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

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Patient reported outcomes in non-instrumented lumbar fusion surgery

A Randomized Controlled Trial of ABM/P-15 vs allograft with 5 years follow-up

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This study was reviewed and approved by the Scientific Ethics Committee of the Region of Southern Denmark (S-20120012).

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Abstract

Study Design: Randomized clinical trial

Objective: To compare five-year Patient Reported Outcomes (PROs) in patients with degenerative spondylolisthesis treated with decompression and non-instrumented posterolateral fusion with either 15 amino acid residue (ABM/P-15) or allograft.

Summary of Background Data: Two-year follow-up data from a Randomized Clinical Trial comparing ABM/P-15 versus allograft showed that despite a higher overall fusion rate of 59% in the ABM/P-15 group compared to 35 % in the allograft graft group, PROs were similar between the two groups.

Methods: Patients with spinal stenosis due to degenerative spondylolisthesis (DS) were enrolled in the study and randomized 1:1 to either ABM/P-15 (mixed 50/50, 5cc/level) or allograft bone (30g/level), both mixed with local bone graft. PROs were collected at baseline and at 12, 24 and 60 months post-operative.

Results: The two groups were similar in terms of gender distribution, age and number of levels fused at baseline. Of 101 subjects enrolled, 98 were available for follow-up at one year, 92after two and 82 patients after 5 years. Patients in both groups reported clinically and statistically significant improvements in all PROs from baseline to post-operative on all PROs. At 5 year follow-up no significant differences were seen for leg pain (ABM/P-15=25.8 vs 32.0, p=0,10) , EQ5D (ABM/P-15=0.81 vs 0.74, p=0,74) or ODI (ABM/P-15=18.6 vs 27.0, p= 0.42) Back pain (ABM/P-15=22.5 vs 38.4, p=0,01) were statistically significant better in the ABM/P-15 group.

Conclusion: At five-year follow-up, patients who had non-instrumented posterolateral fusion augmented with ABM/P-15 had better back pain scores compared to the allograft only group, despite showing similar PROs at two years.

Keywords: ABM/P-15; non-instrumented fusion; decompression; degenerative spondylolisthesis; patient reported outcomes; lumbar fusion

Level of evidence: 1

key points

- This is a five-year follow-up evaluating the patient reported outcomes from a randomized clinical trial comparing ABM/P-15 (mixed 50/50) or allograft bone (30g/level) both mixed with local bone graft.
- There were 50 patients in the ABM/P-15 group and 51 patients in the allograft group. The two groups were similar in terms of gender distribution, age and preoperative health-related quality of life scores.
- Patients in the ABM/P-15 group had greater improvement in PROs compared to the allograft group at five-year follow-up.

Mini Abstract (50 words)

Patients with lumbar degenerative spondylolisthesis undergoing non-instrumented posterolateral fusion surgery with AMB/P-15 (N=51) had had lower back pain scores (VAS = 22,5) compared to allograft bone (N=50, VAS = 38,4, p=0.01) at five-years follow-up.

Introduction:

Patients with Lumbar Spinal Stenosis with severe disability and no improvement with non-surgical treatment are referred to a surgical evaluation and possible surgery (1). Surgical spinal decompression is offered to regain walking ability and reduce pain. When instability is present concomitant fusion is considered. Some studies show superior clinical outcomes in patients with spondylolisthesis who have had concomitant fusion compared decompression alone (2, 3).

Obtaining adequate fusion in elderly patients is challenging due to poorer osteoblast proliferation in elderly patients. Even the gold standard, iliac crest bone graft, may not be adequate to achieve fusion. We previously published the primary outcome results of a Randomized Controlled Trial (RCT) comparing 15 amino acid residue (ABM/P-15) to allograft in non-instrumented lumbar fusion surgery (4). Despite obtaining an overall fusion rate of 59% in the ABM/P-15 group compared 35 % in the allograft graft group, patient reported outcomes (PROs) 2 years post operatively were similar. There is little knowledge regarding longer-term results.

The purpose of the present study is to report on PROs, on the same cohort of patients five years after surgery.

Materials and methods

Study design. This is a 5 year follow-up study on a double-blind single center RCT in patients undergoing lumbar spinal decompression and non-instrumented posterolateral fusion randomized 1:1 comparing ABM/P-15 (I-Factor ™, Cerapedics, USA) to allograft bone both mixed with local harvested autograft. We have reported on two year PROs and fusion rates in a previous publication (4).

The study was conducted according to the Consolidated Standard of Reporting of Reporting, the CONSORT guidelines (5) and Danish legislation. Prior to 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 with an extension in 2019. The study is registered in ClinicalTrials.gov June 13, 2012 (NCT01618435).

From March 2012 to April 2013 all patients aged 60+ with Lumbar Spinal Stenosis (LSS) and concomitant degenerative spondylolisthesis (DS) referred to a major degenerative spine center were screened. Inclusion criteria were severe reduction of walking ability due to spinal stenosis, spinal stenosis on 1-2 levels with spondylolisthesis verified by MRI and lateral standing radiographs, completion of a minimum of 3 months of non-surgical therapy with little or no effect and no sign of dementia as evaluated by the Mini Mental State Examination (MMSE)(6). 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 ASA score (7) of 3 or higher as determined by an anesthesiologist. Further exclusion criteria were cancer, orthopedic or rheumatologic disease of the lower limb.

Randomization and Surgical Technique

Of 195 consecutive patients evaluated, 101 met the inclusion criteria and agreed to participate in the study. The patients were randomized in blocks of 20 with 10 ABM/P-15 and 10 allograft patients in each block. Assignment of the treatment arm was made immediately prior to surgery in the surgical theatre after the patient were anesthetized, allowing both the investigator and patient initially to remain blinded to the treatment arm. The patients and investigators were un-blinded two years after the index surgery.

All patients were decompressed at the affected levels with either a laminotomy or a laminectomy. The posterolateral gutters were prepared by decortication of the transverse processes. In the allograft group the local harvested autograft was mixed with up to 30 grams of morselized fresh frozen femoral head at each fusion level. In the ABM/P-15 group the harvested local autograft was mixed with 5 cc of ABM/P-15 putty at each level.

Patient reported Outcomes

Demographic data regarding age, height, weight, gender and co-morbidity were collected from paper questionnaires prior to the surgery. PROs including Visual Analog Scales (VAS) (8) for back (BP) and Leg Pain (LP), Oswestry Disability Index (ODI)(9,10) and EuroQOL-5D (EQ-5D)(11) were collected pre-operatively on the day of admission and at 12, 24 and 60 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.

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. For longitudinal PRO data, repeated measures ANOVA with baseline scores as co-variates were used to compare PROS between the two treatment arms at 12, 24 and 60 months after surgery. Fisher's exact test was used to determine differences in proportions between the two treatment groups. Threshold p-value was set at <0.05.

Results

The preoperative demographic data were similar between the two groups (Table 1). Five years postoperative 2 patients were deceased leaving 99 patients for follow-up (Figure 1). Both groups reported clinically and statistically significant improvements in all PROs from baseline to post-operative on all outcome measures with no difference at one and two year follow-up (Table2). At 5 years improvements in all PROs were seen in both groups from baseline to five years. Patients in the ABM/P-15 group had greater improvement in PROs compared to the allograft group, but this was only statistically significant for back pain. Fusion results for this cohort have been previously published (4) with an overall fusion rate of 59% in the ABM/P-15 group compared 35 % in the allograft graft group.

Discussion

Previous reported results of this double blind randomized clinical trial showed that adding ABM/P-15 to local bone graft had higher fusion rates compared to local bone graft with allograft in patients undergoing non-instrumented posterolateral fusion for spondylolisthesis (4). The entire cohort showed statistically and clinically relevant improvement from baseline to one year follow-up with no deterioration over the

following year and no difference between the two groups. This finding is in line with the results published by Fischgrund et al (12) who randomized seventy-six patients with degenerative lumbar spondylolisthesis to either instrumented or noninstrumented posterolateral intertransverse-process arthrodesis obtaining significant higher fusion rates in the instrumented group. Two years post-operative the higher fusion rate was not reflected in improvement of pain in the back and lower extremities.

In the present study PROs in the ABM/P-15 group were unchanged between two and five years follow-up whereas PROs in the allograft group deteriorated. This may be explained by Herkowitz and Kurz(3) reported on cohort of 50 patients with degenerative lumbar spondylolisthesis randomized to either decompression alone or decompression with concomitant intertransverse-process arthrodesis with a mean follow-up of 3 years. The patients with concomitant arthrodesis reported significantly better results of pain relief in the back and lower limbs. These results indicate that obtaining fusion when treating symptomatic spinal stenosis patients with concomitant degenerative lumbar spondylolisthesis prevents deterioration of the gained results of the surgical treatment over time.

There are weaknesses to this study. Despite an overall high five year follow-up rate there were great variations in the response rates to the different outcome items, especially the respond rate to ODI were disturbing low. Further both the patients and authors of the present study were un-blinded after the two year follow-up data were processed.

The strengths of the study were the RCT design, a very homogenous group of participants with regards to the diagnosis, all patients having LSS due to degenerative lumbar spondylolisthesis and no difference in baseline demographics.

Conclusions:

Over a five-year follow-up period, patients who had non-instrumented posterolateral fusion augmented with ABM/P-15 had lower back pain scores compared to the allograft only group, despite showing similar patient reported pain scores at two years follow-up.

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Table 1

Table 1. Summary of pre-operative demographic data			
	ABM/P15	Allograft	p-value
N	59	51	
Age, years, mean (SD)	71,4 (6,3)	70.1 (6,8)	0,357
BMI, kg/m^2, mean (SD)	27,4 (4.03)	26,9 (3,9)	0,437
Female, N (%)	35 (72%)	39 (80%)	0,357
Smoker, N (%)	2 (4%)	0 (0%)	0,243
Diabetes, N (%)	7 (14%)	6 (12%)	0,970
Hypertension, N (%)	31 (63%)	22 (45%)	0,068

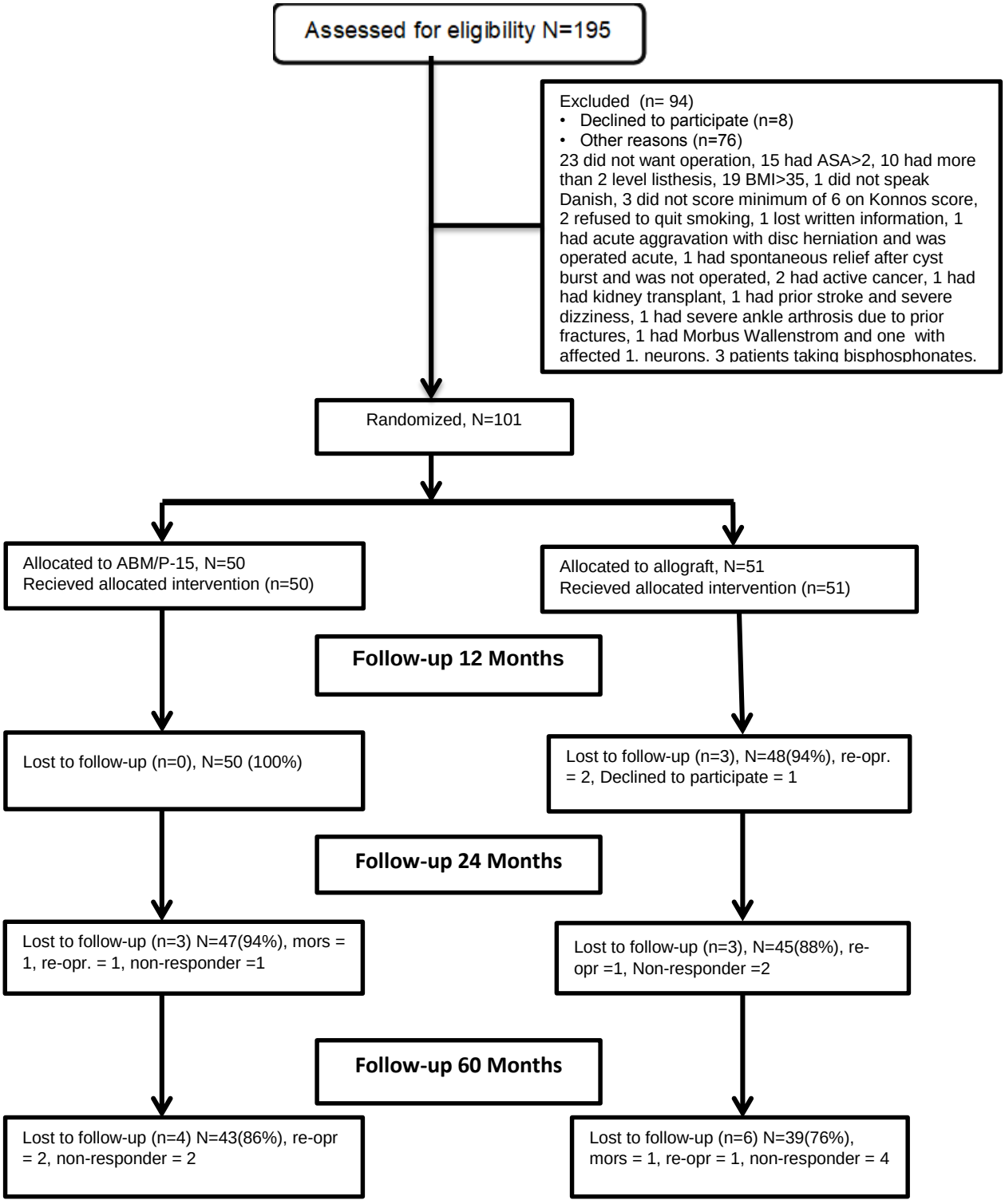
Table 2

Table 2. Summary of Patient Reported Outcomes data			
	ABM/P15	Allograft	p-value
Back Pain VAS, [N] Mean (SD)			0.013
Pre-operative	[50] 56.4 (24.9)	[51] 55,0 (24,9)	
12 month post-operative	[50] 22,1 (25,2)	[47] 20,7 (21,3)	
24 month post-operative	[47] 16,1 (23,2)	[45] 22,3 (25,2)	
60 month post-operative	[43] 22,5 (29,1)	[38] 38,3 (29,8)	
Leg Pain VAS, [N] Mean (SD)			0.105
Pre-operative	[50] 67,4 (17,2)	[51] 64,6 (21,0)	
12 month post-operative	[49] 25,8 (28,5)	[47] 22,7 (24,8)	
24 month post-operative	[46] 25,4 (28,1)	[44] 22,8 (27,8)	
60 month post-operative	[43] 25,8 (30,0)	[39] 32,0 (31,1)	
Oswestry Disability Index, Mean (SD)			0.416
Pre-operative	[50] 37,2 (14,4)	[51] 41,6 (13,6)	
12 month post-operative	[43] 20,4 (14,5)	[45] 19,7 (16,0)	
24 month post-operative	[36] 21,2 (14,7)	[35] 23,7 (16,3)	
60 month post-operative	[32] 18,6 (14,6)	[33] 27,0 (17,3)	
EuroQOL-5D			0.736
Pre-operative	[49] 0,42 (0,29)	[51] 0,41 (0,31)	
12 month post-operative	[50] 0,78 (0,22)	[48] 0,78 (0,22)	
24 month post-operative	[46] 0,80 (0,23)	[44] 0,77 (0,24)	
60 month post-operative	[41] 0,81 (0,25)	[37] 0,74 (0,24)	

Figure 1 Legends

CONSORT Flow Diagram

Figure 1


Assessed for eligibility N=195
Excluded (n= 94)
• Declined to participate (n=8)
• Other reasons (n=76)
23 did not want operation, 15 had ASA>2, 10 had more than 2 level listhesis, 19 BMI>35, 1 did not speak Danish, 3 did not score minimum of 6 on Konnos score, 2 refused to quit smoking, 1 lost written information, 1 had acute aggravation with disc herniation and was operated acute, 1 had spontaneous relief after cyst burst and was not operated, 2 had active cancer, 1 had had kidney transplant, 1 had prior stroke and severe dizziness, 1 had severe ankle arthrosis due to prior fractures, 1 had Morbus Wallenstrom and one with affected 1. neurons, 3 patients taking bisphosphonates.
Randomized, N=101
Allocated to ABM/P-15, N=50
Recieved allocated intervention (n=50)
Allocated to allograft, N=51
Recieved allocated intervention (n=51)
Follow-up 12 Months
Lost to follow-up (n=0), N=50 (100%)
Lost to follow-up (n=3), N=48(94%), re-opr. = 2, Declined to participate = 1
Follow-up 24 Months
Lost to follow-up (n=3) N=47(94%), mors = 1, re-opr. = 1, non-responder =1
Lost to follow-up (n=3), N=45(88%), re-opr =1, Non-responder =2
Follow-up 60 Months
Lost to follow-up (n=4) N=43(86%), re-opr = 2, non-responder = 2
Lost to follow-up (n=6) N=39(76%), mors = 1, re-opr = 1, non-responder = 4