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Int J Spine Surg 2016, 10 ()
doi: https://doi.org/10.14444/3012
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Preliminary Results of Bioactive Amniotic Suspension with Allograft for Achieving One and Two-Level Lumbar Interbody Fusion

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Abstract

Background

Bone graft material for lumbar fusion was historically autologous bone graft (ABG). In recent years alternatives such as allograft, demineralized bone matrix (DBM), ceramics, and bone morphogenetic protein (BMP) have gained favor, although the complications of these are not fully understood. Bioactive amniotic suspension (BAS) with allograft is a new class of material derived from human amniotic tissue.

Methods

Eligible patients receiving a one or two level lumbar interbody fusion with Nucel, a BAS with allograft, were contacted and scheduled for a mininmim 12 month follow-up visit. Patients were evaluated for fusion using CT's and plain radiographs. Clincal outcomes, including ODI, VAS back and leg were collected, as well as comorbidities including BMI, smoking status, diabetes and previous lumbar surgery.

Results

One-level patients (N=38) were 71.1% female with mean age of 58.4 ± 12.7 and mean BMI of 30.6 ± 6.08. Two-level patients (N=34) were 58.8% female with mean age of 49.3 ±10.9 and mean BMI of 30.1 ± 5.82. Kinematic fusion was achieved in 97.4% of one-level patients and 100% of two-level patients. Baseline comorbidities were present in 89.5% of one-level patients and 88.2% of two-level patients. No adverse events related to BAS were reported in this study.

Conclusion

Fusion status is evaluated with many different biologics and varying methods in the literature. BAS with allograft in this study demonstrated high fusion rates with no complications within a largely comorbid population. Although a small population, BAS with allograft results were encouraging for one and two-level lumbar interbody fusion in this study. Further prospective studies should be conducted to investigate safety and efficacy in a larger population.

KEYWORDS: LUMBAR FUSION, BONE GRAFT, BIOACTIVE AMNIOTIC SUSPENSION, ALLOGRAFT, BONE GRAFT ALTERNATIVE, NUCEL

VOLUME 10 ARTICLE 12 DOI: 10.14444/3012

Introduction

Autologous bone graft (ABG) is still considered by many as the gold standard of graft material for spinal fusion, as it comprises all of the properties of an ideal graft: osteoinduction, osteoconduction, and osteogenesis. In addition, ABG for grafting purposes offers complete histocompatibility and has shown excellent fusion rates.[1] However, the use of ABG in spinal fusion has progressively declined in recent years due to the well-documented complications associated with harvesting of the graft itself.[2,3] Other shortcomings of ABG include variability in graft quality and limited availability. These issues have prompted the search for alternatives of bone grafting materials that are equally as effective as ABG in achieving arthrodesis.

Alternatives to ABG include various forms of allograft, demineralized bone matrix (DBM), ceramics, and bone morphogenetic protein (BMP). Many of these options meet results shown by the gold standard, but lack long term data; specifically complica-

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tions are not fully understood.[4] BMP possesses potent osteoinductive properties and has produced superior results to iliac crest bone graft in fusion procedures.[5,6] However, many adverse events have been reported [7-9] since the FDA's approval of BMP for lumbar interbody fusion in 2002.

NuCel© belongs to a new class of bioactive amniotic suspension (BAS) material derived from human amniotic tissue. NuCel has historically been used in spine and orthopedic applications; however there is significant interest and on-going research in wound healing. The allograft tissues, consisting of amniotic membrane and cells from the amniotic fluid and the amniotic membrane, are collected during elective cesarean sections.All donors are properly consented before tissue donation and are screened according to FDA and AATB standards. Standard production cryopreservation techniques, including controlled-rate freezing, are used to preserve native cell viability. NuCel has been on the market since 2009, with over 25,000 doses implanted to date. In that time there have been no reported complaints related to immune reactions or other safety issues. In a different orthopedic application, specifically treatment of knee osteoarthritis,[10] testing of the immune response was evaluated by evaluating C-reactive protein, erythrocyte sedimentation rate, T cells, B cells, and natural killer cells. Additionally, serum was assayed for IgG, IgA, IgM and IgE over the course of 1 year. These data showed that there was no significant immune response caused by the product.

For BAS use in spinal fusion, human amniotic fluid has shown to be a source of mesenchymal stem cells that are known to be pluripotent, capable of differentiating into many cellular phenotypes, including osteocytes.[11-13] Several studies have shown successful outcomes in the application of amniotic fluid in soft-tissue wound healing [14] and in several orthopedic conditions, including cartilage, ligament, and bone [15,16] repair. BAS can be used as an adjunct to allograft bone substitute to promote arthrodesis in spinal fusion procedures. To the best of our knowledge there have been no studies previously performed to analyze the use of BAS in the spine. The goal of this study is to report the preliminary results of a novel BAS product derived from amniotic fluid in patients receiving lumbar interbody fusions.

Methods

One-hundred retrospectively identified subjects met the inclusion/exclusion criteria for this IRB approved study. Each subject must have been treated with BAS (NuCel, Nutech Medical, Birmingham, AL) during the course of a one or two-level lumbar interbody fusion between L1-S1. The surgical approach and interbody cage implanted were at the discretion of the surgeon. Minimally invasive posterior fixation was utilized on all patients with percutaneous pedicle screws, no posterior fusion was performed. The indications for surgery for patients were most commonly spondylolisthesis, spondylosis, radiculopathy and DDD. There were a small number of patients that had a herniated nucleus pulpous. All patients were treated at a single center with surgeries being performed by two fellowship trained spine surgeons. In addition, patients prospectively must have been willing and able to undergo a CT scan and xrays and able to complete patient centered outcome questionnaires. Subjects were excluded from the study if they: were pregnant, had been experiencing back pain due to acute trauma; had evidence of back pain secondary to any infectious agents, metabolic bone diseases, or malignancy; had any autoimmune disease history; had any recent history of chemical or alcohol dependence; or if they were currently experiencing any major mental illness.

Retrospectively identified patients eligible for the study were contacted via telephone and were scheduled for a one-time prospective follow-up appointment. Informed consent was obtained from the patient at the follow-up visit, before any study specific procedures were performed. During the visit, subjects completed two questionnaires and received a CT scan and plain radiographs of the lumbar spine.

Clinical outcomes were based on neurologic status and two different patient centered outcome questionnaires, including: visual analog pain scale (VAS) and Oswestry Disability Index (ODI).The VAS determined the amount of pain experienced in each of: the lower back, right lower extremity, and left lower extremity. The VAS and ODI scores obtained during

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the follow-up visit were compared to scores that were obtained from the subject pre-operatively

Plain radiographs of the lumbar spine in anteroposterior view, lateral bending view, as well as lateral views in flexion and extension positions and non-contrast computerized tomography (CT) scans of the lumbar spine were captured at the follow-up visit. CT was preformed using a Siemens Somatom Emotion 16 with 0.6 mm slice width. The CT scans and X-rays were assessed for fusion by an independent radiologist. Fusion was scored according to the alphanumeric scale as described in Figure 1.

Surgeons commonly assess fusion as a combination of bridging bone and lack of motion at the index level.[17-19] Therefore, lateral flexion-extension radiographs were also evaluated for evidence of motion greater than five degrees at the operative level. Kinematic fusion was defined as a combined measure of CT fusion classification of 2A or 3A, with radiographic confirmation of less than five degrees of motion on the flexion-extension films.[19,20]

Patient medical history was reviewed for demographic information and the presence of comorbidities including; smoking, diabetes, previous lumbar spine surgery (PLS), and Body Mass Index (BMI) categorized according to NIH standards as overweight (≥25 and <30), or obese (≥30).

Results

Fifty-eight one-level patients and 42 two-level patients met inclusion/exclusion criteria, with 38 (one-level) and 34 (two-level) patients that consented to participate in the study. The prospective follow-up visit was a minimum of 12 months post-operation with average of 27.3 months for one-level patients and 28.2 months for two-level patients. Seventeen one-level patients and 18 two-level patients reached 24 months follow-up. Demographics for the one and two-level patients are included as Table 1.

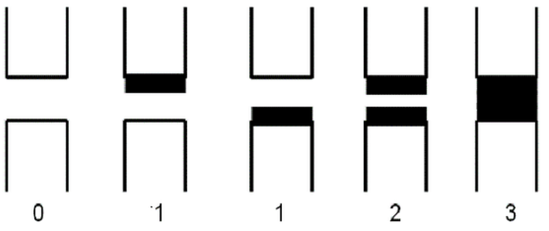

Fig. 1. CT Classification of Spinal Fusion. 0 – No bony ingrowth; 1 – Cranial downgrowth or caudal upgrowth; 2 – Cranial downgrowth and caudal upgrowth but NOT bridging; 3 – Complete bridging trabecular bone fusion; A – No evidence of supplemental fixation failure/no halo seen; B – Evidence of supplemental fixation failure/halo seen.

The levels treated from L1-S1 are stratified in Table 2 and Table 3, the most treated level was L4-L5 for one-level and L4-S1 for two-level patients.

Surgical approach was left to the discretion of the surgeon. Of the 38 one-level patients, ALIF (14) and LLIF (15) were the most common surgical approaches with TLIF (9) being utilized for the remaining patients. The two-level approach most commonly used was ALIF (25), with the remaining patients receiving LLIF (7) and TLIF (1). One two-level patient re-

Table 1. Patient Demographics.

Demographic	**One-Level**	**Two-Level**
N (No.)	38	34
Age (Mean ± SD)	58.4 ±12.7	49.3±10.9
BMI (Mean ± SD)	30.6±6.08	30.1±5.82
Male (%)	11 (28.9)	14 (41.2)
Female (%)	27 (71.1)	20 (58.8)

Table 2. Levels treated in one-level patients.

One-Level	
Levels Treated	No. Patients
L1-L2	1
L2-L3	1
L3-L4	6
L4-L5	20
L5-S1	10

Table 3. Levels treated in two-level patients.

Two-Level	
Levels Treated	No. Patients
L2-L4	1
L3-L5	9
L4-S1	24

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ceived a combined approach of TLIF and LLIF.

Fusion Status

Fusion status was available and graded for all enrolled patients. Representative examples of a 2A and 3A fusion status are included as Figure 2 and Figure 3.

The patient results of the CT fusion classification and radiographic fusion success are included in Figure 4 and Figure 5.

For two-level patients fusion status was further stratified by levels with Figure 6 reporting fusion status

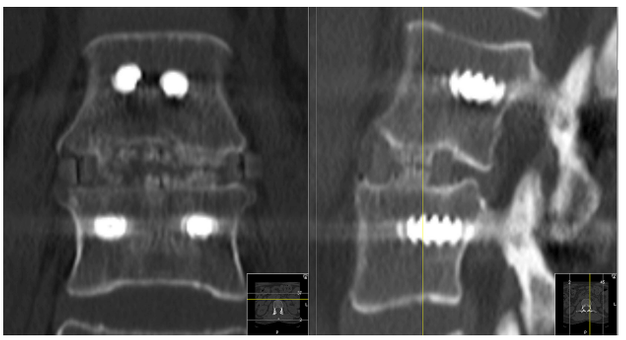

Fig. 2. Representative example of 2A fusion status

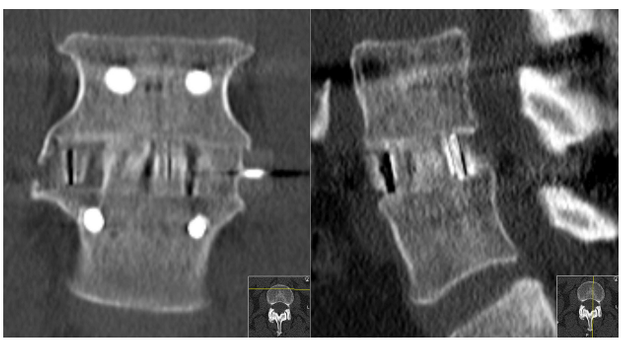

Fig. 3. Representative example of 3A fusion status.

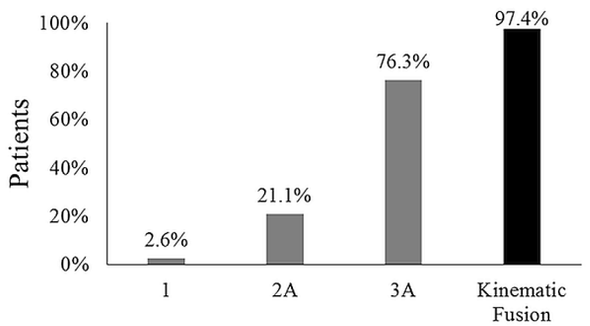

Fig. 4. One-level fusion status.

out of 68 total treated levels.

Applying the definition of kinematic fusion (minimum 2A status and flexion/extension confirmation < 5 degrees motion in the segment), 97.4% of one-level patients and 100% of two-level patients were clinically fused. When combining the one and two-level patients the total fusion rate by levels was 99.1%. The single one-level patient that was not clinically fused, received a CT fusion status of 1 and had motion at the index level. The CT status did not have an alpha grade, because the patient had posterior hardware removed in a subsequent surgery. The patient experienced right side low back pain that began 6 months post-operatively and persisted. After undergoing multiple injections to the hardware site that improved the pain, the patient underwent a hardware removal 18 months post-operatively. Seven months after removal of the hardware, the patient reported a score of zero for VAS back pain.

The CT fusion rate was analyzed in conjuction with surgical approach. The stratification of the data into smaller groups by surgical approach limited the ability to perform any realible statistical tests, so the raw data is presented in Table 4.

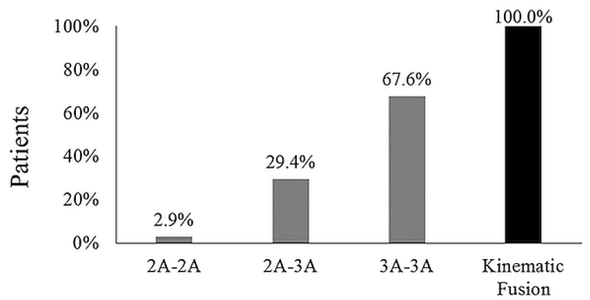

Fig. 5. Two-level fusion status by patient.

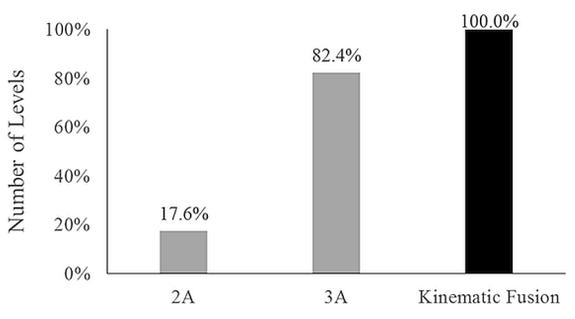

Fig. 6. Two-level fusion status by level.

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Comorbidities

In the one-level patient population, 89.5% of patients had at least one comorbidity and 65.8% had two or more. At least one comorbidity was present in 88.2% of two-level patients with 29.4% having two or more.

Comorbidities for both the one and two-level patient population are further stratified in Table 5.

The one and two-level population included only 10.5% and 11.8% respectively of patients without a comorbidity. Fifty percent of all patients were obese at the time of surgery, with 39.5% of the one-level patients being obese in combination with another comorbidity. Smoking patients were 28.9% of the one-level population and 23.5% of two-level population. All smoking patients in the one-level population had at least one other comorbidity, while 14.7% of the two-level patients had another comorbidity in addition to smoking. Diabetes, as expected, was present in the overweight and obese populations, with 26.3% of one-level and 11.8% of two-level patients having diabetes.

Outcomes

All patients answered a VAS back/leg questionnaire and ODI at the post-operative visit, although not every patient had a pre-operative value. Figure 7 and Figure 8 below include all available patients with pre-operative and post-operative outcomes.

Patients reported average VAS back improvement of 22.2 (one-level) and 27.0 (two-level. VAS leg improvement for right and left legs respectively was 15.9 and 8.0 for one-level and 14.0 and 19.1 for two-level. One-level patients' ODI scores improved on average 18.5 points and two-level scores improved 14.7 points.

Table 4. Fusion Status by Surgical Approach.

	CT Fusion Status			
Approach	**1**	**2A**	**3A**	**Total Levels**
ALIF	0	11	53	64
LLIF	0	7	23	30
TLIF	1	2	9	12

Table 5. One and two-level patient comorbidities.

No. of Comorbidities	Comorbidities	One-Level	Two-Level
None	N/A	4 (10.5%)	4 (11.8%)
Total of Patients with No Comorbidities		**4 (10.5%)**	**4 (11.8%)**
One	Overweight	3 (7.9%)	6 (17.6%)
	Obese	4 (10.5%)	11 (32.4%)
	PLS	2 (5.3%)	0 (0.0%)
	Smoking	0 (0.0%)	3 (8.8%)
Total of Patients with One-Comorbidity		**9 (23.7%)**	**20 (58.8%)**
Two	Smoking / PLS	1 (2.6%)	0 (0.0%)
	Overweight / PLS	5 (13.2%)	1 (2.9%)
	Overweight / Smoking	1 (2.6%)	2 (5.9%)
	Overweight / Diabetes	1 (2.6%)	1 (2.9%)
	Obese / Smoking	5 (13.2%)	2 (5.9%)
	Obese / Diabetes	3 (7.9%)	2 (5.9%)
Total of Patients with Two-Comorbidities		**16 (42.1%)**	**8 (23.5%)**
Three	Overweight / Smoking / PLS	1 (2.6%)	0 (0.0%)
	Overweight / Diabetes / PLS	1 (2.6%)	0 (0.0%)
	Obese / Smoking / Diabetes	1 (2.6%)	0 (0.0%)
	Obese / Diabetes / PLS	4 (10.5%)	1 (2.9%)
	Obese / Smoking / PLS	2 (5.3%)	1 (2.9%)
Total of Patients with Three Comorbidities		**9 (23.7%)**	**2 (5.9%)**

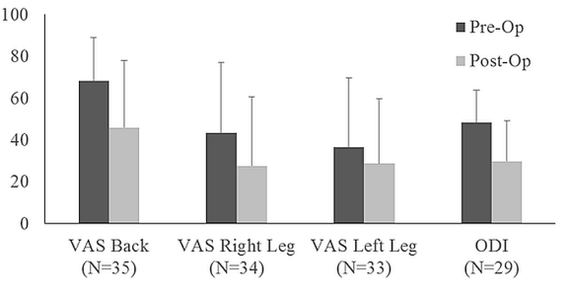

Fig. 7. One-Level Clinical Outcomes preoperative and postoperative. Error Bars show standard deviation from the mean.

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DOI: 10.14444/3012

Discussion

The nature of this study incorporated a largely comorbid patient population, with 89.5% of one-level patients and 88.2% of two-level patients having at least one comorbidity. It has been reported that multilevel surgery, and patients with comorbidities, such as rheumatoid arthritis and smoking have a higher risk of reduced fusion.[21-25] In this study 97.4% of one-level patients and 100% of two-level patients achieved a kinematic fusion. In Andersen, et al. the fusion rate (determined by radiographic bridging trabecular bone) for pre-operative smokers was 84.8% compared to 91.1% for non- smokers. The fusion rate reduced to 81.8% if the patient was smoking more than 10 cigarettes daily. Anayzing patients that smoked post-operatively the fusion rate was reduced to 77.8%, regardless of their smoking status pre-operatively. The authors used predictive statistics, and determined that smoking more than 10 cigarettes a day pre-operatively doubled the risk of a non-union.[24] In this study, 28.9% of one-level and 23.5% of two-level patients smoked, but 100% of smoking patients achieved kinematic fusion. In prospective studies, the exclusion criteria typically do not allow high risk comorbidities. In Malham, et al. only 9.2% of patients smoked, and morbid obesity was an exclusion while our study included 50.0% of one-level patients and two-level patients that met the NIH definition of obese (BMI≥30).[26]

Fusion Rate

Review of literature indicates that ALIF with ABG has long been the gold standard of treatment for symptomatic degenerative lumbar disc disease.[21,27,28] However alternatives, such as allograft and multiple synthetic materials, have recently gained favor due to the complications of harvesting ABG (increased donor site morbidity, blood loss and operation time).[27,29,30]

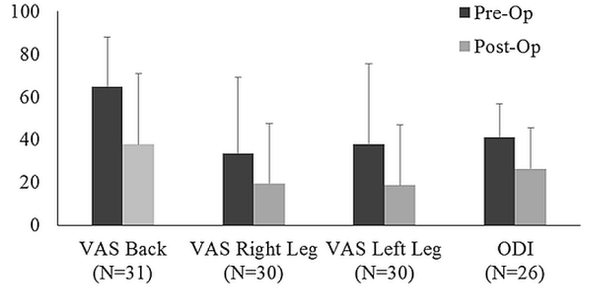

Fig. 8. Two-Level Clinical Outcomes preoperative and postoperative. Error Bars show standard deviation from the mean.

In the current study, 38 one-level patients and 34 two-level patients received interbody fusion with allograft and BAS. One-level patients had a kinematic fusion rate of 97.4%. One patient in the one-level population did not achieve clinical, fusion after she experienced painful hardware and required a subsequent surgery to remove the posterior screws and rods. Although multilevel fusion is published as a risk for non-union,[24,25] 100% of the two-level patients achieved kinematic fusion. The combined one and two-level kinematic fusion rate by number of levels treated was 99.1%.

A specific paper of interest, Santos et al., compared fusion rates using five different methods of evaluation after surgical fusion using autologous bone. Four methods used plain radiographs for evaluation, while the last used CT. The fusion rates using plain radiograph evaluation ranged from 74% to 96%, while the fusion rate with CT was 65%. [31] The CT method of fusion evaluation is a more stringent criteria than plain radiographs, regardless of the bone graft material utilized. The study presented here used CT evaluation of fusion with a 3A status showing full fusion. The levels reaching a 3A fusion were 76.3% of one-level surgeries and 82.4% of two-level surgeries, indicating evaluation by plain radiographs could show a higher fusion rate.

Rates of fusion in the literature vary depending on graft material and the method used to evaluate fusion. Table 6 is a review of the recent literature of fusion rates using various graft material and fusion analysis method. Overall, rhBMP-2 has reported fusion rates from 83% to 98%.[26,32,33] The lower end of the fusion rate occurred when rhBMP-2 was combined with ICBG or LBG, while the highest fusion rate was seen in a prospective study using only rhBMP-2 in the cage. B2A peptide shows strong fusion rates at 100%, when utilized in the larger studied dosage.[19] At 12 months, ABG has the lowest fusion rates between 73%-82%, as reported across multiple studies.[19,34,35] Silicate-substituted calcium phosphate lumbar fusion

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rates using CT were reported as 76.2% and 80% in two separate reported studies.[36,37] The NuCel fusion rate of 99.1% for all treated levels is a comparative fusion rate with other published results of synthetic bone grafts in lumbar fusion.

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Table 6. Published Fusion Rates for Bone Grafts.

Author	Evaluation of Fusion	Graft Material	Comorbidities	Time	Fusion Rate
Dimar et al. (2006)[32]	CT : Solid Unilateral or bilateral fusion	rhBMP-2/CRM	Workers comp - 13.2% Spinal litigation- 3.8% Smoking- 32.1%	12 months	90.6%
		ICBG	Workers comp -17.8% Spinal litigation - 15.6% Smoking - 22.2%	12 months	73.3%
Jenis and Banco (2010)[37]	CT: Graft consolidation on a least 2 contiguous cuts and in at least 2 of 3 planes	Silicate-substituted calcium phosphate (Actifuse, Baxter)	Smoking-9.5% Diabetics- 9.5%	12 months	76.2%
Nagineni et al. (2012)[36]	CT: Graft consolidation on a least 2 contiguous cuts and in at least 2 of 3 planes	Silicate-substituted calcium phosphate (Actifuse, Baxter)	Smoking – 11%	~12 months	80% (Lumbar only)
Nandyala et al. (2014)[38]	CT: Presence of bridging trabecular bone on at least 2 consecutive coronal and sagittal images ,blurring of the bone-graft endplate junction, and absence of radiologic cleft within fusion mass	A Silicate-substituted calcium phosphate (Actifuse, Baxter)	Workers comp – 38.5% Smoking – 30.8%	12 months	65.4%
		rhBMP-2 (INFUSE, Medtronic, Inc.)	Workers comp – 26.9% Smoking – 26.9%	12 months	92.3%
Roh et al. (2013)[39]	Radiograph : Presence of bridging bone across endplates or from endplates to interspace disc plugs	rhBMP-2 (INFUSE, Medtronic, Inc.)	Not available	12 months	83.5%
		Allogenic Morphogenic protein (OsteoAMP, Advanced Biologics)	Not available	12 months	93.3%
Park et al (2013)[33]	CT : Presence of bridging trabecular bone on at least 2 images and cortication of the peripheral edges of the fusion mass	rhBMP-2 (INFUSE, Medtronic) with LBG	Not available	12 months	85.7%
		rhBMP-2 (INFUSE, Medtronic) with ICBG	Not available	12 months	83.4%
Malham, et al. (2014)[26]	CT : Presence of bridging trabecular bone	rhBMP-2 (INFUSE, Medtronic, Inc.)	Smoking-9.2% Diabetes-2.3% Hypertension-7.6% Depression-3.8% Prior lumbar surgery-14.5%	12 months	96.5% ALIF 97.8 Hybrid
Ammerman, et al. (2013)[17]	If patient asymptomatic: Radiographic evidence of bridging bone with no motion – 100% of patients evaluated with radiograph or If patient symptomatic : CT evidence of bridging bone	Allograft cellular bone matrix containing mesenchymal stem cells (MSCs) and osteoprogenitor cells combined with DBM and cancellous bone (Osteocel Plus, Nuvasive)	Osteoporosis - 4.3% Diabetes - 13.0% Smoking - 4.3% Chronic steroid use - 4.3%	12 months	92.3%
Tohmeh et al. (2012)[40]	Fluoroscopy-guided radiography (FGX)- 98% of patients evaluated with FGX or CT: Complete ossification with some component of endplate involvement. – One patient (3%) was evaluated with CT	Allograft cellular bone matrix containing mesenchymal stem cells (MSCs) and osteoprogenitor cells combined with DBM and cancellous bone (Osteocel Plus, Nuvasive)	Tobacco use - 12.5% Coronary Artery Disease - 47.5% Diabetes - 20% COPD - 5% Steroid use - 8% Any prior spine surgery - 65%	12 months	90.20%
Sardar, et al. (2015)[19]	Based on Medical Metrics Inc. (Houston, Texas) criteria using CT and radiographs: Evidence of bridging bone Less than 50% radiolucency Less than 5 degrees of motion and less than 3 mm translation	B2A peptide (Prefix 150, BioSET, Inc)	Not available	12 months	50%
		B2A peptide (Prefix 750, BioSET, Inc)	Not available	12 months	100%
		ICBG	Not available	12 months	77.80%

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Author	Evaluation of Fusion	Graft Material	Comorbidities	Time	Fusion Rate
Lauweryns, et al. (2015)[34]	CT : Presence of bridging trabecular bone	ABM/P-15 (i-FACTOR, Cerpedics, Inc.)*	BMI 25-30 - 40% BMI >30 - 20% Tobacco use - 27.5% Diabetes - 12.5%	12 months	97.78%
		ABG		12 months	82.22%
Thaler et al. (2013)[41]	Radiograph: Bony bridging, bony continuity between endplate, trabecular structure in anterior bone and lack of radiolucent lines CT: 30% of endplate to endplate bridging anteriorly. Continuous intersegmental bridging in posterior column.	β – TCP (Chronos, Synthes)	Smoking – 32.4% Previous lumbar surgery adjacent to index level – 23.5%	12 months	Radiographic – 47.7% CT – 61.4%
Berjano,et al. (2015)[35]	CT: Evidence of bridging trabecular bone from lower endplate to upper endplate	Synthetic bone graft comprised of calcium phosphate granules and hydroxyapatite (Attrax, Nuvasive)	Not available	12 months	83%
		Nanocrystals -nanohydroxyapatite-based bone graft substitute (Nanostim, Medtronic)	Not available	12 months	100%
		ABG	Not available	12 months	75%
		Calcium triphosphate	Not available	12 months	89%
Kurd et al. (2014)[18]	CT : Brantigan, Steffee, Fraser method[42] Radiographs : < 5 degrees motion	Osteconductive - allografts, tri-calcium phosphate (Vitoss, Orthovita, Inc), silicate-substituted calcium phosphate (Actifuse, ApaTech), ceramics (Mastergraft, Medtronic), and hydroxyapatite products (nannOss, Pioneer)	BMI (mean, SD) - 32.5, 7.1 Smoking - 39.2%	12 months	93.75%
		Osteoinductive - rhBMP-2 (Infuse Kit, Medtronic), demineralized bone matrices (Grafton DBM Matrix, Medtronic, Progenix DBM Putty, Medtronic), and stem cell-based products (Osteocel Plus, Nuvasive Inc)	BMI (mean, SD): 30.6, 6.4 Smoking (%): 36.1%	12 months	87.18%

*Not available for sale in the USA.

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Clinical Outcomes

Patient clinical outcomes indicated that one and two-level BAS fusion patients improved from pre-operative scores. Average ODI improvement was 18.5 and 14.7 for one and two-level patients respectively. VAS back pain for one and two-level patients improved 22.2 and 27.0 points. VAS leg pain improvement for right and left legs was 15.9 and 8.0 (one-level) and 14.0 and 19.1 (two-level). Literature is unclear on an accepted minimum clinically important difference (MCID) for patient outcomes. Carragee and Cheng[43] reported the patient's pain should be reduced to 30 mm or less, with ODI improvement of at least 20 points to meet MCID. Copay et al. analyzed MCID and found that an ODI improvement of 12.8 was appropriate, while back pain needed to improve by 11.6 mm and leg pain 16.4 mm.[44] Malham et al., in an rhBMP-2 study reported improvement in ODI from 50.5 to 24.0. VAS back was pain reduced from 64 mm to 26 mm.[26] Outcomes after allograft cellular bone matrix are reported as ODI improvement from 45.7 to 27.1, VAS back improved from 74 mm to 34 mm, and VAS leg improved from 68 mm to 38 mm. The BAS patient outcomes reported here meet some of the variable MCID requirements reported in the literature, but the improvements are not as large as other bone graft studies. However, the large number of comorbidities in these patients should be considered when reviewing the patient outcomes in comparison to prospective studies with restrictive inclusion/exclusion criteria.[6,26]

Adverse Events

No adverse events related to BAS were reported during this study. Although one patient required subsequent surgery to remove painful hardware, it was unrelated to bone graft material. The morbidities associated with ABG, such as blood loss, abnormal sensation, and long term pain at the donor site have been well documented.[27,29,30] The complications with rhBMP-2 remain unclear and controversial, but include increased cancer risk, ectopic bone formation, and hematoma.[45-48] The Osteocel Plus studies did not report any adverse events related to the graft material, but the number of patients in these studies were small.[17,40] Given the small number of patients enrolled on this and other studies, adverse events should continue to be collected and reviewed on larger scale studies of bone graft substitutes.

Limitations

The largest limitation to this study was its retrospective nature. Clinical data is rarely available for all patients in a retrospective study and this study was no exception. The follow-up rate was reasonable for a retrospective study, but is not the same level as a prospective RCT. However, this retrospective study included a largely comorbid population allowing for a "real conditions of use" study of BAS in lumbar spinal fusion. Although this study has limitations, the high fusion rates and lack of any related adverse events in this population are promising. Further prospective studies should be conducted to investigate safety and efficacy of NuCel in a larger patient population.

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Disclosures & COI

Pierce Nunley, MD is a consultant for Nutech Medical, and received clinical and research support from Nutech Medical. Eubulus J. Kerr III, MD, Philip A. Utter, MD, David A. Cavanaugh, MD, Kelly A. Frank, MS, Devan Moody, Brian McManus, and Marcus B. Stone, PhD received clinical and re-

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search support from Nutech.

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Published 18 April 2016.
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