distributed between the two study groups showing the success of stratified randomization.

Both study groups were comparable with regard to gender, age, height, weight/body mass index (Table 2), diagnosis group (infection/osteitis, tumor, congenital/degenerative spine disease, trauma/nonunion, nontraumatic foot deformities (Table 3A); location of the index surgical procedure (Table 3B); type and extent of the bone graft. Three patients treated with the collagen fleece needed bone grafting for the following diagnoses: avascular necrosis of the femoral head, benign bone cyst of the femur, and giant cell tumor of the femur.

Fourteen surgeons applied and judged the materials in this investigation. They were introduced into the study design and the scoring system during two all-day meetings before the start of the clinical part of the study.

Table 1. Study Inclusion and Exclusion Criteria

Inclusion criteria:
Necessity for harvesting cortico-cancellous blocks of cancellous bone from the iliac crest as autologous grafts to fill up any other bone defect
Ages between 18 and 80 years
Patients to be treated on an in-patient basis
Low-molecular or low-dose conventional heparin for prevention of thromboembolism
Females of childbearing age routinely using effective contraception
Exclusion criteria:
Pregnancy or planned pregnancy
Breast-feeding
Participation in a clinical trial within 30 days prior to randomization
No or limited self-competence, or psychiatric or emotional problems
History of alcohol and/or drug abuse
Cardiovascular or respiratory disease resulting in a very high anesthetic or operative risk
Coagulopathy
Autoimmune disease
Uncontrollable arterial hypertension
Decompensated renal failure
Hepatic diseases or medication influencing coagulation
Systemic infections
Inflammations at the iliac crest to be operated on
Malignancies
Hypersensitivity or contraindication to one or more components of Bone Seal or the collagen fleece (Lyostypt)
Steroid medication or immunodeficiency

Table 2. Demographic Data and Donor Site Areas of the Study Groups (Safety Analysis for 113 Cases)

	Bone Seal	Collagen Fleece
Male	33	38
Female	22	20
Mean age in years (SD)	48.3 (15.4)	46.1 (15.7)
Mean height in cm (SD)	171 (9.6)	174 (8.3)
Weight in kg (SD)	77 (16.7)	79 (16.0)
Body mass index (SD)	26.4 (4.6)	26.3 (4.8)
Donor site area in cm^2 (SD)	11.5 (6.3)	10.3 (4.4)

Table 3A. Indications for Autologous Bone Grafting From the Iliac Crest (Intention-to-Treat Analysis for 109 Cases)

Diagnosis Group	Bone Seal	Collagen Fleece
Infection/osteitis	3	4
Tumor	0	2
Congenital/degenerative spine disease	21	21
Trauma/non-union	29	26
Nontraumatic foot deformity	1	2
Sum	54	55

Table 3B. Locations of the Surgical Procedure (Intention-to-Treat Analysis for 109 Cases)

Location of the Surgical Procedure	Bone Seal	Collagen Fleece
Spine	21	23
Femur	7	8
Calf	10	13
Foot/ankle joint	7	5
Shoulder/clavicle/humerus	3	2
Hand/forearm	4	2
Not available	2	2
Sum	54	55

After harvesting tricortical cortico-cancellous blocks or removal of a cortical strut for cancellous bone graft harvesting from the anterior or posterior iliac crest, a maximum of three units of either Bone Seal or collagen fleece was used to mechanically occlude the bleeding bone surface. The amount used was at the surgeon's discretion. A Robinson-type drain was inserted close to the donor site. The wound was closed in layers. Patients were observed-up clinically and by routine laboratory studies until the end of their in-patient care or until any untoward medical event either had subsided or was assessed as not being related to the product investigated. The mean follow-up period was 15 days in the Bone Seal group and 16 days in the collagen fleece group, respectively.

Bone Seal is a wax-like, completely resorbable and biologically degradable material made of 75 weight-% of low-molecular weight (molecular mass 1000) polymers of glycero-oligolactic-coglycolic acid. Twenty-five weight-% of polyethylene glycol (molecular mass 8000) is added to improve the handling of Bone Seal. A package unit of Bone Seal is rod-shaped, 40 mm in length, 6 mm in diameter, and weighs 1.6 g. It is packed in a sterile aluminum foil and easily stored at 10 to 25°C. Before application, the rod should be gently kneaded into a leaflet form rendering it softer and improving its application to the bleeding bone surface.

Lyostypt is a standard medical material for local hemostasis after bone graft harvesting with a long record of clinical efficacy and safety. It is a rectangular fleece (50 × 80 mm) with 10 cm^2 containing 100 mg of absorbable collagen of bovine origin.

The "Bleeding Score." The primary efficacy parameter was the compound metric parameter bleeding score. The bleeding score was the sum of the three variables "secondary intraoperative bleeding," "drainage volume," and the volume of the hematoma/seroma at the donor site as determined by ultrasound study 5 to 7 days after surgery (Table 4). The ultrasound measurement of the postoperative hematoma aided in the quantification of the total postoperative blood loss from the donor site. To maximize adherence to the study protocol and to avoid weekends, the ultrasound study was scheduled within a range of 3 days (from the 5th to the 7th day postoperatively). Judging from clinical experience, negligible quantities of blood continue to enlarge the already formed wound hematoma while resorption of the hematoma has hardly begun during this period. The bleeding score could adopt values between 3 (most favorable) and 9 (least favorable) points.

Table 4. Definition of the "Bleeding Score"

Variable/Points	1	2	3
Secondary intraoperative hemorrhage	None*	Little†	Much‡
Drainage volume 48 hours postoperatively	<150 mL	150–250 mL	>250 mL
Hematoma volume (ultrasound study)	<2 cm^3	2–6 cm^3	>6 cm^3

*None = immediate hemostasis after application of the topical hemostat.
†Little = delayed hemostasis within three minutes after application of the topical hemostat or secondary new hemorrhage.
‡Much = persistent hemorrhage.

Table 5. Definition of the "Manageability Score"

Variable/Points	1	2	3
Administration properties	Very Good	Satisfactory	Poor
Sticking to instruments	None	Moderate	Strong
Sticking to gloves	None	Moderate	Strong
Sticking to the swab	None	Moderate	Strong
Modeling properties	Very good	Satisfactory	Poor

The "Manageability Score" and "Applicability Score." Additional efficacy parameters were the manageability score and the applicability score. The manageability score was defined as the sum of 1 to 3 points assigned to 5 variables that were meant to reflect the ease and comfort with which the surgeon was handling the investigational product (Table 5). The "applicability score" comprised the 2 variables "adhesion to bleeding bone" and "wet-stability" of the investigational product (Table 6). It was designed to characterize the local performance of the product at the donor site and could vary from 2 (very good) to 6 (very poor) points.

The "Wound Healing Score." For the evaluation of the product safety, a wound healing score was defined as the weighted sum of 1 to 3 points assigned to 5 variables (Table 7). Purulence at the donor site was considered to have the most negative effect on wound healing. The score could take values from 13 (favorable) to 39 (unfavorable) points.

Statistical Analysis. As at the beginning of the study, no data had been available for the expected variation of the bleeding score; sample size calculation was initially based on the efficacy parameter "drainage volume" within 48 hours after surgery with an expected volume of 200 mL and an expected SD of 45 mL for a standard collagen fleece. At a significance level of $\alpha = 0.05$ [a maximum difference in the drainage volume of 30 mL (15%), for which equivalence could still be assumed, and with a power of 80% ($\beta = 0.2$)], equivalence of Bone Seal and the collagen fleece (Lyostypt) could be demonstrated for one-sided statistical hypothesis testing, if the intention-to-treat set (full analysis set) contained at least 63 patients per treatment group (1:1-randomization). According to Bauer and Kohne,[29] a two-stage adaptive interim analysis plan was applied to terminate the study as early as possible. The gain in information

Table 6. Definition of the "Applicability Score"

Variable/Points	1	2	3
Adhesion to bleeding bone	Very good	Satisfactory	Poor
Wet-stability	Very good	Satisfactory	Poor

Table 7. Definition of the "Wound Healing Score"

Variable/Points	Weighting	1	2	3
Induration	1	None	Moderate	Strong
Edema	1	None	Moderate	Strong
Dehiscence	3	None	Moderate	Strong
Hematoma	3	None	Moderate	Strong
Purulence	5	None	Moderate	Strong

manifested in the P value observed at each interim analysis was used to adaptively calculate the sample size for the next stage.

Confirmatory analysis was performed on the primary efficacy variable of the intention-to-treat set. All other statistical analyses were carried out on an exploratory basis. A one-sided Mann-Whitney *U* test for equivalence with a 5% level of significance was employed for confirmatory analysis of the primary efficacy parameter bleeding score. Exploratory analysis was applied to the secondary efficacy parameters "manageability," "applicability," and "wound healing" using the Mann-Whitney *U* test for metrically scaled parameters and the Cochran-Mantel-Haenszel test for ordinally scaled parameters, respectively, with the same level of significance, testing the null-hypothesis of no difference.

The study protocol was approved by the institutional review board at each study center and by the pertinent legal authorities. The trial was performed in accordance with the Declaration of Helsinki including all its revisions and the Somerset West Amendment of 1996 and in compliance with EN 540, ISO 14155, and Good Clinical Practice.

■ Results

The one-sided Mann-Whitney *U* test with a type-I error of 5% showed equivalence of the primary efficacy parameter bleeding score for both study groups. For either study group, the mean scores took favorably low values (Table 8). With regard to each single dimension of the bleeding score, more higher (i.e., less favorable, scores were calculated for the Bone Seal group; Table 9). The comparison of the median raw values for the drainage volume within 48 hours after surgery (50 ml, range 30–120 ml, in the Bone Seal group and 50 ml, range 25–80 ml, in the collagen fleece group) and the volume of the hematoma/seroma as determined by ultrasound (0.5 cm^3, range 0–2.5 cm^3, in the Bone Seal group and 0.2 cm^3, range 0–5.9 cm^3, in the collagen fleece group) did only show minor, statistically not significant differences between the two study groups.

Table 8. Confirmatory Analysis of the Primary Efficacy Parameter "Bleeding Score" for the Intention-to-Treat Set (109 Cases) Using a One-Sided Mann-Whitney *U* test for Equivalence With a 5% Level of Significance

	Bone Seal	Collagen Fleece
No. of cases	54	55
Mean (SD) "bleeding score"	4.5 (1.3)	4.2 (1.2)
Median (Q1–Q3) "bleeding score"	4 (4–5)	4 (3–5)
P value </> significance level	0.00046 < 0.05	

Table 9. Distribution of the "Bleeding Scores" and Descriptive Statistical Analysis

Bleeding Score	Bone Seal (Cases)	Collagen Fleece (Cases)
3	10	19
4	26	16
5	7	12
6	6	7
7	3	0
8	2	1
Sum	54	55
Mean (SD)	4.5 (1.3)	4.2 (1.2)
Median (Q1–Q3)	4 (4–5)	4 (3–5)
Range	3–8	3–8

The median bleeding score significantly varied from 4 to 6 points in between the study centers but showed almost no difference between the two study groups at each single study center. Irrespective of the study group, the bleeding score was significantly 1 point higher (less favorable) for cases undergoing spinal surgery as compared with cases undergoing upper or lower extremity surgery (5 and 4 points, respectively; $P < 0.01$).

Bone Seal had significantly higher (less favorable) "manageability scores" (Table 10). It was significantly more inconvenient in handling than the standard collagen fleece.

Application of the collagen fleece resulted in significantly higher mean "applicability scores" (Table 11). Thus, Bone Seal appeared to be more suitable for the occlusion of bleeding bone surfaces of the iliac crest than the collagen fleece.

The "wound healing score" did not significantly differ between the two study groups throughout the follow-up period (Table 12). Cases of purulence did not occur. Within a possible range of 13 to 39 points, the highest mean score was 14.6 on day 3 in the collagen fleece group. Thus, on average, no impairment of wound healing was observed.

With the exception of the C-reactive protein (CRP) and the blood glucose concentration, differences in the routine laboratory parameters between the two study groups were generally small and not statistically significant. As a marker of the postoperative systemic inflammatory reaction, the CRP rose to a significantly higher level (67 mg/L) in the collagen fleece group than in the Bone Seal group (48 mg/L; $P < 0.01$). Contrary to this finding, more patients in the Bone Seal group shifted

Table 10. Distribution of the "Manageability Score" in the Two Study Groups

	Bone Seal	Collagen Fleece
No. of cases	54	55
Missing cases	12	3
Mean (SD) score	9.1 (2.3)	7.5 (1.9)
Median (Q1–Q3) score	10 (7–11)	7 (6–9)
Range	5–13	5–14
P value	$P < 0.01$	

Table 11. Distribution of the "Applicability Score" in the Two Study Groups

	Bone Seal	Collagen Fleece
No. of cases	54	55
Missing cases	2	1
Mean (SD) score	3.13 (0.9)	4.15 (0.98)
Median (Q1–Q3) score	3 (2–4)	4 (4–5)
Range	2–5	2–6
P value	$P < 0.01$	

from CRP levels within reference range before surgery to elevated CRP levels the day after surgery than patients in the collagen fleece group ($P < 0.01$). No clinical relevance could be attributed to a significantly higher median rise in the blood glucose concentration on day 1 after surgery in the collagen fleece group (16 mg/dL versus 4 mg/dL; $P < 0.01$).

Seven out of 55 patients in the Bone Seal group incurred a total of 10 adverse medical events. Seventeen adverse medical events were seen in 13 of 58 cases in the collagen fleece group. The most frequent adverse events were a hematoma at the donor site and postoperative anemia. Only four adverse events (three cases of a hematoma, one case of a postoperative anemia) were judged to be possibly related to the medical material. One case of a moderate hematoma occurred in the Bone Seal group, the others occurred in the collagen fleece group.

In summary, Bone Seal was as effective in topical hemostasis as the collagen fleece and clinically safe. It showed better adhesion to the donor site, although the collagen fleece was easier to handle.

■ Discussion

The results of the present study demonstrate the clinical efficacy and safety of a novel hemostatic material compared with a standard hemostatic material with a proven record of clinical safety and effectiveness.[27,28] For the present study, safety related to the wound healing score and the absence of adverse events.

The efficacy of collagen-derived hemostatic agents has been established in standardized animal studies[19,27,30–33] and clinically in man.[12,28,34–36] Only a few controlled clinical studies compare two or more hemostatic materials.[37] Harris *et al*[12] measured the weights of a surgical and a hemostatic sponge applied to the trochanteric osteotomy site in total hip arthroplasty to quantify the hemostatic efficacy of gelatin paste, gelatin sponge/bovine thrombin, and microfibrillar collagen. During a 3-minute interval, the spontaneous reduction in bleeding was 11% in controls, 47% after microfibrillar collagen, 75% with the gelatin sponge soaked in thrombin, and 85% with the gelatin paste. In a multicenter study, Sherman *et al*[38] compared the efficacy of a composite of bovine fibrillar collagen and bovine thrombin with a collagen sponge applied using manual pressure to the iliac crest bone graft donor site in 19 patients. The duration of bleeding was measured by a stopwatch up to a maximum of 10 minutes. The authors used the time elapsed until bleeding had subsided to a slight oozing and the time elapsed until complete hemostasis as parameters of efficacy. The median time to achieve complete hemostasis was more than six times shorter in the experimental group compared with the controls. Unfortunately, the authors did not comment on the numbers of patients excluded from the study for various reasons.

Zwischenberger *et al*[39] used a hemorrhage grading scale to compare two different collagen-based hemostatic sponges (Hemostagene, Coletica, S.A., Lyon, France/Actifoam, MedChem Products, Inc., Woburn, MA versus Helistat, Integra Life Sciences, Inc., Plainsboro, NJ) in 60 patients undergoing cardiac surgery. A single observer quantified the bleeding intensity by discriminating low-grade bleeding (Grade 1–3), medium-grade bleeding (Grade 4–6), and high-grade or brisk bleeding (Grade 7 and above) every 3 minutes after application of the sponge. The material investigated was considered successful, if hemostasis was achieved within 10 minutes after its application. Both products had a similar success rate of 75 and 77%, respectively. Although a single evaluator was employed, the wide range of distinct bleeding quantities may have distorted reproducibility. In a prospective, randomized, and controlled multicenter trial, Oz *et al*[40] compared the efficacy of Gelfoam/thrombin and bovine thrombin added to a gelatin matrix (FloSeal) in 93 patients undergoing cardiac surgery. The investigational products were only to be used after standard methods of hemostasis had failed. Bleeding severity was quantified as either "oozing" or "heavy bleeding." The primary endpoint was the presence of continued bleeding recorded 1, 2, 3, 6, and 10 minutes after the application of the hemostatic product. A secondary endpoint was the time to cessation of bleeding. The number and sites of the bleeding source were not controlled. The hemostatic

Table 12. Distribution of the "Wound Healing Scores" in the Two Study Groups

	Day 2 Postop.		Day 3 Postop.		Day 5–7 Postop.		Day 8–14 Postop.		Day 15–21 Postop.	
Device	Bone Seal	Collagen Fleece	Bone Seal	Collagen Fleece	Bone Seal	Collagen Fleece	Bone Seal	Collagen Fleece	Bone Seal	Collagen Fleece
Mean (SD) score	14.1 (1.7)	14.3 (2.3)	14.0 (1.7)	14.6 (2.4)	13.9 (1.7)	14.2 (1.9)	13.6 (1.4)	13.7 (1.3)	13.2 (0.8)	13.4 (1.0)
Median (Q1–Q3) score	13 (13–16)	13 (13–16)	13 (13–16)	13 (13–16)	13 (13–14)	13 (13–16)	13 (13–13)	13 (13–14)	13 (13–13)	13 (13–13)
Range	13–20	13–23	13–19	13–23	13–20	13–20	13–19	13–23	13–16	13–23
P	0.98		0.38		0.29		0.31		0.48	

effect was solely determined during surgery. Secondary hemorrhage was not determined. In a prospective, controlled, and randomized neurosurgical trial with 198 patients, Krüger[28] reported on the superior hemostatic efficacy and inferior handling properties of the collagen fleece (Lyostypt) used as the control material in the present study compared with gelatin foam (Marbagelan). The author and the multiple evaluators used the variables "applicability," "sticking to the instrument," "plasticity," "adhesion to bleeding surfaces," "wet stability," and "hemostatic effect" and rated each numerically from 1 (unfavorable) to 5 (favorable).

In contrast to these studies, the bleeding score employed in the present study gives a close approximation of the real local blood loss. The observational classes of the parameter "secondary intraoperative bleeding" (none, little, much) were clearly defined and simple, providing a high degree of reproducibility at the seven study centers. Although the median "bleeding score" significantly varied from 4 to 6 points in between the study centers, it almost showed no difference between the two study groups at each single study center. Irrespective of the study group, the bleeding score was significantly 1 point higher (less favorable) for cases undergoing spinal surgery as compared with cases undergoing upper or lower extremity surgery (5 and 4 points, respectively; $P < 0.01$). This variation is therefore probably correlated to the extent of bone grafting or to differences in the surgical technique at each single center.

The "wound healing score" used in the present study simultaneously reflects efficacy and safety. Because prevention of a hematoma is associated with a low incidence of impaired wound healing and overt infection,[1,41,42] the clinical finding of a hematoma was weighted with the factor three. The weighting of the 5 parameters of the "wound healing score" was introduced to allow for a better discrimination of differences between the two study groups. Cases of purulence did not occur and the observed scores were generally low. Only two findings of a rise in serological inflammation markers were indicative of a possible wound healing disorder. The absence of infection in the present study is atypical for cohorts of patients after iliac crest bone graft harvesting with a reported infection rate of up to 10%[5] and may be attributed to a bias. As the reported infection rate of up to 10% refers to retrospective studies, this bias seems typical for the few controlled comparative clinical studies of hemostatic materials and probably reflects the safety maximally achievable. The real safety in clinical use is dependent on the manageability and the applicability of the product.

In the absence of significant differences in the location of the index surgery, the type of surgical diagnosis, and the size of the donor site, the statistically greater increase in the postoperative CRP levels of the in the collagen fleece group may be attributed to the extent of the index surgery. Another explanation is an individual disposition because of the greater number of patients showing already elevated CRP levels before surgery in the collagen fleece group as compared with the Bone Seal group.

According to the results of the present study, the disadvantage of slightly poorer handling properties of Bone Seal as compared with the collagen fleece (Tables 5 and 10) is counterweighted by better adhesion to the bleeding bone surface and wet-stability (Tables 6 and 11). A similar safety performance of Bone Seal and collagen fleece can therefore be anticipated for the clinical use. In contrast to most hemostatic agents, Bone Seal does not rely on an activation of the coagulation cascade or on thrombocyte aggregation for hemostatic effectiveness. Bone Seal has favorable biologic properties. It is completely resorbable and degradable with excretion of its components from the body within weeks after application.[43] Similar to the above mentioned efficacy and safety studies of earlier hemostatic materials, efficacy and safety of the novel investigational product may be anticipated for bleeding bone surfaces at various anatomic sites.

■ Key Points

- A prospective, controlled, open, randomized multicenter study was performed to compare the efficacy, safety, and handling properties of a novel topical hemostat to that of a collagen fleece after iliac bone graft harvesting.
- The application of the novel material is similar to that of bone wax, but it is cleared from the body within 4 weeks.
- It is as effective and safe as the conventional collagen fleece.
- The novel material showed better adhesion to the bleeding bone surfaces, but its handling was a little more complicated.

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