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Allograft plus OP-1 enhances ossification in posterolateral lumbar fusion: A seven year follow-up

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KEYWORDS

Lumbar spine
Fusion
Spinal arthrodesis
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ABSTRACT

Purpose: To study the results of the combination of allograft plus BMP-7 in comparison with allograft alone in posterolateral lumbar arthrodesis.
Patients and Methods: A blinded controlled consecutive prospective cohort of skeletally mature patients study. One hundred and ten patients underwent posterolateral lumbar instrumented arthrodesis. Allograft randomly compacted onto either the right or the left side of the articular and the posterior aspect of the transverse processes of lumbar spine. The same procedure performed on the contralateral side, but allograft was previously mixed with osteogenic protein (OP-1). Clinical, x-ray and CT-scan long follow-up performed. Univariable and multivariable logistic regression analyses.
Results: More bone continuity was found with allograft plus OP-1 than with allograft alone ($p > 0.0038$). The amount of bone mass was greater on the OP-1 side ($p < 0.001$). No local or systemic adverse effect were noted.
Conclusions: Allograft on one side plus allograft with BMP-7 on the other achieved a fusion rate of 93 per cent. Allograft combined with BMP-7 was more effective than allograft alone.

Introduction

Surgical treatment for the spine is often aimed at achieving the fusion of a painful or unstable segment. The technique employed consists fundamentally of combining an instrumentation system for mechanical stabilization with a biological substance for bone formation enhancement [1]. Grafting enhances bone fusion, and therefore permanent stability, with bone autograft being the gold standard of graft materials.

However, the availability of autograft is limited. Furthermore, unacceptable pseudarthrosis rates have been reported with the use of autogenous bone graft in spinal surgery [2]. In addition, up to 25% of patients have reported substantial and persistent morbidity associated with the harvesting of autogenous iliac crest bone [3], making it necessary to seek an alternative to autograft. Such bone-graft substitutes should match and if possible improve on the fusion rates achieved with autologous bone grafting techniques, while avoiding the morbidity of bone graft harvesting and raising the quantity of graft material available. Many bone graft substitutes and cell therapy approaches have been proposed [4,5], with allograft being most commonly considered.

Allograft is an important osteoconductive agent, and although concern exists about disease transmission and immunogenicity, despite the large number of allograft recalls, there is only one documented case of probable disease transmission to a spine surgery patient, which concerned a human immunodeficiency virus infection transmission in 1988. To the best of our knowledge, no report on bacterial disease transmission from the use of allograft bone to spinal surgery patient has been published. Consequently there appears to be no overt risk associated with the use of allograft bone in spinal surgery [6].

On the other hand, bone morphogenetic proteins (BMPs) are a group of growth factor proteins within the transforming growth factor-b (TGF-b) superfamily of growth factors. BMPs stimulate osteoprogenitor cells from the host bed, and over the last decade they have been used as an alternative to autograft in lumbar fusion [7,8]. Since BMP molecules combined in vivo to form heterodimers would be much more potent osteoinductive agents than individual BMP molecules, their combination with allograft as a carrier appears to be an excellent approach for bone promotion in lumbar spinal surgery.

Therefore, a combination of allograft together with BMP may achieve a better fusion rate than the use of allograft or BMP alone. Since carriers with structural integrity are more desirable in posterolateral

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lumbar fusion, because they maintain a space around the transverse processes in which the fusion mass can form, allograft, furthermore, appears to be a good carrier.

The objective of this paper is to study the results of the combination of allograft together with BMP-7 in comparison with allograft alone in posterolateral lumbar arthrodesis. The operative hypothesis is that allograft + BMP-7 achieves better fusion rates than allograft alone; the null hypothesis is that both achieve the same fusion rate, while the alternative one is that allograft alone achieve a better fusion rate than allograft + BMP-7. This research was approved by the Local Committee for Clinical Trials and Research.

Material and methods

Surgical procedure

In a prospective consecutive cohort of skeletally mature patients, a posterolateral lumbar intertransverse process arthrodesis of the L4-L5 segment was performed, and at least one level above and one below were fused (Table 1). Inclusion criteria included skeletal maturity and medical recommendation for primary posterolateral lumbar spinal fusion, while exclusion criteria were prior revision surgery, nosocomial infection, or treatment with drugs interfering with bone metabolism. The conventional surgical fusion technique was the same in each case, and it was always performed by the same surgeon and surgical team. The host bone was denuded until bleeding was observed, and screws (Xia®, Stryker™, Kalamazoo, USA) for conventional posterolateral transpedicular fixation fluoroscopically-guided introduced. Bone denudation was completed, and two batches of 30 cc allograft chips were prepared, one with allograft and the other with a mixture of allograft plus a 3.3 mg dose of BMP-7 (OP-1 eptotermin alfa, Ossigraft®, Stryker™, Kalamazoo, USA). Randomization was then performed using a computerized method by a blinded independent researcher, not included as an author. One of these batches was then randomly compacted onto either the right or the left side of the spine to the lateral aspect of the articular and the posterior aspect of the transverse processes, and the other one was compacted onto the contralateral side. Subsequently, rods were connected within the pedicular screws, after which careful haemostasis was carried out and devitalized muscle removed. Finally, soft superficial low-pressure drainage was introduced, well distant from the allograft + OP-1. In all cases, the patient remained in bed for two to three days, and was then allowed and encouraged to walk with the help of a walker. Within a week, the patient was discharged from hospital. Results were studied for both study groups (Group A: allograft alone. Group B: allograft + OP-1).

Number of patients

The number of patients needed for the study was calculated in accordance with the binomial power calculations published by UCLA [9]. According to the literature, the differences between the groups – autograft/allograft and autograft/BMPs – could be up to 35% [9], and so 18 patients (18 cases per group) would be needed to obtain a success (fusion) probability of 0.65 in group A and of 0.95 in group B (30% difference between the groups). We enlarged the sample to 110 patients to compensate for possible exclusions or follow-up loss. All of them were enrolled from 2002 to 2006, and by the time of the final outcome, the study had, at least, 7 years follow-up.

Thirty-six patients were excluded because of infection (five cases), prior associated surgical procedures (seven cases), general disease (four cases), exitus (one case), lost to follow-up (14 cases), or incomplete follow-up (five cases). Therefore, we finally studied 74 patients (probability 0.65 group A/0.85 group B; power 0.80; probability null hypothesis rejection: $p = 0.05$; two-sided test: 20% expected differences, overheading for 0.15 probability).

Follow-up

All patients were clinically and radiographically followed up at months 3, 6, 12, 24, and then annually.

- Clinical. Pre and post-operative clinical examination was conducted using the Oswestry [10] low back pain disability questionnaire, preoperatively, two year-postoperatively and at the end of follow-up.
- Images. At the conclusion of follow-up (range: 84–132 months), conventional AP and lateral x-rays together with a planar and a 3-D reconstruction CT-scan (high speed spiral 1mm-acquisition CT-scan) were performed. CT-scan was performed only once: at two year (24 months) follow-up.
  - Fusion: For the diagnosis of fusion we followed a modification of the approach taken by Tan et al. [11] for structural allograft fusion. Grade I (complete fusion) full central trabecular continuity, and Grade II (partial fusion) partial trabecular continuity were grouped as "*bone continuity*"; Grade III (unipolar non-union) denoting superior or inferior non-union of the central allograft with partial trabecular discontinuity centrally, and Grade IV (bipolar pseudarthrosis) were grouped as "*no bone continuity*".
  - Bone amount was defined as the sum of bone differences from one side to the other. This was measured using a millimetric

Table 1.
Statistical profile for all patients

	n	Mean (yr)	Median (yr)	Range (yr)
Age	74	45.29	44	21–73
	n	Female	Male	Total
Gender	74	28 (38%)	46 (62%)	74
	Lumbar spinal stenosis	Disc pathology	Vertebral fractures	Degenerative spondylolisthesis
Diagnosis	15 (20.27%)	40 (54%)	10 (13.5%)	8 (10%)
	n	<3 levels	>3 levels	
Level fused	74	54 (73%)	20 (27%)	
	Median	Mean	SD	Range
Preoperative Oswestry	68	65.88	16.29	36–90
	Median	Mean	SD	Range
Postoperative Oswestry	30	29.76	14.34	10–72