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A Prospective, Randomized Controlled Clinical Trial of Anterior Lumbar Interbody Fusion Using a Titanium Cylindrical Threaded Fusion Device

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Study Design. A prospective, randomized, controlled clinical trial comparing a cylindrical threaded titanium cage to a femoral ring allograft control for anterior lumbar interbody fusion.

Objective. To compare these two implants with regard to arthrodesis. Secondary outcome measures included pain relief, neurological status, and general health status.

Summary of Background Data. Anterior lumbar interbody fusion is a well-accepted procedure using trapezoidal femoral ring allografts or cylindrical titanium cages. Clinical and biomechanical studies evaluating these two distinct constructs are numerous; however, no prospective, randomized study comparing them has been done.

Methods. A multicenter trial of 140 patients: 78 were randomized to the cylindrical threaded titanium cage device treatment arm and 62 patients randomized into the control group. All had autogenous iliac crest bone graft packed into the device. All patients had a single-level stand-alone anterior lumbar interbody fusion at either the L4–L5 or L5–S1 interspace for symptomatic degenerative disc disease. Radiographic fusion data were collected as well as multiple types of outcome data, including pain/disability scores, neurologic status, and overall health.

Results. At 12 months, 97% of the cylindrical threaded titanium cage device group and 40% of the control group demonstrated radiographic fusion. At 24 months, 97% of the cylindrical threaded titanium cage group and 52% of the control group showed radiographic fusion. These fusion rate differences are statistically significant ($P <$ 0.001). The Oswestry and neurologic scores were not significantly different between groups.

Discussion. This is the first prospective, randomized, multicenter clinical trial that compares fusion cage results to control data.

Conclusion. Cylindrical threaded titanium cages have a higher fusion rate, comparable improvements in clinical outcome (Oswestry, Low Back Pain Questionnaire, SF-36), and fewer secondary supplemental fixation procedures compared to the femoral ring allograft control. [Key words: anterior lumbar interbody fusion, Interbody fusion cage, prospective trial, femoral ring allograft, INTER FIX Threaded Fusion Device] **Spine 2004;29:113–122**

The use of interbody fusion cages has increased markedly over the past 5 years, and it is now estimated that 5,000 cages are implanted monthly in the United States.[1] It has been shown that interbody cages effectively achieve fusion[2–5] and that the use of interbody cages can be cost effective.[6,7] Further, it has been shown that achieving successful fusion correlates with better clinical outcomes.[7] While several prospective studies have been undertaken on different interbody fusion devices,[2–4] none of these studies has been designed as a prospective, randomized, multicenter clinical trial that compares fusion cage results to control data.

The INTER FIX Threaded Fusion Device was developed by Medtronic Sofamor Danek for use in spinal fusion procedures in skeletally mature patients with degenerative disc disease. The device is also indicated for use in patients with no more than Grade 1 lumbar spondylolisthesis or retrolisthesis at a single level. INTER FIX device implants are to be used with autogenous bone graft and implanted *via* an open anterior approach. The following study was conducted as a prospective, randomized, multicenter study to determine the safety and effectiveness of the INTER FIX device in the treatment of patients with symptomatic lumbar degenerative disc disease.

History. The INTER FIX device has been distributed in Europe since 1995 and has been marketed in at least 20 countries. The U.S. Food & Drug Administration approved the Premarket Approval application for the INTER FIX device on May 14, 1999. This approval covers the use of the device with autologous bone graft in spinal fusion procedures *via* the open anterior approach for patients with degenerative disc disease at one level from L2–S1, including those with Grade 1 or less spondylolisthesis or retrolisthesis.

Device Design and Preclinical Testing. The INTER FIX device is a hollow, threaded cylinder with a removable end cap (Figure 1). The device was originally approved for 18 sizes with diameters from 12 mm to 20 mm and lengths from 20 mm to 29 mm with end cap components. Subsequently, 8 additional size devices, with 22- or 24-mm diameters, have received a marketing clearance from the Food & Drug Administration. The information presented and the results of the clinical trial, however,

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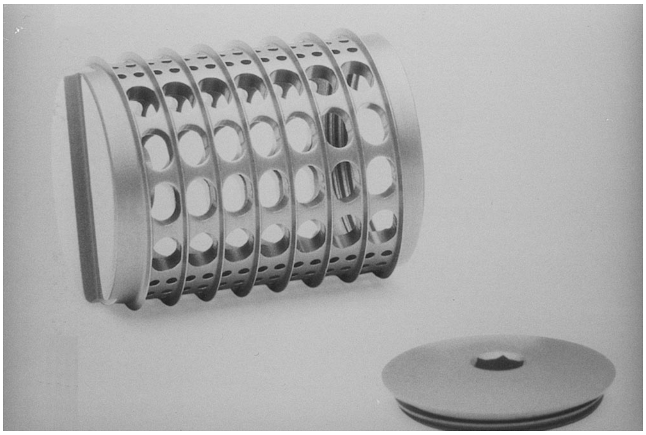

Figure 1. INTER FIX Threaded Fusion Device.

are based on the 18 original sizes that were used in the clinical trial. The end caps provide strength while reducing metal volume and increasing the space available for autograft. Each cylinder component has a 30° included angle self-tapping V-thread over the entire outer surface of the implant and a 45° chamfer at the ends to facilitate insertion into the prepared intervertebral cavity. Each cylinder component has multiple through-holes that are to be placed cephalad and caudad and multiple small transverse holes to enhance vascularization of the graft within the device. The INTER FIX device is manufactured from titanium alloy (Ti-6Al-4V).

Biomechanical laboratory testing to characterize the mechanical properties of the INTER FIX device included static compression testing, cyclic fatigue testing, and stability testing, which was comprised of stiffness testing, insertion torque, and push-out testing. The INTER FIX device failed at an average compression load of 79,797 N without breakage and cyclic load testing of 5 million cycles of compression loads ranging from 880 N to 9,600 N without failure. Using a combined loading (compression, bending moment, and shear) test fixture that enhanced simulation of a dynamically loaded spine, breakage did not occur at 5 million cycles at a maximum bending moment of 135 N-m, which is a substantially greater load than the bending moment of 33 N-m that the motion segment can resist before sustaining damage. In another "combined" loading mechanical test, which also attempted to replicate the complex lumbar loading situation *via* a compression shear apparatus, the INTER FIX device has a strength of 30,570 N and 4,000 N in static and fatigue (5×10^6 cycles) loading situations, respectively. This compares favorably with estimate maximum *in vivo* loads of 2,200 N and 1,400 N, respectively. Based on these data, the INTER FIX device appears to provide a significant safety factor over the complex *in vivo* loading situation.[15]

Clinical Trial. The purpose of this clinical trial is to determine the safety and efficacy of the INTER FIX device for treatment of symptomatic degenerative disc disease and to compare it with a completely biologic femoral ring allograft implant (Figure 2).

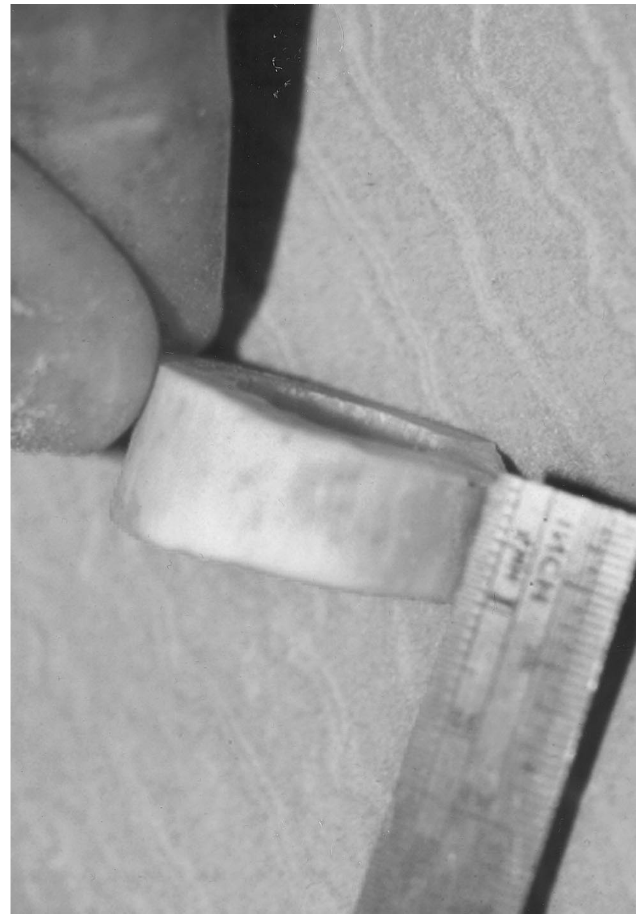

Figure 2. Femoral ring allograft.

Methods

A prospective, randomized, multicenter clinical trial of the INTER FIX device was conducted in the United States to determine the safety and effectiveness of the anterior spinal use of the INTER FIX device in the treatment of patients with symptomatic degenerative disc disease. A total of 140 patients were entered into the study at 13 study sites. The following is the list of investigators participating in the prospective, randomized study:

- Avi Bernstein, MD, Park Ridge, IL
- Gary Michelson, MD, Los Angeles, CA
- Courtney Brown, MD, Lakewood, CO
- Robert Pashman, MD, Los Angeles, CA
- Craig Callewart, MD, Dallas, TX
- Richard Salib, MD, Minneapolis, MN
- Guy Danielson, MD, Tyler, TX
- Rick Sasso, MD, Indianapolis, IN
- Edgar Dawson, MD, Los Angeles, CA
- Robert Watkins, MD, Los Angeles, CA
- Alexander Hadjipavlou, MD, Galveston, TX
- Douglas Weiland, MD, Clearwater, FL
- Scott Kitchel, MD, Eugene, OR

Seventy-eight patients were randomized to the INTER FIX device treatment arm (Figure 3), and 62 patients were random-

Figure 3. Lateral radiograph of INTER FIX.

Figure 4. Lateral radiograph of femoral ring allograft 3 months postoperative.

ized to the control group (Figure 4). Investigational patients were treated with the INTER FIX device filled with autogenous bone derived from the iliac crest. Control patients were treated with femoral ring allograft also filled with iliac crest-derived autogenous bone. All patients underwent an anterior surgical approach for a single-level interbody fusion. Patients had at least 6 months of nonoperative treatment before surgical intervention, including physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs. The clinical trial was designed as an equivalence trial, to determine if the INTER FIX device outcomes are no worse than those of the control, according to methods described by Blackwelder.[10] Patients enrolled in the study had symptomatic degenerative disc disease diagnosed by symptoms of intractable leg and/or back pain with positive diagnostic imaging findings. In addition, patients had to exhibit spinal instability as defined by >4 mm of translation or >5° of angulation on flexion–extension radiographs, have single-level symptomatic involvement from L2–S1, and have no greater than Grade 1 spondylolisthesis. The positive diagnostic imaging findings for patients enrolled in the study, as noted by intractable leg and/or back pain in the presence of instability, included at least one of the following: 1) herniated nucleus pulposus as documented by MRI, CT, or myelographic techniques, 2) collapse of disc space of >2 mm as determined by anteroposterior and lateral radiographs, 3) scarring and/or thickening of the anulus fibrosis, ligamentum flavum, and/or facet joint capsule, 4) osteophyte formation on the vertebral endplates, 5) osteophyte formation or hypertrophy of the facet joint, or 6) disc disruption manifested by resorption and narrowing of the disc space. Specifically excluded from the clinical trial were patients who had a previous anterior interbody fusion procedure at the involved spinal level; had osteopenia, osteoporosis, or osteomalacia; or required bone growth stimulation. Contraindications to use of INTER FIX device use were active infection at the operative site or patients with an allergy to titanium or titanium alloy. No posterior instrumentation could be present at the surgical level.The primary outcome variable tested in this study was fusion. Other outcome measures included pain relief, neurologic status, and general health status. All radiographs were interpreted by an independent board-certified radiologist, and patients completed subjective data surveys independently. Demographic information of the patients in the clinical trial is presented in Table 1. The demographic characteristics of both treatment groups were similar.Each patient had to agree to participate in the research protocol and each was assigned by random selection, with neither surgeon nor patient knowing whether they would receive a cage or an allograft until after the consent was signed.

Surgical Procedure. Preoperative planning required the identification of which intervertebral disc to operate on followed by selecting the proper size construct by using templates which were designed for use with plain radiographs, CT, or MRI scans. Care was taken to match the scale of magnification on the radiographic study.

Table 1. Demographic Information

	INTER FIX Device	Control
Age (yr) (mean [range])	N = 77 41.0 [18–64]	N = 62 41.2 [27–59]
Weight (lb) (mean [range])	N = 77 170.5 [100–270]	N = 62 172.8 [109–250]
Height (in.) (mean [range])	N = 76 66.6 [60–75]	N = 62 67.9 [60–74]
Sex [frequency (%)]		
Male	30 (39.0)	33 (53.2)
Female	47 (61.0)	29 (46.8)
Tobacco used [frequency (%)]		
Yes	23 (29.9)	20 (32.3)
No	54 (70.1)	42 (67.7)
Workers' Compensation [frequency (%)]		
Yes	32 (42.1)	22 (35.5)
No	44 (57.9)	40 (64.5)
Taking preoperative medication for pain [frequency (%)]		
Yes	59 (76.6)	46 (74.2)
No	18 (23.4)	16 (25.8)
Previous back surgery [frequency (%)]		
Yes	32 (41.6)	27 (43.6)
No	45 (58.4)	35 (56.5)

The INTER FIX device was implanted through an anterior spinal approach, either transperitoneal or retroperitoneal. The amount of great vessel release and retraction was limited to that required for insertion of the instruments and constructs. Both double barrel outer sleeve and single barrel outer sleeve methods of implant placement were available. Two cages are inserted in the disc space. The double barrel procedure is presented here.

A standard block discectomy is recommended. The centering pin should be used to fluoroscopically confirm the midline of the disc. Measurement of the available space for the selected device size was carried out using the blunt proximal end of the double barrel outer sleeve and compared with the preoperative radiographic template. While holding the double barrel, the necessary width of the discectomy was identified and marked. Disc material was removed from the defined space with a scalpel, rongeur, or curette. The procedure proceeded with size-specific instrumentation for the appropriate diameter INTER FIX device.

Distraction shafts were placed to distract the vertebral bodies before vertebral reaming. The double barrel outer sleeve is firmly seated into the disc space replacing the distractor. An appropriate size reamer is selected, depth stop adjusted, and disc space prepared. Several passes of the reamer should be undertaken. Any remaining intradiscal disc, bone, or anular material is removed with the rongeur.

The INTER FIX device is filled with autogenous bone using a bone press. The end cap is affixed and the device is placed in the corresponding inserter. The device is then advanced into place, checking depth with lateral fluoroscopy. The optimal position of the INTER FIX device is slightly countersunk from the anterior surface and within the lateral margins of the vertebral bodies. Two INTER FIX devices should be implanted side by side at the surgical level. The long axis of the INTER FIX device should be in the anteroposterior direction.

Standard wound closure was then carried out. No other fixation was used in patients in this study. Ambulation was initiated when tolerated usually on the day of surgery. A corset or thoracic lumbosacral orthosis was sometimes used after surgery for immobilization.

Table 2. Successful Fusion Rates (%) at 6, 12, 24, and 48 Months

Treatment Group	6 Months	12 Months	24 Months	48 Months
INTER FIX device	95.0 (38/40)	96.7 (58/60)	97.0 (64/66)	92.0 (23/25)
Control	10.9 (6/55)	40.4 (21/52)	51.9 (27/52)	42.1 (8/19)

The surgical technique for the control was the surgeon's standard method of anterior spinal implantation of the femoral ring allograft. A block discectomy of the entire disc and preparation of the endplates with complete removal of the cartilage while preserving the subchondral bone was done. The femoral ring allograft was cut with an oscillating saw to exactly match the interspace in distraction. The intramedullary canal of the trapezoidal ring was packed with autogenous iliac crest cancellous bone. As with the INTER FIX device, no other fixation was used in patients in the study. The same postoperative regimen was also recommended for the control device.

Patients were evaluated before surgery, perioperatively, and after surgery at 3, 6, 12, and 24 months following surgery. The protocol also stipulated that patients had to be evaluated biennially until the last patient had reached his/her 24-month evaluation. Therefore, 48-month data are available for some of the patients. Evaluations included the assessment of fusion at the involved level, pain/disability status, neurologic status, and general health status. The results have since been updated as of May 2000, with data on all available patients in the randomized study. Also, additional data on patients who have been evaluated at 48 months after surgery are included. The inclusion of the 48-month results is for information purposes; however, because of the partial information, these data will not be discussed. It is noteworthy that the 48-month results are consistent with those at 12 and 24 months postoperative. Approximately one third of all the patients in the randomized group have reached this time point.

Results

Fusion

Fusion was determined using anteroposterior, lateral, and flexion–extension radiographs that were interpreted by an independent board-certified radiologist at 6, 12, and 24 months after surgery. Arthrodesis was based on the spinal level showing evidence of bridging trabecular bone, translational stability (≤3 mm), angular motion stability (<5°), and the absence of radiolucent lines around more than 50% of the implant(s). Patients requiring secondary surgeries resulting from nonunions were considered as having failed fusions and were included in the fusion calculations. Fusion data are presented in Table 2. At 12 months, 96.7% of the INTER FIX device group and 40.4% of the control group demonstrated radiographic fusion. At 24 months, 97.0% of the INTER FIX group and 51.9% of the control group showed radiographic fusion. The data demonstrates that the INTER FIX device is not only no worse than the

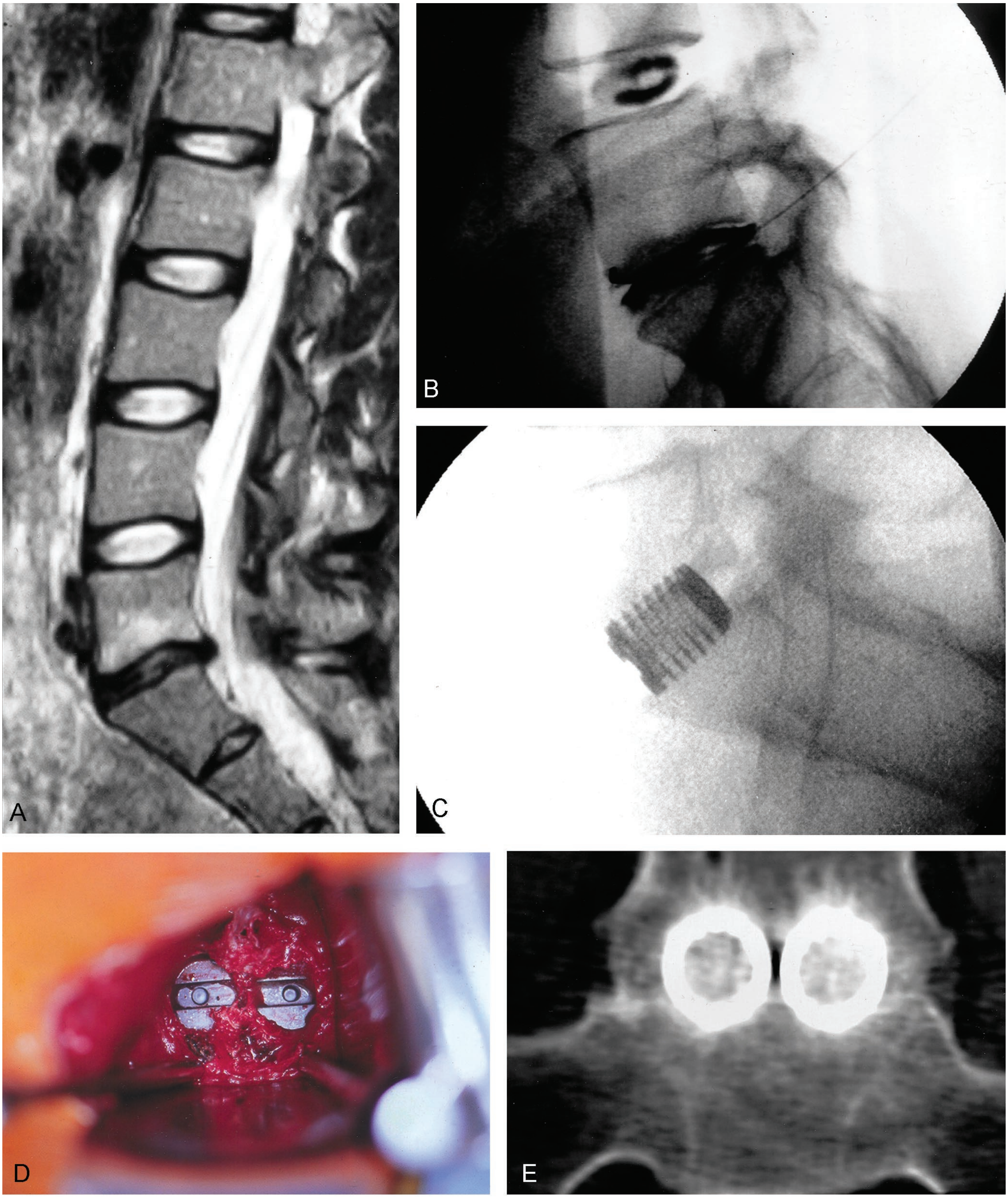

Figure 5. **A:** Preoperative sagittal T2-weighted MRI with degeneration of the L5–S1 disc and a normal L4–L5 disc. **B:** Discogram with morphologic abnormality of the L5–S1 disc and a large posterior anular tear. The L4–L5 disc is anatomically normal. Exact concordant 10/10 pain was reproduced at L5–S1. The L4–L5 injection caused no pain. **C:** Postoperative lateral radiograph with INTER FIX cages in good position. **D:** Intraoperative picture of the two cages implanted at the L5–S1 interspace. **E:** Coronal CT scan 1 year postoperative. Bone has grown through and around the cages.

control ($\Delta < 0.01$) but that the INTER FIX device fusion rates were superior to the control rates at 6, 12, and 24 months ($P < 0.001$) (Figure 5).

Pain/Disability

Pain and the disability resulting from pain were assessed using the Oswestry Low Back Pain Disability Questionnaire. This questionnaire was administered before surgery and at each postoperative visit. The Oswestry Questionnaire evaluates the patient's response to 10 questions that focus on pain, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and ability to travel. Responses range from zero to five, and the lower numerical score represents a better pain and disability status with regard to each variable. The total score is determined by summing the scores to individual questions and dividing that total by the maximum possible total score to yield a percentage score. A lower score is characteristic of less pain and disability. Mean Oswestry Questionnaire scores are presented in Table 3. The mean overall scores significantly improved in all groups compared with the preoperative scores ($P < 0.001$). The INTER FIX device group showed improvement from a mean preoperative value of 51.1 to a mean value of 33.7 at 6 months, 32.9 at 12 months, and 29.5 at 24 months. The control group preoperative mean value was 52.7, falling to 38.4 at 6 months, 34.4 at 12 months, and 31.5 at 24 months. There was no statistical difference between the treatment groups.

Neurologic Evaluation

All patients in the clinical trial underwent neurologic evaluation before surgery and after surgery at every follow-up visit. The neurologic assessment tool addressed motor function, sensory, reflexes, and degree of straight leg raising producing pain. An algorithm was developed to transform the detailed scores for each parameter into an overall classification representing maintenance or improvement in neurologic status at a given postoperative time as compared with their preoperative neurologic status. Overall neurologic status maintenance or improvement is based on demonstrating maintenance or improvement in at least three of the four categories. Table 4 shows the distributions of patients in the treatment groups having a maintenance or improvement in neurologic condition following surgery. Overall values for the INTER FIX device group were 97.2% at 6 months, 100% at 12 months, and 97.0% at 24 months. The control group overall values were 98.3% at 6 months, 100.0% at 12 months, and 95.6% at 24 months. There were no statistically significant differences between the randomized INTER FIX device group and the control group at these time periods ($P > 0.05$).

General Health Status

The general health status of all study patients was assessed using the Medical Outcomes Study 36-item Short Form Health Survey (SF-36). Patients completed this self-administered test before surgery and at each postoperative visit. The test consists of 36 questions involving eight subscales of health status: physical function, role-physical, pain index, general health perception, vitality, social function, role-emotional, and mental health. These eight subscales can be summarized further into two measures pertaining to physical health (PCS) and mental health (MCS). The PCS is based primarily on the physical functioning, role-physical, bodily pain, and general health scales. The MCS is based on the vitality, social function, role-emotional, and mental health scales. Higher numbers represent increasing improvement. Table 5 presents the mean PCS and MCS results for the two treatment groups. All the postoperative scores were higher than the preoperative scores indicating improvement. The INTER FIX device group showed mean score improvement in PCS scores of preoperative value of 28.3 to 35.3 at 6 months, 37.9 at 12 months, and 39.8 at 24 months. Mean MCS scores improved from a preoperative value of 42.2 to 24-month value of 46.8. Control mean values of PCS and MCS at preoperative, 6-, 12-, and 24-month follow-up were 28.5/41.9, 36.4/47.1, 37.0/46.9, and 37.3/51.0, respectively. There were no statistically significant differences at any time period between the investigational and control groups in the mean change in PCS and MCS scores postoperative compared with the preoperative value ($P > 0.05$).

Adverse Effects

Table 6 presents the nature and frequency of adverse events through the latest evaluation of the patients. The most common and serious adverse effects were intraoperative vascular, neurologic injuries or spinal events, such as disc herniation or foraminal stenosis. A total of 9 (11.5%) intraoperative vascular events occurred in patients in the INTER FIX device group and 2 (3.2%) vascular intraoperative injuries occurred in the control group. In the INTER FIX device group, 14 (17.9%) neurologic events occurred compared with 16 (25.8%) neurologic events in the control group. Spinal events occurred in 11 (14.1%) of the INTER FIX device group and 4 (6.5%) in the control group. Sacroiliac pain occurred in 7 (8.9%) of the INTER FIX device treatment group and 3 (4.8%) of the control group while 4 (5.1%) of the INTER FIX device group had back pain compared with 14 (22.5%) of the control group. In the INTER FIX device group, 5 (6.4%) had incisional pain, as did 8 (12.9%) of the control group. While there were no occurrences of implant displacement or loosening or implant breakage in the INTER FIX device group, there were 6 (9.7%) and 5 (8.1%), respectively, in the control group. There was only one death in the study of a patient in the control group (1.6%) that resulted from cardiac arrest and was not associated with the implant. None of the adverse event rates for the INTER FIX device group was statistically higher than those for the control group. The rates of implant breakage, implant loosening/displacement, back pain, and other pain in the control group were statistically higher ($P < 0.05$) than those for the INTER FIX device group.

Some of these adverse events led to surgical interventions subsequent to clinical trial surgery. These surgeries were classified as revision, removal, supplemental fixation, and reoperation. The definitions for these classifications are as follows:

Table 3. Mean Oswestry Pain/Disability Scores

Treatment Group	Preoperative	6 Months	12 Months	24 Months	48 Months
INTER FIX device	51.1 (N = 77	33.7 (N = 73	32.9 (N = 66	29.5 (N = 69	23.7 (N = 29
Control	52.7 (N = 60	38.4 (N = 57	34.4 (N = 53	31.5 (N = 48	14.8 (N = 15

- *Revision*—A procedure that adjusts or in any way modifies the original implant configuration (*e.g.*, adjusting position of original configuration, removal with replacement of component, adding a fixation screw to the bone graft).
- *Removal*—A procedure that removes one or more components of the original implant configuration without replacement of any components.
- *Supplemental fixation*—A procedure in which additional instrumentation not approved as part of the protocol is placed.
- *Reoperation*—A procedure that involves any surgical procedure that does not remove, modify, or add any components.

These results are summarized in Table 7. The INTER FIX device group had a significantly fewer number of supplemental fixations compared with the control group ($P = 0.003$).

Discussion

Although several interbody fusion devices are currently marketed, none of these cages has been subjected to the rigors of a prospective, randomized, multicenter clinical trial until now. This clinical trial of the INTER FIX Threaded Fusion Cage is therefore a landmark study, which demonstrates the superior results of increased fusion rates using the INTER FIX device compared with the control of treatment involving a femoral allograft ring filled with autogenous bone.

Rapoff *et al*[8] studied the stability of the spine following INTER FIX device implantation. The biomechanical testing included the effects of the device on spinal stiffness and the implant insertion torque and push-out properties. Stiffness testing was performed using lumbar calf spines evaluating stiffness in flexion–extension, axial torsion, axial loading, and lateral bending using the intact spine as a baseline. Results showed that the spines instrumented with the INTER FIX device were stiffer than intact spines and spines with resected posterior elements in flexion, extension, and overall. The overall stiffness testing results were comparable to SpineTech's BAK device. The INTER FIX device instrumented spines were significantly stiffer in extension. Insertion torque and push-out testing using human cadaveric spines were performed on both the INTER FIX and BAK devices. Results for the two devices were similar and the INTER FIX device was found to be resistant to migration and push-out.

Sandhu *et al*[9] reported on the use of the INTER FIX device for single-level anterior lumbar interbody fusion procedures in sheep comparing this to iliac crest dowels and interbody decortication. Six-month evaluation, including manual palpation of fusion site and histology, showed 100% fusion to palpation and 37% complete fusion by histologic evaluation in the INTER FIX group. Radiographic evaluation, which included measurement of interbody distraction and angulation, was carried out at 2, 4, and 6 months after surgery. The INTER FIX device maintained disc space height over time. The iliac crest dowel group also had a 100% fusion rate but demonstrated more collapse of the interbody space at follow-up.

Prospective, multicenter randomized clinical trials are the gold standard of scientific studies. While these studies are required for pharmaceutical testing, they are rarely done in a surgical setting.[11,12] The lack of prospective, randomized orthopedic studies and prevalence of poor study designs and analysis is reported throughout the orthopedic literature.[13,14] The prospective, randomized clinical trial design limits bias, although it does not completely eliminate it in the surgical setting because of surgeon familiarity with specific techniques and proce-

Table 4. Neurological Maintenance or Improvement Rates (%) at 6, 12, 24, and 48 Months

Treatment Group	Motor Function	Sensory	Reflexes	SLR	Overall
6 months					
INTER FIX device	100.0 (72/72)	95.8 (69/72)	88.9 (64/72)	96.7 (59/61)	97.2 (70/72)
Control	100.0 (58/58)	100.00 (58/58)	93.1 (54/58)	98.0 (49/50)	98.3 (57/58)
12 months					
INTER FIX device	100.0 (66/66)	98.5 (65/66)	93.9 (62/66)	96.3 (52/54)	100.0 (66/66)
Control	100.0 (52/52)	98.1 (52/53)	92.5 (49/53)	97.9 (47/48)	100.0 (52/52)
24 months					
INTER FIX device	100.0 (67/67)	98.5 (66/67)	88.1 (59/67)	93.3 (56/60)	97.0 (64/66)
Control	97.8 (44/45)	91.1 (41/45)	95.6 (43/45)	93.0 (40/43)	95.6 (43/45)
48 months					
INTER FIX device	100.0 (27/27)	92.6 (25/27)	85.2 (23/27)	100.0 (27/27)	100.0 (27/27)
Control	100.0 (14/14)	92.9 (13/14)	92.9 (13/14)	100.0 (14/14)	100.0 (14/14)

Table 5. Mean PCS and MCS Scores at 6, 12, 24, and 48 Months

	Preoperative		6 Months		12 Months		24 Months		48 Months	
Treatment Group	PCS	MCS	PCS	MCS	PCS	MCS	PCS	MCS	PCS	MCS
INTER FIX device	28.3 N=77	42.2 N=77	35.3 N=71	46.5 N=71	37.9 N=66	46.3 N=66	39.8 N=68	46.8 N=68	41.8 N=29	48.8 N=29
Control	28.5 N=61	41.9 N=61	36.4 N=55	47.1 N=55	37.0 N=53	46.9 N=53	37.3 N=48	51.0 N=48	47.8 N=15	51.9 N=15

dures.[11] In this clinical trial, however, all surgeons participating were competent and familiar with both the investigational and control procedures, thereby minimizing any bias that could result from surgical technique variations. Because this was a multicenter study, surgical bias in terms of reproducibility was also minimized.

There were other important design features of this clinical trial, including the use of the independent board-certified radiologist for interpretation of postoperative films. This served to eliminate bias and standardize the interpreted results. A very specific definition of fusion was utilized, requiring that evidence of bridging trabecular bone, translational stability (≤3 mm), and angular motion stability (< 5°) be present, and the absence of radiolucent lines around >50% of the implant(s) be evident for fusion to be considered to have occurred. Finally, the patients themselves supplied the subjective data *via* the Oswestry Disability Scale and the SF-36, keeping these data free of the clinician's interpretation and bias. All these factors further support the validity of this clinical trial.

One of the more difficult areas to evaluate in any lumbar fusion study is the subjective measure of patient outcome. Two measures were used in this study to measure patient improvement, the Oswestry Low Back Pain Questionnaire and the SF-36. Using both these measures, patients had improvement when the INTER FIX device was used compared with preoperative values. The mean INTER FIX results were also better initially and at 3, 6, 12, and 24 months than the results from the control group for both the Oswestry and SF-36 measurements. There were no statistically significant differences between the control and experimental groups in regards to Oswestry, SF-36, or neurologic scores. The improvement seen in both groups is likely more a function of the approach itself (anterior lumbar interbody fusion) rather than what material or device was implanted or whether fusion actually occurred. Although fusion indexes are not inconsequential, many factors are associated with patient satisfaction. Exposure and soft tissue factors are especially important in patient satisfaction outcomes. Traditionally, an anterior approach is correlated with a better outcome despite a lower fusion rate compared with a more soft tissue destructive posterolateral exposure. Fraser[16] found that better outcomes are obtained after anterior interbody fusion than after posterolateral fusion with internal fixation despite a higher fusion rate in the latter group.

The INTER FIX device was found to be not only statistically equivalent to, but better than, the femoral ring allograft for interbody fusion in rate of fusion. Improvement in terms of clinical outcomes was demonstrated through use of the Oswestry Low Back Pain Questionnaire and the SF-36. There were no statistically significant differences in specific adverse event rates that favored the control group. However, the INTER FIX device group had statistically fewer secondary supplemental fixation procedures. Although there is no statis-

Table 6. Adverse Effects

	Total Adverse Events	
Complication	INTER FIX Device [no. (% of 78)]	Control [no. (% of 62)]
Vascular intraoperative	9 (11.5)	2 (3.2)
Sacroiliac pain	7 (8.9)	3 (4.8)
Neurological	14 (17.9)	16 (25.8)
Back pain	4 (5.1)	14 (22.5)†
Incisional	5 (6.4)	+8 (12.9)
Spinal event	11 (14.1)	4 (6.5)
Urological	2 (2.6)	2 (3.2)
Other	7 (9.0)	5 (8.1)
Other pain		6 (9.7)†
Gastrointestinal	5 (6.4)	5 (8.1)
Retrograde ejaculation	1 (1.3)	
Respiratory	6 (7.7)	1 (1.6)
Leg pain	2 (2.6)	
Trauma	1 (1.3)	
Peritoneal	3 (3.8)	
Vascular postoperative	1 (1.3)	2 (3.2)
Bone fracture	2 (2.6)	
Implant displacement/ loosening		6 (9.7)†
Graft site pain		1 (1.6)
Nonunion*	1 (1.3)	
Nonunion (outcome pending)	1 (1.3)	3 (4.8)
Meningitis		1 (1.6)
Implant breakage		5 (8.1)†
Death		1 (1.6)

* Did not result in second surgery; nonunions that did result in second surgeries appear in Table 7.
† $P < 0.05$.

Table 7. Secondary Surgical Procedures

	INTER FIX Device (N = 77) [no. (%)]	Control (N = 62) [no. (%)]
Revisions	2 (2.6)	3 (4.8)
Removals	1 (1.3)	0 (0.0)
Supplemental fixations	6 (7.8)	17 (27.4)*
Reoperations	12 (15.6)	11 (17.7)

* $P < 0.05$.

tically significant difference between the two groups in regards to intraoperative vascular injury and other intraoperative problems, the number of patients in this study may be too small to detect a difference if indeed it does exist. The authors are currently looking at this issue with a much larger cohort. Intraoperative complications of anterior lumbar interbody fusion through a mini-open retroperitoneal approach using either cylindrical or trapezoidal implants are being compared for future publication.

The results of this prospective randomized study indicate that the INTER FIX device is safe and effective for use in interbody fusion as an improved alternative to femoral ring allograft.

Key Points

- Stand-alone anterior titanium cylindrical threaded interbody fusion cages have a higher fusion rate than stand-alone anterior femoral ring allograft.
- Improvements in clinical outcome were similar in both groups.
- Intraoperative complications were higher in the cylindrical threaded cage group compared with the trapezoidal femoral ring control cohort but did not reach statistical significance.

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Point of View

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This article meets the “gold standard” for scientific studies, as it is prospective, randomized, and multicentered. The field of clinical spinal research is difficult in part because of the many variables present. This study attempted to limit the variables by using strict inclusion criteria and evaluating only one variable, the merit of cylindrical metal implants compared with cortical ring implants. The goal of the study appears to have been achieved by showing that the fusion rate and the clinical outcomes using cylindrical metal implants are at least as good as or better than those obtained with cortical ring implants.

Interpretation of the results, however, raises the question of why the clinical outcomes are similar in the face of fewer apparently solid fusions in the control group (cortical rings). If the objective of surgery is to relieve pain by elimination of motion, higher fusion rates should result in better clinical outcomes.[1] The authors quote Fraser,[2] implying that the anterior approach may be responsible for a better outcome than can be achieved with the posterolateral approach. In this paper, however, the same anterior approach was used in both study groups. A closer look at the adverse events reported of “back pain” and “other pain” in the control group may be reflective of the greater number of failed unions in the cortical ring group. This factor may not be well represented in the Oswestry or SF-36 scores. Another possible explanation may be that despite the radiographic appearance, there may have been larger numbers of nonunions in the cylindrical metal implant group. If, indeed, the number of solid fusions were similar in both groups; the clinical outcomes being similar would make sense.

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The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication.
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Determination of solid fusion is often very difficult using presently available radiographic technology. The authors correctly used the present standard for assessment of fusion, using evidence of bridging bone, radiolucent lines, and motion studies. The fundamental difficulties with these methods are further compounded by the variable of bone implants compared with metal implants. The radiographic assessment can be improved using more accurate methods such as high resolution CT scans with reconstructions (as in Figure 5E). Even this technique is not foolproof, I would urge that future prospective studies hold to this higher standard, especially for those whose primary outcome variable is fusion.

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