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RANDOMIZED TRIAL

Efficacy of i-Factor Bone Graft *versus* Autograft in Anterior Cervical Discectomy and Fusion

Results of the Prospective, Randomized, Single-blinded Food and Drug Administration Investigational Device Exemption Study

Paul M. Arnold, MD,[*] Rick C. Sasso, MD,[†] Michael E. Janssen, MD,[‡] Michael G. Fehlings, MD, PhD,[§] Joseph D. Smucker, MD,[†] Alexander R. Vaccaro, MD, PhD,[¶] Robert F. Heary, MD,[||] Ashvin I. Patel, MD,[**] Benoit Goulet, MD,[††] Iain H. Kalfas, MD,[‡‡] and Branko Kopjar, MD, PhD[§§]

Study Design. A prospective, randomized, controlled, parallel, single-blinded noninferiority multicenter pivotal FDA IDE trial.

Objective. The objective of this study was to investigate efficacy and safety of i-Factor Bone Graft (i-Factor) compared with local autograft in single-level anterior cervical discectomy and fusion (ACDF) for cervical radiculopathy.

Summary of Background Data. i-Factor is a composite bone substitute material consisting of the P-15 synthetic collagen fragment adsorbed onto anorganic bone mineral and suspended in an inert biocompatible hydrogel carrier. P-15 has demonstrated bone healing efficacy in dental, orthopedic, and nonhuman applications.

Methods. Patients randomly received either autograft (N = 154) or i-Factor (N = 165) in a cortical ring allograft. Study success was defined as noninferiority in fusion, Neck Disability Index (NDI), and Neurological Success endpoints, and similar adverse events profile at 12 months.

Results. At 12 months (follow-up rate 87%), both i-Factor and autograft subjects demonstrated a high fusion rate (88.97% and 85.82%, respectively, noninferiority $P = 0.0004$), significant improvements in NDI (28.75 and 27.40, respectively, noninferiority $P < 0.0001$), and high Neurological Success rate (93.71% and 93.01%, respectively, noninferiority $P < 0.0001$). There was no difference in the rate of adverse events (83.64% and 82.47% in the i-Factor and autograft groups, respectively, $P = 0.8814$). Overall success rate consisting of fusion, NDI, Neurological Success and Safety Success was higher in i-Factor subjects than in autograft subjects (68.75% and 56.94%, respectively, $P = 0.0382$). Improvements in VAS pain and SF-36v2 scores were clinically relevant and similar between the groups. A high proportion of patients reported good or excellent Odom outcomes (81.4% in both groups).

Conclusion. i-Factor has met all four FDA mandated noninferiority success criteria and has demonstrated safety and efficacy in single-level ACDF for cervical radiculopathy. i-Factor and autograft groups demonstrated significant postsurgical improvement and high fusion rates.

Key words: anterior cervical discectomy and fusion, arthrodesis, cervical radiculopathy, cervical spine, degenerative disc disease, fusion, i-Factor bone graft, P-15 small peptide.

Level of Evidence: 1

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From the [*]University of Kansas Medical Center, Kansas City, KS; [†]Indiana Spine Group, Carmel, IN; [‡]Center for Spine Disorders, Thornton, CO; [§]University of Toronto Spine Program and Toronto Western Hospital, Toronto, Ontario, Canada; [¶]Rothman Institute at Jefferson, Philadelphia, PA; [||]Rutgers-New Jersey Medical School, Newark, NJ; [**]Kennedy-White Orthopaedic Center, Sarasota, FL; [††]Montreal Neurological Institute, Montreal, Quebec, Canada; [‡‡]Cleveland Clinic, Cleveland, OH; and [§§]Univer-University of Washington, Seattle, WA.

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The device(s)/drug(s) that is/are the subject of this manuscript is/are being evaluated as part of an ongoing FDA-approved investigational protocol (IDE) or corresponding national protocol for utilization of i-Factor Bone Graft in the application described in this investigation.

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Address correspondence and reprint requests to Paul M. Arnold, MD, University of Kansas Medical Center, Department of Neurosurgery, Mail Stop 3021, 3901 Rainbow Blvd., Kansas City, KS 66160;
E-mail: parnold@kumc.edu

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Anterior cervical discectomy and fusion (ACDF) is a standard-of-care treatment for cervical radiculopathy that does not respond to conservative care.[1–3] ACDF has traditionally been performed using iliac crest autograft as the preferred interbody graft material. Although efficacious with respect to fusion, iliac crest autograft harvest is associated with significant morbidity,[4–6] which has led to the increased use of local autograft bone or alternatives such as allograft bone, synthetic grafts, demineralized bone, ceramics, calcium phosphates, and

bone morphogenetic proteins.[7–23] Local autograft bone may be of insufficient volume or of uncertain quality. Alternative materials have not been evaluated in rigorous randomized, controlled studies for use in ACDF. Currently, there is no bone graft product approved by the United States Food and Drug Administration (FDA) for use in ACDF.

P-15 is a novel synthetic, 15-amino acid polypeptide peptide that mimics the cell-binding domain of Type I collagen[24,25] and is able to signal a mechanical and biochemical communication pathway that ultimately results in new bone formation.[26,27] The P-15 peptide enhances cell migration[26] and induces osteoblast cell proliferation and differentiation.[28] P-15 appears to enhance the differentiation of human bone marrow stromal cells into osteoblasts and cause them to produce and secrete osteogenic factors that drive other cells into an osteoblastic phenotype.[28] P-15 is specific to anchoring-dependent connective tissue mesenchymal cells, including osteogenic cells, and therefore does not induce bone formation in the absence of these cells. The receptor-mediated anchorage of osteoblasts by P-15 initiates a number of signal transduction pathways that lead to the synthesis of growth factors, cytokines, and bone morphogenetic proteins.

i-Factor Bone Graft (Cerapedics, Inc., Westminster, CO) (i-Factor) is a composite bone substitute material consisting of the P-15 adsorbed onto anorganic bone mineral and suspended in an inert biocompatible hydrogel carrier. Evidence of the bone-forming ability of this synthetic bone graft combination has been demonstrated in pre-clinical models and clinical investigations.[29–35]

This analysis presents the safety and efficacy outcomes of the multicenter FDA Investigational Device Exemption (IDE) noninferiority single-blinded clinical trial of i-Factor *versus* local autograft in single-level ACDF for the treatment of symptomatic cervical degenerative disc disease (DDD).

MATERIALS AND METHODS

A prospective, randomized, controlled, multicenter clinical trial was conducted at 22 sites in North America to investigate the safety and efficacy of i-Factor compared with standard-of-care autograft (clinicaltrials.gov NCT00310440.) Patients underwent instrumented ACDF and received either i-Factor or local autograft in a cortical allograft ring implanted into the target vertebral interspace prior to placement of the screw-plate fixation device.

Objectives

Primary objectives were to evaluate noninferiority for (1) fusion; (2) neurological outcomes; and (3) Neck Disability Index (NDI) functional outcomes in patients 12 months following instrumented single-level ACDF for symptomatic cervical disc disease. The primary safety objective was to assess difference in overall adverse event (AE) rates between the i-Factor and autograft arms. Secondary objectives were to compare Visual Analog Scale (VAS) neck and arm/shoulder pain scores; SF-36v2 Physical (PCS) and Mental (MCS) component summary scores, and self-rating of outcomes with Odom's criteria.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are provided in Table 1. Key inclusion criteria were radiographic evidence of DDD and preoperative VAS neck and arm/shoulder pain scores >4 and NDI >30. Key exclusion criteria were multilevel symptomatic cervical disc disease, history of prior fusion and/or prior decompression at the index level, or history of acute cervical injury or instability due to trauma.

Surgical Technique

A traditional anterior cervical approach was performed with intraoperative radiographic identification of the symptomatic surgical level. Surgeons performed an anterior cervical discectomy with achievement of neural decompression. More than 85% of patients underwent ACDF at C5-C6 or C6-C7. Control subjects received a cortical allograft ring filled with autograft bone collected from osteophytes and endplate preparation during the procedure. Investigational subjects received a cortical allograft ring filled with an average of 0.78 cc (range 0.15–4.0 cc) of i-Factor. Following placement of the ring in the interbody space, an anterior cervical plate was placed spanning the disc space level and fixed with screws. Patients were discharged to home on the basis of the usual routine of the operating surgeon.

Endpoints

The four coprimary endpoints were fusion, change in NDI, Neurological Success, and safety evaluated as rate of *any* AEs. Successful fusion was based on roentgenographic examination (anteroposterior, lateral, flexion, and extension) showing evidence of bridging trabecular bone between the involved motion segments, and translational motion <3 mm and angular motion <5°. Qualitative evaluations of evidence of bridging bone were performed by two blinded radiologists from the central radiology laboratory (Medical Metrics, Inc., Houston, TX); a third radiologist was involved in case of a tie. If there was lack of evidence of bridging bone on 12-month plain roentgenograms, a computed tomography (CT) scan was used to make the final determination of fusion status. The criteria for fusion on CT scan were trabecular bone formation patterns within the intervertebral disc space or bridging bone formation that crossed the interspace. Change in NDI was the difference between pre-operative and 12-month NDI scores. The NDI is a validated questionnaire that assesses the patient's disability during activities of daily living.[36] Neurological outcomes were assessed in motor, sensory, and reflex domains specific for the cervical spine. An independent, blinded adjudicator rated subjects as Neurological Success (maintenance or improvement) or failure (decline). The rate of *any* AEs was based upon the regulatory definition of any untoward medical occurrence in a clinical investigation subject.

Secondary endpoints were VAS neck and arm/shoulder pain scores, SF-36v2 PCS and MCS scores,[37] and patient-rated outcome using Odom criteria.[38] The composite endpoint of overall success at 12 months was defined as fusion success, neurological success, NDI success

TABLE 1. Inclusion and Exclusion Criteria

Inclusion criteria
Age between 18 and 70 yrs
Radiographically determined discogenic origin including at least one of the following characteristics: degenerated/dark disc on MRI; decreased disc height compared with adjacent levels on radiographic film, CT, or MRI; and disc herniation on CT or MRI
Radicular symptoms by history and physical exam, including at least one of the following characteristics: arm/shoulder pain; decreased reflexes; decreased strength; and abnormal sensation
On 0–10 Visual Analog Scale, pain level at arm/shoulder >4 OR pain level at neck >4
Neck Disability Index >30
Involved disc(s) between C3 and C7
Undergoing anterior cervical fusion at a single level
Failed to gain adequate relief from at least 6 weeks of nonoperative treatment
Willing and able to give consent to participate in study
Willing and able to participate in the study follow-up according to the protocol
Willing and able to comply with postoperative management program
Can understand and read English at elementary level
Exclusion criteria
Presence of systemic infection such as AIDS, HIV, or active hepatitis
Presence of significant metabolic disease that in the surgeon's opinion might compromise bone growth, such as osteoporosis or osteomalacia
Taking medication for the prevention of osteoporosis
Presence of circulatory, cardiac, or pulmonary problems that could cause excessive surgical risk
Presence of active malignancy
Nondiscogenic source of symptoms (*e.g.*, tumor, etc.)
Multiple level symptomatic degenerative disc disease
Previous cervical fusion
Previous cervical decompression at the same level
Acute cervical trauma or instability (*i.e.*, subluxation >3 mm on flexion/extension radiographic film)
Undergoing treatment for tumor or bony traumatic injury to the cervical spine
Presence of rheumatoid disease of the cervical spine
Presence of myelopathy
Pregnant or planning to become pregnant in the next 2 years
Posterior cervical spine procedure scheduled
More than one level to be operated on for any cause

(NDI improvement of >15), and absence of reoperations and device-related serious AEs.

Patient Population

A total of 319 patients were enrolled between June 2006 and May 2013 at 19 sites in the United States and three in Canada. Four patients were excluded from the investigational arm and two from the control arm for the efficacy analysis due to protocol deviations. Patients were evaluated in person pre-operatively and then postoperatively at 6 weeks, 3, 6, 9, 12, 18, and 24 months and thereafter annually. Patients were blinded to the treatment assignment. The 12-month follow-up rate was 134/161 (83.23%) in the i-Factor group and 139/152 (91.45%) in the autograft group, for an overall follow-up rate of 87% (Figure 1).

Data Processing and Statistical Methods

Randomization was performed using opaque sequenced envelopes. The sequence was generated centrally using random permuted blocks of sizes two and four and stratified by site. Data were collected using electronic case report forms (eCRFs). Data quality was monitored by independent study monitors to assure that the data were true, accurate, complete, and reliable. In addition, the FDA performed several independent audits of the source data at various investigative sites and at the central data management center.

Noninferiority margins and statistical success criteria were pre-specified in the statistical analysis plan approved by the FDA prior to study initiation. The efficacy evaluation (fusion, change in NDI, and Neurological Success) was based on a noninferiority statistical approach and the safety evaluation (rate of AEs) was based on a superiority statistical approach. Fusion and Neurological Success outcomes were tested using the Wald asymptotic approach[39] and change in NDI using the analysis of covariance (ANCOVA) adjusting for baseline NDI value. The one-sided alpha value for noninferiority testing was set to 0.025, and the superiority two-sided alpha was set to 0.05. Study success was based on rejection of all three efficacy noninferiority null hypotheses and on favorable testing of the safety hypothesis. No multiplicity adjustment is required for this statistical approach. Secondary endpoints were analyzed using a superiority approach and ANCOVA for continuous variables and Fisher exact test for categorical variables. All analyses were performed using the imputed data and intent-to-treat approach.

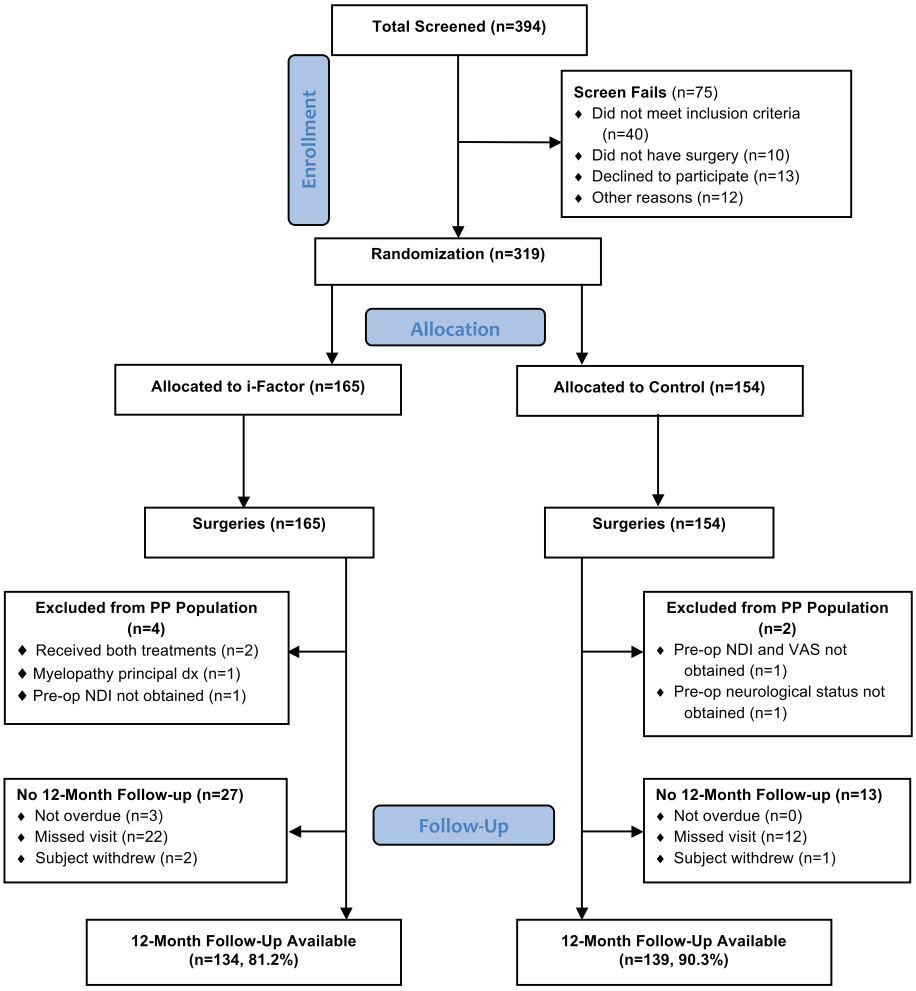

Figure 1. CONSORT flow diagram.

Missing values for fusion outcome were imputed by last value carry forward using nine months observation, if available. Missing follow-up scores for NDI, SF-36v2, and VAS were assumed to be missing at random and were accounted for using a multiple imputations procedure. Neurological Success and Odom criteria were not imputed. After imputation, fusion data were available for 145/161 (90.06%) of i-Factor subjects and 141/139 (92.76%) of autograft subjects; neurological success was available for 143/161 (88.82%) and 143/152 (94.08%) of i-Factor and autograft subjects, respectively. NDI, VAS pain, and SF-36v2 were multiply imputed for all 313 subjects (100.00%).

The initial sample size was set as the largest of the sample size estimates for the three coprimary endpoints and was 164 subjects (82 in each study arm) based on estimated fusion rate of 95% and power of 85%. On the basis of the pre-planned adaptive statistical design, a blinded sample size re-estimate controlled by the independent Data Safety and Monitoring Board was performed when 114 subjects had 12 months' follow-up data available.[40] At that time, the sample size was increased to 250 evaluable subjects in order to maintain pre-determined minimum study-wide power of 80%. The final sample size was set to 313 subjects to account for 20% loss to follow-up.

Ethics

Approval from investigational review boards (IRBs) or research ethics boards were obtained at each site, and each subject provided written informed consent to participate in the study.

RESULTS

Demographics

Demographics, clinical metrics, functional metrics, and index surgical level data are presented in Table 2. Average age, symptom duration, gender, comorbidities, and evidence of current tobacco use were similar in both populations. Pre-operative VAS neck and arm/shoulder pain scores, NDI scores, and SF-36v2 PCS and MCS scores were similar between the groups.

Primary Endpoints

At 12 months, all three coprimary efficacy endpoints met the pre-determined statistical success criterion for noninferiority

TABLE 2. Study Population Baseline Demographic Comparison

Characteristic	i-Factor (n = 161)	Autograft (n = 152)	P*
Age (yrs) mean ± SD	47.7 ± 9.8	45.7 ± 9.4	0.0653
Body mass index mean ± SD	28.6 ± 6.0	29.1 ± 5.7	0.4970
Symptom duration (mo) mean ± SD	18.5 ± 24.2	25.6 ± 35.7	0.1779†
Gender (% male)	42.24%	37.50%	0.4201
Current tobacco use (% yes)	20.50%	27.63%	0.1472
Clinical			
VAS—Neck/shoulder (mean ± SD)	6.6 ± 2.4	6.7 ± 2.4	0.6874
VAS—Arm (mean ± SD)	7.0 ± 2.0	6.9 ± 2.0	0.8128
Functional			
NDI (mean ± SD)	50.6 ± 13.2	52.7 ± 14.4	0.1955
SF36 (PCS) (mean ± SD)	35.2 ± 7.4	34.3 ± 7.0	0.2810
SF36 (MCS) (mean ± SD)	40.6 ± 12.8	40.9 ± 13.1	0.8253
Surgical level			0.5376‡
C3/C4 (%)	2.48%	2.63%	
C4/C5 (%)	11.18%	7.24%	
C5/C6 (%)	43.48%	50.00%	
C6/C7 (%)	42.86%	40.13%	

*P values are for the independent two-sample t-test for continuous variables and Fisher exact test for categorical variables, if not indicated otherwise.
†Wilcoxon signed-rank test.
‡Chi-square test.

between the i-Factor and autograft groups (Table 3). Successful fusion was observed in 88.97% of i-Factor subjects and in 85.82% of autograft subjects ($P = 0.0004$, noninferiority). Average improvement in NDI was 28.75 and 27.40 in i-Factor and autograft groups, respectively ($P < 0.0001$, noninferiority). Neurological success was 93.71% and 93.01% in i-Factor and autograft groups, respectively ($P < 0.0001$, noninferiority). Finally, 83.64% of i-Factor subjects and 82.47% of autograft subjects had one or more AEs ($P = 0.8814$).

Overall Success

To achieve overall success, a patient had to achieve success in all of the individual coprimary endpoints. i-Factor subjects demonstrated higher overall success rate than control subjects (68.75% and 56.94%, respectively, $P = 0.0382$) (Table 3).

Secondary Endpoints

Improvement in VAS neck and arm/shoulder pain scores and SF-36v2 PCS and MCS scores were similar between the i-Factor and autograft groups. There was no difference in improvement in the two groups relative to each other (Table 4). With respect to Odom criteria, more than 80% of patients in both groups reported their improvement as either "excellent" or "good." There was no difference in Odom criteria between the i-Factor and autograft groups at 12 months (Table 4).

Adverse Events

The most common complication in both groups was axial pain (39.13% and 36.84% in the i-Factor and autograft groups, respectively, $P = 0.7271$), postoperative residual radiculopathy (19.25% and 18.42% in the i-Factor and autograft groups, respectively, $P = 0.8858$), and dysphagia (19.25% and 19.74% in the i-Factor and autograft groups, respectively, $P = 1.0000$) (Table 5). New radiculopathy was more common in autograft subjects than in i-Factor subjects (18.42% and 10.56%, respectively, $P = 0.0537$). Also, new intractable neck pain was more frequent in autograft subjects than in i-Factor subjects (10.53% and 4.35%, respectively, $P = 0.0497$). There were no reports of allergic reactions associated with i-Factor. Regarding other complications, two autograft subjects developed chronic lymphocytic leukemia, and one i-Factor subject developed a bone hemangioma in the lumbar spine and one developed renal cancer. Three i-Factor subjects had subsequent surgeries: one a reoperation for supplemental fixation; one involving the above adjacent level only; and one involving both the index and above adjacent levels. Six autograft subjects had subsequent surgeries: four reoperations; one involving the above adjacent level, and one involving both the index and above adjacent levels.

DISCUSSION

The results of this clinical trial demonstrate that i-Factor is safe and effective treatment for symptomatic radiculopathy due to single-level cervical disc disease. In this FDA IDE pivotal, randomized, controlled, noninferiority study, i-Factor reached all four FDA mandated success criteria for use in ACDF compared with autograft controls. Outcomes in subjects treated with i-Factor were similar to those treated with autograft bone on all evaluated measures. Furthermore, the rate of AEs was similar between the

TABLE 3. Primary Endpoints at 12 Months

Test Parameter	i-Factor	Autograft	Difference	95% CI	Noninferiority Margin	*P*
Fusion (% fused)	129/145 (88.97%)	121/141 (85.82%)	3.15%	(−4.54 to 10.84)	−10%	0.0004†
Improvement in NDI Score (BL-12M)*	28.75 (25.81, 31.69)	27.40 (24.35, 30.45)	1.35	(−2.81 to 5.51)	−11	<0.0001†
Neurological success (% improved)	134/143 (93.71%)	133/143 (93.01%)	0.70%	(−5.07 to 6.47)	−15%	<0.0001†
Adverse events (% patients with *any* AE)	138/165 (83.64%)	127/154 (82.47%)	1.17%	(−7.07 to 9.41)	Not Applicable	0.8814‡
Overall success*	99/143 (68.75%)	82/144 (56.94%)	11.81%	(0.72–22.88)	Not Applicable	0.0382‡

**Overall success is defined as radiological evidence of fusion, improvement in NDI of >15 points, neurological success and re-operation, device explantation, or device-related SAE.*

†*Noninferiority test.*

‡*Superiority test.*

i-Factor and autograft subjects. Finally, a composite endpoint of overall success outcomes consisting of fusion, functional gains, neurological success, and absence of major complications, was superior in i-Factor subjects. More than two out of three subjects treated with i-Factor were classified as overall success, 12% more than in the autograft group.

Outcomes in i-Factor treated patients were clinically relevant. NDI improvements of 29 points exceeds substantial clinical benefit (SCB) threshold of 9.5; SF36 PCS improvement of 10 points exceeds SCB threshold of 6.5 and VAS Pain at neck of 4.5 and arm of 4.9 exceed SCB threshold of 3.5.[41]

Our findings corroborate with pre-clinical and clinical experience of prior investigations of bone healing activity of P-15. In a New Zealand rabbit study, Scarano *et al.*[34] demonstrated the ability of P-15 to improve the healing potential of cortical bone defects.[35,42] In a human study

TABLE 4. Secondary Endpoints: Difference in Score Between Baseline and 12 Months

	i-Factor (n = 161)		Autograft (n = 152)		
Test Parameter	Least Squares Mean	95% Confidence Intervals	Least Squares Mean	95% Confidence Intervals	*P*
VAS					
Neck pain	4.45	4.00–4.90	4.39	3.96–4.82	0.8257
Arm pain	4.89	4.44–5.34	4.85	4.40–5.30	0.9010
SF-36v2					
Physical health component	10.02	8.39–11.66	9.95	8.25–11.65	0.9520
Physical function	9.22	7.60–10.84	9.58	7.97–11.19	0.7497
Physical role limitation	13.52	11.57–15.46	13.56	11.47–15.65	0.9756
Bodily pain	14.67	12.96–16.38	13.90	12.16–15.64	0.5373
General health	1.10	−0.49 to 2.70	0.73	−0.78 to 2.25	0.7381
Mental health component	8.33	6.66–10.01	8.21	6.48–9.95	0.9204
Emotional well-being	7.93	6.40–9.46	7.80	6.18–9.42	0.9101
Emotional role limitation	10.02	7.88–12.16	10.27	8.27–12.27	0.8651
Social functioning	12.12	10.23–14.02	11.69	9.75–13.63	0.7478
Energy/fatigue	8.94	7.32–10.55	8.78	7.04–10.52	0.8976
Odom criteria	P-15 Putty (n = 129)	%	Autograft (n = 129)	%	0.9929*
Excellent	80	62.0%	80	62.0%	
Good	25	19.4%	25	19.4%	
Fair	16	12.4%	15	11.6%	
Poor	8	6.2%	9	7.0%	

**Chi-square for statistical difference between P-15 Putty and autograft.*

TABLE 5. Complications at 12 Months by Study Arm

	i-Factor (N = 161)	% of N	Autograft (N = 152)	% of N	*P*
Pseudarthrosis and nonunion	14	8.69%	15	9.87%	0.8458
Dural tear	1	0.62%	0	0.00%	1.000
Retropharyngeal hematoma/airway obstruction	0	0.00%	1	0.66%	1.000
Horner syndrome	0	0.00%	1	0.66%	1.000
Partial or complete vocal cord paralysis (hoarseness)	4	2.48%	1	0.66%	0.3720
Dysphagia	31	19.25%	30	19.74%	1.000
Dysphonia	1	0.62%	2	1.32%	0.6132
Superficial infection	4	2.48%	0	0.00%	0.1232
New radiculopathy	17	10.56%	28	18.42%	0.0537
Graft subsidence	2	1.24%	0	0.00%	0.4988
Cardiopulmonary event	1	0.62%	0	0.00%	0.4988
Worsening of the neurological status	0	0.00%	2	1.32%	
Postoperative radiculopathy/ radiculitis	31	19.25%	28	18.42%	0.8858
Axial pain (nuchal or periscapular pain or neck fatigue)	63	39.13%	56	36.84%	0.7271
New intractable neck pain	7	4.35%	16	10.53%	0.0497
Adjacent segment degeneration	9	5.59%	13	8.55%	0.3781

evaluating treatment of long bone fracture nonunion using P-15, Gomar *et al.*[32] demonstrated that a majority of patients achieved radiographic healing. In a periodontal bony defect clinical study, P-15 yielded a higher amount of new bone formation than anorganic bone mineral (ABM)-only controls.[30,43] Moreover, the i-Factor group yielded a statistically significant higher number of patients with >90% filling of the original defect with new bone than the ABM-only group.[30,43]

The 12-month rates reported in this study are consistent with the rates reported in the literature. Luszczyk *et al.*[44] reported fusion rates in single-level ACDF with allograft and a locked anterior cervical plate in five control arms of FDA IDE studies of cervical arthrodesis. At 24 months postoperative, the rates ranged from 84.5% to 96%. Karikari *et al.*[45] reported similar fusion rates (92.6%) in their meta-analysis of 35 studies, although it was unclear at what time after surgery the fusion was evaluated in the included studies.

The similar nature of functional and arthrodesis outcomes with respect to the autograft control in this study suggests a positive effect of this graft material in this fusion environment. In situations when iliac crest bone harvesting is considered in anterior cervical spinal arthrodesis, use of i-Factor would eliminate any potential risks associated with autograft harvesting.

Safety profile of patients receiving i-Factor was similar to that of the autograft group. There were no reports of allergic-type reactions to i-Factor, and there was no evidence of carcinogenic effect of i-Factor. Subsequent surgeries among the i-Factor patients were uncommon—only three patients had such event compared with six in the autograft group.

There are limitations of our study. Our study has involved patients who met detailed inclusion and exclusion criteria and were willing to participate in randomized controlled trial. Patients in clinical practice may differ from the patients enrolled in this study. Next, some patients were not unavailable at 12 months follow-up. We accounted for such data by using pre-specified imputation approaches. We also performed multiple statistical sensitivity analyses to address this issue and have arrived to same conclusions suggesting that missing follow ups do not bias our results. For practical reasons, surgeons were not blinded to the treatment assignment. However, assessment of fusion and neurological success was performed by independent blinded adjudicators and assessment of functional and quality of life outcomes was self-reported by blinded subjects.

In conclusion, ACDF is effective and safe treatment for cervical radiculopathy due to DDD. Use of i-Factor in ACDF is effective and safe and it results in similar and on some metrics superior outcomes compared with local autograft bone.

➢ Key Points

- ❑ The investigational i-Factor Bone Graft demonstrated similar radiographic fusion rates to autograft bone at 12 and 24 months.
- ❑ Clinical and patient-reported outcomes, including Neurological Success, VAS neck and arm/shoulder pain, NDI, and SF-36v2 health survey and PCS/ MCS scores, were similar in both cohorts at all postsurgical time frames, with both cohorts

demonstrating clinically significant improvements from pre-surgical baseline.

- ❑ The safety profile of i-Factor was similar to that of local autograft.

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