Evaluation of Interspinous Process Distraction Device (X-STOP) in a Representative Patient Cohort

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Key words
- Interspinous device
- Neurogenic intermittent claudication
- Spinal stenosis
- X-STOP

Abbreviations and Acronyms
FDA: Food and Drug Administration
IDE: Investigational Device Exemption
PF: Physical function
PS: Patient satisfaction
SS: Symptom severity
ZCQ: Zurich Claudication Questionnaire

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OBJECTIVE: **To test the hypothesis that the level of clinical efficacy reported in the investigational device exemption (IDE) study of the X-STOP device that led to its approval by the U.S. Food and Drug Administration could also be achieved in patients who are representative of the population approved for treatment, irrespective of whether they met all the stringent requirements of the IDE study.**

METHODS: **A retrospective analysis was conducted of a consecutive series of 31 patients who received the X-STOP interspinous process distraction device as treatment for neurogenic intermittent claudication. Outcome was assessed at an average of 2 years after surgery by use of the Zurich Claudication Questionnaire (ZCQ), which used the definition of clinical success used in the IDE study.**

RESULTS: **On the basis of the ZCQ, clinically significant improvement occurred in 38% of the evaluable patients (21 patients), compared with 48.4% in the IDE study; at the sites other than those of the device's inventors, the improvement level was 37%. Four patients needed additional surgery, which was a rate comparable with that reported in the IDE study.**

CONCLUSIONS: **The success level in the controlled IDE study that established the safety and efficacy of the X-STOP device was achieved in a representative patient cohort that did not necessarily meet all the strict requirements of the IDE plan. Nevertheless, the overall results were not good, suggesting that the ZCQ definition of success might not have captured the true outcome of surgical treatment with the X-STOP device.**

INTRODUCTION

Neurogenic intermittent claudication secondary to lumbar spinal stenosis is commonly manifested by lower back pain and/or weakness in the legs, with symptoms exacerbated by standing or lumbar extension and relieved by sitting or lumbar flexion (9). The pathophysiology of neurogenic intermittent claudication likely involves ischemia of the lumbrosacral nerve roots resulting from compression by surrounding structures (4, 8). Patients with symptomatic lumbar stenosis who do not respond to conservative treatments may be treated by surgical decompression. Another alternative is a titanium interspinous process distraction device that prevents extension and causes slight flexion between the stenosed lumbar vertebrae (X-STOP, St. Francis Medical Technologies, Inc., Alameda, California, USA).

The X-STOP device was approved by the U.S. Food and Drug Administration (FDA) on the basis of a multicenter investigational device exemption (IDE) study in which investigators reported improvement in function and lessening of symptoms at 2 years after implantation of the device (12, 15). Although the criteria for assessing clinical success differed somewhat between the IDE study (12) and the published report (15), both the FDA evaluation and the report concluded that device implantation was clinically successful. The IDE study had both detailed inclusion/exclusion criteria and strict reporting and monitoring requirements. Other studies of the X-STOP device have been published (2, 6, 10), but the question whether clinical success comparable with that achieved in the IDE study might also be obtained in a more representative patient cohort has not been directly addressed.

We tested the hypothesis that the reported level of clinical efficacy could also be achieved in patients representative of the population approved by the FDA for treatment, irrespective of whether the patients met all the stringent requirements of the original study. We accomplished this by analyzing a consecutive series of patients who had received the X-STOP device in accordance with the conditions listed in the device labeling.

METHODS

Patients

Patients who underwent X-STOP placement during 2006 and 2007 were studied. The patients received the device in accordance with its package insert information but not necessarily in accordance with all the inclusion/exclusion criteria stipulated in the original study (Table 1). The indications for use in our consecutive series were patients aged 59 or older who were experiencing neurogenic intermittent claudication secondary to radiologically confirmed diagnosis of lumbar spinal stenosis, who

SPINE

Table 1. Inclusion and Exclusion Criteria for the Original Study (12)

Inclusion
- 50 years or older
- Leg/buttock/groin pain, with or without back pain, that can be completely relieved by flexion such as when sitting in a chair. If back pain is also present, it must be partially relieved when flexed.
- Can sit for 50 minutes without pain
- Can walk 50 feet or more
- Narrowing of the lumbar spinal canal, nerve root canal or intervertebral foramen at 1 or 2 levels using CT scans and/or MRI where the area of spinal canal is 50% less when compared to segments above and below
- Has completed at least 6 months of conservative therapy, which may include physical therapy, bracing, systemic or injected medications
- Signed Patient Informed Consent document
- Physically and mentally willing and able to comply
- Lives in immediate area and has no plans to relocate to another geographic area before completion of the study, or lives outside the immediate area and will comply with the scheduled postoperative visits with a prearranged and designated physician

Exclusion
- Cannot sit for 50 minutes
- Cannot walk more than 50 feet
- Unremitting pain in any spinal position
- Axial back pain only without leg/buttock/ groin pain
- Fixed motor deficit
- Cauda equina syndrome defined as neural compression causing neurogenic bowel (rectal incontinence) or bladder (bladder retention or incontinence) dysfunction
- Severe symptomatic lumbar spinal stenosis at >2 levels
- Significant instability of the lumbar spine
- Has had any surgery of the lumbar spine
- Significant peripheral neuropathy
- Acute denervation secondary to radiculopathy
- Significant scoliosis (Cobb angle >25°)
- Significant peripheral vascular disease
- Spondylolisthesis >Grade 1 at affected level
- Sustained pathologic fractures of the vertebrae or multiple fractures of the vertebrae and/or hips
- Severe osteoporosis of the spine or hip (DEXA and NOF definition; BMD <2.5 SD below mean in the presence of one or more fragility fractures)
- Obesity (BMI >40 kg/m^2)
- Active systemic disease such as AIDS, HIV, hepatitis
- Active infection
- Angina, active rheumatoid arthritis, advanced diabetes, or systemic disease that would affect study outcome
- Paget's disease at involved segment or metastasis to the vertebrae
- History of narcotic abuse
- Allergy to any component of the device such as titanium
- Immunologically suppressed, or has received steroids at any dose daily for >1 month within last 12 months
- Involved in study of another investigational product
- Pregnant or planning to become pregnant

CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; NOF, National Osteoporosis Foundation; BMD, bone mineral density; SD, standard deviation; BMI, body mass index.

experienced pain relief in flexion, and who underwent at least 6 months of nonoperative treatment. The contraindications were spinal anatomy of disease that would prevent implantation of the device or cause the device to be unstable, cauda equina syndrome, severe osteoporosis in the spine or hip, systemic infection, or infection at the implantation site (12).

All patients had lumbar stenosis that was confirmed by magnetic resonance imaging and flexion-extension radiographs of the lumbar spine. Each patient had stenosis at only one level with pain that was relieved or decreased by sitting or by flexion of the lumbar spine. All patients had undergone conservative management that included nonsteroidal anti-inflammatory drugs, physical therapy, activity modification, and/or epidural steroid injections but with negligible benefit. The patients had no previous surgery on the lumbar spine and no more than grade one spondylolisthesis. The study was approved by the institutional review board for human research.

Surgery

Under mild intravenous sedation, the patient was placed in a flexed lateral decubitus position, and the location for X-STOP insertion was determined by the use of fluoroscopy. The overlying skin was infiltrated with lidocaine and epinephrine, and the skin was incised in the midline. The paraspinous muscles were elevated while the interspinous ligament was protected. A dilator was placed from one side of the interspinous ligament to the other, as close as possible to the lamina. After the ligament was pierced, a series of increasingly larger dilators were inserted to create an opening in the interspinous ligament. A sizing instrument with a gauge was then placed and distracted until the ligament was tight. After the device size was thus determined, the device was inserted and the locking wing was connected and locked. The wound was irrigated with antibiotic-containing saline and closed with absorbable sutures. Antibiotic was administered intravenously within 1 hour of making the skin incision, and at least three doses of antibiotic were given within 24 hours after surgery. The surgical technique was described in more detail elsewhere (14).

Outcome Assessment

The Zurich Claudication Questionnaire (ZCQ), which was completed by the patient during a visit to the clinic or by means of a telephone interview, was used to assess treatment outcome. The questionnaire consisted of 18 questions that relate to symptom severity (SS; seven questions), physical function (PF; five questions), and overall patient satisfaction (PS; six questions) (7, 11). SS questions were scored 1 to 5; those in the other two components of the test were scored from 1 to 4. The scores from each component were averaged. An average score of 1 was the best-possible score (no pain, no functional limitation, "very satisfied," in the respective components). The

ZCQ measure is reproducible, valid, and sensitive (11).

In the published study (15), the ZCQ data were evaluated various ways to address specific questions. In the IDE study, the primary outcome variable, called clinically significant improvement or clinical success, was defined as a PS score of less than 2.5 points and improvements of at least 0.5 points in both the SS and PF scores. After 2 years, the fraction of X-STOP patients who met the ZCQ criteria was 48.4%. Under the hypothesis that the results would be no worse in our patient sample, it can be shown that N = 31 patients is sufficient to test the hypothesis with a statistical power of about 80% (one-tailed test at a significance level of 5%) to detect a 25% decrease in the fraction of patient successes (48.4% down to 36.3%). The criteria for the power analyses were chosen arbitrarily. We recognized that any *a priori* calculation would be an overestimation because some patients would likely be lost to follow-up and/or not respond to treatment during the planned follow-up period, and that the use of a two-tailed test would result in a lower estimated statistical power. Nevertheless, relying on the power calculation solely as general guidance for the choice of the size of the patient series, a consecutive series of 31 patients who received the X-STOP device were enrolled in the study. As in the FDA study, the outcomes were evaluated 2 years after device implantation, on average, using the ZCQ criteria (12).

RESULTS

Of 31 patients enrolled in the study, 25 responded to the questionnaire, 3 of whom were excluded because of postsurgery morbidity that confounded the ZCQ data (two cases of trauma, one involving a stroke). One additional patient was excluded because of device failure that occurred too early in the study to provide useful data. In the remaining 21 patients, clinically significant improvement occurred in 8 patients (38%; Table 2).

One patient had a surgical complication that involved a superficial wound infection, which resolved with oral antibiotics with no further intervention. The device was removed from four patients; two had decompressive laminectomies and two had

Table 2. Two-Year Follow-Up Data from Patients Treated for Neurogenic Intermittent Claudication Using the X-STOP Device

Subject	Age (years)	Sex	Follow-Up Time (months)	Symptom Severity		Physical Function		Patient Satisfaction	ZCQ Success
				Before	After	Before	After		
1	65	F	22	3.6	3.3	1.6	1.6	3.8	No
2	75	F	24	3.3	3.0	2.0	1.8	1.8	No
3	57	M	15	4.0	1.0	3.4	1.2	1.2	Yes
4	71	F	30	4.2	3.7	2.4	1.6	2.2	Yes
5	70	F	16*	3.3	4.1	2.4	1.6	2.2	No
6	89	F	18	3.4	3.3	1.8	3.2	2.7	No
7	78	F	26	4.7	4.6	3.0	3.4	2.5	No
8	63	M	18*	4.1	3.9	3.2	2.8	3.2	No
9	78	M	27	3.1	3.1	1.2	3.0	3.3	No
10	83	M	23	3.4	3.3	3.4	3.6	3.8	No
11	71	M	25	3.0	3.4	2.2	3.6	2.5	No
12	59	F	18	3.0	1.9	2.0	1.0	1.0	Yes
13	76	M	27	2.9	2.9	2.0	2.0	3.5	No
14	78	F	27	3.4	1.0	3.4	1.0	1.0	Yes
15	75	F	20	2.3	2.3	3.2	3.2	2.3	No
16	80	F	27	3.6	1.9	1.2	1.2	1.5	Yes
17	79	F	26	4.1	2.3	2.4	2.8	2.2	No
18	81	F	27	3.3	1.9	2.0	1.2	1.7	Yes
19	70	M	25	3.4	1.0	3.2	1.0	1.0	Yes
20	69	F	26	3.4	1.7	3.0	2.4	1.3	Yes
21	77	F	33	2.1	2.1	3.0	3.2	2.5	No
Mean ± SD	73.5±8.0		23.8 ± 4.7	3.4 ± 0.6	2.6 ± 1.0	2.5 ± 0.7	2.2 ± 1.0	2.2 ± 0.9	

Outcome assessed by use of the indicated components of the Zurich Claudication Questionnaire (ZCQ). Spine level L4—5 except L3—4 in subjects 1, 5, 9, 18, 19, and L2—3 in subject 4.
*$P < 0.05$.

fusions. In the latter two patients, instability and epidural scarring was seen at the level where the device had been placed.

DISCUSSION

The X-STOP device was approved by the FDA after a randomized controlled study involving highly selected patients in which the primary outcome variable was clinically significant improvement, as assessed using the ZCQ (IDE study). The proportion of X-STOP patients in the IDE study who satisfied the ZCQ criteria was 48.4% (15). We addressed the question whether a similar level of success could be achieved in patients selected in accordance with the FDA-approved device labeling but who did not necessarily meet all the inclusion/exclusion criteria and patient-management conditions applied in the original study.

We found that 38% of the evaluable patients (8 of 21) exhibited clinically significant improvement as assessed on the basis of the ZCQ criteria (**Table 2**). There was a fairly high attrition rate. Of the 31 devices implanted, 25 responses were obtained, 3 of which were excluded. If it were assumed that all 9 nonresponses/exclusions were failures, then the ZCQ success rate would be 26% (8/31).

It could be argued that our lower success level (38% compared with 48.4%) was attributable to our less-restrictive inclusion/exclusion criteria, higher mean patient age, or smaller patient group. However, probably the better view is that our success level was materially identical to the original success level except for the influence of the unique skill of the inventor. When the patients in the IDE study who were enrolled at the sites of the device's inventors were excluded, the proportion of successful patients was 37% (12).

Evidence from published X-STOP studies not explicitly designed to evaluate the criticality of the FDA-IDE inclusion/exclusion criteria suggests that the ZCQ success rate varies depending on the relative mix of various uncontrolled factors in a particular study. In an evaluable group of 24 patients from a consecutive series of 37 patients, median age about 72 years, at 12 months the respective improvements in SS, PF, and PS were 54%, 33%, and 71%; the fraction of patients in which all three improvements occurred was not given but could not have been greater than 33% (10). In a consecutive series of 10 patients, mean age 71 years and mean follow-up time 11 months, the FDA clinical-success level was 20% (6). In a study involving 62 patients, mean age approximately 64 years, 31% had a good outcome on the basis of the ZCQ criteria (2). Overall, whether or not the stringent conditions from the original study were followed, the present evidence indicates that the ZCQ success level was 20% to 48.4%.

The randomized controlled IDE study that resulted in FDA approval of the X-STOP device reported that the SS component of the ZCQ score improved by 45.4% in the patients who received the device compared with 7.4% in the control group; the respective results for the PF ZCQ component were 44.3% and 0.4%. In other studies, authors also evaluated X-STOP outcome data in this manner (5). Nevertheless, comparisons of average values can sometimes be misleading because large improvements in only a few patients can markedly increase a group average. For this reason, the primary end point in the IDE plan was defined as the fractional number of patients who showed clinically significant improvement (12).

Defining a clinical success in terms of a particular numerical combination of values arbitrarily assigned to categorical ZCQ variables facilitated objective evaluation of the X-STOP group (12). At the level of an individual patient contemplating X-STOP surgery, a reasonable way of interpreting the reported range of the clinical success rate is that the patient has a 20% to 48.4% chance of some meaningful improvement in pain and/or function. However, several other important outcomes do not formally contribute to the interpretation, even though they are directly pertinent to a decision to use the device. One example is the occurrence of device failures necessitating its removal, the rate of which varied widely depending on the study (13). Device removal effectively lowers the estimated chance of success because it results in the omission of data from reoperated X-STOP patients (who obviously were not treated successfully).

Another important but unweighed outcome involves the complications associated with device removal (an event that merits consideration because the X-STOP device is labeled for use in patients as young as 50 years). Instability and/or scarring at the operative site may complicate or compromise any additional needed surgery. Finally, negative results and/or complications are probably underreported because of sampling bias (3). All these factors combine to suggest that even the modest 20% to 48.4% ZCQ success rate is probably an overestimation of the true clinical impact of the X-STOP device (1).

In summary, when using the FDA/ZCQ definition of clinical success, we achieved results in a representative patient cohort that were essentially the same as those found in the IDE study when the unique skill of the inventor was removed (12). Nevertheless, the overall clinical results were not good.

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LEGACY

Harvey Cushing's Early Treatment of Meningiomas: The Untold Story

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Key words
- Harvey Cushing
- Meningiomas

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BACKGROUND: **In his 1938 monograph, Cushing tabulated 313 meningioma cases treated throughout his career at the Johns Hopkins and the Peter Bent Brigham Hospitals. Of these, 18 patients were treated at the Johns Hopkins Hospital. Cushing provided basic demographic, perioperative, and outcomes data in his tables, but the operative details for many of his early meningioma cases have not been previously described.**

METHODS: **After institutional review board approval, and through the courtesy of the Alan Mason Chesney Archives, the surgical files for the Johns Hopkins Hospital from the period 1896 to 1912 were reviewed. Cases diagnosed as endothelioma or dural endothelioma were selected for further analysis.**

RESULTS: **Of the 14 patients with available records, 1 were male. The mean age was 34.4 years. Nine patients (64.3%) died during their inpatient stay. Cushing used staged resections in an attempt to minimize blood loss, morbidity, and mortality, albeit with limited success.**

CONCLUSIONS: **The operative details demonstrate Cushing's early attention to hemostasis, and use of staged resections in patients with large, highly vascular meningiomas. Cushing's first 18 cases of meningiomas, treated while a young attending physician at the Johns Hopkins Hospital, are not the most elegant operations in his lengthy series, but serve as an illustration of his ability to transform clinical challenges into opportunities for improvement.**

INTRODUCTION

During the 19h century, the nomenclature surrounding intracranial tumors, in particular meningiomas, was fraught with confusion; these tumors were referred to by a variety of terms, including tumeurs fongueuses, fungus durae matris, myeloid tumors, acervuloma, and tumeur fibroplastique (6). Virchow offered sarcoma and psammoma as alternate descriptions, whereas Golgi offered endothelioma as a compromise (6). However, the debate continued, with surgeons and pathologists from both sides of the Atlantic contributing potential terminology for these tumors, with the term meningioma being widely accepted, although it was already known that these tumors arose not from the meninges, but from "the cell clusters principally associated with the arachnoidal villi" (6).

Attempts were made to further subdivide these meningiomas, based largely on histopathologic appearance. Percival Bailey offered an elaborate subdivision: mesenchymatous, angioblastic, meningotheliomatous, psammomatous, osteoblatic, fibroblastic, melanoblastic, lipomatous, and generalized sarcomatosis of the meninges (2, 6). Harvey Cushing, in his 1938 monograph, offered a detailed description of meningiomas, dividing his case series into 29 distinct populations based on tumor location and behavior, with reference to histopathologic characteristics.

In this monograph, Cushing tabulated the 313 meningioma cases treated throughout his career at the Johns Hopkins