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ORIGINAL STUDY

Demineralized bone matrix versus autogenous bone graft for thoracolumbar anterior single-level interbody fusion

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In thoracolumbar fracture treatment, autogenous iliac crest bone grafting (ICBG) is the standard procedure to achieve anterior single-level fusion. To avoid associated problems of graft harvesting, intervertebral cages are an alternative, but cannot provide biological fusion. Therefore, investigations on fusion-enhancing adjuncts to cages are performed to find biomaterials with biological features comparable to bone grafts. This study is the first prospective randomized trial in literature to compare the results of demineralized bone matrix (DBM putty) plus cage vs. ICBG in anterior fusion procedures for thoracolumbar fractures.

Thirty patients underwent posterior bisegmental instrumentation and anterior stabilization by (I) titanium cage with DBM putty (n=15), or (II) autogenous ICBG (n=15).

After nine months, biological fusion occurred in 80% and 57% *(p≈0.24)*, respectively. Extent of clinical recovery was 82.5%±17.3% vs. 80.4%±12.9% *(p≈0.90)*. Loss of kyphosis correction amounted to -1.4°±2.1° vs. -1.6°±4.1° *(p≈0.91)*.

Fracture treatment with DBM plus titanium cage showed promising 9-months-results in this pilot study on 30 individuals.

Keywords : biological fusion ; demineralized bone matrix (DBM) ; iliac crest bone graft ; fracture ; thoracolumbar ; randomized controlled pilot study.

INTRODUCTION

Successful thoracolumbar fracture treatment requires biological fusion to maintain the surgically reconstructed spinal profile. With a posteroanterior approach's fusion rate of 87-100%, autogenous iliac crest bone grafting (ICBG) represents the standard procedure in single-level anterior fracture treatment *(18,19)*. Graft harvesting, however, is a major drawback due to significant donor site pain jeopardizing therapeutic outcome *(20)*. Infection and haematoma rates of the harvesting site, intensity of post-surgical iliac crest pain, incidence of iatrogenic nerve lesions, and occurrence of iliac crest fractures diminish the acceptance of ICBG in contemporary spine surgery. To avoid graft harvesting and associated problems, alternative surgical techniques have been developed.

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For permanently restoring the spinal profile the use of cages combined with autologous bone from the fracture site has evolved as most promising alternative, and is superior to ICBG in bisegmental anterior reconstructions *(9)*. Autologous platelet-rich plasma concentrates (PRP) in combination with local bone from the fracture site showed similar fusion rates in shorter time intervals compared to ICBG, but failed to provide clinical advantages concerning pain reduction or functional recovery *(10,22)*. Recombinant human bone morphogenetic protein (rhBMP) has yielded anterior fusion rates of 95-100%. However, its clinical success was limited by postoperative occurrence of radicular pain *(17)* or vertebral osteolysis *(14)*. Synthetic bone ceramics combined with bone marrow aspirates or autologous bone attain fusion rates of over 85% after 2-3 years, regardless of anterior, posterolateral, or posterior fusion procedures *(5,7,12).* Also as an adjunct to bone marrow or autogenous bone, demineralized bone matrix (DBM) promoted posterolateral fusion rates similar to autograft in degenerative disease or trauma after 12-24 months *(3,4,11,23)*.

This pilot study was designed to compare the results of DBM putty plus titanium cage with those of autologous ICBG for thoracolumbar fractures requiring anterior single-level fusion in a limited study-size.

PATIENTS AND METHODS

During 26 months, 30 consecutive patients with traumatic thoracolumbar fractures were enrolled in a single-centre, prospective randomized controlled study and allocated to one of two study arms using computer-generated block randomization. Inclusion criteria were acute fractures of the thoracolumbar spine requiring anterior single-level fusion (i.e. incomplete burst/burst-split fractures with adjacent single-level intervertebral disc lesion, and their combinations with flexion-distraction or rotational injuries) in individuals aged 18-65 years. Exclusion criteria were osteoporotic vertebral fractures or pre-diagnosed osteoporosis.

Treatment scheme comprised (1) initial posterior stabilization after treatment of life-threatening concomitant injuries, (2) elective anterior stabilization after individual recovery from initial treatment, (3) removal of internal fixation devices after 9 months. All patients underwent bi-level posterior fixation in prone position. For anterior stabilization, a titanium cage (SynMesh, Synthes Inc., Oberdorf, Switzerland) with 5 cc DBM putty placed left-lateral to the cage was used in the trial, and autogenous ICBG in the control group. All individuals additionally received anterolateral single-level locking plate fixation (TeleFix, Synthes Inc., Oberdorf, Switzerland). Enrolled subjects had been informed about study contents, inherent risks and complication profiles of both treatment options. Informed consent was obtained from all individual participants included in the study. The patients' age at the time of trauma, gender, BMI (body-mass-index), ASA (American Society of Anesthesiologists)-class, nicotine consumption, regular NSAID (non-steroidal anti-inflammatory drug)-intake after anterior fusion, and posttraumatic neurological deficits were recorded for assessing baseline differences between the groups. Pre-operative radiological examinations included plain radiographs of the injured spinal level in two planes, and computed tomography (CT) scans with sagittal and coronal reformations of the fractured and at least two adjacent vertebrae (SOMATOM Sensation, 64-slice CT scanner, Siemens Inc., Erlangen, Germany). Magnetic resonance imaging (MRI) was restricted to individuals with post-traumatic neurological deficits. After posterior instrumentation, pedicle screw positions were controlled by CT. The anterior procedure was performed in right lateral position of the patient, and comprised partial corporectomy of the fractured vertebra, discectomy of the destroyed adjacent intervertebral disc, and defect reconstruction via left lateral approach. Injuries of the thoracic and upper lumbar spine (above L2) were treated using video-assisted thoracoscopic surgery. Vertebrae below L1 were accessed by left-lateral lumbotomy. A split posteroanterior procedure justified a second CT scan to visualize TeleFix locking screw positions, or persisting spinal stenosis caused by dislocated posterior fragments. Radiographic examinations in standing position (two planes)

were stipulated post-surgically, at 3-6, and after 9 months. Another CT scan with sagittal and coronal reformations was conducted after 9 months to determine biological fusion (primary efficacy outcome) requiring contiguous bony bridging of both adjacent vertebrae in at least two consecutive sagittal or coronal CT-reformation slices. In the trial group, density alterations in DBM application sites were determined by evaluating post-surgical and final CT-scans in three different filters of

(1) >-1000 Hounsfield units (HU ; corresponding to the density of air),

(2) >+100 HU (corresponding to the density of cancellous bone), and

(3) >+500 HU (corresponding to the density of cortical bone)

based on a technique described by Hartmann et al., using the software "syngo Volume" (Siemens, Erlangen, Germany) for SOMATOM CT scanners *(10)*. Successful fusion after DBM treatment required confirmation through measurable density increase within the partition of >+100 HU or >+500 HU.

Severity of pre-traumatic back pain and related functional limitations in activities of daily living (ADL) were individually analysed with the VAS (visual analogue scale) Spine Score (13). The total score ranges from 0-100 points, with higher numbers indicating less complaints and better subjective function. Recovery of pre-traumatic functionality (secondary efficacy outcome) was documented at follow-up (3-6 and 9 months) using the same score. Good clinical results were indicated by score deficits of less than 20% compared to pre-traumatic levels. Deficits of 20-40% or more than 40% were estimated as mediocre or unsatisfying clinical outcomes, respectively. Lateral radiographs were evaluated for monosegmental kyphosis angle and loss of correction (LOC) until final follow-up (secondary efficacy outcome).

Procedure-related major complications requiring revision surgery were recorded separately for each group. The study adheres to the CONSORT statement.

Statistics : Values are given as the mean and standard deviation (SD). Nominal data are given as frequencies. Student's t-test was used for comparing continuous variables, and Fisher's exact test for categorical variables. A *p-value* of less than 0.05 was considered significant.

Ethics : All procedures involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. The trial was registered before enrolment of the first participant by the local ethics committee (date of issue: 03/19/2008, registration number: 38/08).

RESULTS

Injuries comprised incomplete burst fractures (n=15), burst-split fractures (n=6), flexion-distraction (n=8), and rotational injuries (n=1). Two patients were polytraumatized, 6 had additional extremity or chest trauma. In the trial group, the upper injury of a two-level fracture (T8, T12) was treated without an additional anterior locking plate and therefore excluded from further considerations because of discordance with study requirements. Anterior stabilization was performed in levels T11-T12 (n=7), T12-L1 (n=15), L1-L2 (n=5), and L2-L3 (n=3). Baseline characteristics were similar in both groups (Table I).

Posterior internal fixation was performed percutaneously in 2 individuals of the trial, and 7 individuals of the control group (CD Horizon Longitude, Medtronic Sofamor Danek, Memphis, TN, USA). In the other cases, open reduction and internal fixation was conducted (USS II, Synthes Inc., Oberdorf, Switzerland). Posterior instrumentation was performed 4.5±6.0 days after trauma. Anterior stabilization followed another 4.5±2.1 days later. A 36-year-old control group patient (non-smoker, ASA-class 2, BMI 22.8 kg/m^2, regular post-surgical NSAID-intake) was lost to follow-up due to relocation.

Final CT scans took place after 10±3 months (trial group: 10±4 months, control group: 10±1 months). Contiguous intervertebral bridging was found in 13 trial, and 8 control group patients (Fig. 1).

Density increase in DBM application sites was most pronounced in the filter for cancellous bone

Table I. — Baseline characteristics. Differences between trial and control group were not significant

Characteristic	trial group (n=15)	control group (n=15)	*p-value*
Age (years)	40.9±11.9	45.5±12.0	0.30
Sex female – n (%) male – n (%)	6 (40.0) 9 (60.0)	7 (46.7) 8 (53.3)	0.72
BMI (kg/m^2)	24.2±3.5	24.5±2.7	0.82
ASA-class	1.6±0.5	1.8±0.4	0.25
Smoking status smoker – n (%) non-smoker – n (%)	8 (53.3) 7 (46.7)	4 (26.7) 11 (73.3)	0.15
NSAID consumer status NSAID – n (%) no NSAID – n (%)	14 (93.3) 1 (6.7)	12 (80.0) 3 (20.0)	0.30
Posttraumatic neurological deficits – n (%)	1 (6.7)	1 (6.7)	1.00

BMI body mass index; *ASA* American Society of Anesthesiologists; *NSAID* non-steroidal anti-inflammatory drug.

(>+100 HU: 62±138 HU; >+500 HU: 19±236 HU, >-1000 HU: 32±165 HU). Restricting those CTs from evaluation, that were carried out earlier than 9 months after surgery (n=1), densitometry indicated significant cancellous bone formation (*p≈0.016*, Fig. 2) and confirmed fusion in 12 trial group patients by increasing density values for cancellous (101±111 HU, *p≈0.009* ; 95%-CI:

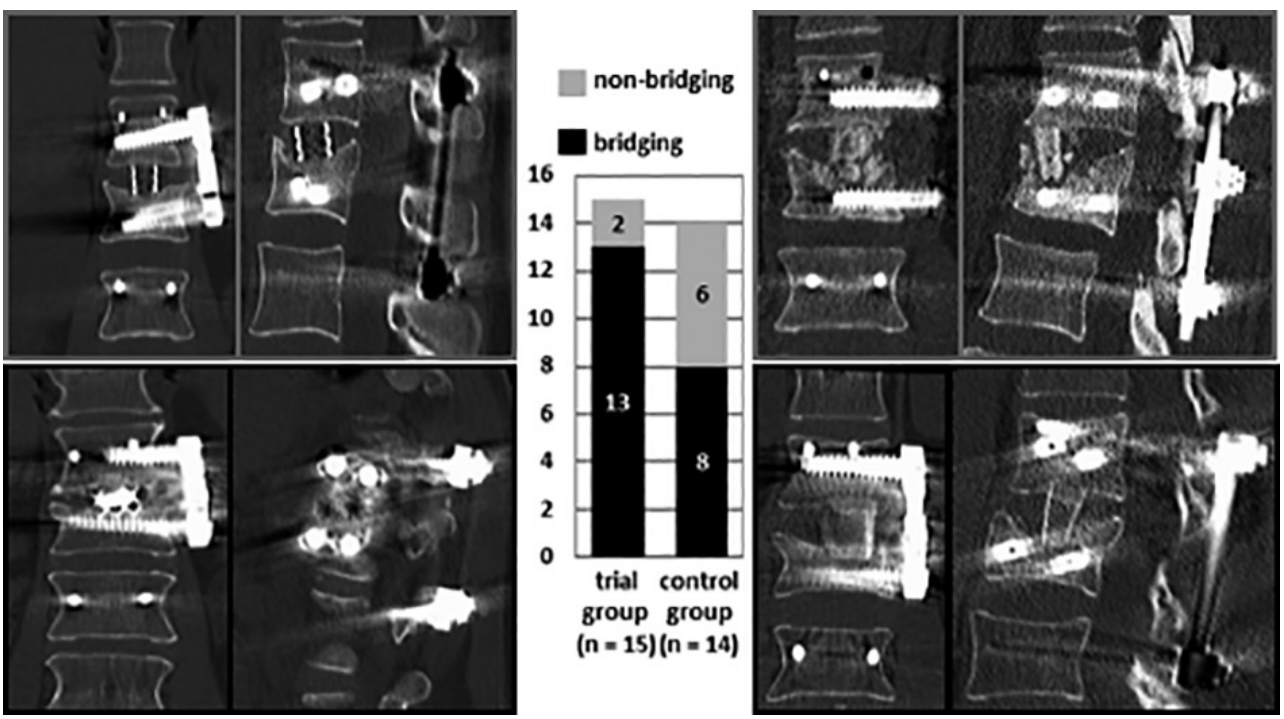

Figure 1. – Left side: examples of the trial group's results (coronal and sagittal reformations of CT scans at final follow-up). Non-bridging (left upper side) was found in 2 cases, and successful bridging (left lower side) in 13 cases. Right side: examples of the control group's results (coronal and sagittal reformations of CT scans at final follow-up). Pseudarthrosis (right upper side) was found in 6 cases (the example shows inferior pseudarthrosis of the graft), and contiguous bridging (right lower side) in 8 cases. The centre shows rates of intervertebral bridging and non-union after nine months in trial and control group.

Table II. — Summary of results. Differences between trial and control group results were not significant

Result		trial group (n=15)	control group (n=15)	*p-value*
Intervertebral result	bridging – n (%) non-bridging – n (%)	13 (86.7) 2 (13.3)	8 (57.1)[b] 6 (42.9)[b]	0.11
Densitometry of bridged sites (trial group only, n=13)				
density increase in filter of >+100 HU		101±111 HU		
density increase in filter of >+500 HU		70±151 HU		
Biological fusion result	fusion – n (%)	12 (80.0)	8 (57.1)[b]	0.24
	non-union – n (%)	3 (20.0)	6 (42.9)[b]	
VAS Spine Score	pre-traumatic 3-6 months-follow-up 9 months-follow-up	93±9 68±20 77±17	90±9 65±17[b] 73±16[b]	0.50 0.66 0.74
VAS Spine Score deficit after 9 months		16±16	17±12[b]	0.69
Single-level kyphosis angle (°)	post-traumatic post-surgery 9-months-follow-up	-18.7±6.6 -8.4±4.0[a] -9.8±4.7	-16.1±6.5 -5.5±5.1 -7.2±5.6[b]	0.31 0.10 0.19
LOC (°)		-1.4±2.1	-1.6±4.1[b]	0.91

[a] n=14: post-surgical plain radiographs in standing position were not performed in the case of a post-traumatic paraplegic patient; [b] n=14: follow-up data were not available for one patient of the control group; *HU* Hounsfield units; *VAS* visual analogue scale; *LOC* loss of correction.

[31.0; 172.1]) or cortical bone (70±151 HU, $p\approx0.11$; 95%-CI: [-20.3; 183.7]).

Under these specifications, biological fusion rates were 12/15 (80%) in the trial, and 8/14 (57%) in the control group ($p\approx0.24$, Table II).

Average pre-traumatic and follow-up VAS Spine Score values are shown in Table II and Figure 3.

Functional deficits equalled 17.5±17.3% (16±16 points) in the trial, and 19.6±12.9% (17±12 points) in the control group (Table II) indicating an average good clinical 9-months-result in both groups. Significant differences in clinical results were not found in any respect. After nine months, fusion success and clinical result did not strongly correlate:

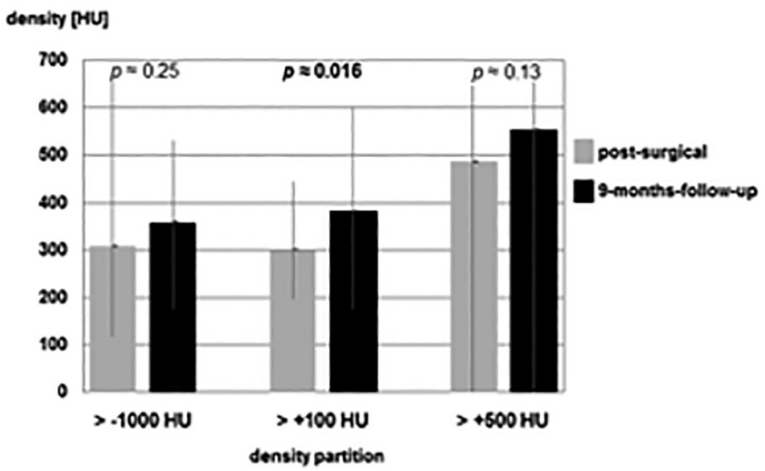

Figure 2. – Mean density increase within the partition of >-1000 HU, >+100 HU, and >+500 HU after 9 months. Only within the partition of >+100 HU (cancellous bone), a significant density gain could be found ($p\approx0.016$; n=14).

Table III. — Intervertebral and clinical results at 9-months-follow-up. After DBM application (trial group), successful biological fusion required contiguous bridging *and* densitometric confirmation through increasing (=positive) density values for cancellous or cortical bone (partition of >100 or >500 HU) in DBM application sites.

patient	group	age (years)	gender	BMI (kgm^{-2})	ASA	nicotine consume	NSAID intake	neurological deficit	bridged site	densitometric result:		biological fusion result	VAS Spine Score deficit
										>100HU	>500HU		
1	DBM	51	female	25.3	1	no	yes	no	+	-59.1	-50.7	NU	20.3%
2	ICBG	43	male	30.3	2	no	yes	yes	-			inferior NU	20.1%
3	ICBG	46	male	21.7	2	yes	yes	no	-			inferior NU	30.1%
4	DBM	38	male	21.3	2	yes	yes	no	+	132.7	13.6	fusion	45.6%
5	DBM	29	female	19.5	1	no	yes	no	+	-80.6	27.8	fusion	4.6%
6	ICBG	40	male	22.2	2	yes	yes	no	-			inferior NU	25.7%
7	ICBG	35	female	26.6	2	no	yes	no	+			fusion	20.1%
8	ICBG	52	male	27.5	2	yes	no	no	+			fusion	10.6%
9	ICBG	61	female	23.6	2	no	yes	no	+			fusion	12.0%
10	DBM	44	female	23.5	1	no	yes	no	+	297.1	108.4	fusion	20.6%
11	ICBG	59	female	27.7	2	no	yes	no	+			fusion	20.1%
12	DBM	42	male	22.8	2	yes	yes	yes	+	59.0	22.3	fusion	3.9%
13	ICBG	22	female	20.5	1	no	yes	no	-			bipolar NU	0.2%
14	DBM	49	female	20.6	2	no	yes	no	+	215.6	69.5	fusion	2.3%
15	DBM	27	female	20.9	1	yes	yes	no	-	12.4	0	NU	3.6%
16	DBM	24	female	22.6	1	no	yes	no	+	11.6	72.0	fusion	19.3%
17	DBM	45	male	23.4	1	no	yes	no	+	42.0	-1.9	fusion	22.1%

18	DBM	56	male	32.4	2	yes	yes	no	-	-248.3	0	NU	16.4%
19	ICBG	42	female	22.5	2	no	no	no	+			fusion	30.6%
20	DBM	43	male	29.3	2	yes	yes	no	+	182.3	10.1	fusion	59.6%
21	ICBG	65	female	23.0	2	no	yes	no	+			fusion	5.7%
22	ICBG	36	male	22.8	2	no	yes	no				lost to follow-up	
23	DBM	43	male	25.4	2	no	yes	no	+	18.3	15.9	fusion	2.3%
24	DBM	42	male	24.8	2	yes	no	no	+	-9.6	22.1	fusion	5.9%
25	ICBG	54	female	24.6	2	no	yes	no	+			fusion	4.8%
26	ICBG	30	male	25.4	1	yes	yes	no	-			superior NU	0.0%
27	DBM	19	male	27.8	2	yes	yes	no	+	173.8	39.4	fusion	9.0%
28	DBM	62	male	24.2	2	yes	yes	no	+	176.3	581.5	fusion	11.8%
29	ICBG	53	male	23.7	2	no	no	no	+			fusion	31.6%
30	ICBG	45	male	25.4	1	no	yes	no	+			fusion	33.6%

DBM demineralized bone matrix; HU Hounsfield units; BMI body mass index; ASA American Society of Anesthesiologists; NSAID non-steroidal anti-inflammatory drug; VAS visual analogue scale; ICBG iliac crest bone grafting; NU non-union

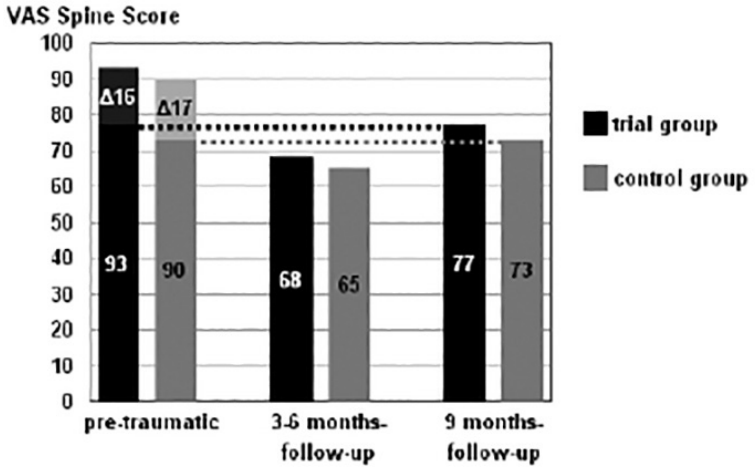

Figure 3. – Course of VAS Spine Score (ADL-VAS) from a pre-traumatic state over the first (3-6 months post-surgery) to the second follow-up (9 months post-surgery) without inter-collective differences at any time.

Successful fusion and good clinical result, or non-union and mediocre/unsatisfying clinical outcome met in 9/15 (60%) of trial and 7/14 (50%) of control group patients, respectively (Table III).

During follow-up, monosegmental LOC was comparable in both groups (Table II).

In the trial group, procedure-related major complications comprised post-surgical hematothorax indicating re-thoracotomy two days after anterior stabilization (n=1), symptomatic pneumothorax after chest tube removal requiring chest re-drainage (n=1), and pedicle screw misplacements needing correction (n=2). In the control group, post-surgically recognized strut graft dislocation (n=1), and subfascial hematoma after posterior instrumentation (n=1) indicated revision surgery.

DISCUSSION

DBM is a non-pooled human cortical bone graft substitute showing variable concentrations of biologically active growth factors (BMPs) in each batch which leads to different biological activities with unpredictable fusion rates *(2,25)*. It has frequently been applied as graft enhancer or filling material for cages in disc replacement surgeries, but was never used in a controlled comparative anterior-fusion fracture-treatment study.

ICBG was selected for control group treatment, as it is still considered the gold standard in anterior single-level fusion *(6,11)*. The rationale behind the trial group's combination of DBM with a cage was to compensate DBM's weight bearing inability. Fusion assessment was restricted to DBM application sites between cage and locking plate system to largely exclude an eventual cage-related impact on fusion success.

In trauma surgery, spinal fusion frequently involves temporary posterior transfixation of intact adjacent segments. To prevent transfixed intervertebral discs and facet joints from irreversible degenerative alteration, posterior fixation devices should be removed timely *(15,24)*. On the other hand, destabilization through early posterior release might jeopardize anterior fusion. We therefore determined fusion success at 9 months, prior to removal of internal fixation, even if some sites had not yet biologically fused. This could have negatively influenced fusion rates. But in order to document an eventual faster fusion success after DBM treatment, we decided to assess fusion after 9 months, even if this meant to report comparatively low fusion rates for autograft.

The evaluation of biological fusion strongly depends on an examiner's opinion, resulting in high inter-observer variability. Although the

Tübinger Score *(1)* provides an instrument for quantifying ICBG fusions with an inter-observer reliability of 0.81-1.00, its worth in evaluating DBM putty fusions is limited. In ICBG, the graft is located centrally in the intervertebral space, which allows the Tübinger score to be applied using coronal CT-reformations. After DBM putty treatment, however, fusion success was determined in a non-central region between cage and locking plate. With the cage occupying the intervertebral centre, the Tübinger score rates considerable areas as non-fused. This leads to minor scorings, since fused sites in the trial group are regularly restricted to the left hemi-side of the intervertebral space. Therefore, we rejected to use this score. In 2001, McAfee et al. published criteria that were supposed to indirectly indicate successful bony fusion including computed tomographic evidence, limitations of acceptable residual segment mobility on plain inclination-reclination radiographs, and the reduction of clinical complaints *(16)*. Basically, radiological assumption of successful fusion is supported, if clinical complaints or hints for the existence of non-union are missing. However, discrepancies between clinical and radiological results have been reported in the past *(8)*. Having analysed the outcomes of 52 individuals with a successful posterolateral fusion rate of 90%, Schnee et al. found good clinical results in only 60% *(21)*. In our series, fusion in combination with mediocre or unsatisfying clinical results (31.0%), as well as non-union combined with asymptomatic individuals (13.8%) could be encountered (Table III), again questioning the correlation between clinical and radiological outcome. We did not perform inclination-reclination radiographs due to their evaluative inaccuracy and inter-observer variability. To us, CT represents the most reliable instrument for fusion evaluation. But DBM is not radiopaque, so that fused sites are not visible until bridged by sufficiently mineralized bone. Therefore, DBM application sites were additionally assessed through CT densitometry. After 9 months, we recorded significantly increasing density values within the partition of >+100 HU in the region of interest, indicating cancellous bone formation. Investigations on cortical bone formation (>+500 HU), meanwhile, did not demonstrate significant density alterations. The partition of >-1000 HU (value for density of air) was incorporated as validity proof. As expected, a statistically significant density increase was not detected using this filter. Measurements were influenced through artifact-related image distortion caused by closely neighboring metal implants (cage, locking plate system). Assuming a constant artifact-influence over time, we concluded that subtraction of corresponding measurements eliminated artifact-induced errors. CT densitometry was performed in the trial group, exclusively, due to a lack of more suitable instruments for fusion confirmation. In the control group, we judged this method inappropriate for evaluating graft incorporation at bony interfaces, as contact zones between vertebral body and graft can generate positive densitometric results despite biological failure, when graft sclerosis causes an increase in density, which should be interpreted as graft degradation rather than as biological fusion *(16)*.

Complications occurred more often in the trial group (4 vs. 2 events). However, the rate of specific complications attributable to anterior fracture treatment was balanced with one in each group (hematothorax/graft dislocation). Adverse events, like e.g. subfascial hematoma after posterior stabilization, pedicle screw misplacements, or pneumothorax after chest tube removal, have no correlation to anterior fracture-treatment mode.

A clear limitation in this trial is the sample size of only 15 patients per study arm making conclusions difficult to be drawn. This pilot trial, however, was designed to indicate, whether DBM could be an alternative to ICBG in the fractured human spine at all. Another limitation is the study's follow-up schedule with an unsharpness of 3-6 months for the first, and transgression of more than 1 month at final follow-up in 2 trial, and 5 control group patients. These uncertainties might distort results. The median's difference of 0.5 months at final follow-up between groups might have promoted slightly higher fusion rates after DBM treatment. However, with respect to complication rates and notable effort of surgical therapy, conservative treatment should alternatively be considered whenever surgical stabilization constitutes a relative indication.

CONCLUSIONS

In this pilot study, anterior single-level interbody fusion with DBM plus titanium cage for thoracolumbar fracture treatment showed comparable results to ICBG in terms of procedure-specific major complication rates and primary/secondary efficacy outcomes after 9 months. Despite limited study-size, results are encouraging on the quest for alternative autograft-independent anterior fusion approaches. Comprehensive approval of the efficacy of DBM, however, requires e.g. a multicentric study design for an adequate recruitment volume.

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