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Radiographic Analysis: 110 Consecutive ACDF Procedures Utilizing Novel Growth-factor Allograft

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Abstract

Introduction: Anterior Cervical Discectomy and Fusion (ACDF) procedures are a staple for addressing persistent pain and radiculopathy associated with of the degeneration, herniation and/or failure of interbody nucleus propulsi. Autograft arguably remains the gold standard after facing stiff competition from recombinant biologic alternatives that provided supra-physiologic quantities of singular growth factor to support bony remodeling. The alternative, novel allograft growth factor used in this series, provides the full complement of growth factors available from the native donor tissue many shown to play integral roles related to specific cascades involved with bony remodeling. Serial radiography is retrospectively assessed for efficacy is supporting fusion.

Methods: An Institutional Review Board was consulted and a waiver granted for retrospective evaluation of the state of fusion captured in radiology accrued during the routine follow-up associated with post-surgical care of patients requiring a surgical intervention where the novel allograft growth factor was utilized. A single, fellowship trained orthopedic surgeon collected data regarding 110 consecutive ACDF procedures that included at least one level where the novel allograft growth factor was included over a period from Nov 2018 thru Nov 2022. Criteria for considering an ACDF intervention included pain, radiculopathy, stenosis, kyphosis, myelopathy, pseudoarthrosis (prior), instability, cord compression, herniated nucleus propulsi (HNP), degenerative disc disease, and/or scoliosis. A collagen matrix scaffold or equivalent carrier was rehydrated using novel allograft growth factor for each of the surgical interventions reviewed. The resulting graft mass was positioned within interbody cages utilized at each level requiring intervention. An independent radiologist assessed serial radiography collected using the Brantigan, Steffee and Fraser criteria to classify state of fusion.

Results: At three months 70 of 162 (43.2%) levels were deemed fused with 85 of 162 (52.5%) deemed partially fused and the remaining 7 of 162 (4.3%) levels reporting with limited evidence of fusion. At six months 90 of 150 (60.0%) levels were deemed fused with 55 of 150 (36.7%) deemed partially fused and 5 of 150 (3.3%) reporting with limited evidence of fusion. At twelve months 114/129 (88.4%) levels were deemed fused 14/129 (10.9%) deemed partially fused and 1/129 (0.8%) demonstrating limited evidence of fusion. At eighteen months 131/133 (98.5%) levels were deemed fused 1/133 (0.8%) deemed partially fused and 1/133 (0.8%) demonstrating limited evidence of fusion. At twenty-four months 132 of 133 (99.2%) levels were deemed fused with the remaining level (0.8%) deemed partially fused.

Conclusion: This novel allograft growth factor demonstrates success with regards to supporting bony fusion desired as a result of an ACDF intervention. This multi-factored approach to supporting fusion includes a number of known growth factors shown to benefit a number of biologic cascades pivotal to bony remodeling including osteoinductive, angiogeneic, proliferative and chemotactic roles. These parallel relationships work collaboratively to contribute to successful bony remodeling and may improve patient outcomes. Further clinical assessment is warranted to better understand the full potential of this novel growth factor allograft.

Keywords: ACDF • Cervical • Spine • Biologic • Novel • Allograft • Growth factor • Radiographic analysis

Introduction

Anterior Cervical Discectomy and Fusion (ACDF) procedures are a staple for addressing sequelae observed including persistent pain and radiculopathy associated with of the degeneration, herniation and/or failure of nucleus propulsi and the resulting stenosis.

Autograft arguably remains the gold standard after facing stiff competition from recombinant biologic alternatives that provided supra-physiologic quantities of singular growth factor to support bony remodeling. This single factor approach led by rhBMP2, has mixed success in the off-label applications associated with ACDF procedures where Ratko reported moderate evidence that off-label use of rhBMP2 in anterior cervical spine fusion increases cervical swelling and related complications [1]. Nonetheless, biologics have seen continued use in an effort to better support bony remodeling associated with successful fusion, [2,3] increasingly in patients where comorbidities may pose a substantial challenge to successful healing [4,5].

The alternative, novel allograft growth factor used in this series, provides the full complement of growth factors sourced from the allograft donor, in the therapeutic quantities recovered from the native tissue. Many of the growth factors recovered have been shown to play integral roles related to specific cascades involved with bony remodeling. Research into additional, supplemental factors such as Fibroblast Growth Factors 1 and 2 (FGF-1. FGF-2), [6,7] Platelet-Derived Growth Factor (PDGF), [8] Insulin-like Growth Factor (IGF-1), [9] Vascular Endothelial Growth Factor (VEGF),[10] and/or Transforming Growth Factor Beta (TGF-β), [11,12] which are all expressed in this novel growth-factor allograft, have demonstrated value with regard to important osteoinductive, angiogenic, proliferative and chemotatic cascades

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required for successful fusion. Serial radiography was retrospectively assessed to evaluate efficacy in supporting fusion.

Materials and Methods

A single, fellowship-trained orthopedic surgeon collected data regarding 110 consecutive ACDF procedures detailing 107 patients that included at least one level where the novel growth-factor allograft was included over a period from Nov 2018 thru Nov 2022. The cohort (n=107) included 39 males (36.4%) and 68 females (63.6%). The median age was 54.7 years with the youngest reporting to be 32.4 years and the most senior at 83.3 years.

From the cohort 100 patients were assessed for related comorbidities which revealed 35//100 (35.0%) patients had no indication of a comorbidity, 33//100 (33.0%) reported hypertension, 20/100 (20.0%) reported diabetes, 14/100 (14.0%) reported a thyroid condition, 11/100 (11.0%) reported heart disease, 10/100 (10.0%) reported osteoporosis, 9/100 (9.0%) reported rheumatic disease, 6/100 (6.0%) reported high blood pressure, 4/100 (4.0%) reported kidney disease, 3/100 (3.0%) reported lung disease, 2/100 (2.0%) reported stroke, 1/100 (1.0%) reported osteoarthritis, and 1/100 (1.0%) reported a history of cancer as detailed on (Table 1).

Of the 100 patients assessed for comorbidities, additional review detailed smoking status, any return to the ER/OR and any infection that required treatment following surgery. With regards to smoking 48/100 (48.0%) had a history of smoking. From the portion reporting a history of smoking, 30/48 (62.5%) identified as former smokers and 18/48 (37.5%) identifying as an active smokers as captured in (Table 2). 88/100 (88.0%) patients assessed did not require any return visit to the ER/OR. Of the remaining 12/100 (12.0%) patients a return to the ER/OR was reported for the following reasons: 6/100 (6.0%) patients required an surgical extension or additional levels to the initial procedure, 3/100 (3.0%) patients required a surgical revision to the posterior-lateral articulation, 1/100 (1.0%) patient required a subsequent bilateral laminectomy and 2/100 (2.0%) patients reported a return to the ER: one for neck pain which resolved upon removal of stabilization collar and another for calf pain to rule out DVT. Of the 100 assessed a single patient 1/100 (1.0%), reported infection at the site of incision which was resolved with Levaquin.

Additionally BMI assessment was conducted on 95 patients from the group which revealed, 2/95 (2.1%) were below normal weight standards reporting a BMI of less than 18.0 kg/m^2, 16/95 (16.8%) were within normal weight standards reporting a BMI greater than or equal to 18.0 to 24.9 kg/m^2, 35/95 (36.8%) were classified as overweight reporting a BMI greater than or equal to 25-29.9 kg/m^2, and 42/95 (44.2%) were classified as obese reporting a BMI greater than or equal to 30 kg/m^2. Within the subcategory of those defined as obese, 28/42 (66.7%) fall within Obesity class I(BMI 30-34.9 kg/m^2); 11-42 (26.2%) fall within Obesity class II (BMI 35-39.9 kg/m^2); and three of 42 (7.1%) fall within Obesity class III also referred to as severe, extreme or massive obesity (BMI ≥40 kg/m^2) () as noted with (Table 3). Of the 110 interventions reviewed 46/110 (41.8%) procedures involved one level, 37/110 (33.6%) procedures involved two levels, 20/110 (18.2%) procedures involved three levels and 7/110 procedures involved four levels (6.4%) detailed on (Table 4). From the 110 procedures performed, 1/207 (0.04%) levels evaluated included C2-C3, 33/207 (15.9%) levels evaluated included C3-C4, 51/207 (24.6%) levels evaluated included C4-C5, 63/207 (30.4%) levels evaluated included C5-C6, 54/207 (26.1%) levels evaluated included C6-C7 and 5/207 (2.4%) levels evaluated included C7-T1 as demonstrated on (Table 5). It should be noted the 107 patient cohorts includes three patients which each contribute two procedures: two patients receiving distinct intervention to adjacent levels and a single patient receiving subsequent intervention to an adjacent level and revision to the initial level of intervention. Of the criteria for considering an ACDF intervention 91/107 (85.0%) patients reported pain, 81/107 (75.7%) reported radiculopathy, 66/107 (61.7%) reported stenosis, 22/107 (20.5%) reported kyphosis, 18/107 (16.8%) reported myelopathy, 9/107 (8.4%) reported pseudoarthrosis (prior), 8/107 (7.5%) reported instability, 4/107 (3.7%) reported cord compression, 4/107 (3.7%) reported Herniated Nucleus Propulsi (HNP), 2/107 (1.9%) reported degenerative disc disease, and 1/107 (0.9%) patients included scoliosis as demonstrated in (Table 6). A collagen containing scaffold or equivalent carrier was rehydrated using novel growth-factor allograft for each of the surgical interventions reviewed. The surgeon elected to utilize a collagen-mineral matrices in 71/110 (64.5%) procedures, demineralized bone fibers in 38/110 (34.5%) and a single instance (0.9%) of a demineralized bone matrix as demonstrated in (Table 7). The resulting graft mass was positioned within interbody cages utilized at each level requiring intervention. Of the interbody cages implanted 149/207 (72.0%) were of titanium construction with the remaining 58/207 (28.0%) cages consisting of PEEK design. An Institutional Review Board was consulted, and waiver granted for retrospective evaluation of the state of fusion captured in radiology accrued during the routine follow-up associated with post-surgical care of patients requiring a surgical intervention

Table 1. Comorbidities expressed (n=100).

No indication of comorbidity	35/100 (35.0%)
Hypertension	33/100 (33.0%)
Diabetes	20/100 (20.0%)
Thyroid Condition	14/100 (14.0%)
Heart disease	11/100 (11.0%)
Osteoporosis	10/100 (10.0%)
Rheumatic disease	9/100 (9.0%)
High blood pressure	6/100 (6.0%)
Kidney disease	4/100 (4.0%)
Lung disease	3/100 (3.0%)
Stroke	2/100 (2.0%)
Osteoarthritis	1/100 (1.0%)
History of cancer	1/100 (1.0%)

Table 2. Smoking status (n=100).

Non-smoker	52 (52.0%)
History of smoking	48 (48.0%)
Former smoker	30/48 (62.5%)
Active smoker	18/48 (37.5%)
Total	100

Table 3. BMI classification at time of procedure (n=95).

Below weight (BMI ≤ 18.0 kg/m^2)	2	(2.1%)
Normal weight (BMI ≥ 18.0 to 24.9 kg/m^2)	16	(16.7%)
Overweight (BMI ≥ 25 to 29.9 kg/m^2)	35	(36.5%)
Obesity class | (BMI ≥ 30 to 34.9 kg/m^2)	28	(29.2%)
Obesity class II (BMI ≥ 35 to 39.9 kg/m^2)	11	(11.5%)
Obesity class III (BMI ≥ 40 kg/m^2)	3	(3.1%)
Total	95	(100.0%)

Table 4. # of levels included per procedure (n=110).

One level	46/110 (41.8%)
Two level	37/110 (33.6%)
Three level	20/110 (18.2%)
Four level	7/110 (6.4%)
Total	110 (100.0%)

Table 5. Intervention by level (n=207).

C2-C3	1/207 (0.4%)
C3-C4	33/207 (15.9%)
C4-C5	51/207 (24.6%)
C5-C6	63/207 (30.4%)
C6-C7	54/207 (26.1%)
C7-T1	5/207 (2.4%)
Total	207

where the novel growth-factor allograft was utilized. Radiology was grouped within reporting windows of 3, 6, 12, 18, and 24 months--including a margin of error of ±1.5 months. An independent radiologist assessed serial radiography collected sequentially using the Brantigan, Steffee and Fraser criteria to classify state of fusion (Table 8).

Results

At three months 70/162 (43.2%) levels were deemed fused, 85/162 (52.5%) deemed partially fused and the remaining 7/162 (4.3%) levels reporting limited evidence of fusion. At six months 90/150 (60.0%) levels were deemed fused, 55/150 (36.7%) deemed partially fused and 5/150 (3.3%) reporting limited evidence of fusion. At twelve months 114/129 (88.4%) levels were deemed fused 14/129 (10.9%) deemed partially fused and 1/129 (0.8%) demonstrating limited evidence of fusion. At eighteen months 131/133 (98.5%) levels were deemed fused 1/133 (0.8%) deemed partially fused and 1/133 (0.8%) demonstrating limited evidence of fusion. At twenty-four months 132/133 (99.2%) levels were deemed fused with the remaining level (0.8%) deemed partially fused (Table 9). The cohort was stratified into respective groups relative to the number of levels receiving allograft. It should be noted that for patients undergoing a single-level intervention, evidence of fusion was seen in 96.9% of patients at 6 M. This segment of the cohort demonstrates evidence of fusion in 100% of remaining cohort at 24 M (Table 10).

Discussion

This retrospective review of a cohort of patients undergoing ACDF surgical intervention was designed to review the safety and fusion success with a novel growth-factor allograft product. While the safety concern in the cervical spine are documented with single recombinant growth factor options such as rh-BMP2, [1-15] no adverse events tied to the application of this novel growth-factor allograft were reported for this cohort. While data is limited, the lack of adverse safety events is very encouraging, arguably indicating the graft presented no evident safety concerns as used in the interventions and for the duration of this analysis. Additionally, as demonstrated by the reporting of 98.5% fusion at 18M, this novel growth-factor allograft has proven to be efficacious.

Early success with regards to recombinant BMP-2 and BMP-7 application was followed by categorical assessments by Blokhuis TJ, et al. concluding "concerns about safety and costs have arisen, as well as the reality that the application of BMPs does not guarantee union in difficult cases."[16] Blokhuis went on to note "This implicates that BMP application is not the final solution," with regards to the meta-analysis conducted.

Nonetheless study around additional growth factors known to play critical roles in bony remodeling has demonstrated the value of non-BMP growth factors including VEGF, IGF and TGF-βamong others. For instance, VEGF has been shown to contribute in each of the four cross-functional corners of the remodeling paradigm including demonstrated structural density improvements when used alongside BMPs [17]. Additionally, Schmidmaier's work with IGF and TGF-β demonstrated the early benefit of natural cascades that contribute to healthy remodeling of bone [18]. The variation in the biologic cascades that each of these factors contributes to has been resolved into osteoinductive and osteoconductive components, working in tandem with angiogenic, proliferative and chemotactic cascades. These parallel relationships appear to contribute greatly to healthy remodeling insomuch as bony fusion is concerned.

While the benefit of osteoinductive factors such as BMP are well documented, [19-21] successful bony remodeling benefits from angiogenic, proliferative and chemotactic cascades succeeding in equally collaborative proportions [22-24]. The growth factor concentrations represented in this novel allograft are more closely aligned with physiological levels presumed to work more mechanistically in tandem with the body. Several of the individual growth factors included with this novel growth-factor allograft are documented with regards to osteoinductive, [6-8] angiogenic, [25,26] proliferative [27,28] and chemotactic [11-29] roles governing each process involved in the successful remodeling of bone, with many individual factors contributing cross-functionally across multiple processes. Additional pre-clinical and clinical evaluation will benefit the working knowledge of this novel growth factor allograft and its multitude of growth factors.

Conclusion

The novel allograft growth factor used to support bony fusion was found to be efficacious in this retrospective study of interbody fusions done in the lumbar spine. This donor-derived growth factor offers an allograft solution that

Table 6. Cohort diagnosis pool (n=107).

Pain	91/107 (76.5%)
Radiculopathy	81/107 (68.1%)
Stenosis	66/107 (55.5%)
Kyphosis	22/107 (18.5%)
Myelopathy	18/107 (15.1%)
Prior pseudoarthrosis	9/107 (7.6%)
Instability	8/107 (6.7%)
Cord Compression	4/107 (3.4%)
HNP	4/107 (3.4%)
Degenerative Disc DZ	2/107 (1.7%)
Scoliosis	1/107 (0.8%)

Table 7. Breakdown by scaffold (n=110).

Collagen-mineral matrix	71 (64.5%)
Demineralized bone fiber	38 (34.6%)
Demineralized bone matrix	1 (0.9%)
Total Procedures	112

Table 8. Classification of interbody fusion success: Brantigan Steffee Fraser (BSF).

(BSF) BSF-3: Radiographical fusion: Bone bridges at least half of the fusion area with at least the density originally achieved at surgery, radiographical fusion through one cage (half of the fusion area) is considered to be mechanically solid fusion even if there is lucency on the opposite side
BSF-2: Radiographical locked: Pseudoarthrosis is indicated by lucency visible in the middle of the cages with solid bone growing into the cage from each vertebral endplate
BSF-1: Radiographical pseudoarthrosis is indicated by collapse of the construct, loss of disc height, vertebral slip, broken screws, displacement of carbon cage, or significant resorption of the bone graft, or lucency visible around the periphery of the graft or cage

Table 9. Results by level.

Reporting Window	3M	6M	12M	18M	24M
BSF-3:	70	90	114	131	132
BSF-2:	85	55	14	1	1
BSF-1:	7	5	1	1	0
# of levels	162	150	129	133	133
BSF-3 @	43.2%	60.0%	88.4%	98.5%	99.2%
BSF-2 @	52.5%	36.7%	10.9%	0.8%	0.8%
BSF-1 @	4.3%	3.3%	0.8%	0.8%	0.0%

Table 10. Single-level results by level (n=46).

Reporting Window	3M	6M	12M	18M	24M
BSF-3:	21	25	30	33	34
BSF-2:	15	6	5	3	1
BSF-1:	1	1	1	1	0
# of levels	37	32	36	37	35
BSF-3 @	56.8%	78.1%	83.3%	89.2%	97.1%
BSF-2 @	40.5%	18.8%	13.9%	8.1%	2.9%
BSF-1 @	2.7%	3.1%	2.8%	2.7%	0.0%

provides a safe, effective alternative in scenarios where autograft availability is limited or contraindicated. Additionally, this allograft tissue option contains a myriad of growth factors involved in bone healing which may be more successful in a bone fusion surgical setting as compared to single-factor recombinant options currently available.

Acknowledgement

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Conflict of Interest

None.

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