Original Study

Clinical outcomes for anterior cervical discectomy and fusion with silicon nitride spine cages: a multicenter study

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Background: Intervertebral spacers made of silicon nitride (Si_3N_4) are currently used in cervical and thoracolumbar fusion. While basic science data demonstrate several advantages of Si_3N_4 over other biomaterials, large-scale clinical results on its safety and efficacy are lacking. This multicenter retrospective study examined outcomes for anterior cervical discectomy and fusion (ACDF) using Si_3N_4 cages. Results were compared to compiled metadata for other ACDF materials.

Methods: Pre-operative patient demographics, comorbidities, changes in visual analog scale (VAS) pain scores, complications, adverse events, and secondary surgical interventions were collected from the medical records of 860 patients who underwent Si_3N_4 ACDF at four surgical centers. For comparison, MEDLINE/PubMed and Google Scholar searches were performed for ACDF using other cage or spacer materials. Nine studies with 13 cohorts and 736 patients met the inclusion criteria for this control group.

Results: Overall, the mean last-follow-up for all patients was 319±325 days (10.6±10.8 months), with the longest follow-up being 6.5 years. In comparison to the metadata, patients from the Si_3N_4 groups were older (57.9±12.2 *vs.* 56.8±11.1 y, P=0.06) and had higher BMI values (30.0±6.3 *vs.* 28.1±6.5, P<0.01), but gender and smoking were not different. The Si_3N_4 patients reported significant improvements in VAS pain scores at last follow-up (i.e., pre-op of 71.0±22.1 *vs.* follow-up of 36.4±31.5, P<0.01). Although both preoperative and last-follow-up pain scores were higher for Si_3N_4 patients than the control, the overall change in scores (ΔVAS) was similar. From pre-op to last-follow up, ΔVAS values were 35.4±34.3 for patients receiving the Si_3N_4 implants versus 34.4±27.3 for patients from the meta-analysis (P=0.56). The complication and reoperation rate for the Si_3N_4 and the metadata were also comparable (i.e., 7.39% and 0.31% versus 9.79% and 0%, P=0.17 and 0.25, respectively).

Conclusions: ACDF outcomes using Si_3N_4 implants matched the clinical efficacy of other cage biomaterials.

Keywords: Anterior cervical discectomy and fusion (ACDF); clinical outcomes; silicon nitride

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Introduction

Anterior cervical discectomy and fusion (ACDF) is performed to restore intervertebral height and alignment and to relieve neck and radicular pain. The procedure uses either allogenic spacers or abiotic cages (containing a central lumen for bone graft) to facilitate fusion. Autograft is still

Table 1 Inclusion and exclusion criteria

Inclusion criteria:
≥18 years of age
Cervical radiculopathy and/or myelopathy as diagnosed by their respective spine surgeon based on patient history, physical examination, and radiographic assessment
No improvement in symptoms within ≥ 6 weeks of conservative therapy
All studies with a surgical date at least 6 months prior to initiation of the data collection process
Exclusion criteria:
Corpectomy
Anterior/posterior fusion
Cervical trauma or neoplasm
Preoperative infection

considered to be the gold standard for spacers due to rapid bone healing, but it is limited by harvest site morbidities (1). Structural allograft is also commonly used as a spacer, but it lacks curative effectiveness and has the finite possibility for disease transmission (1). Due to these limitations, synthetic cage materials including titanium, polyetheretherketone (PEEK), tantalum, and silicon nitride (Si_3N_4) have largely displaced allogenic spacers (2-4). The BAK cage, which was subjected to extensive clinical trials in the 1990s, is often cited as the first truly abiotic spacer that was successfully employed in cervical and lumbar fusion (5,6). However, it is not well known that porous silicon nitride (Si_3N_4) actually predated the BAK cage by about 6 years (7). Si_3N_4 spacers were introduced in a small human clinical trial in Australia beginning in 1986. They now have the longest clinical history of any spacer—exceeding 30 years (8). Partially based on these results, Si_3N_4 was cleared by the US FDA as intervertebral devices in 2008. Although it now has a 10-year history in the USA and EU, only a limited number of case reports and small single-center retrospective studies, along with one randomized controlled trial, have been published (9-13).

The purpose of this study was to augment these data with a significant retrospective review consisting of 860 patients at four US surgical centers. Preoperative patient demographics, pain scores, comorbidity data along with post-operative last follow-up pain scores, complications, adverse events, and secondary surgical interventions (SSI) were extracted from patients' records. Results were compared with a meta-analysis of nine studies, consisting of 13 cohorts and 736 patients who underwent similar ACDF procedures using other commonly accepted spacers or cages. The hypothesis of this comparative analysis was that Si_3N_4 cages would produce similar clinical outcomes to the other allogenic spacers or synthetic cages.

Methods

Retrospective chart review of patients receiving Si_3N_4 spacers

Following required reviews of the study protocol, an independent trained evaluator reviewed the medical charts of all patients who underwent ACDF by each of four surgeons working at different medical centers between November 2017 and June 2018. Patient information and data remained anonymous and in compliance with IRB standards. A total of 860 patients had ACDF procedures. Inclusion criteria are listed *Table 1*. Data were recorded from both digital and active or archival hard copy files.

The Si_3N_4 cervical spacers used in these procedures are shown in *Figure 1*. The spacers were produced in two footprints—14 mm × 12 mm and 16 mm × 14 mm—with heights ranging from 5 to 12 mm and two lordotic angles—0° and 6°. A total of 1,482 Si_3N_4 devices were implanted. *Figure 2* provides a breakdown of the number of single and multilevel operations for each center. Overall, 50.0% of the patients had single-level, 35.6% 2-level, 12.8% 3-level, and 1.6% four-level procedures. *Figure 3* shows the number of implants placed at each segmental level from C2/C3 through C7/T1. Most of the patients (86.7%) received implants at C4/C5 through C6/C7.

Surgical procedures

Each surgeon used a standard Smith-Robinson surgical approach for ACDF (14). After complete discectomy with release of the posterior longitudinal ligament (PLL) and decompression of the uncinate process, vertebral endplates were prepared while maintaining their structural integrity. Bone graft consisting of local morselized autograft, sometimes supplemented with morselized allograft or a synthetic bone extender, was placed into the lumen of the spacer. Appropriately-sized Si_3N_4 cages were then implanted and anterior plate/screw fixation was used according to surgeon preference. Patients were mobilized soon after surgery without cervical orthoses. Upon discharge, they

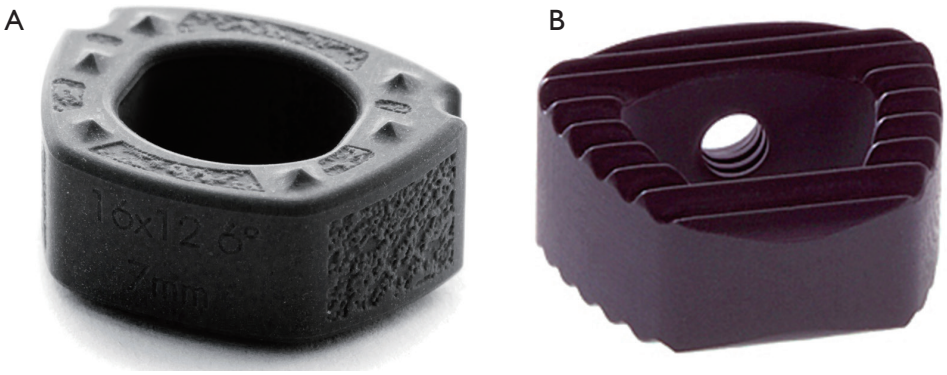

Figure 1 Si_3N_4 cervical implants: (A) Valeo™ IC; (B) Valeo™ IIC.

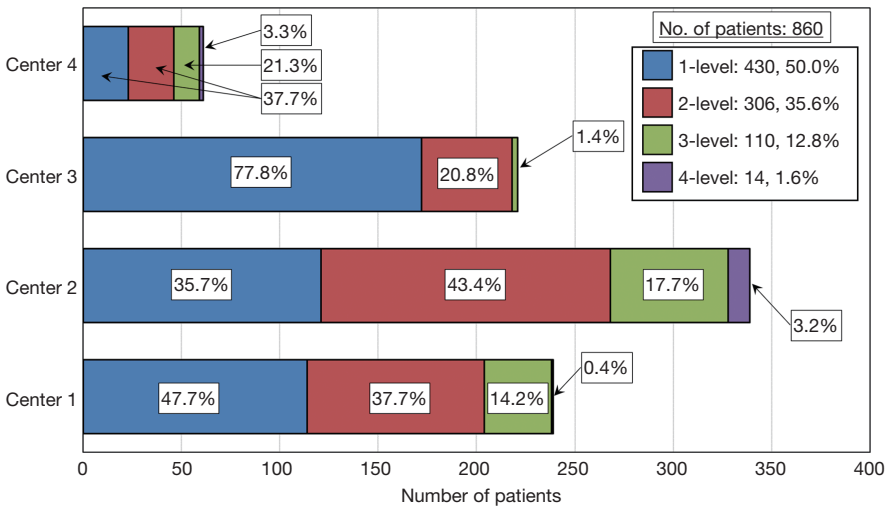

Figure 2 Number of patients, levels, and percentages at each of the four surgical centers.

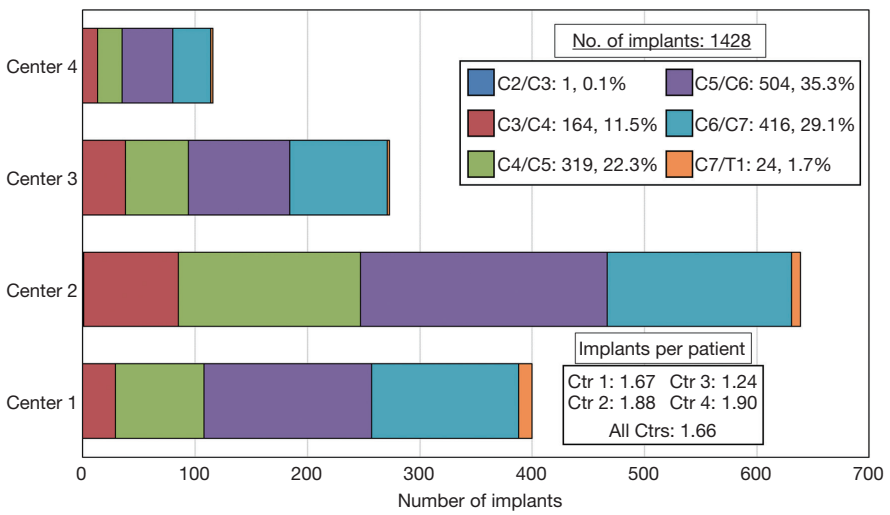

Figure 3 Number of implants per level at each of the four surgical centers.

were instructed to restrict lifting to less than ~4.5 kg (<10 lbs.) during the initial recovery period of 6 weeks and no more than ~11.3 kg (25 lbs.) between 6 and 12 weeks. They were also instructed to avoid repetitive bending or twisting of the neck for at least 3 months.

Data acquisition

Preoperative demographic data (age, gender, height, weight, BMI, and diagnoses), comorbidity conditions (smoking, diabetes, hypertension, osteoporosis, osteopenia, tumor, and other), and post-operative results (days to last follow-up, pain scores, complications, adverse events, and secondary surgical interventions) were extracted from the medical charts. Pain scores were assessed using the visual analog scale, zero being "no pain" and ten being the "worst pain imaginable." Pain scores were taken as the maximum of either neck, arm, or bodily pain at each follow-up visit. For consistency with the metadata, scores were converted to a zero to 100-point scale. Complications and adverse events included hematomas, hoarseness, infection, nerve damage, pseudarthrosis, or recurrent symptoms. Secondary surgical interventions were compiled for patients experiencing screw migration, adjacent-level disease (ALD), and pseudarthrosis (i.e., delayed, or non-union).

Meta-analysis

A meta-analysis was performed to quantitatively assess and compare differential changes in pain scores, complications, adverse events, and SSI for patients implanted with Si_3N_4 cages versus other commonly used ACDF spacers or cages. MEDLINE/PubMed was searched for relevant publications using a human clinical query with the search terms of "(Anterior Cervical Discectomy and Fusion) AND (Pain) AND (VAS)" along with filters for years (2000 to 2019), abstract and full text in English, and Adults (≥19 years of age). The output was augmented by a Google Scholar search with the added terms of "(Standard Deviation) OR (Confidence Interval)". Article titles and abstracts were then compared, and duplicates removed. Additional ACDF clinical papers were identified from a number of published systematic reviews and meta-analyses (15-23) and by manual searches. Papers were excluded if the reported studies were for follow-up periods of <6 months or if they lacked quantifiable statistical data for pre- and follow-up pain scores. Of the remaining articles, those selected for inclusion had statistically similar pre-op demographics. This resulted in the inclusion of nine studies which consisted of 13 cohorts and 736 patients (24-32). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for included articles is shown in *Figure 4* (33).

Statistical analysis

Statistical analyses including metadata comparisons were performed using MedCalc Ver. 18.6 – 64 bit (Ostend, Belgium). Ordinal data were analyzed using Student's *t*-tests whereas nominal results used proportionality assessments including Chi-squared and Fisher's exact tests. Significance was set at P values of <0.05. Biomedical Statistical Consulting (Wynnewood, PA USA) assisted in performing the meta-analysis.

Results

Pre-op diagnoses, demographics, and comorbidities

Admission records showed that most patient diagnoses were either spondylosis (35.9%), spinal stenosis (32.6%), or disc herniation (20.1%). Complete etiological data are shown in *Table 2*. Of the 860 patient records included in the study, the average age was 57.9±12.2 years, 46.5% were female, and the average BMI score was 30.0±6.3. There were no statistical differences between the four centers for gender or BMI. However, patients in Center 4 were statistically younger than the remaining three centers (i.e., 52.8 versus 57.9 years, P<0.01). Pre-op comorbidities are presented in *Table 3*. The patient count in this and subsequent tables or charts does not total to the original enrollment due to the fact that some data were missing from patients' records. There was a smaller proportion of patients from Center 3 that were smokers (7.7% versus 20.3%, *cf*., *Table 3*, P<0.01) and there was also a higher percentage of patients from Center 4 with hypertension (36.1% versus 24.1%, *cf*., *Table 3*, P=0.04). Heterogeneity tests were conducted for differences in these demographic and pre-op comorbidities. Based on these calculations, the centers were considered to have homogeneous statistics for gender (I^2=18.4%, P=0.30), BMI (I^2=13.7%, P=0.32), and diabetes (I^2=51.5%, P=0.10) but heterogeneous data for age (I^2=78.7%, P<0.01), smoking (I^2=92.4%, P<0.01), and hypertension (I^2=71.2%, P=0.02). Also, as shown in *Figures 2* and *3*, each center performed a significant number of multilevel surgeries. This ranged from ~95% of the patients in Center 2 to ~25% for Center 1.

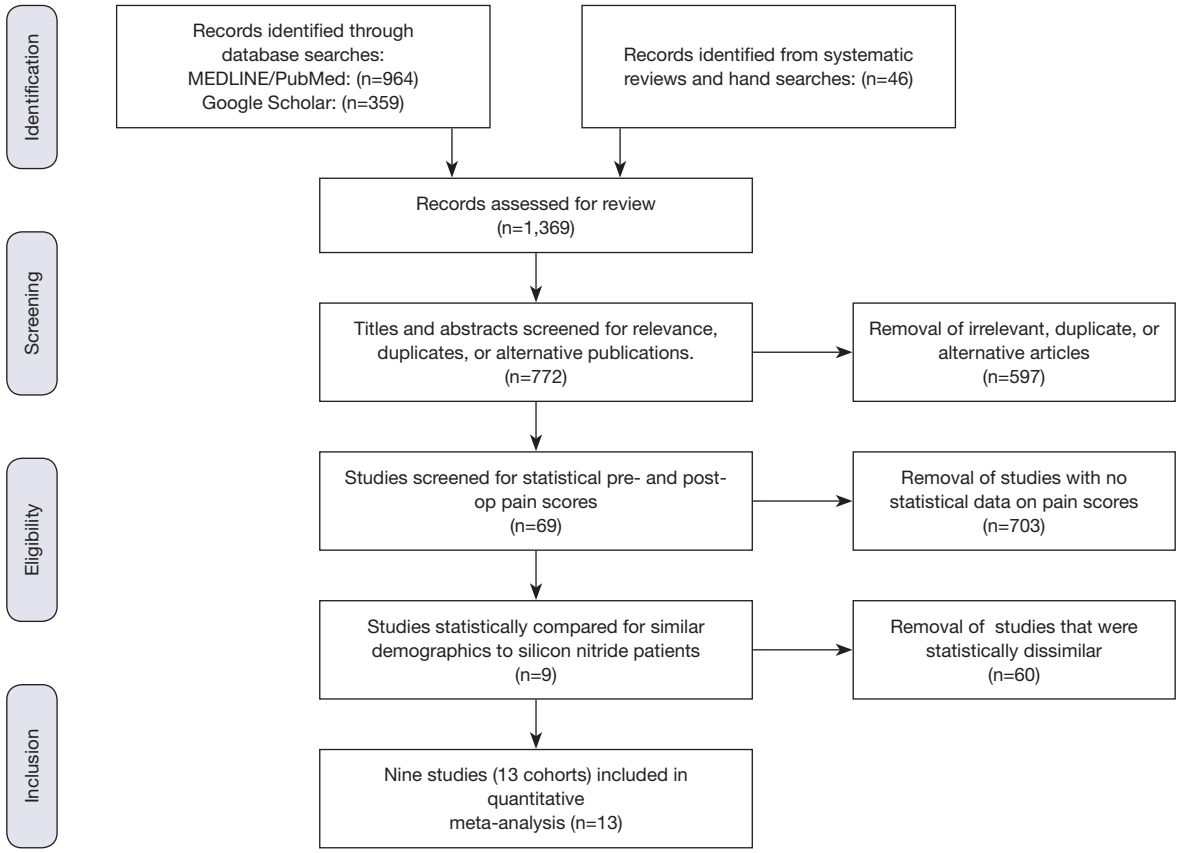

Figure 4 PRISMA flow diagram for selection of included studies.

Table 2 Patient diagnoses

Diagnosis	n	%
Spondylosis	309	35.9
Spinal stenosis	280	32.6
Disc herniation	173	20.1
Degenerative disc disease	35	4.1
Radiculopathy	21	2.4
Post-traumatic deformity	19	2.2
Spondylolisthesis	18	2.1
Spinal instability	2	0.2
Infectious discitis	2	0.2
Congenital stenosis	1	0.1

There was also considerable heterogeneity between the centers with respect to single versus multilevel operations (I^2=96.2%, P<0.01). Only Centers 2 and 4 were statistically equivalent in the number of multilevel implantations (P=0.19). Combined, these data suggest that the patients comprising this study were drawn from a broad range of pre-op cervical maladies which are typical of conditions generally encountered by spine surgeons in the US population.

Clinical outcomes

Average time to last-follow-up for each of the four surgical centers is presented in *Table 4*. Significant differences were noted in last follow-up periods with Center 3 having the shortest period (209±264 days, 7.0±8.8 months) and Center 2 having the longest (430±397 days, 14.3±13.2 months). The overall longest follow-up also occurred for Center 2 at 2,351 days (~6.5 y). Clinical results for changes in VAS pain scores for the four centers are provided in *Table 5*. Patients from each center experienced significant reductions in VAS pain scores (P<0.01) from pre-op to last follow-up. A summary of VAS pain scores for each center along

Table 3 Pre-op comorbidities by surgical center

Ctr	Smoking			Hypertension			Diabetes			Total n
	n	%	P†	n	%	P†	n	%	P†	
1	52	21.8	0.61	60	25.1	0.75	40	16.7	0.94	239
2	88	26.0	0.03	65	19.2	0.07	67	19.8	0.24	339
3	17	7.7	<0.01	60	27.1	0.36	33	14.9	0.48	221
4	18	29.5	0.09	22	36.1	0.04	5	8.2	0.08	61
Total	175	20.3	1.00	207	24.1	1.00	145	16.9	1.00	860

†, P value for each center in comparison to average value for all centers.

Table 4 Days to last follow-up by surgical center

Center	n	Avg	SD	Max	Min	P value†
1	237	270	227	974	0	0.03
2	333	430	397	2,351	0	<0.01
3	220	209	264	1,277	14	<0.01
4	61	301	208	869	0	0.67
Total/Avg	851	319	325	2,351	0	1.00

†, P value for each center in comparison to average for all centers.

Table 5 Change in Pain Scores (ΔVAS) from pre-op to last follow-up by surgical center

Center	n	Avg	SD	Max	Min	P value†
1	195	42.6	37.0	100	−40	0.01
2	284	30.7	32.4	100	−70	0.05
3	53	37.0	31.8	100	−30	0.74
4	60	32.8	32.3	100	−20	0.57
Total/Avg	592	35.4	34.3	100	−70	1.00

†, P value for each center in comparison to average value for all centers.

with their statistical significance is shown in *Figure 5*. Patients from Center 1 had the largest reductions in pain (42.6 points) with patients from Center 4 showing the smallest change (32.8 points). Overall, 81.7% of the patients from the four centers reported an improvement in pain at ≤2-year follow-up. Of this total, 20.4% showed minimal reductions of less than 20 points, while 50.4% had >40-point change at their last-follow-up. These data were also heterogeneous between the four centers: pre-op (I^2=74.8%, P=0.01), last follow-up (I^2=71.8%, P=0.01), and ΔVAS (I^2=71.0%, P=0.02). Separate correlation analyses indicated no observable trends associated with any of the pre-op demographics, comorbidities, or number of surgical levels.

Box and whisker plots for pain scores are provided in *Figure 6* as a function of last follow-up period. The largest reduction in pain occurred in the post-operative periods up to two years. Mean values dropped from 71-points for pre-op to 34.3-, 31.1-, 30.6-, and 28.8-points for the periods of <3, 3-6, 6-9, and 9-12 months, respectively. Thereafter, pain scores moderately increased for the remaining patients at 1–2 years (38.4 points) and >2 years (52.8-point), but they never returned to their pre-op levels. The increase in the later follow-up periods is not surprising because these

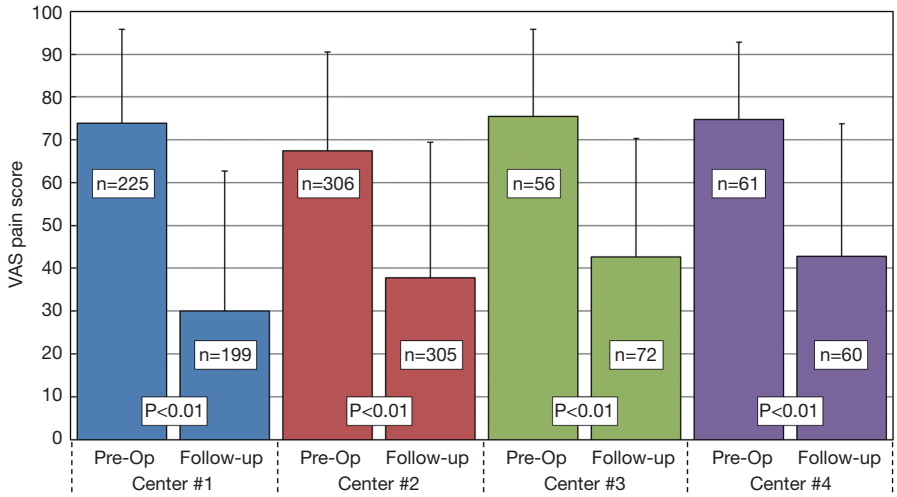

Figure 5 Pre-op and last follow-up cervical VAS scores for the four participating surgical centers.

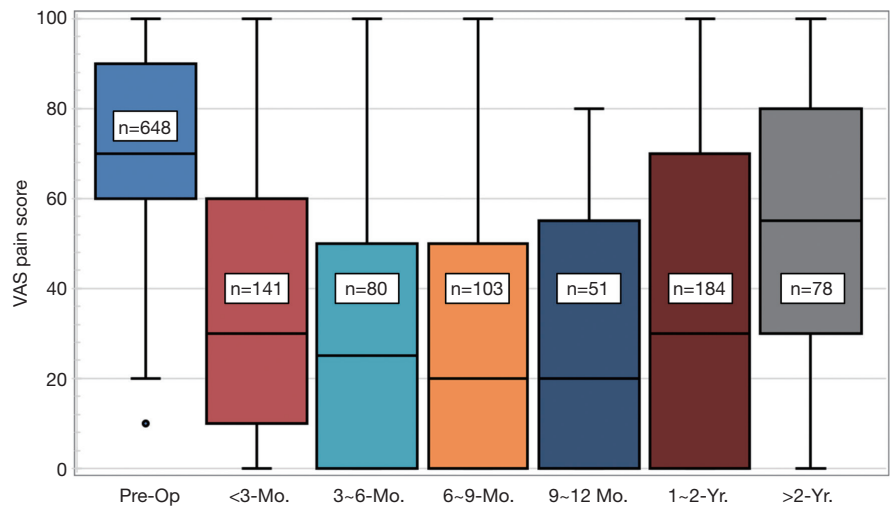

Figure 6 Box and whisker plot of VAS pain scores as a function of follow-up period.

patients had a higher percentage of diabetes (24.8% versus 16.9%, P<0.01) and hypertension (31.6% versus 21.4%, P=0.02), or had undergone a greater number of multilevel procedures (60.4% versus 50.0%, P<0.01). There were two revision surgeries associated with this group as well.

Meta-analysis

Clinical results from nine ACDF studies which included 13 cohorts and 736 patients were selected for comparison with the Si_3N_4 data. Although a significant number of studies were originally considered, the majority failed to meet the inclusion criteria of single to multilevel ACDF procedures with similar demographics. Most studies had much younger patient populations (i.e., typically >10-year differential). The nine included studies contained seven retrospective reviews and two prospective trials for various ACDF materials. Brief synopses of the selected papers are provided in *Table 6*. Two of the studies compared 2-level ACDF with 1-level anterior cervical corpectomy and fusion (ACCF). An additional two studies examined 3- or 4-level ACDF using PEEK cages, with and without anterior plating. One prospective study compared multilevel ACDF with multilevel posterior laminoplasty and a second prospective study examined the effect of racial ethnicity on ACDF outcomes. The remaining studies examined either the clinical important

Table 6 Summary of meta-analysis studies

Author	No. of patients	Study type, materials, and methods	Clinical outcomes
Oh *et al.* (24) 2009	14	Retrospective review of 2-level ACDF using iliac crest bone (ICB) spacers or PEEK cages versus 1-level cervical corpectomy and fusion (ACCF)	Both ACDF and ACCF provided similar acceptable clinical results
Song *et al.* (25) 2013	43	Retrospective review of 3- and 4-level ACDF using PEEK cages and anterior plating	High fusion rates with low complications and good maintenance of lordotic angle
Auffinger *et al.* (26) 2013	30	Retrospective review to assess the minimum clinically important differences for patients undergoing ACDF due to cervical spondylotic myelopathy. The type of spacer or cage was not reported	The SF-36 form was found to be the most effective measurement method
Burkhardt *et al.* (27) 2013	80	Retrospective review of prospectively collected data comparing 2-level ACDF using ICB spacers, or Ti and PEEK cages to ACCF for treatment of spondylotic myelopathy	Both ACDF and ACCF were found to be similar, safe, and effective methods
Seng *et al.* (28) 2013	64	Prospective non-randomized trial comparing multilevel ACDF and anterior plating with multilevel posterior laminoplasty. The ACDF procedure used fibular allograft or an unspecified cervical cage filled with autograft	Both methods were found to provide comparable clinical results
Elsamadicy *et al.* (29) 2016	140	Retrospective review of data on two multilevel ACDF patient cohorts—one pretreated for depressive symptoms prior to surgery. The specific ACDF method and cage or spacer were not reported	Pre-treatment of patients for depression significantly improved their perception of pain and functional disabilities
Elsamadicy *et al.* (30) 2016	60	Prospective non-randomized multilevel ACDF trial comparing pain scores and functional outcomes versus racial ethnicity (black and white). The specific ACDF method and cage or spacer were not reported	There were no statistical differences in ACDF outcomes based on racial ethnicity
Chaudhary *et al.* (31) 2017	220	Retrospective review of two multilevel ACDF patient cohorts—one receiving tracheal retraction exercises (TRE) to decrease the occurrence of post-surgical dysphagia. PEEK cages, local harvested autograft from osteophytes, and titanium plate fixation were used	TRE were found to significantly reduce the incidence of post-surgical dysphagia
Kim *et al.* (32) 2018	68	Retrospective review of a two cohort ACDF study for 2- and 3-level ACDF patients with stand-alone PEEK cages—with and without subsidence	There were no clinically significant differences between patients with and without subsided implants

ACDF, Anterior cervical discectomy and fusion.

methodologies for assessing ACDF outcomes and the effect of preoperative depression management, or tracheal retraction exercises on ACDF results.

Table 7 provides a comparison of the pre-op demographics and comorbidities for the Si_3N_4 group and the metadata. There were no statistical differences in gender, age, and smoking for the two groups (i.e., P=0.06 to 0.55). However, BMI values for the Si_3N_4 patients were significantly higher than the metadata (i.e., 30.0 versus 28.1, P<0.01). Remarkably, this difference was universally found for most of the studies initially reviewed for inclusion in the meta-analysis. In fact, only 7 of the 69 studies considered for inclusion had BMI similar values to the Si_3N_4 group, yet most failed to have appropriate demographics (i.e., age, gender) and only three were eventually included in the final meta-analysis. This observation suggests that on average the Si_3N_4 patients of this study bordered on being morbidly obese as compared with most other published ACDF trials.

Table 8 shows the clinical results for the Si_3N_4 group and the compiled metadata. VAS pain scores for the Si_3N_4

Table 7 Pre-op demographics for ACDF with Si_3N_4 or allogenic bone and other abiotic spacers

Demographic	Si_3N_4			Meta-data			P value
	N	n/Avg	%/SD	N	n/Avg	%/SD	
Gender/F	860	400	46.5%	736	353	48.0%	0.55
Age	859	57.9	12.2	719	56.8	11.1	0.06
BMI	852	30.0	6.3	294	28.1	6.5	<0.01
Smoking/yes	860	175	20.3%	450	107	23.8%	0.40

ACDF, anterior cervical discectomy and fusion.

Table 8 Clinical outcomes for ACDF with Si_3N_4 or allogenic bone and other abiotic spacers

Outcome	This study			Meta-data			P value
	n	Avg/total	SD/%	n	Avg/total	SD/%	
Change in VAS pain scores	592	35.4	34.3	713	34.4	27.3	0.56
Complications and adverse events	47	636	7.39%	41	419	9.79%	0.17
Secondary surgical interventions (SSI)	2	636	0.31%	0	419	0.00%	0.25

ACDF, anterior cervical discectomy and fusion.

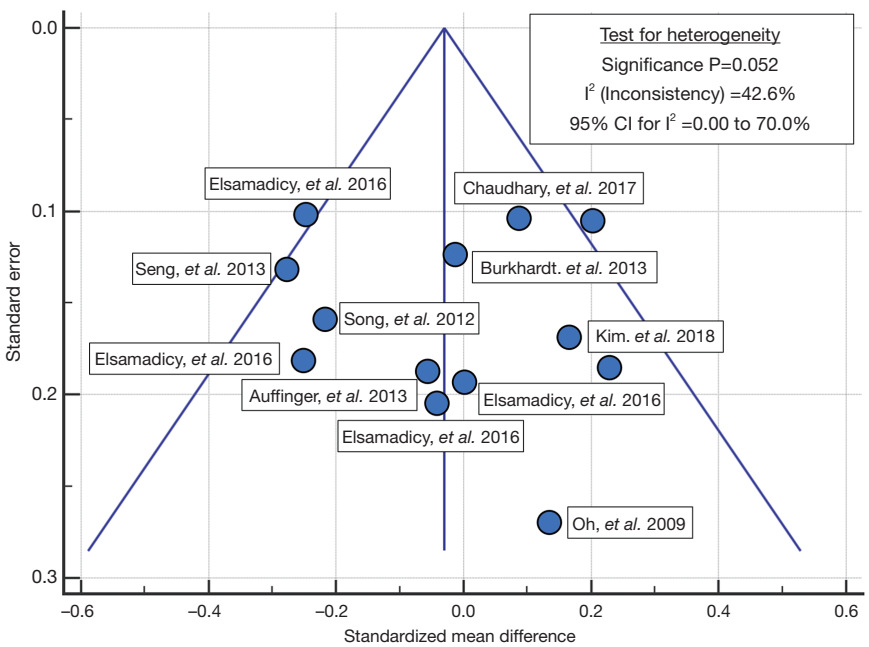

Figure 7 Funnel plot for meta-analysis studies and cohorts.

patients were higher at both pre-op and last follow-up when compared with the metadata, but the overall changes in pain scores (ΔVAS) were statistically equivalent. The higher pre-op and last follow-up pain scores for the Si_3N_4 patients of this study may have been a consequence of patient hypertension, diabetes, and related comorbidities. A heterogeneity test for this metadata is provided in the funnel plot of *Figure* 7. This test compares mean and 95% confidence intervals for changes in VAS pain scores for the 13 meta-analysis cohorts to the mean and pooled 95% confidence interval from this

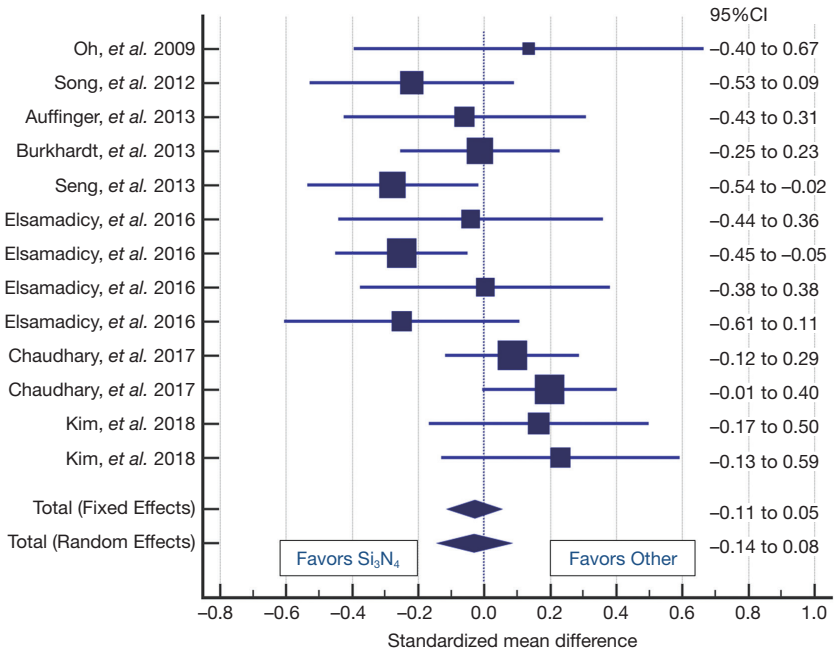

Figure 8 Forest plot comparing changes in VAS pain scores for meta-data and the four surgical centers.

Si_3N_4 study. The test indicates reasonable homogeneity of the data (I^2 =42.6%, P=0.052). A subsequent forest plot, using the same comparative data, is given in *Figure 8*. The results of the forest plot compliment the statistical analysis of *Table 8* and suggest that changes in pain scores between the two groups were essentially equivalent under either fixed or random effects assumptions.

Table 8 also shows that complications or adverse events and secondary surgical interventions (SSI) were also statistically equivalent. The complication rate of the Si_3N_4 patients was ~7.4% compared to ~9.8% for the metadata (P=0.17). There were two SSI incidents for the Si_3N_4 patients and none for patients included in the meta-analysis (P=0.25). Additional details on complications, adverse events, and SSI are provided in *Table 9*. A recurrence of symptoms was the most common complication within the Si_3N_4 group (n=20, 3.1%), followed by additional diagnoses of adjacent level disease (n=13, 2.0%). Revision surgeries were performed on two patients for the malposition and back-out of a screw and an unresolved hematoma. Although the complication rate for the metadata was slightly higher than for Si_3N_4, the incidence of adverse events was broader ranging from respiratory discomfort and dysphagia to hematomas and urinary tract infections. There were no reported revisions for the metadata.

Discussion

Clinical effectiveness of Si_3N_4

Although Si_3N_4 has a long and valued history as an industrial ceramic (34), it has only been approved for clinical use during the past decade. The material exhibits many qualities desired in spine fusion cages, such as mechanical integrity (35), enhanced osteoconductivity (36-38), bacteriostasis (39-42), and improved radiolucency (12,43). There is a misperception among surgeons that all ceramics are brittle; but in fact, Si_3N_4 is one of the strongest and toughest biomaterials known (44,45). Si_3N_4 has ten-times the strength and toughness of PEEK and can withstand failure loads equivalent to medical titanium (46). Recent studies have shown that Si_3N_4 is no more prone to subsidence than any other biomaterial used in cervical spinal fusion (47). In pre-clinical studies, its unique surface chemistry, topography, and hydrophilicity not only upregulate osteogenic activity to achieve faster fusion, but also simultaneously prevent bacterial adhesion and biofilm formation (48-53). Thus, while some claim that the ideal spine biomaterial has yet to be identified (3), others suggest that Si_3N_4 may be the obvious future choice (54,55).

The present study is the largest one of its kind; reporting multi-center clinical evidence of the safety and efficacy

Table 9 Complications, adverse events, and secondary surgical interventions for this study in comparison to the meta-data

Author	No. of patients	Complications and adverse events		Secondary surgical interventions (SSI)		Description of complications, adverse events, and SSI
		n	%	n	%	
This study 2019	636	47	7.4	2	0.3	Hematoma [2]; surgical site infection [1]; hoarseness [4], non-union [1]; recurrent symptoms [20]; adjacent level disease [13]. Secondary surgical interventions were performed for: screw back-out [1]; and hematoma [1]
Oh *et al.* (24) 2009	14	0	0	0	0	No complications, adverse events, or secondary surgical interventions
Song *et al.* (25) 2012	43	10	23.3	0	0	Respiratory discomfort [3]; swallowing difficulty [4]; hoarseness [1]; superficial infection [1]; continued pain at donor site [1]
Auffinger *et al.* (26) 2013	30	1	3.3	0	0	Post-operative atrial fibrillation with rapid ventricular rate [1]
Burkhardt *et al.* (27) 2013	68	14	20.6	0	0	Details on specific complications were not provided in the paper
Seng *et al.* (28) 2013	64	5	7.8	0	0	Hematoma [2]; vocal cord paresis [1]; superficial wound infection [1]; dermatome numbness [1]
Elsamadicy *et al.* (29) 2016	140	6	4.3	0	0	Urinary tract infection [3]; pneumonia [2]; durotomy [1]
Elsamadicy *et al.* (30) 2016	60	5	8.3	0	0	Urinary tract infection [2]; durotomy [1]; pneumonia [1]; surgical site infection [1]
Chaudhary *et al.* (31) 2017	220	NA†	NA†	NA†	NA†	No complications or adverse events were included or discussed in the paper
Kim *et al.* (32) 2018	68	NA†	NA†	NA†	NA†	This study specifically examined clinical outcomes for patients with and without subsidence. Thirty-seven patients had subsidence and thirty-one did not. There were no clinical differences

†, data were not provided in the article or the provided data was not clinically relevant to this comparative analysis.

of Si_3N_4 in cervical fusion. Si_3N_4 was the first synthetic material used in spinal arthrodesis, with a 30-patient cohort undergoing fusion in the mid-1980s (8). While that study addressed lumbar fusion, the VAS pain scores were similar to those observed in the present study. Initial reductions of up to 47 points were seen during the first 5-years post-operatively with lower reductions further out (i.e., 35 points at 10 years). Complication rates were higher (n=11, 36.7%) in the lumbar study, reflecting a rudimentary design of the spinal implants used at the time.

Following this seminal work, several additional studies have described the performance of Si_3N_4 in cervical fusion. For instance, Ball *et al.* published a 36-month retrospective clinical comparison of the osseointegration and fusion performance of Si_3N_4 versus PEEK spacers (9). Those data showed no differences in 36-month outcomes, but early fusion and pain score results suggested the superiority of Si_3N_4 over PEEK cages. A subsequent retrospective study by Smith *et al.* compared Si_3N_4 cages to fibula-based allograft spacers (10). In their 92-patient study, the implants were assessed for fusion, osseous integration, and subsidence for up to 24-month. The results demonstrated that both materials were effective in achieving acceptable arthrodesis at ≥12 months, but earlier periods favored the use of the Si_3N_4. At 3-, 6-, and 12-month follow-up, Si_3N_4 patients showed faster fusion, greater osseous integration, and lower subsidence. Lastly, a 24-month prospective randomized clinical trial of ~100 patients compared PEEK and Si_3N_4

spacers in ACDF (56). The PEEK cages were packed with autograft while the Si_3N_4 spacers had porous ceramic cores (i.e., no bone graft was used). Both groups had comparable clinical and radiographic outcomes at 24-month, indicating the non-inferiority of Si_3N_4 when compared to PEEK. The study also showed that Si_3N_4 was highly effective in generating solid fusion even without added autograft bone chips.

Preoperative demographics and comorbidities

The patients of the present study were older and had higher BMI values than comparative metadata. A significant percentage of the Si_3N_4 patients were diabetic, hypertensive, or smokers. Successful bone fusion can be challenging with age-related comorbidities, but reports from at least two studies suggest that reduction in pain scores in elderly patients may be equivalent to younger counterparts (57,58). This finding is consistent with the present study. Additionally, three studies by Sielatycki *et al.* (59), Narain *et al.* (60), and Srinivasan *et al.* (61) correlated the effect of obesity on patient reported outcomes for elective ACDF. Although VAS pain scores were not monitored in these studies, other clinical measures suggested that obese patients were no more likely to experience greater perioperative complications or post-operative functional disabilities than patients with normal body mass indices. Similarly, Mayo *et al.* found that preoperative smoking did not affect post-operative pain scores (62).

Diabetes and hypertension are common comorbidities in the general population, but have increased coincidence for older patients undergoing cervical spine surgery (63). The present study suggests that patients with these comorbidities were more likely to have poorer clinical outcomes. This finding is consistent with other ACDF studies suggesting that these conditions lead to longer hospital stays (64), higher complication rates and adverse events (65), more revisions (66), and higher odds ratios for readmission and/or multilevel surgeries (66).

Minimum clinical important differences in pain scores

In the present study, the average reduction in pain scores (ΔVAS) with Si_3N_4 spacers was between 30.7- to 42.6-points. Several studies have attempted to address the minimum clinically important difference (MCID) for changes in VAS pain associated with ACDF surgery (26,67-69). The concept of MCID can be simply stated as "the smallest change in pain that is important to the patient" (67). There is a considerable range in MCID values (0 to 100-point scale) from these studies, including a 21.4- to 26-point spread for neck pain, 25- to 41-point for arm pain, and 19.5 for general bodily pain. An additional ACDF review by Kersten *et al.* suggested MCID for pain ranges between 25- to 26-points for neck, 25- to 46-points for arm, and 15 to 25-points for general bodily pain (70). MCID values can vary greatly based on patients' diagnoses, the specific surgical procedure, and the MCID calculation method itself (71). Because of this, definitive MCID values for patients undergoing ACDF surgery have yet to be clearly established (68). Nevertheless, although the present study did not differentiate between anatomical pain locations, an estimate of ≥40-points appears to be a conservative MCID benchmark.

A large multi-surgeon study by Carreon *et al.* attempted to clearly define the MCID for ACDF (67). They followed self-reported pain scores on 505 patients for one-year. Although the demographics of the patients were different than the present study (i.e., younger and with a higher percentage of females), the indications for treatment and pre-op neck pain were similar. Conversely, their average change in VAS pain from pre-op to follow-up was only 23-points compared to 35.4-points in the present study (*cf.*, *Table 8*). Despite this smaller reduction, they calculated the MCID to be ≥25-points for either neck or arm pain. Using this standard, only 44.6% and 45.5% of their patients had perceptible neck and arm pain reductions, respectively. In contrast, in the present study, 50.4% of the patients reported pain reductions of ≥40-point. This direct comparison further supports Si_3N_4's effectiveness as an arthrodesis device in the cervical spine.

Limitations

The present study is limited by its retrospective design. While patient data was collected from medical charts using a prescribed protocol by an independent examiner, the prior recording of each patient's data was not. Therefore, the use of a consistent set of clinical evaluation tools including validated pain or disability indices and questionnaires was not possible. The simple patient reported outcome of VAS pain was the only clinical measure, but even so, neck, arm, and bodily pain were not clearly separated and categorized. Nevertheless, zero to 10 (or zero to 100) pain scales are simple to administer and evaluate. An additional limitation is the lack of a consistent last follow-up period between the four centers. The study was also limited by a lack of

contemporaneous controls, (i.e., no corresponding ACDF data with other cage materials were available from the four clinical sites). Instead, previously reported metadata were used for comparison of clinical outcomes. Lastly, although the data were acquired by an unbiased medical records contractor, subsequent analyses were done by the study authors who believe in the benefits of Si_3N_4 spinal spacers. Nonetheless, the statistical analyses and comparison to previously-published metadata fairly represent expected outcomes by other practitioners and surgical centers.

Conclusions

In this large-scale clinical review of patient demographics, comorbidities, and clinical outcomes, a total of 1,428 Si_3N_4 spacers were implanted during single- and multi-level ACDF. Of 860 patients studied, the majority received multilevel procedures. Patient follow-up averaged 10.6±10.8 months. When compared to other published ACDF studies, the Si_3N_4 patients of the present study were older, with a higher incidence of comorbidities, particularly those related to obesity, hypertension, and diabetes.

The nine studies that were selected for a comparative meta-analysis had similar demographics and multilevel procedures. The metadata consisted of 13 ACDF cohorts and 736 patients. The analyses suggest that ACDF with Si_3N_4 cages was at least as safe and effective as similar procedures that relied on structural bone autograft, PEEK, or titanium alloy fusion cages. Although the four centers in this study were heterogeneous in pre-op patient demographics, comorbidities, and pre- and post-op clinical outcomes, the compiled ordinal and nominal data were similar to the selected meta-analysis, suggesting overall equivalence. Lastly, comparative MCID analyses demonstrated that Si_3N_4 cages were equivalent, if not superior to other commonly used ACDF devices in pain reduction.

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Footnote

Conflicts of Interest: Drs. GC Calvert, GV Huffmon 3rd, WM Rambo Jr, and MW Smith were consulting surgeons to Amedica Corporation during the course of this study. The study was designed and funded by Amedica Corporation (now SINTX Technologies), Salt Lake City, UT USA, of which Dr. Bryan J. McEntire and Dr. B. Sonny Bal are officers and employees.

Ethical Statement: The authors are solely accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Due to the retrospective nature of the study, informed consent by the respective IRBs of each surgical center was not required. However, none of the patients' personal data was disclosed, and their records remain fully secured and in compliance with IRB standards.

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