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Basic Science

Allograft alone versus allograft with bone marrow concentrate for the healing of the instrumented posterolateral lumbar fusion

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Abstract

BACKGROUND CONTEXT: Spondylodesis in the operative management of lumbar spine diseases has been the subject of numerous studies over several decades. The posterolateral fusion (PLF) with pedicle screw fixation is a commonly used procedure.

PURPOSE: To determine whether the addition of bone marrow concentrate (BMC) to allograft bone increases fusion rate after instrumented posterior lumbar fusion.

STUDY DESIGN: The study was prospective, randomized, controlled, and blinded.

METHODS: Eighty patients with degenerative disease of the lumbar spine underwent instrumented lumbar or lumbosacral PLF (22 men, 58 women; body mass index less than 35 for a good visualization of the PLF in the X-rays). In 40 cases, the PLF was done with spongious allograft chips alone (Group I, age 62.7 years in average, range 47–77 years, level of fusion 1–2). In another 40 cases, spongious allograft chips were mixed with BMC (Group II, age 58.5 years in average, range 42–80, level of fusion 1–3), including the mesenchymal stem cells (MSCs). Patients were scheduled for anteroposterior and lateral radiographs 12 and 24 months after the surgery and for computed tomography scanning 24 months after the surgery. Fusion status and the degree of mineralization of the fusion mass were evaluated separately by two radiologists blinded to patient group affiliation. The bony mass was judged as fused if there was uninterrupted bridging of well-mineralized bone between the transverse processes or sacrum, with trabeculation indicating bone maturation on least at one side of the spines.

RESULTS: In Group I at 12 months, the bone graft mass was assessed in X-rays as fused in no cases (0%) and at 24 months in four cases (10%). In Group II, 6 cases (15%) achieved fusion at 12 months and 14 cases (35%) at 24 months. The statistically significant difference between both groups was proven for complete fusion at both 12 ($p=.041$) and 24 months ($p=.011$). Computed tomography scans showed that 16 cases (40%) in Group I and 32 cases (80%) in Group II had evidence of at least unilateral continuous bridging bone between neighboring vertebrae at 24 months ($p<.05$).

CONCLUSIONS: We have confirmed the hypothesis that the autologous BMC together with the allograft is a better alternative for PLF than the allograft alone. The use of autologous MSCs in form of BMC in combination with allograft is an effective option to enhance the PLF healing.

Keywords: Lumbar spine; Posterolateral fusion; Allograft; Bone marrow concentrate; Mesenchymal stem cells; Fusion rate

FDA device/drug status: Not applicable.

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Introduction

Spondylodesis in the operative management of lumbar spine diseases has been the subject of numerous studies over several decades. Posterolateral fusion (PLF) with pedicle screw fixation is a commonly used procedure. Autologous bone harvested from the iliac crest via a second surgery is supposed to be a ''gold standard'' graft material because of its osteoconductive and osteoinductive potential, unfortunately, there is a substantial frequency of morbidity after the harvest procedure, associated especially with donor site pain [1]. Allografts provide an alternative source of bone graft for PLF. The disadvantage of the washed fresh-frozen allograft is the generally accepted lack of osteoinductive potential [2].

Bioactive growth factors are presently being considered as therapeutic possibilities to enhance the healing of different mesenchymal tissues. Apart from other cells, bone marrow concentrate (BMC) also contains platelets and mesenchymal stem cells (MSCs). There are over 1,500 proteins within platelets and among them are growth factors stored in platelet α granules [3]. Mesenchymal stem cells have demonstrated benefits in the regeneration of different tissues of the musculoskeletal system [4]. The concept of BMC is to concentrate bone marrow aspirate and increase the numbers of platelets (and their growth factors) in addition to MSCs. Bone marrow concentrate is a fully autogenous material that can enhance the osteoinductive potential of the fresh-frozen allografts.

The aim of this study was to investigate the validity of BMC addition to allografts in instrumented lumbar PLF surgery and confirm or refute the hypothesis that autologous BMC together with the allograft is a better alternative for PLF than the allograft alone.

Material and methods

Sample selection

Between February 2009 and March 2010, 80 patients (22 men, 58 women) who had degenerative disease of the lumbar spine underwent instrumented lumbar or lumbosacral PLF at the authors' institution. Cases with vertebral fractures, infections, or spinal neoplasms were excluded from the study. Additional exclusion criteria consisted of nonrigid instrumentations, medication affecting bone mineralization (eg, corticosteroids), body mass index higher than 35, systemic diseases, blood disease and/or immunosuppressant treatment and/or dicoumarol therapy, and immunosuppressant and/or neoplastic and/or infectious diseases. For all patients, the operation was a primary surgical procedure in lumbar or lumbosacral spine. The study was designed to meet ethical standards and was approved by the ethical committee of the authors' institution.

Study design

The study was prospective, randomized, controlled, and blinded. All patients provided informed consent and afterward were scheduled for the operation at random using a predefined computer schedule (Random Number Generator Software 7.0; Microsoft Corp., Redmond, WA, USA). In 40 cases, instrumented PLF was done with spongious allograft chips alone (Group I). In another 40 cases, spongious allograft chips were mixed with BMC (Group II) (Fig. 1). Instrumentation was restricted to rigid pedicle screw system in both groups (S4; B/Braun-Aesculap, Tuttlingen, Germany). The demographic characteristics were similar in both groups regarding gender, age, and the number of levels fused (Table 1).

Surgical procedure

The PLF was performed in all cases in accordance with the standard general practice; beds for allografts were decorticated and spongious bone chips were implanted on each side of the spine. All allografts were delivered by an authorized bonebank institution. Sterile graft harvest from proximal or distal femur is routinely done within 12 to 24 hours of death using a sterile technique. The grafts are preserved until use by freezing them fresh. The fresh-frozen method consists of washing the graft with antibiotic solution and then cooling to −70°C. After slow defrosting in the operating theater, the allograft material (90 g) was morselized with the Luer forceps into small chips. The chips obtained were washed in sterile Ringer solution (with added antibiotics, Gentamycin). Afterward, the solution was removed from the bone chips in a closed syringe by means of active suction. The quantity of bone chips that were finally used depended on the number of fused segments. All patients received prophylactic antibiotic therapy for 24 hours after surgery and were braced for 3 months with a standard soft orthotic device. Full activities were resumed afterward.

Bone marrow concentrate preparation

In Group II, a total of 100 mL of bone marrow aspirate was harvested from both posterior iliac crests, with the

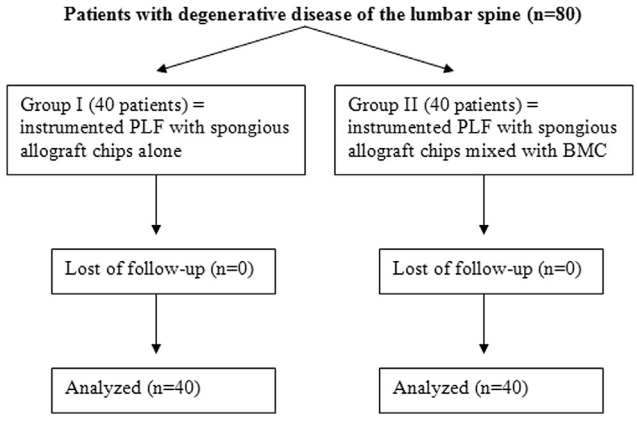

Fig. 1. CONSORT diagram shows the randomization of patients into two groups. PLF, posterolateral fusion; BMC, bone marrow concentrate.

Table 1
Demographic characteristics of both groups (Group I=PLF was done with spongious allograft chips *alone*; Group II=spongious allograft chips were mixed *with BMC*)

Gender	Number	Age (y) (min–max)	Number of levels fused (min–max)
Group I			
Male	10	67.6 (60–77)	1.2 (1–2)
Female	30	61.1 (47–74)	1.2 (1–2)
Total	40	62.7 (47–77)	1.25 (1–2)
Group II			
Male	12	62.6 (59–66)	1.83 (1–3)
Female	28	56.7 (42–80)	1.85 (1–3)
Total	40	58.5 (42–80)	1.85 (1–3)

PLF, posterolateral fusion; BMC, bone marrow concentrate; min, minimum; max, maximum.

patient positioned prone under general anesthesia just before the surgery. The bone marrow harvesting was performed simultaneously by both surgeons with two Yamshidi marrow needles (Somatex, Teltow, Germany) inserted about 2 to 3 cm deep into the iliac crests. Bone marrow was aspirated into 10-mL plastic syringes that were internally coated with calcium-heparin solution. Only small fractions of marrow (2–3 ml) were aspirated to maximize the harvesting of the MSCs and minimize dilution by peripheral blood. The harvesting was repeated and several perforations were made into different points in the iliac crests until a total of 100 mL of bone marrow aspirate was collected. The harvested bone marrow was processed in the operating theater using a dedicated centrifuge (Jouan B4i; Jouan, Saint-Herblain, France) at 20°C. The marrow was centrifuged for 15 minutes at 500 rpm and separated into leukocytes with platelets and erythrocytes fractions. Leukocytes (with residual platelets) were concentrated, approximately 10 times, together with MSCs. The isolated buffy coat with the maximal concentration of nucleated bone marrow elements was obtained from centrifuge tubes by an experienced physician, hematologist, with sterile pipettes, 1.0 mL from each tube providing 10 mL of BMC. An mL of BMC was used for the MSCs count control. The remaining 9 mL of BMC was mixed with sucked-out spongious bone chips (90 g) that were subsequently applied to the decorticated beds on each side of the spine. The content of MSCs was estimated with a flow cytometer FC 500 (Beckman-Coulter Cytomics, Nyon, Switzerland) following four-type protocol (genotypes CD45− and CD34− with coexpressions of CD 90+ and CD 105+). The achieved MSCs concentration was 0.01% to 0.02% (1.74×10^4/L on average; range: 1.06–1.98×10^4/L) of all nucleated bone marrow elements (1–10×10^6/L) in all specimens.

Radiologic follow-up protocol

Postoperative follow-up for 2 years was decided because it has been proposed to be the time required to definitively evaluate the solidity and stability of spine fusion [5]. Patients were scheduled for protocol follow-up anteroposterior and lateral radiographs 12 and 24 months after the surgery. Fusion status and the degree of mineralization of the fusion mass were evaluated separately by two independent experienced radiologists blinded to patient group affiliation. The bony mass on each side of the spine was evaluated and judged as fused if there was uninterrupted bridging of well-mineralized bone between the transverse processes or sacrum laterally to the instrumentation, with trabeculation indicating bone maturation at least on one side (right or left). Lower mineralization of the fusion mass was rated as absent, mild (<50%) (Fig. 2), moderate (>50%) (Fig. 3), or extensive (near 100%) (Fig. 4) as published by Lowery et al. [6] on the less mineralized side (right or left). Because the sensitivity of X-ray interpretation for lumbar spine arthrodesis is up to 70% [7], the status of the fusion was additionally evaluated by the same radiologists using computed tomography (CT) scans 24 months after the surgery. The CT imaging protocols consisted of 1 mm of continuous nonoverlapping axial slices that were made without a bone filter and of sagittal and coronal reconstructions. Fusion success was defined as the presence of continuous trabecular bone connecting the transverse processes on at least one side (right or left). In multilevel fusion cases, the least mineralized segment was evaluated (Fig. 5).

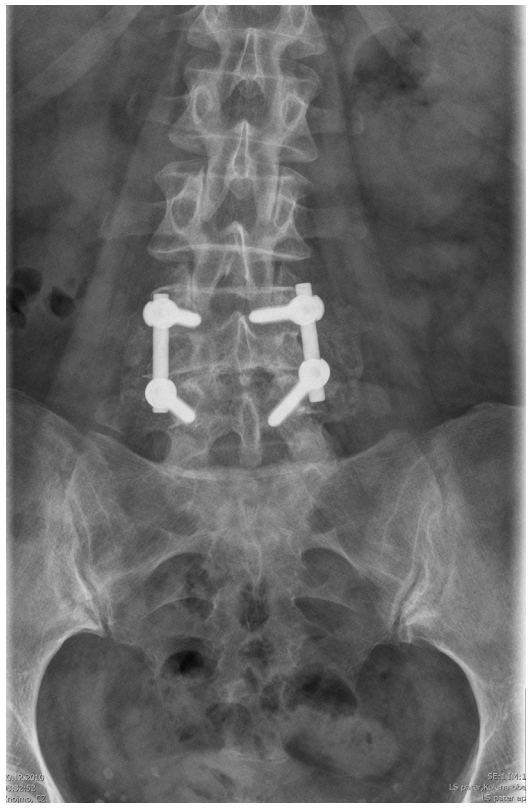

Fig. 2. X-ray (anteroposterior projection) of the lumbar spine with mild fusion (<50%).

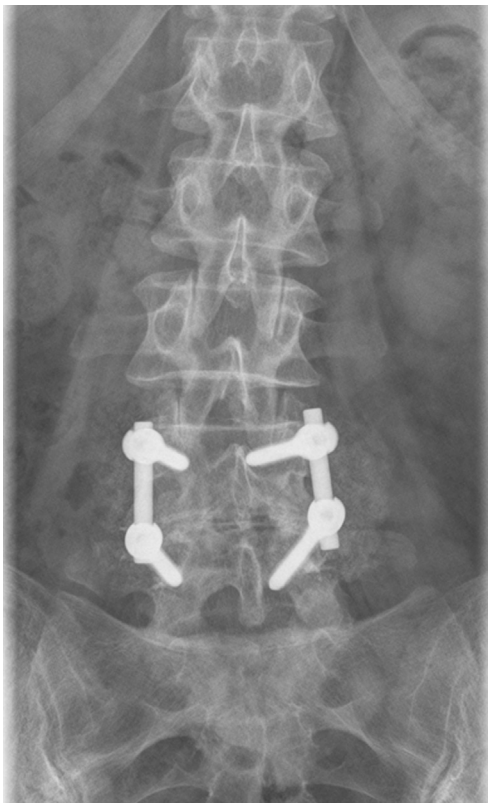

Fig. 3. X-ray (anteroposterior projection) of the lumbar spine with moderate fusion (>50%).

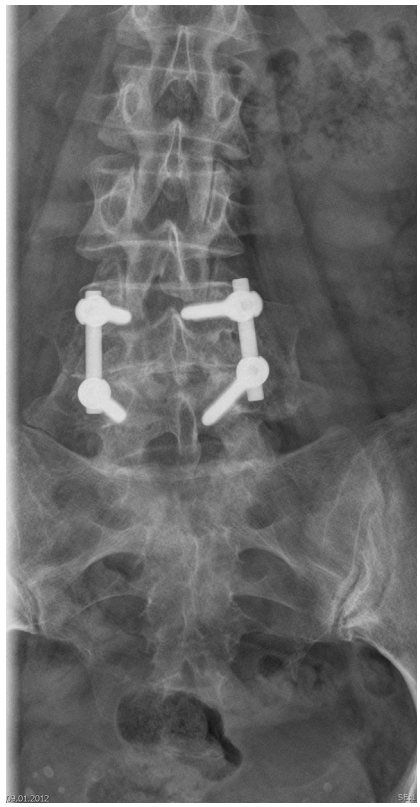

Fig. 4. X-ray (anteroposterior projection) of the lumbar spine with extensive fusion.

Statistical analysis

Statistical comparisons were based on the recorded follow-up radiologic data. The work was designed as a superiority study. All the data were evaluated statistically using the STATISTICA 9.0 software (StatSoft, Prague, Czech Republic). For comparing demographic and preoperative characteristics in both groups, p values were determined from the analysis of variance for continuous variables. To compare the degree of the mineralization of the fusion mass between both groups, the Mann-Whitney *U* test and chi square were used to assess the postulated hypothesis. A p value less than .01 was considered statistically significant.

Results

Of the 80 patients who underwent surgery, no patient died or was lost from the study and all were available for each of the radiologic assessments and last CT follow-up controls 2 years after surgery. Computer randomization provided similar distribution of demographic and preoperative measures. There were no statistically significant differences between both groups regarding preoperative diagnosis (degenerative disc disease vs. degenerative spondylolisthesis), gender, age, or the number of levels fused (p>.05 for all comparisons). There were no significant differences in the mean hospital stay lengths between both groups (average 11.8 days in Group I and 12.0 days in Group II; the confidence interval 95%, p=.72). Two complications occurred in each of the two groups, hematoma with subsequent revision surgery and drainage during the first week postoperatively. No patient in the groups required further surgery for any reason. No other adverse events were observed in either group.

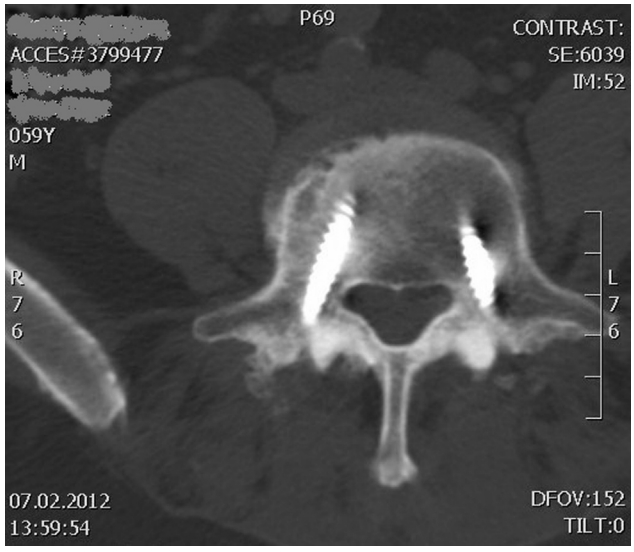

Fig. 5. Computed tomography scan of lumbar vertebrae with fusion success on the left.

Radiographic evaluation reported significant differences between the two groups regarding protocol-defined fusion success. Table 2 shows mean values that were achieved in the two groups with regard to the aforementioned rating ($p<.01$). In Group I at 12 months, the bone graft mass lateral to the instrumentation was assessed as fused in no cases (0%) and at 24 months in four cases (10%). In Group II, 6 cases (15%) achieved fusion at 12 months and 14 cases (35%) at 24 months. The statistically significant difference between both groups (with the advantage for Group II) was proven for complete, extensive fusion at 12 and 24 months. The moderate mineralization rating (>50%) also displayed a difference between both groups at 12 (5% in Group I and 20% in Group II) and 24 months (10% in Group I and 20% in the Group II). There were similar proportions of cases with a mild mineralization rating (<50%) in the two groups at 12 (10% in Group I and 15% in Group II) and 24 months (15% in the Group I and 0.5% in Group II). And there were also different percentages of absent mineralization ratings in the two groups at 12 (85% in Group I and 50% in Group II) and 24 months (65% in Group I and 40% in Group II). Complete agreement was achieved in the interpretations of fusion status and bone mineralization by the two radiologists.

Computed tomography scans showed that 16 cases (40%) in Group I and 32 cases (80%) in Group II had evidence of at least unilateral continuous bridging bone between neighboring vertebrae at 24 months. There were no differences between single- and multilevel PLFs in either group. Information about CT scanning results is provided in Table 3. Computed tomography investigation revealed more complete fusion than standard radiographs in the two groups (12 cases, 30% more in Group I and 16 cases, 40% more in Group II).

Discussion

The instrumented PLF is a commonly accepted surgical procedure and overall the most common technique performed to obtain fusion in the lumbar spine [8]. It provides substantial benefit for patients with degenerative disc disease [9]. The biological process of bone formation requires two critical elements: osteoinductive-osteogenic elements, factors (bone morphogenetic proteins) and cells that are able to cause the osteoblastic differentiation and an osteoconductive scaffold. Autografts possess both of these properties. Although the use of autologous bone graft to achieve a solid fusion is the preferred standard and is by far the most common source of graft [8], obtaining bone from the iliac crest has several disadvantages, including increased operation time, blood loss, and chronic donor site pain [1]. Allograft excludes these problems and can serve as an alternative option, but it is lacking in the osteoinductive potential and osteogenic cells because of the processing that it undergoes to decrease its antigenicity [2].

Animal studies have been performed to investigate how to achieve PLF more successfully using autograft material, allograft material, and BMC. Urrutia et al. [10] proved that autograft produces a higher fusion rate than allograft in the spinal fusion in a rabbit model. Cheng et al. [11] found that allograft when combined with recombinant human bone morphogenetic protein-4 effectively produces new bone formation and fusion in the rabbit PLF model. Peterson et al. [12] worked with BMC in athymic rats and demonstrated that bone marrow cells alone produce sufficient bone in vivo to fuse the lumbar spine in this model. Rao et al. [13] also confirmed the positive effect of BMC in an in vivo mouse PLF model. A transitional study from animal to human PLF models was published by Boden et al. [14]. They performed a prospective animal (rhesus monkey) and human clinical pilot trial using an extract containing bone morphogenetic proteins (Ne-Osteo) for PLF and found that this product added to the demineralized bone matrix and allograft is capable of achieving a continuous spine fusion mass.

There are also clinical studies focusing on allograft material in PLF in the literature. Jorgenson et al. [15] compared autograft with allograft in the PLF in the same patient and found out that allograft is inferior to autograft.

Table 2
Numbers of patients regarding X-ray evaluation of the mineralization of the fusion mass according to Lowery et al. [6]

	Group I	Group II			Group I	Group II	
X-rays	12 mo	12 mo	p	X-rays	24 mo	24 mo	p
0%	34	20	.038	0%	26	16	.047
<50%	4	6	**.042**	<50%	6	2	.002
>50%	2	8	**.024**	>50%	4	8	**.035**
100%	0	6	**.041**	100%	4	14	**.011**
Chi square	*13.73*	*p=.0035*		*Chi square*	*11.27*	*p=.0104*	

PLF, posterolateral fusion; BMC, bone marrow concentrate.

Note: *Group I*=PLF was done with spongious allograft chips alone; *Group II*=spongious allograft chips were mixed with BMC; *0%*=mineralization of the PLF is absent; *<50%*=mild mineralization of the PLF; *>50%*=moderate mineralization of the PLF; *100%*=total mineralization of the PLF; *chi square* in italics=final score of the chi square with p value; p value in bold=the p value of the Mann-Whitney *U* test.

Table 3
Numbers of patients and percentage of fusion success regarding results of CT imaging (Group I=PLF was done with spongious allograft chips *alone*; Group II=spongious allograft chips were mixed *with BMC*; fusion success (n)=the number of patients with PLF fused; fusion not success (n)=the number of patients with PLF nonfused)

	Group I	Group II
Fusion success (n)	**16**	**32**
Fusion not success (n)	24	8
Percentage (%)	**40**	**80**
Chi square	11.72	p=.003

CT, computed tomography; PLF, posterolateral fusion; BMC, bone marrow concentrate.

Bolded values represent the number of patients and percentage of fusion success of the posterolateral fusion. Unbolded values represent the number of patients with no fusion success.

They do not even recommend that allograft be used in the PLF. An et al. [16] conducted a very similar study using autografts and allografts in the same patient undergoing an instrumented lumbar PLF and demonstrated that the autograft side had achieved a solid fusion much more frequently than the allograft side. However, autograft harvesting from the iliac crest causes significant incidence of donor site pain that is persistent in patients over many years [17]. To avoid complications from autograft harvest surgery, many methods have been used to promote allograft (or bone substitute) bone formation potential for the PLF, combining magnetic fields [18], pulsed electromagnetic fields [19], direct current stimulation [20], or bone morphogenetic protein [21–23], despite the fact that the extent of fusion has relatively little bearing on the patient reported outcomes of pain and functional status.

Bone marrow concentrate seems to be another option on how to promote PLF healing. The primary bone-forming cell in the body is the osteoblast (the extracellular bone matrix is produced by the osteoblasts). Its precursor is the MSC. Mesenchymal stem cells are multipotent cells with the ability to proliferate and differentiate into muscle, cartilage, adipose, and also into bone cells (osteoblasts). The differentiation process is regulated by growth factors. Mesenchymal stem cells are more present in the bone marrow aspirate and BMC than in peripheral blood [24]. Bone marrow based grafts include techniques that focus on collecting the cellular elements (together with regulating proteins) of the bone marrow through aspiration.

In contrast to autografts, allografts and bone substitutes do not contain any autologous osteogenic cells and are coupled with poor osteoinductive properties. An addition of autologous BMC to bone allografts or substitutes represents an option on how to deliver autologous progenitor cells with osteogenic potential and osteoinductive factors to the osteoconductive scaffold. Gan et al. [25] used bone marrow derived MSCs combined with bone substitute (beta-tricalcium phosphate) in the PLF and reported that 95.1% of cases had positive spinal fusion results. Bansal et al. [26] used hydroxyapatite with beta-tricalcium phosphate mixed with BMC for the PLF. Fusion was evident in CT scans at the 1-year follow-up in all 30 cases. Calcium sulfate pellets soaked in BMC were used for the PLF by Niu et al. [27]. In contrast to both the aforementioned studies with beta-tricalcium phosphate, they recorded only a 45.5% fusion rate. Kitchel [28] used mineralized collagen bone graft substitute combined with BMC for the PLF and achieved a fusion rate of 80%, proved with CT scanning. He achieved an 84% fusion rate using autograft.

As mentioned previously, allograft by itself is not an effective material as a posterior onlay graft for the PLF in adult surgery [15,16]. Only one clinical trial concerning the use of autologous BMC in combination with the allograft material for the PLF has been published so far by Taghavi et al. [29]. Eighteen patients underwent instrumented PLF (7 single- and 11 multilevel) with a minimum 2-year follow-up. A diagnosis of nonunion was based on exploration during a revision surgery, dynamic radiographs, or CT scans. All single-level PLFs achieved solid fusion, whereas multilevel surgeries had a fusion rate only of 63.6% (seven cases). They concluded that BMC in combination with allograft is appropriate as an autograft substitute only in single-level PLF.

We have proved that allograft together with BMC produces a higher fusion rate than allograft alone in the instrumented lumbar posterolateral spinal fusion. The use of autologous MSCs in the form of BMC in combination with allograft is an effective alternative to autologous bone grafts for enhancing the PLF. We have achieved similar results to, for example, Dimar et al. [30], who have reported with iliac crest bone autograft in instrumented PLF (83.9% fusion rate). We agree with other authors [15,16] that allograft alone should not be used in the PLF. We have confirmed the hypothesis that the autologous BMC together with the allograft is a better alternative for the PLF than the allograft alone.

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