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Clinical Study

Randomized double blind clinical trial of ABM/P-15 versus allograft in noninstrumented lumbar fusion surgery

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Abstract

BACKGROUND CONTEXT: Due to poor bone stock in the elderly, a noninstrumented fusion is commonly performed in Scandinavia when instability is present. Allograft bone is often used as graft extender with consequent low fusion rates. The use of 15 amino acid residue (ABM/P-15) has shown superior fusion rates in dental and cervical spinal surgery but no clinical studies have been conducted in noninstrumented lumbar fusion surgery.
PURPOSE: To evaluate patient reported outcomes (PROs) and the intertransverse fusion rate in noninstrumented posterolateral fusion with either ABM/P-15 or allograft.
STUDY DESIGN: Double-blind randomized clinical trial.
PATIENT SAMPLE: Patients 60 years or older with degenerative spondylolisthesis undergoing decompression and noninstrumented posterolateral fusion.
OUTCOME MEASURES: Visual analog scales for back and leg pain, Oswestry Disability Index and EuroQoL-5D.
METHODS: One hundred one patients were enrolled in the study and randomized 1:1 to either ABM/P-15 (mixed 50/50, 5cc/level) or allograft bone (30 g/level), both mixed with local bone graft. PROs were collected at baseline and at 12 and 24 months after surgery. The patients underwent 1-year postoperative fine cut computed tomography-scans (0.9 mm) with reconstructions, independently evaluated by three reviewers. Fusion status was concluded by consensus of two of the three as "fusion" or "no fusion."
RESULTS: There were 49 patients available for analysis in both cohorts. The two groups were similar in terms of sex distribution, age, and number of levels fused. The fusion rate was significantly higher in the ABM/P-15 group with 50% fused compared with 20% in the allograft group. PROs at baseline and at all follow-up time points were similar between the two groups.
CONCLUSIONS: Patients undergoing noninstrumented posterolateral fusion augmented with ABM/P-15 had a statistically significantly higher fusion rate compared with allograft when evaluated with postoperative fine cut computed tomography-scans (0.9 mm) with reconstructions. However, this did not translate to better clinical outcomes.

Keywords: Decompression; Degenerative lumbar spinal stenosis; Degenerative anterolisthesis; Posterolateral fusionLumbar fusion surgery

FDA device/drug status: Not applicable.

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Introduction

Lumbar spinal stenosis (LSS) is one of the most common indications for spinal surgery [1,2]. This prevalence is expected to increase over the next few decades due to an increase in the aging population in industrialized countries [3]. Surgical decompression is offered to regain walking ability, reduce pain, and increase survival rate [4]. When instability is present, or in cases where postoperative instability and subsequent severe low back pain is expected [5,6], concomitant fusion is considered. Studies show superior clinical outcomes in patients with spondylolisthesis who have had concomitant fusion [7,8] compared with decompression alone. Hence, it is common to add fusion to decompression in LSS patients with degenerative listhesis (DS) [9,10]. In Scandinavia, noninstrumented fusion is the standard of care for patients 60 years and older. The rationale for not using instrumentation despite the lower rates of fusion is the higher risk of poor fixation, loosening of the instrumentation and prolonged surgical time [11–13].

With an increase in the aging population in industrialized countries, it is expected that there will be greater number of patients requiring spinal fusion surgery for lumbar degenerative conditions with instability. Obtaining adequate fusion in elderly patients is challenging due to poorer osteoblast proliferation in the older compared to younger patients [13].

Autologous bone remains the gold standard graft in fusion surgery. However, in elderly patients, the quantity of locally harvested autologous bone from the decompression is often inadequate to obtain fusion [13], necessitating the use of graft extenders. In an attempt to avoid peri- and postoperative complications in harvesting additional donor bone from the iliac crest [14,15], allograft bone is used in Scandinavia. The use of allograft is labor intensive as it has to be processed and stored. In addition, the donor must be screened at least twice for potential contagious diseases. For these reasons, an acceptable bone graft extender, enhancer or substitute would be a welcome addition to the available options for the spine surgeons performing fusions.

Bone graft enhancers and extenders exist but they have not been without potential problems. Enhancers such as rhMBP-2 have been shown to increase fusion. However, there have been reports of increased radiculopathy and heterotopic ossification associated with its use [16]. The osteoinductive properties of allograft have also been open to debate. Studies have shown that different manufacturers and even different lots from the same manufacturer may have different osteoinductive capabilities [17].

A novel inorganic bovine-derived hydroxyapatite matrix combined with a synthetic 15 amino acid residue (ABM/P-15, Peptide Enhanced Bone Graft), as a substitute for autologous bone graft, is available in the market. It has been shown to promote bone formation in periodontal defects in humans and enhances cell proliferation, cell attachment, cell differentiation, osteogenesis, and biofilm suppression in animal and in-vitro studies [18–22]. ABM/P-15 is not osteoinductive by the normal definition because it does not induce bone to readily form soft tissues. This is a key safety feature of ABM/P-15 compared with rhBMP-2 which has shown to induce ectopic bone formation and osteoclast-mediated bone resorption [16]. ABM/P-15 has previously been studied in spine surgery [23,24]. However, no studies have been conducted in lumbar spine noninstrumented fusion surgery.

This study reports the results of an randomized controlled trial comparing ABM/P-15 versus allograft in noninstrumented lumbar fusion surgery. The purpose is to evaluate the rate of radiographic intertransverse fusion in patients with symptomatic LSS due to DS undergoing lumbar spine decompression and noninstrumented posterolateral intertransverse fusion with ABM/P-15 (mixed 50/50) or allograft bone (30 g/level), both mixed with local bone graft, using 1-year postoperative fine-cut computed tomography (CT) scans and to compare patient reported outcomes (PROs) at 12 and 24 months after surgery.

The study was conducted according to the CONSORT (Consolidated Standard of Reporting of Reporting) guidelines [25] and Danish legislation. Before inclusion each patient gave written informed consent for research use and publication of their data. Approval from the Scientific Ethics Committee of the Region of Southern Denmark (S-20120012) was obtained. The study is registered in ClinicalTrials.gov June 13, 2012 (NCT01618435).

Materials and methods

This was a prospective, randomized, double-blind single center trial in patients undergoing lumbar spinal decompression and noninstrumented posterolateral fusion randomized 1:1 comparing ABM/P-15 (I-, Cerapedics, USA) to allograft bone both mixed with local harvested autograft.

From March 2012 to April 2013, all patients aged 60 and older with LSS and concomitant DS referred to a major degenerative spine center were screened for inclusion. Inclusion criteria were severe reduction of walking ability due to spinal stenosis, a minimum score of 7 on Konno's "History of Examination Characteristic" [26], central spinal stenosis on 1–2 levels with spondylolisthesis verified by magnetic resonance imaging and lateral standing radiographs, completion of a minimum of 3 months of nonsurgical therapy with little or no effect and no sign of dementia as evaluated by the Mini Mental State Examination [27]. Exclusion criteria were previous spinal fusion surgery or fracture within the previous year, comorbidities limiting walking ability, such as cardiovascular or pulmonary disease with an American Society of Anesthesiologists score [28] of three or higher as determined by an anesthesiologist. Further exclusion criteria were cancer, orthopedic, or rheumatologic disease of the lower limb.

Randomization

Of 195 consecutive patients evaluated by the investigator, 101 met the inclusion criteria and agreed to participate

in the study. Before the study, sealed envelopes were prepared allowing 1:1 randomization in blocks of 20 with 10 ABM/P-15 and 10 allograft patients in each block. Assignment of the treatment arm was made just before surgery in the surgical theatre after the patient were anesthetized, allowing both the investigator and patient to remain blinded to the treatment arm, but not the surgeon. Sample size was determined using an expected 10-point greater improvement in the Oswestry Disability Index (ODI) in the ABM/P-15 group compared with the Allograft group, with a standard deviation of 17 at an α=0.05 and beta of 0.80.

Surgical technique

All patients were decompressed at the affected levels with either a laminotomy or a laminectomy. Nine surgeons participated in this trial and were equally distributed between the two cohorts. The posterolateral gutters were prepared by decorticating the transverse processes. The total volume of local autograft bone from the decompression was collected and weighed in grams. No bone from the iliac crest was harvested.

In the allograft group, the harvested local autograft was mixed with 30 grams of morselized fresh frozen femoral head at each fusion level (30 grams in one-level fusions and 60 grams in two-level fusion). In the ABM/P-15 group, the harvested local autograft was mixed with 5 cc of ABM/P-15 putty at each level (5 cc in one-level and or 10 cc in two-level fusions). The resultant graft material was divided equally to be used in posterolateral gutters of the fusion. Femoral head allograft costs DK5000 (US $754) and 5 cc of ABM/P-15 costs DK5695 (US $859). Postoperatively, patients were braced for 3 months with a soft brace, instructed not to lift more than 2 kg and to avoid maximal flexion, extension, and rotation.

Demographic data regarding age, height, weight, gender, and comorbidity were collected from paper questionnaires before the surgery. Surgical data, including duration of surgery, postoperative drain output, total estimated blood loss, and levels of fusion were collected perioperatively. PROs including Visual Analog Scales (VAS) [29] for back and leg pain, Oswestry Disability Index [30,31], and EquroQOL-5D [32] were collected at baseline on the day of admission and at 12 and 24 months after surgery by mail. Missing surveys were considered missing and were not imputed. If there were not enough items to calculate a score for the EQ-5D or ODI, these were considered missing as well.

Patient reported outcomes

VAS for back and leg pain

Visual analog scale [29] for back and leg pain is a respondent completed, unidimensional measure of pain intensity using a continuous scale on a horizontal line 100 mm in length, anchored by “no pain” (score of 0) and “worst imaginable pain” (score of 100). The respondent is asked to place a mark on the VAS line at the point that represents their pain intensity. The score is determined by measuring the distance between the “no pain” anchor and the patient’s mark, providing a range of scores from 0 to 100 [21,22].

ODIThe ODI [30,31] is a self-administered questionnaire measuring “back-specific function” on a 10-item scale with six response categories each. Each item scores from 0 to 5 which are transformed into a 0−100 scale. Patients with scores between 0 and 20 have Minimal Disability, between 21 and 40 have Moderate Disability, between 41 and 60 have Severe Disability, 61−80 are crippled and 81−100 are bed-bound or exaggerating their symptoms.

EuroQOL-5D

The EQ-5D-3 Level [32] consists of two pages − a descriptive system and a visual analogue scale (EQ VAS). The descriptive system has five dimensions − mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each has three levels − no problems, some problems, and extreme problems. The respondent indicates his/her health state by marking the box with the most appropriate statement in each of the five dimensions. The EQ VAS records the respondent’s self-rated health on a vertical, visual analogue scale where the endpoints are “Best imaginable health state” and “Worst imaginable health state.” The scoring algorithm for the population of the United Kingdom was used to assign a value, or index score, that incorporates UK population-based preference weights 1. The EQ-5D scores for the UK population range from −0.59 (worse than death) to 1.0 (full health), with a score of 0 indicating death [32].

Fusion evaluation

One-year postoperative fine-cut CT-scans (0.9 mm) with reconstructions were evaluated independently by three reviewers unaware in which arm the subject was enrolled. The reviewers evaluated the CT scans in EasyViz (Medical Insight, version 7.4.7-263.el6.final), a PACS workstation, using axial cuts with sagittal and coronal reconstruction viewed simultaneously. Each decompressed level (for example L2/L3) has two intertransverse spaces, one on each side. Each intertransverse space was evaluated separately generating two values for each of the operated segments. The fusion status of the decompressed level was decided as fused if at least one of the intertransverse spaces were fused. Fusion was defined as a continuous osseous bridge extending over the intertransverse space. The fusion status of each intertransverse space was determined as described by Carreon et al. [33] by agreement between two of the three reviewers as “fused” or “nonfused.”

Statistics

All data collected were entered in EPIDATA/EXCEL and exported to STATA for statistical analysis. All patients were treated as allocated. Continuous variables that were normally distributed were compared using unpaired *t* tests

and Wilcoxon-Mann-Whitney and Kruskal-Wallis test for non-normally distributed continuous variables. For longitudinal data such as the PROs, repeated measures analysis of variance with baseline scores were used to compare the two treatment arms. Fisher exact test was used to determine differences in proportions between the two treatment groups. Threshold p value was set at <.05.

No prior power analysis was made regarding fusion status.

Results

During the 1-year follow-up period, three patients had revision surgery – one had a recurrent stenosis, one had a same level disc herniation and a facet cyst, and one had adjacent level stenosis. These three were excluded from the analysis leaving 98 patients (49 in each group) available for analysis. The preoperative demographic and baseline PROs were similar between the two groups (Table 1). Although patients in the ABM-P15 group had a statistically significantly lower Mini Mental State Examination scores (28.59) compared with the Allograft group (29.16, p=.024), this is probably not clinically relevant. Approximately 90% of the spondylolisthesis were low grade and number of patients with two-level slips was similar between the two groups: eight in the Allograft group and 14 ABM/P-15 group (p=.133). The perioperative data including operative time, blood loss, and length of hospital stay was similar between the two groups. The amount of local bone harvested from the decompression was similar between the two groups as well (Table 2).

Table 1
Summary of demographic and baseline data

	ABM/P15	Allograft	p Value
N	49	49	
Age, years, mean (SD)	71.35 (6.33)	70.12 (6.76)	.357
BMI, kg/m^2, mean (SD)	27.42 (4.03)	26.85 (3.86)	.437
Female, N (%)	35 (71%)	39 (80%)	.347
Diabetes, N (%)	7 (14%)	6 (12%)	.970
Hypertension, N (%)	31 (63%)	22 (45%)	.068
Mini Mental State Examination (MMSE) Score	28.59 (1.38)	29.16 (1.06)	.024
Patient reported outcomes			
Back pain Visual Analog Scales (VAS), Mean (SD)	5.87 (2.42)	5.47 (2.60)	.437
Leg pain VAS, Mean (SD)	6.75 (1.71)	6.67 (2.06)	.832
Oswestry Disability Index, Mean (SD)	36.73 (14.56)	41.59 (13.70)	.094
EuroQOL-5D	0.55 (0.21)	0.54 (0.21)	.793
Grade of listhesis			.869
Grade 1	46 (94%)	45(91%)	
Grade 2	3 (6%)	4 (9%)	
Levels of listhesis			.218
1- level	35 (71%)	41 (82%)	
2- level	14 (28%)	8 (18%)	

Table 2
Summary of perioperative data

Perioperative data	ABM/P15	Allograft	p Value
Length of stay, days, mean (SD)	4.63 (2.14)	5.37 (2.51)	.123
Operative time, minutes, mean (SD)	114.92 (28.65)	106.15 (27.99)	.133
Estimated blood loss, mL, Mean (SD)	289.06 (281.60)	253.33 (187.76)	.467
Weight of local decompressed bone, mean (SD)	6.33 (3.56)	5.92 (5.20)	.648
Weight of allograft, mean (SD)	0.00	34.38 (10.70)	
Volume of ABM/P15, Mean (SD)	7.81 (3.08)	0.00	
Surgical levels fused			.218
One-level	35 (71%)	41 (82%)	
Two-level	14 (28%)	8 (18%)	

Fusion rate

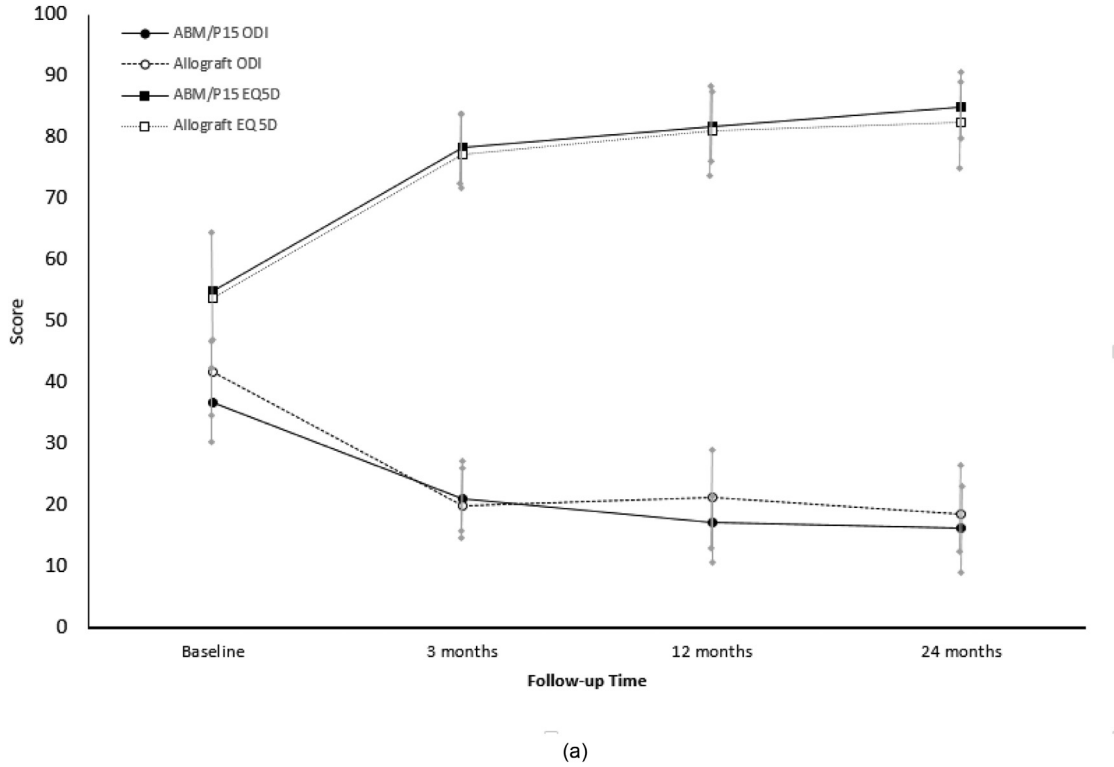
The number of surgical levels between the two groups was similar. As each level of consists of two intertransverse gutters, a total of 240 intertransverse sides or segments were evaluated, 126 in the ABM/P-15 group and 114 in the allograft group. As shown in Table 3, 63 of 126 (50%) intertransverse gutters in the ABM/P-15 group were classified as fused compared to 23 of 114 (20%) in the allograft (<0.001). Even when stratified into one- and two-level fusions, the fusion rates remain significantly higher in the ABM/P-15 group compared with the allograft group (Table 3). Based on the data available, the current sample size has a power of 0.8052 for the observed delta of 0.28 in the fusion rate.

Patient reported outcomes

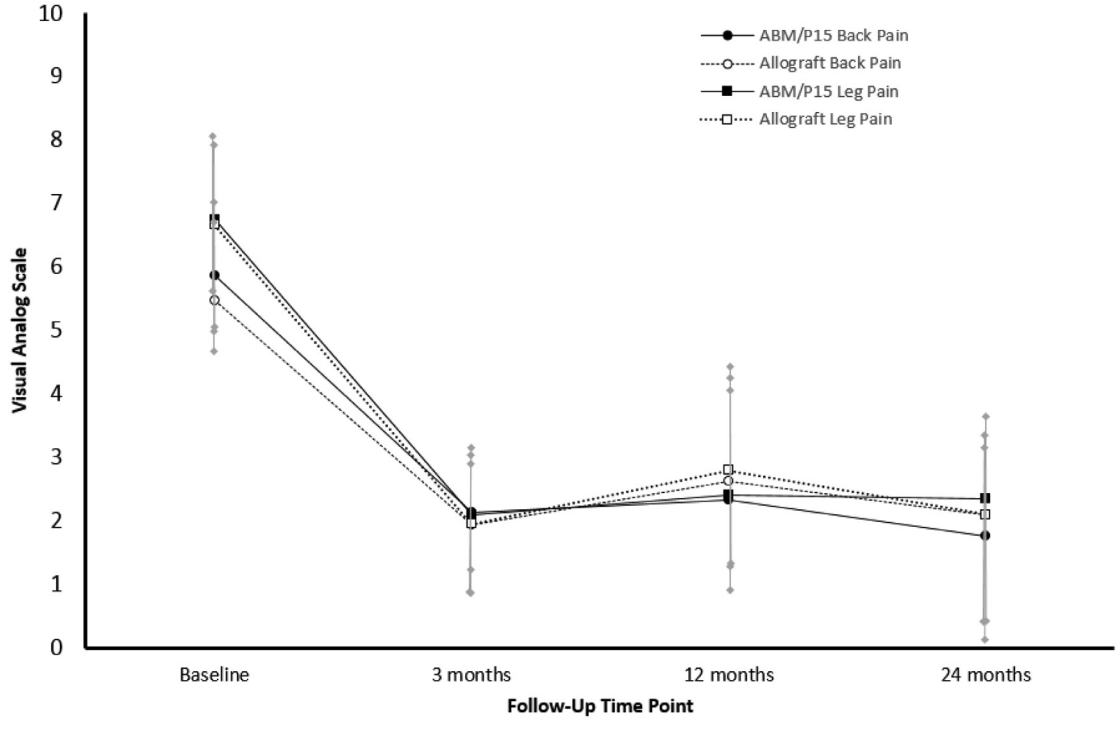
Forty-six (94%) subjects in the ABM-P15 and 45 (92%) had PROs available at the 24 month follow-up time point. In both cohorts, there were statistically significant improvements in all outcome scores from baseline to 3 months after surgery that was sustained at 1 and 2 years after surgery (Figure). However, there were no statistically significant

Table 3
Summary of fusion data

	ABM/P15	Allograft	p Value
One-level fusions			
Number of intertransverse spaces	70	82	
Presence of bridging bone across transverse processes	29 (41%)	17 (21%)	.007
Two-level fusions			
Number of intertransverse spaces	56	32	
Presence of bridging bone across transverse processes	34 (61%)	6 (32%)	.001
Total			<.000
Number of intertransverse spaces	126	114	
Presence of bridging bone across transverse processes	63 (50%)	23 (20%)	



(a)



(b)

Figure. Patient reported outcomes in the ABM/P-15 (solid markers) and the Allograft group (open markers) showing similar (Left) leg and back pain visual analog scores and (Right) EuroQOL-5D and Oswestry Disability Index scores.

Table 4
Summary of patient reported outcomes data

	ABM/P15	Allograft	p Value
N	49	49	
Back pain VAS, Mean (SD)			
Baseline	5.87 (2.42)	5.47 (2.60)	.493
3 mo postoperative	2.13 (1.94)	1.93 (1.79)	
12 mo postoperative	2.31 (2.81)	2.61 (2.81)	
24 mo postoperative	1.68 (2.47)	1.99 (2.27)	
Leg pain VAS, Mean (SD)			.665
Baseline	6.75 (1.71)	6.67 (2.06)	
3 mo postoperative	2.09 (2.36)	1.95 (2.33)	
12 mo postoperative	2.39 (3.03)	2.62 (2.96)	
24 mo postoperative	2.15 (2.71)	2.10 (2.68)	
Oswestry Disability Index, Mean (SD)			.261
Baseline	36.73 (14.56)	41.59 (13.70)	
3 mo postoperative	21.10 (18.68)	19.80 (15.28)	
12 mo postoperative	16.91 (14.86)	21.85 (21.44)	
24 mo postoperative	15.45 (16.39)	17.65 (16.82)	
EuroQOL-5D			.804
Baseline	0.55 (0.21)	0.54 (0.21)	
3 mo postoperative	0.78 (0.13)	0.77 (0.16)	
12 mo postoperative	0.81 (0.18)	0.81 (0.19)	
24 mo postoperative	0.85 (0.19)	0.83 (0.16)	

differences in the PROs between the two groups at any time point (Table 4).

Discussion

The results of this double blind randomized clinical trial show that adding ABM/P-15 to local bone graft increases fusion rates compared with local bone graft with allograft in patients undergoing noninstrumented posterolateral fusion for spondylolisthesis. The proportion of patients achieving fusion in the ABM/P-15 groups was twice that in the allograft group in both one and two level fusions.

These findings are similar to the findings of Lauweryns and Raskin [34] who report that ABM/P-15 has equal or greater efficacy compared with autograft bone. The low fusion rate, especially in the allograft group, evaluated with thin slice 3D CT images corresponds with the fusion rates reported by Andersen et al. [35].

The patients in the control arm of this study received allograft bone along with the local bone graft. Allograft bone is readily available and is widely accepted for use in anterior cervical discectomy and fusion. Allografts in ACDF are under compression and are in contact with cancellous bone, providing a better environment to produce fusion. However, there is a small risk of infectious disease transmission. Since allograft bone is mostly harvested from femoral heads taken during hip replacement surgery in older patients, the quality of the allograft is not optimal either.

In a posterolateral fusion, the graft is not under compression and the transverse processes and laminae are mostly cortical bone. This produces a less than optimal environment for fusion. In addition, the current surgical standard in Denmark is the use of noninstrumented fusion, especially in elderly individuals. The thought is that elderly patients already have poor bone stock which places them at risk of inadequate pedicle screw purchase and screw pullout [12]. Adding instrumentation also increases operative time, which may increase risk of the perioperative complications in the elderly [13].

Giannoudis et al. [36] emphasizes the importance of stability, osteoinductive, osteogenetic, and osteoconductive properties in the fusion site to generate optimal conditions for achieving a solid fusion. ABM/P-15 contributes to this, as it contains the small peptide P-15, which is not only an osteoconductive scaffold, but has osteoinductive properties including stimulating osteoblast differentiation, improved osseointegration, and adhesion of mesenchymal cells [20,21] There were no postoperative complications, such as, radiculopathy or excessive seroma formation, that could be directly attributable to ABM/P-15.

Interestingly, the improved fusion rate did not translate to improved patient-reported outcomes. This is similar to a previous prospective randomized trial of patients with degenerative spondylolisthesis [9] which showed that even in the 36% of patients that had nonunion, their clinical results were graded good to excellent. The authors concluded that development of a fibrous union or partial fusion may stabilize the motion segment enough to prevent progressive slip and recurrence of symptoms. This may especially hold true in the present study, as all patients were older than 60 years old and may have fewer physical demands. Longer follow-up is probably needed to truly assess the effect of nonunion on clinical outcomes. Previous studies on noninstrumented posterolateral fusions found that with longer follow-up, the results in patients with pseudarthrosis began to deteriorate. At average 7-year follow-up, 86% of patients with solid fusion had good-to-excellent results compared with only 56% of patients with pseudarthrosis [37].

There are limitations to this study. Although noninstrumented fusion is standard of care in Scandinavia, fusion with instrumentation is more widely used in other countries such as the United States and may limit the generalizability of this study. Using a noninstrumented fusion creates a more challenging environment for fusion compared with instrumented fusion. This may account for the lower rates of fusion compared with previously published reports. Other criteria such as demineralized bone or autograft were not included in the study design. The status of the fusion was determined using fine-cut CT scans which still carry inaccuracies compared with the gold-standard of surgical exploration. The strengths of the study were the randomized controlled trial design, a very homogenous group of participants with regards to the diagnosis, all patients having LSS due to degenerative lumbar spondylolisthesis, a high follow-up rate and that the blinding was ensured until after the statistical analysis was performed.

Conclusions

ABM/P-15 in combination with local harvested autograft significantly increases the intertransverse fusion rates compared with allograft in patients undergoing one to two-level noninstrumented posterolateral fusion for degenerative spondylolisthesis. This did not translate to improved patient reported outcomes in this 2-year follow-up study. Longer follow-up is needed to fully assess the impact of ABM/P-15 compared with allograft on patient reported outcomes.

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Supplementary material

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2020.01.009.

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