The First 18 Months Following Food and Drug Administration Approval of Lumbar Total Disc Replacement in the United States: Reported Adverse Events Outside an Investigational Device Exemption Study Environment

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ABSTRACT

Background

Introduction of a new surgical technology may result in higher rates of adverse events compared with rates reported in the study performed to gain regulatory approval. The purpose of our study was to describe the incidence of reported adverse events during the first 18 months following US Food and Drug Administration (FDA) approval of the first lumbar arthroplasty device available in the United States and to discern data trends.

Methods

Reports of adverse events submitted to the FDA in patients receiving the Charité artificial disc were reviewed and pooled by similarity. We analyzed 135 medical device reports filed with the FDA regarding the Charité artificial disc between October 26, 2004, and April 26, 2006. Sixteen reports were excluded for lack of information regarding cause or because described events were vague or unrelated to the procedure.

Results

Rate of adverse events reported to the FDA as a percentage of devices of which the device manufacturer was aware had been dispensed at 6, 12, and 18 months following approval was 0.58%, 2.34%, and 2.13%, respectively. The adverse event reported most frequently through 18 months was anterior migration with reoperation (0.65%); other reported adverse events were, in decreasing order, sizing and malposition errors resulting in reoperation (0.36%), posterior element fracture resulting in reoperation (0.30%), major vascular injury requiring a blood transfusion (0.23%), and subsidence requiring reoperation (0.20%). Three non–device-related patient deaths were reported following FDA approval. The reported rate of sizing/malposition errors leading to reoperation of 0.36% was the same rate as that seen in the investigational device exemption (IDE) study of the Charité artificial disc. All other reported rates were lower than rates of the same events reported in the study.

Conclusions

Medical device reporting is an important yet highly anecdotal and incomplete event-tracking process. However, it is the principal means available in the United States for obtaining information on the clinical performance of a device after its approval for sale and does provide some data, albeit imperfect, in this regard. The cumulative medical device reports through the 18 months following FDA approval, measured against the number of devices dispensed, suggests a rate of adverse events that either tracks or is somewhat less than that reported in the IDE study. This suggests that a repeat of the "cage rage," a "lumbar arthroplasty rage," has not yet occurred.

Key Words lumbar arthroplasty, total disc replacement, adverse events, complications. ***SAS Journal.*** **Winter 2007; 1; 8–11.** DOI: SASJ-2006-0001-RR

INTRODUCTION

New medical technology, particularly new surgical technology, may yield higher rates of complications or adverse events in its initial use beyond controlled studies. The most recent example of this phenomenon in spine surgery is the "cage rage" of the late 1990s, during which adverse events and outcomes did not match the results of the investigational device exemption (IDE) study leading to regulatory approval. In general, randomized, controlled, multicenter studies of a new surgical device are performed by investigators with a high level of knowledge, experience, and technical expertise. Indications and contraindications for the device are strictly adhered to as described in study protocols. Rates for the

most common adverse events in US Food and Drug Administration (FDA)–regulated studies are generally included in peer-reviewed publications and are additionally available from the FDA[1] through the Freedom of Information Act.

Following regulatory approval and introduction of a new surgical device to the market, the environment in which the device is used is of necessity less well controlled than during its premarket evaluation process. The Charité artificial disc (DePuy Spine, Raynham, Mass) was the first FDA-approved artificial disc prosthesis for the treatment of lumbar degenerative disc disease. The approved indications are specific to treatment at 1 level, either the L4-5 or the L5-S1 disc. The purpose of our study was to determine the incidence of adverse events reported to the FDA following approval of the device and to attempt to discern whether these data provided new or additional information about the device's performance.

MATERIALS AND METHODS

FDA regulations stipulate that any medical device manufacturer must report to the FDA within 30 days[2] all known deaths or serious injuries that come to its attention and are associated with use of the medical device in question. This process depends in large measure on input from surgeons and hospitals as well as from sales distributors and representatives. The medical device reporting process is exempt from the protected health information provisions of the Health Insurance Portability and Accounting Act (HIPAA), but this fact is not widely known.

Reports submitted to the FDA of adverse events in patients receiving the Charité artificial disc were reviewed and pooled by similarity. We reviewed reports for the first 18 months following FDA approval of the device (October 26, 2004–April 26, 2006) and divided these reports by time frame into 3 groups: 0 to 6 months, 6 to 12 months, and 12 to 18 months postapproval. The manufacturer shared information with us about the number of devices implanted for each time frame. The number of devices implanted was based on the number of devices shipped as replacements for used devices, not the total number of devices shipped and does not include initial sets of implants shipped to hospitals. This provides a strong approximation of the number of devices actually implanted. The policy of DePuy Spine is to report all known reoperations following implantation of the Charité artificial disc, even when the implanting surgeon stated that the reoperation had nothing to do with the device or its design.

We identified a total of 135 reports. Of these, 16 were excluded because they contained insufficient information to categorize the event reported or because the reports described events that were thought to be vague or completely unrelated to the surgical procedure, such as "patient has osteoporosis following disc replacement surgery."

STATISTICAL METHODS

Statistical comparisons were not performed. We report only unadjusted percentages, obtained by dividing the number of adverse events by the approximate number of devices implanted as described.

RESULTS

The rate of reported adverse events was 0.58% (10 of 1714) in the 0- to 6-month time frame and increased to 2.34% (95 of 4055) cumulatively at 12 months but remained steady at 2.13% (119 of 5575) cumulatively at 18 months. Specific event rates are detailed in Table 1, which contains rates of each event type divided cumulatively by time frame.

Between 0 and 6 months following approval, the rate of reported adverse events was 0.58% (10 of 1714). Between 6 and 12 months, the rate of reported adverse events was 3.63% (85 of 2341). Between 12 and 18 months, that rate decreased by more than half to 1.58% (24 of 1520). The adverse event most frequently reported through 18 months was anterior migration with reoperation (0.65%; 36 of 5575). Sizing and malposition errors resulting in reoperation were reported to have occurred in 20 cases (0.36%), and 17 cases (0.30%) of posterior element fracture resulting in reoperation were reported. A major vascular injury requiring a blood transfusion was reported to have occurred in 13 cases (0.23%). Subsidence requiring reoperation was reported to have occurred in 11 cases (0.20%). All other reported events numbered fewer than 10.

Following FDA approval, 3 patient deaths occurred, each of which appeared to be unrelated to the device. These patients died because of a confirmed or suspected pulmonary embolus, which was presumably caused in part by the anterior approach. One patient died in the hospital 2 days after surgery of a suspected pulmonary embolus, but the family refused to allow an autopsy. One patient slipped on a ground-level object and fell. A revision procedure was performed. The patient developed a pulmonary embolus 2 days after the revision procedure and later died. The third patient was turned in bed by a nurse following surgery and died from a subsequent pulmonary embolus. No known device-related deaths have occurred since FDA approval.

Table 1 contains the reoperation rates at each time point. The cumulative rate of reported reoperations through 18 months was 1.61% (90 of 5575), which was lower than the rate of reoperations in the IDE study3 of 5.43% (15 of 276). The rate of reported reoperations from 0 to 6 months was 0.35% (6 of 1714). From 6 to 12 months, the reported reoperation rate increased to 2.61% (61 of 2341) but decreased from 12 to 18 months to a rate of 1.51% (23 of 1520).

Table 1

Postapproval Key Adverse Events and Overall Reoperation Rates Compared With the Investigational Device Exemption (IDE) Study

	6 mos Post-FDA Approval (N = 1714)	12 mos Post-FDA Approval (N = 4055) (Cumulative)	18 mos Post-FDA Approval (N = 5575) (Cumulative)	IDE Study (N = 276)
Adverse event, n (%)				
Anterior migration with reoperation	1 (0.06)	28 (0.69)	36 (0.65)	3 (1.09)
Sizing/malposition with reoperation	2 (0.12)	18 (0.44)	20 (0.36)	1 (0.36)
Bone fragment with reoperation	0	2 (0.05)	2 (0.04)	0
End plate fracture	1 (0.06)	6 (0.15)	6 (0.11)	0
Posterior element fracture with reoperation	1 (0.06)	12 (0.30)	17 (0.30)	5 (1.81)
Subsidence with reoperation	1 (0.06)	5 (0.12)	11 (0.20)	0
Posterior migration with reoperation	1 (0.06)	2 (0.05)	4 (0.07)	0
Major vascular injury requiring transfusion	2 (0.12)	13 (0.32)	13 (0.23)	1 (0.36)
Major neurological[a]	0	5 (0.12)	5 (0.09)	13 (4.71)
Deep wound infection	0	2 (0.05)	2 (0.04)	0
Death	1 (0.06)	2 (0.05)	3 (0.05)	1 (0.36)
Total	**10 (0.58)**	**95 (2.34)**	**119 (2.13)**	**24 (8.70)**
Overall reoperations, n (%)				
Reoperations, 360-degree revisions, and off-label reoperations	6 (0.35)	67 (1.65)	90 (1.61)	15 (5.43)

Note. FDA = Food and Drug Administration.

[a]As described by Geisler et al.[4]

DISCUSSION

The overall rate of adverse events at 2.13% compares favorably with the overall rate of the same events reported in the Charité artificial disc IDE study (8.70%),[3,4] although such a comparison should be made with caution. Data generated from the medical device reporting process is highly anecdotal, and even though the process is compulsory for industry, no evidence exists as to the completeness of these data or regarding the statistical reliability of data derived from medical device reports. Statistical analyses other than those basic propositions reported here were not performed for this reason. In August 2004, however, the manufacturer retained an independent contractor to perform a limited surgeon survey to derive some further information as to the completeness and reliability of the medical device reports discussed herein. The surgeon survey, encompassing 30% of the Charité cases performed to that time, did not detect higher rates of events than were already being reported (Richard Toselli, MD, DePuy Spine; personal communication).

In cases without reoperation, only the treating physician is likely to be aware of the adverse event and serves as the sole source for filing a medical device report. In cases with adverse events requiring reoperation, the 2 possible medical device reporting sources are the treating physician and the sales representative, who usually would be present during the reoperation procedure. Given these facts and the anecdotal nature of the reporting process, events without a reoperation may be underreported. By contrast, events with a reoperation and 2 sources for reporting the event are less likely to be underreported.

As previously stated, the study methodology had significant limitations. The study was retrospective. Reports were often incomplete. Follow-up calls to individual surgeons for more details about specific cases were often unsatisfactory, largely because of confusion about the issue of HIPAA compliance, even though reporting of serious adverse events to industry and/or the FDA is exempt from HIPAA-related regulations.

Although the limitations as outlined clearly exist, some inferences from the data may be suggested. The overall reported rate of these adverse events was lower than the same events in patients receiving the Charité artificial disc in the IDE study, as was the reported reoperation rate. Investigational device exemption studies have strict adverse event reporting requirements, but those standards are not currently met post–regulatory approval. The IDE study results were reported up to 24 months, whereas this study reported events only to 18 months, and approximately 70% of the postapproval patients were not yet more than 1 year postsurgery. Given the decrease in overall reported events and reoperations in the 12- to 18-month time frame compared with the 6- to 12-month time frame, the overall rates probably would not increase significantly in this group of patients at 24 months.

It is unclear from the data whether the rate increase in reported events and reoperations from 6 to 12 months compared with 0 to 6 months was caused by increased

vigilance in reporting of events to the manufacturer and the FDA or by a "learning curve effect." If we assume the latter reason, the 6- to 12-month time frame could represent the point at which errors in patient selection or technique were more fully realized.

Sizing and malposition errors requiring reoperation had the same rate of reported events (n = 20, 0.36%) as in the IDE study (n = 1, 0.36%). All other reported events had lower rates than those reported in the IDE study. According to McAfee et al.,[5] placement of the Charité artificial disc greater than 5 mm in either plane was shown to generate a significantly poorer clinical outcome as measured by Oswestry Disability Index 2.06 (score 1–100) and Visual Analogue Scale pain scores (score 1–100). Placement of the prosthesis outside of the annulus laterally is a clear indication for revision. However, given the small number of patients in the IDE study, follow-up on more patients and for a longer term is necessary to identify the threshold of malposition inside the annulus that would indicate need for revision. It is unclear from the filed reports whether errors of malposition necessitated revision.

As a condition of FDA approval, the manufacturer was required to provide training on the device. The manufacturer developed a 1.5-day course that included didactic sessions on the topics of FDA-approved indications, contraindications, clinical results, postoperative care, adverse events, and case reviews. A surgical technique hands-on session was also part of this program. More than 3000 surgeons have completed the course since FDA approval. Researchers cannot properly quantify the effect of this training on adverse events because no spinal device with a similar surgical history, without training, exists that allows a comparison. However, we believe that the training program may have played some role in avoiding the problems of the past (thus far).

The overall reported rate of adverse events in the first 18 months following FDA approval of total disc replacement in the United States suggests that the data derived from the investigational device exemption study, on which the device labeling was based, remain supported by the ongoing clinical data. Even though the methodology available for this survey was limited, the data represent specific trends suggesting that a repeat of the "cage rage" has not occurred thus far with lumbar arthroplasty in the United States. We urge the spine surgeon community to continue to report serious adverse events to industry and the FDA so that our body of knowledge concerning this technology may continue to grow.

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