

Review Article

Pros, cons, and costs of INFUSE in spinal surgery

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Received: 7 December 10

Accepted: 22 December 10

Published: 24 January 11

Surg Neurol Int 2011, 2:10

This article is available from: <http://www.surgicalneurologyint.com/content/1/2/10>

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This article may be cited as:

Epstein NE. Pros, cons, and costs of INFUSE in spinal surgery *Surg Neurol Int* 2011;2:10

Available FREE in open access from: <http://www.surgicalneurologyint.com/text.asp?2011/1/2/76147>

Abstract

Background: INFUSE (recombinant human bone morphogenetic protein-2 [rh-BMP-2]; Medtronic, Memphis, TN, USA) is approved by the Federal Drug Administration (FDA) only for use with the lumbar tapered fusion device (LT Cage; Medtronic) to perform single-level anterior lumbar interbody fusions (ALIF: L2–S1 levels). INFUSE, however, is widely utilized in an “off-label” capacity for anterior and/or posterior cervical, thoracic, and lumbar surgery. Nevertheless, Medicare and other insurance companies, are now increasingly denying reimbursement (average cost of a “large” INFUSE to the hospital without overhead \$5000–6000) to hospitals for INFUSE when utilized “off-label.”

Methods: This commentary looks at several representative studies citing the cons associated with utilizing INFUSE in spinal surgery, contraindications, complications, and cost factors.

Results: There are multiple cons of utilizing INFUSE in an “off-label” capacity for spinal surgery. Direct contraindications include pregnancy, allergy to titanium, allergy to bovine type I collagen or rhBMP-2, infection, tumor, liver or kidney disease, immunosuppression (e.g., lupus, HIV/AIDS); contraindications are also seen in those receiving radiation, chemotherapy, or steroids. Reported complications include exuberant/ectopic bone formation, paralysis (cord, nerve damage), dural tears, bowel–bladder and sexual dysfunction, respiratory failure, inflammation of adjacent tissues, fetal developmental complications, scar, excessive bleeding, and even death. Complications are so prevalent in the anterior cervical spine, that many surgeons no longer use it in this region. Similarly, INFUSE complications and indications for posterior lumbar interbody fusions (PLIFs) and transforaminal interbody lumbar fusions (TLIFs) should also be reexamined.

Conclusions: More surgeons need to question the safety, efficacy, and appropriate “off-label” use of INFUSE in all spine surgeries.

Key Words: INFUSE (rhBMP-2), bone morphogenetic protein, spinal surgery, off-label use

Access this article online

Website:
www.surgicalneurologyint.com

DOI:
10.4103/2152-7806.76147

Quick Response Code:



INTRODUCTION

The use of bone morphogenetic protein INFUSE (recombinant human bone morphogenetic protein-2 [rhBMP-2]; Medtronic, Memphis, TN, USA) in cervical, thoracic, and lumbar spine surgery remains controversial. Despite its Federal Drug Administration (FDA) approval solely for anterior lumbar interbody fusions (ALIFs) with a lumbar tapered fusion device (LT Cage; Medtronic), it has been applied at the discretion of individual surgeons in an “off-label” capacity throughout the spine. Surgeons validate its use based upon the “standard of care.” In this review, we examine the cons of utilizing INFUSE, citing its common (e.g., anterior cervical complications) and not-so-commonly known complications, while also taking a cursory look at its pros. Furthermore, several of the studies look at the major financial implications of utilizing INFUSE. Presently, INFUSE costs hospitals an average of \$5000–6000 for a large package (actual cost without overhead to the hospital). As Medicare and more insurance companies no longer reimburse or are considering cessation of reimbursement for INFUSE used in an “off-label” capacity (anywhere excluding ALIFs), surgeons may have to turn toward other supplements/alternatives to attain fusion.

MATERIALS AND METHODS

Current Status of Approvals for Use of INFUSE

Presently, the FDA has approved INFUSE for use in certain tibial fractures and oral maxillary procedures, along with specific ALIFs with the LT Cage at L2–S1 levels.

Composition of INFUSE

INFUSE consists of two parts. The first is a solution comprised of rhBMP-2 and an absorbable collagen sponge (ACS). The INFUSE protein, a genetically engineered variant, stimulates bone formation. At surgery, the collagen sponge (bovine product consisting of type I collagen which resorbs over time) is impregnated with rhBMP-2, with the latter functioning as a scaffold for new bone formation.

FDA Approval only for ALIF with INFUSE and LT Cage

INFUSE and the LT Cage were originally devised for adult anterior spinal fusions. The combined device is FDA approved for single-level use in the anterior lumbar spine (ALIF) for degenerative disc disease, grade I spondylolisthesis, and/or retrolisthesis at the L2–S1 level. Advantages of this device include avoiding the need for obtaining autograft bone (e.g., iliac crest), shorter surgical procedures (reduced morbidity), and smaller incisions. It may be utilized in patients who have failed, 6 months of conservative, nonsurgical treatment. The surgical

procedure may be performed either “open” or minimally invasively (laparoscopic technique).

“Off-Label” Uses of INFUSE

Although INFUSE is FDA approved for use with the LT Cage to perform ALIFs, it is predominantly utilized “off-label” to perform other types of anterior and/or posterior spinal operations. In the cervical spine, it has been utilized to perform anterior (single or multilevel anterior discectomy/fusion, or anterior corpectomy/fusion) or posterior fusions (fusions with or without laminectomy/decompression). Similarly, anterior and posterior thoracic procedures have utilized INFUSE. The most common “off-label” use is in the posterior lumbar spine where it is utilized to perform posterior lumbar interbody fusions (PLIFs) or transforaminal interbody fusions (TLIFs). INFUSE's utility is predominantly attributed to its ability to enhance fusion rates, decrease the length of some surgeries, and potentially decrease the length of hospital stay. Nevertheless, more data are needed to allow for a more careful consideration of the pros and cons of utilizing INFUSE.

Contraindications for INFUSE

There are multiple contraindications associated with utilizing INFUSE and the LT Cage. Contraindications include pregnancy or in someone who will become pregnant, a history of sensitivity to titanium alloy, allergy to bovine type I collagen, or recombinant human rhBMP-2, infection, tumor, or where bones are not mature (still growing). It is also contraindicated in patients with liver or kidney disease, in those with osteoporosis or metabolic bone disorders, in immunosuppressed patients including those with autoimmune disease (e.g., Lupus, HIV/AIDS), and in those receiving radiation, chemotherapy, or steroids.

Summary of Complications Reported with INFUSE/LT Cage

There are multiple complications reported in conjunction with the application of INFUSE and the LT Cage. Complications include exuberant bone formation at the site of implantation or ectopic bone formation at the site of original insertion/application. Other complications include bending, breakage, loosening, and/or migration of the implant, failure to fuse, paralysis and/or other neurological complications (spinal cord, nerve damage), dural tears, bowel, bladder, and sexual dysfunction, respiratory failure, gastrointestinal problems, damage to adjacent tissues (inflammatory response/swelling), death, fetal developmental complications, scar formation, bleeding which may warrant transfusions, and vascular problems excluding bleeding.

RESULTS

Cons for INFUSE in Cervical Spine Surgery: A

Literature Review

The increased risks associated with utilizing INFUSE for anterior cervical spine surgeries are well publicized. One study systemically assessed 240 articles written between 1990 and 2009 on utilizing INFUSE for cervical, thoracic, and lumbar surgery; only 31 were adequate for inclusion.^[9] In the anterior cervical studies in which INFUSE was utilized as an “off-label” device, there was a 5.8% incidence of postoperative soft tissue swelling/dysphagia. In another retrospective study (2004–2009), clinical outcomes and fusion rates were compared for 260 patients undergoing anterior cervical surgery with INFUSE versus 515 (control) anterior procedures performed without INFUSE.^[15] Complications associated with INFUSE included a significant increase in the length of stay (LOS), hospital charges, airway-related complications e.g., airway obstruction, reintubation/unplanned postoperatively, tracheotomies, ICU admissions, hoarseness, dyspnea, respiratory failure, dysphagia, readmission, and the need to perform percutaneous gastrostomies (PEG). In particular, acute airway obstruction was attributed to marked soft tissue inflammation/swelling occurring between postoperative days 2 and 7, resulting in a marked increase in unplanned intubations and tracheotomies. The authors concluded, therefore, that INFUSE in anterior cervical surgery posed an unacceptable risk to respiratory function.^[15]

In another retrospective anterior cervical study, 35 (23.2%) of 151 patients undergoing anterior discectomy and fusion (138) or anterior corpectomy and fusion (13) developed complications attributed to INFUSE (2003–2004).^[12] Complications included 15 hematomas, 11 of which required surgical removal on postoperative days 4 or 5. Thirteen additional patients required prolonged hospital stays of greater than 48 h or hospital readmission addressing swallowing/breathing problems, or marked swelling without focal hematomas. The authors also concluded that high-dose INFUSE, when utilized during anterior cervical spine surgery, contributed to high complication rates attributed to its generalized inflammatory effect (spread to adjacent structures, increased perioperative complications/morbidity). The authors recommended that the indications for using INFUSE during anterior cervical surgery be reassessed to determine whether it is safe in this location: at what dose, and with what morbidity.^[12]

One case study reported postoperative neurological deterioration attributed to a massive seroma (severe inflammatory response) attributed to INFUSE utilized to perform a posterior occipital/cervical fusion.^[11] A 53-year-old patient, following removal of the resultant seroma, exhibited only a partial recovery. Again, the authors questioned whether INFUSE should be utilized in the posterior cervical spine, and at what dose. They also queried whether surgeons should avoid direct exposure of

paraspinal muscles to INFUSE, and whether prolonged drainage is required where such exposure occurs. Furthermore, they recommended the use of steroids to reduce INFUSE’s inflammatory response.^[11] A combined use of prolonged drainage and steroids, however, may lead to an increased risk of infection.

Cons for INFUSE in Lumbar Spine Surgery

The “off-label” use of INFUSE for lumbar surgery is the most prevalent (compared with cervical or thoracic surgery), and complications (cons) occurring following PLIF and TLIF procedures have become more recognizable. A review of multiple articles regarding the use of INFUSE in the lumbar spine revealed that its “off-label” use with the interbody cage contributed to a 44% resorption rate, a 25% subsidence rate, and a 27% incidence of cage migration.^[9] Another report cited two cases of vertebral osteolysis (bone resorption) following TLIF procedures, likely attributed to a high concentration of INFUSE and/or a violation of the end plates with subchondral cysts.^[11] The third study cited five cases in which INFUSE was utilized “off-label” to perform PLIF and TLIF procedures where new neurological deficits were attributed to significant ectopic bone formation within the spinal canal.^[14] Furthermore, revision surgeries were substantially more “difficult” due to the prolific ectopic ossification attributed to INFUSE. The authors ultimately questioned the relative safety of INFUSE in posterior lumbar spine surgery. In the fourth study, INFUSE was utilized to perform 36 levels of instrumented lumbar fusions (30 patients); surgical procedures included 4 PLIFs and 32 TLIFs.^[8] Interbody spacers were filled with a combination of local autograft and low-dose BMP-2 (1.4 mg/level). This resulted in 33 fusions within an average of 7.1 months, and 2 partial fusions at 6 months (fused by 12 months). However, 5 (16.6%) complications occurred in the 30 patients; 1 nonunion at 12 months (vertebral body osteolysis), 2 “asymptomatic” heterotopic ossifications, and 2 perineural cysts (1 required secondary surgery for revision of the interbody cage). The authors concluded that INFUSE when used for minimally invasive lumbar surgery resulted in a high rate of early fusion but that even “very low dose” BMP resulted in several complications. In the fifth study, complications were assessed up to 3 months following 204 TLIFs performed with INFUSE.^[10] Complications occurred in 47 of 204 (21.6%) patients. Major complications were observed in 13 (6.4%) patients who developed new postoperative neurological deficits. Six of these patients required second operations to address: one poor screw placement, one epidural clot, and four seromas/hematomas. Persistent radiculopathy was noted in six other patients. One patient with vertebral osteolysis resulting in foraminal narrowing/radiculopathy was treated non-surgically. Wound complications were also seen in 6 (2.9%) patients; wound

infection was seen in 3 patients, hematoma/seroma in 1, and persistent drainage/dehiscence in 2 patients. More minor complications were observed in 34 (16.7%) patients.^[10] In the sixth study, a case report, a 55-year-old male underwent a 360° circumferential T8-pelvis fusion for degenerative lumbar disease that utilized multiple units (high dose) of INFUSE.^[4] Several months later, he presented with weight loss, pain, and a solid abdominal mass. On the abdominal CT, ectopic bone growth within the retroperitoneum, contiguous with the original anterior exposure, was found. This specific complication was attributed to the use of “multiple” packages of BMP (INFUSE).

PROS of INFUSE Lumbar Fusions

Multiple reports cite the attributes (pros) of utilizing INFUSE to perform spinal surgery. A prospective, non-blinded, multicenter study involved 46 patients undergoing single-level anterior lumbar discectomy and interbody fusion with INFUSE (ALIF) utilizing allograft bone dowels (other studies used the LT Cages).^[2] Patients were randomized to receive either allograft with INFUSE or allograft with autogenous iliac bone graft (ICBG). Outcomes were assessed utilizing questionnaires, while the fusion was documented with dynamic X-rays and CT scans obtained up to 24 months postoperatively. INFUSE effectively decreased pain, improved outcomes, and contributed to 100% fusion rates compared with lesser outcomes and a reduced fusion rate with ICBG. In another study, complications were assessed (medical records 2003–2006) for a consecutive series of 1037 patients undergoing posterolateral lumbar fusion utilizing INFUSE.^[7] Complications occurred in 190 of 1037 procedures (18.3%): 81 were major (7.8%), while 110 were minor (10.2%). Neurological complications were due to screw positioning (six patients), epidural clots (three patients), new radiculopathy (seven patients), and psoas clots (eight patients documented on CT). Complications directly attributed to INFUSE occurred in 6 (0.6%) patients. Although they concluded that INFUSE was relatively safe and effective in lumbar posterolateral fusion, they readily conceded the marked complications cited for INFUSE in the anterior cervical spine. In a CT-based study, fusion rates of 97.2% were achieved for instrumented one- and two-level posterolateral fusions utilizing INFUSE (rhBMP-2 dose of 12 mg/1.5 mg/ml) with allograft, and lamina and spinous process autograft.^[13] One additional study found that the frequency of wound complications and anaphylaxis was not increased for 96 patients reexposed to INFUSE.^[3] Each patient had a minimum of two operations utilizing INFUSE. The first exposure to INFUSE resulted in 2 (2.1%) wound infections, and 9 minor wound problems without any allergic reactions. The second exposure included 5 (5.2%) wound infections, 11 minor wound problems, and no allergic resections. They concluded that

multiple exposures to INFUSE did not increase the risk of wound infection or allergic reactions.

Costs of INFUSE

Two studies have documented the cost-effectiveness of INFUSE in spinal surgery. In the first, a prospective randomized trial assessed the relative cost-effectiveness and efficacy of INFUSE bone graft (rhBMP-2/ACS: 50 patients) versus ICBG in 52 patients for lumbar fusions in patients over the age of 60.^[6] The Oswestry and SF-36 questionnaires were utilized to assess the outcome, while the fusion status was evaluated with CT scans postoperatively at 2 years. In-patient and out-patient costs were designated by a “dedicated hospital coder.” Interestingly, outcome questionnaires 2 years postoperatively showed nearly comparable results [Table 1]. However, the ICBG demonstrated 20 complications compared with the 8 seen with INFUSE; many of these were attributed to the iliac crest donor sites. Added treatment (16 ICBG patients versus 8 INFUSE), and revision surgery/pseudarthrosis (ICBG 8 reoperations, 5 for pseudarthrosis) versus 2 reoperations for INFUSE (1 with pseudarthrosis) were more typically warranted in the ICBG versus the INFUSE groups. Of interest, the costs at the first admission were nearly the same (ICBG = \$34,235 versus INFUSE = \$36,530), and the costs for second admission were nearly the same (ICBG = \$42,574 versus INFUSE = \$40,131). In

Table 1: Comparison of results for 2 years following fusions utilizing INFUSE versus iliac crest bone graft.^[6]

Variable	INFUSE (50 patients)	ICBG (52 Patients)
Number of patients	50	52
Outcome improvement		
Oswestry questionnaire	15.8	13
SF-36 questionnaire	6.6	7.5
Complications	8	20
Additional treatment	10	16
Revision surgery	2	8
Pseudarthrosis	1	5
Cost of the first admission	\$36,530	\$34,235
Cost of the second admission	\$40,131	\$42,574

Table 2: The perioperative cost of the INFUSE bone graft in posterolateral lumbar spine fusions^[5]

	INFUSE	(50 patients)Iliac crest bone graft (ICBG; 52 patients)
Cost of the first admission	\$24,736	\$21,138
Physician/medical doctor costs	\$5,082	\$5,316
Post-hospital-rehabilitation costs	\$4,906	\$6,820
Total cost up to 3 months postoperatively	\$33,860	\$37,227

the second study, the same authors concluded that the hospital carries the cost burden for using INFUSE in lumbar fusions, but savings include decreased payment for in-patient rehabilitation, hospital reimbursement by decreasing the LOS, physician costs, and outpatient services; [Table 2].^[5] The cost for the first admission was greater for INFUSE (\$24,736) versus ICBG (\$21,138). However, all other costs were greater for the ICBG versus the INFUSE populations: physician costs (\$5316 versus \$5082), postoperative hospital rehabilitation (\$6820 versus \$4906), and total combined costs up to 3 months following the surgery (\$37,227 versus \$33,860).

CONCLUSION

Medicare and other insurers are increasingly not reimbursing institutions for the “off-label” use of INFUSE in spine surgery. Where, when, and how INFUSE is utilized in the future will have to depend on a reexamination of the indications, efficacy, and safety of its use, and its cost to the hospital, typically \$5000–6000 (without overhead).

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