Cost-Effectiveness of Long-Term, Targeted OnabotulinumtoxinA versus Peripheral Trigger Site Deactivation Surgery for the Treatment of Refractory Migraine Headaches

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Background: Chronic migraines affect approximately 2 percent of the U.S. population and cost an estimated $17 billion per year. OnabotulinumtoxinA (botulinum toxin type A) is a U.S. Food and Drug Administration–approved prophylactic medication for chronic migraine headaches and is best injected in a targeted fashion into specific trigger sites. The purpose of this study was to determine the cost-effectiveness of long-term, targeted botulinum toxin type A versus peripheral trigger site deactivation surgery for the treatment of migraine headaches.
Methods: A Markov model was constructed to examine long-term, targeted botulinum toxin type A versus peripheral trigger site deactivation surgery. Costs, utilities, and other model inputs were identified from the literature. One-way and probabilistic sensitivity analyses were performed. An incremental cost-effectiveness ratio under $50,000 per quality-adjusted life-year was considered cost-effective.
Results: The mean cost of peripheral trigger site deactivation surgery was $10,303, with an effectiveness of 7.06; whereas the mean cost of long-term, targeted botulinum toxin type A was $36,071, with an effectiveness of 6.34. Trigger-site deactivation surgery is more effective and less costly over the time horizon of the model. One-way sensitivity analysis revealed that surgery is the most cost-effective treatment in patients requiring treatment for greater than 6.75 years.
Conclusions: Based on this model, peripheral trigger site deactivation surgery is the more cost-effective option for treating refractory migraine headaches requiring treatment beyond 6.75 years. The model reveals that peripheral trigger-site deactivation surgery is more effective and less costly than long-term, targeted botulinum toxin type A over the course of a patient's lifetime. (*Plast. Reconstr. Surg.* 145: 401e, 2020.)

Based on the International Headache Society classification system, chronic migraines are defined as 15 or more headache days per month for more than 3 months. Eight of these headaches must have features of migraine headaches.[1] Chronic migraine headaches affect approximately 1 to 3 percent of the world population (approximately 0.9 percent of U.S. adults) and significantly decrease quality of life.[2–4] Compared to episodic migraine patients, chronic migraine patients use more health care resources, resulting in higher direct cost and a higher indirect cost because of missed work days and decreased productivity.[5] The cost of treating migraine headaches in the United States is estimated at $17 billion per year.[6]

OnabotulinumtoxinA (botulinum toxin type A) is U.S. Food and Drug Administration–approved for the prophylactic treatment of chronic

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migraines. The original Phase III Research Evaluating Migraine Prophylaxis Therapy study, led by neurologists, used 155 U injected in 31 fixed predetermined injection sites over seven head and neck regions, with an additional 40 U injected into eight additional pain trigger sites at the clinician's discretion.[7,8] The proposed mechanism of this injection pattern relies on the theory that pain in migraine headaches is caused by overactivation of pain sensory fibers from intracranial and extracranial blood vessels.[9] It is postulated that botulinum toxin type A affects these pathways by down-regulating the peripheral release of pain mediators and proinflammatory neuromodulators such as glutamate, calcitonin gene-related peptide, substance P, cyclooxygenase 2, and transient receptor potential vanilloid 1.[10–15]

A newer, alternative theory postulates that migraine headache is caused by compression of peripheral nerves at specific trigger sites. This theory was proposed in 2000 by Guyuron et al. after patients who underwent corrugator supercilii resection for cosmetic brow lift reported improvement in migraine headaches.[16] The mechanism whereby peripheral trigger-site deactivation improves or eliminates migraine headaches is based on the physical elimination of trigger sites and is a well-established treatment modality; this procedure is also referred to as migraine surgery.[17–23] Botulinum toxin type A plays an important diagnostic and therapeutic role in migraine headache caused by peripheral trigger site compression. Patients who respond to targeted botulinum toxin type A injection are deemed operative candidates, as they have a high probability of successful trigger site deactivation and elimination of migraine headache.[24,25] In addition to its diagnostic value, botulinum toxin type A also has therapeutic efficacy; Janis et al. reported that botulinum toxin type A is a reasonable long-term treatment modality for patients who respond to targeted peripheral nerve injection (and who either do not want, or do not qualify for, surgery).[25] The targeted injection of botulinum toxin type A has a cost savings benefit, as it requires much smaller doses compared with the Phase III Research Evaluating Migraine Prophylaxis Therapy protocol.

In an era of cost-conscious health care, it is imperative that patients and health insurance providers be informed by evidence-based cost-effectiveness studies. No studies comparing the cost-effectiveness of long-term, targeted peripheral nerve botulinum toxin type A injection to peripheral trigger site deactivation surgery have been published to date.

PATIENTS AND METHODS

We developed a decision-analytic Markov model using TreeAge Pro 2019 software (TreeAge, Williamstown, Mass.) to perform cost-effectiveness analysis of long-term, targeted botulinum toxin type A injection versus peripheral trigger site deactivation surgery for migraine headache from the societal perspective. The model ran in 3-month cycles, reflecting the average duration of action of botulinum toxin type A for a time course of 37.6 years (113 cycles). This was based on mean lifespan (81.1 years) and age at presentation (43.5 years) for the average migraine headache patient.[25,26] The model reflected variable effectiveness for botulinum toxin type A and surgery with different response arms for each: 100 percent effective, 91 to 99 percent effective, 51 to 90 percent effective, 1 to 50 percent effective, and ineffective. For the botulinum toxin type A arm, patients were able to transition between response arms, accounting for the variability in botulinum toxin type A effectiveness between treatment cycles. Ten percent of patients who remained nonresponders to botulinum toxin type A after two cycles stopped botulinum toxin type A therapy and were removed from the model. Patients could not transition between botulinum toxin type A and surgery arms.

Variable definitions for response rates, adverse effects, and costs were determined based on reported rates in the literature. All costs were calculated in 2019 U.S. dollars. Cost-effectiveness was assessed by calculating the incremental cost-effectiveness ratio. We assumed a willingness-to-pay threshold of $50,000 per quality-adjusted life-year gained. We performed one-way sensitivity analyses to investigate the impact of different variables on the incremental cost-effectiveness ratio. We performed probabilistic sensitivity analysis, with 100,000 Monte Carlo simulations, to probe the effects of uncertainty in our variables and assumptions. Normal distributions for cost of surgery (mean, $10,000; SD, $3000), cost of botulinum toxin type A (mean, $624.44; SD, $100), and gamma distribution for number of migraine headaches days per month (mean, 14.0; SD, 3.1) were created for probabilistic sensitivity analysis.

RESULTS

The mean cost per patient undergoing peripheral trigger site deactivation surgery was found to be $10,303, with an effectiveness of 7.06. The mean cost per patient undergoing long-term, targeted botulinum toxin type A injection was calculated

to be $36,071, with an effectiveness of 6.34, yielding an incremental effectiveness of −0.72 quality-adjusted life-year. After 113 cycles, long-term, targeted botulinum toxin type A was dominated by surgery, meaning that botulinum toxin type A had higher cost and lower effectiveness compared with migraine surgery (Fig. 1). One-way sensitivity analysis revealed that migraine surgery became cost-effective after 27 cycles (6.75 years).

Probabilistic sensitivity analysis revealed the mean cost for peripheral trigger site deactivation surgery to be $10,311, with an effectiveness of 7.06. Mean cost for long-term, targeted botulinum toxin type A injection was calculated to be $36,004, with an effectiveness of 6.36. At a willingness-to-pay threshold of $50,000, migraine surgery was found to be cost-effective in 100 percent of cases because botulinum toxin type A is less effective and more costly compared with surgery. The cost-effectiveness scatterplot demonstrates the ranges in distribution between the two treatment arms (Fig. 2).

DISCUSSION

Two prior studies have investigated the economics of the surgical treatment of migraine headache and have similarly found that peripheral trigger site deactivation surgery is a cost-effective treatment option. Faber et al. calculated the long-term costs savings to society of the surgical treatment of migraine headache and found that, despite high up-front costs, the long-term benefits associated with surgery far outweigh the initial costs.[27] The study calculated direct and indirect costs savings after migraine surgery based on patient survey data and provided valuable information related to annual costs savings after peripheral trigger site deactivation surgery. However, it did not compare the cost of migraine surgery to other treatment options. Shauly et al. performed a cost-utility analysis of steroid and neurotoxin injection therapy versus migraine surgery for the treatment of chronic migraines, and found surgery to be the more cost-effective treatment option.[28] This study did not focus specifically on botulinum toxin type A injection therapy, as the analysis mostly included local anesthetic and steroid injections. In addition, it did not examine the costs related to long-term, targeted botulinum toxin type A injections, but rather relied on the more traditional and diffuse injection pattern. The study assumed a 100 percent surgical success rate, and relied on costs from a single academic institution rather than averaging costs across multiple sites. Lastly, this study did not use a Markov model or a probabilistic sensitivity analysis, limiting the generalizability of their results. Although the two aforementioned studies add to the body of literature demonstrating the economic benefits of peripheral trigger site deactivation surgery, they do not provide data directly comparing surgery to long-term, targeted botulinum toxin type A injections. Our study addresses this gap in the literature.

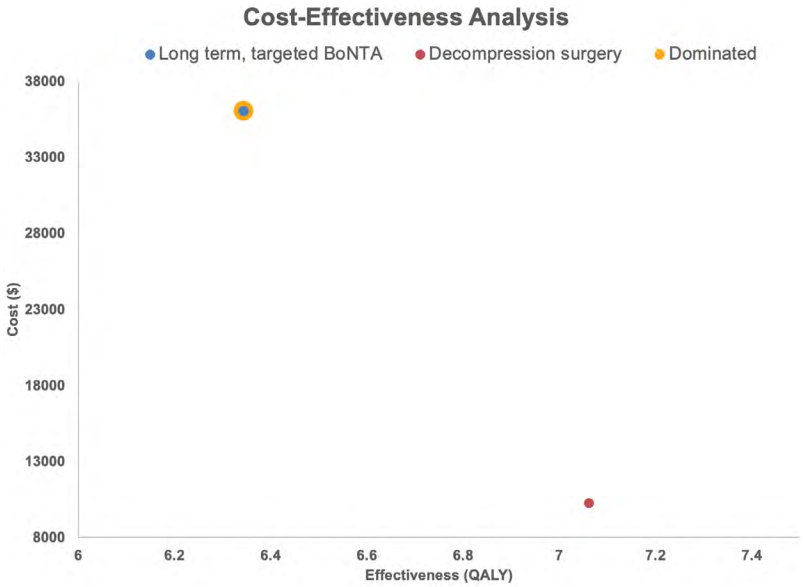

Fig. 1. Cost-effectiveness analysis. *Blue*, long-term, targeted botulinum toxin type A; *red*, trigger site deactivation surgery; *yellow*, dominated. *QALY*, quality-adjusted life-years.

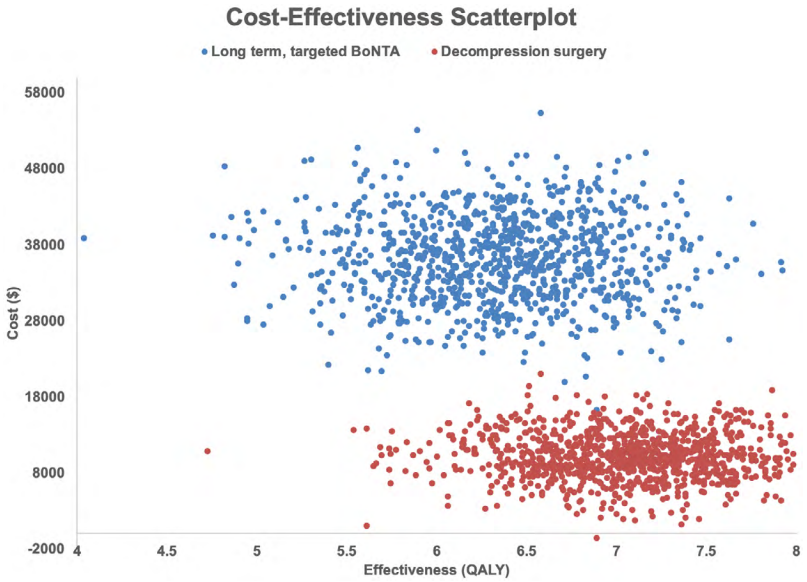

Fig. 2. Cost-effectiveness scatterplot. *Blue*, long-term, targeted botulinum toxin type A; *red*, trigger site deactivation surgery. *BoNTA*, botulinum toxin type A; *QALY*, quality-adjusted life-years.

Our study investigated the cost-effectiveness of long-term, targeted botulinum toxin type A injections versus migraine surgery for the treatment of chronic migraine headaches. Our study specifically analyzed the costs and benefits of targeted botulinum toxin type A injection rather than the higher dose Phase III Research Evaluating Migraine Prophylaxis Therapy protocol. The targeted botulinum toxin type A injection pattern uses 12.5 to 25 U per trigger site compared to 155 to 195 U based on the Phase III Research Evaluating Migraine Prophylaxis Therapy protocol; our study therefore grossly underestimates the cost of botulinum toxin type A for the general population, as most migraine patients receive the Phase III Research Evaluating Migraine Prophylaxis Therapy injection protocol. We chose to compare the targeted botulinum toxin type A injection pattern originally proposed by Behmand et al. and further described by Janis et al. to peripheral trigger site deactivation surgery because targeted botulinum toxin type A injection is based on the same anatomical and physiologic principles that underlie the efficacy of migraine surgery.[25,29]

Our analysis revealed that after 113 cycles (the average length of time from initiation of treatment to death for a migraine headache patient), peripheral trigger site deactivation surgery is the most cost-effective treatment option for migraine headache in 100 percent of cases. Our one-way sensitivity analysis showing that migraine surgery is more cost-effective after 27 cycles (6.75 years) gives a more nuanced description of the inflection point after which migraine surgery becomes cost-effective. This is because the high upfront cost of surgery is not surpassed by the cumulative cost of quarterly botulinum toxin type A injections until 27 treatment cycles. Therefore, in cases of refractory migraine headaches necessitating long-term treatment beyond 6.75 years, the cumulative cost associated with repeated botulinum toxin type A injections over a patient's lifetime far surpass the cost of surgery. In addition, our model did not account for indirect costs such as missed work, parking fees for doctors' appointments, childcare, or personal inconvenience associated with repeated doctors' visits. Including indirect costs into the model would have assuredly further increased the cost of long-term, targeted botulinum toxin type A. Overall, peripheral trigger site deactivation surgery is the most cost-effective treatment option for refractory migraine headaches in patients who are surgical candidates.

Peripheral trigger site deactivation surgery is a well-established treatment for migraine headaches.[17–23] Despite the body of literature demonstrating the safety and efficacy of peripheral trigger-site deactivation surgery for migraine headache, most major insurance companies do not cover surgical treatment for migraine headache because they deem this treatment to be "experimental and investigational."[30–34] Of note, some insurance carriers require a neurologist, ophthalmologist, pain specialist, or headache specialist to

inject botulinum toxin to be covered under their policies, precluding plastic surgeons from treating migraine headache patients with botulinum toxin type A.[35] In 2018, the American Society of Plastic Surgeons published a position statement summarizing the overwhelming evidence of the benefits of migraine surgery for migraine headache.[36] The position statement includes data from prospective and randomized controlled trials demonstrating the efficacy of trigger-site deactivation surgery, with the vast majority of patients experiencing great improvement or complete elimination of migraine headaches.[19,20,37,38] Based on this body of data, the American Society of Plastic Surgeons position paper states that surgery should not be considered "experimental," but rather a standard treatment option that should be integrated into the care model for refractory chronic migraine headaches. The results of our study add further support for this position, as migraine surgery is not only clinically efficacious, but cost-effective, as well.

The limitations of our study are based largely on the level of evidence of data from prior studies used to generate our model. We mitigated the effects of this with the probabilistic sensitivity analysis in which we varied the values for cost of surgery and botulinum toxin type A and the number of migraine headache days per month. In addition, the lack of universal inclusion criteria among the studies used for our model inputs limits the generalizability of our results. In particular, studies investigating the use of botulinum toxin type A are limited to patients who suffer from chronic migraines, whereas studies investigating peripheral trigger site deactivation surgery include patients who suffer from episodic and chronic migraines. In addition, we were not able to control for or exclude studies that included patients who suffer from rhinogenic migraine headaches; rhinogenic migraine headaches do not respond to botulinum toxin type A, whereas septoplasty and turbinate reduction have been shown to effectively address this trigger site.[21,39,40] This limitation was also addressed in the probabilistic sensitivity analysis in which we varied the number of migraine days per month and the effectiveness of botulinum toxin type A and surgery. Lastly, our model did not account for alternative treatments after surgical failure, as there is no consensus on management of recalcitrant migraine headaches after failed surgery; treatments range from reoperation to steroid injections to fat grafting.[41–43]

Our study adds to the growing body of literature that supports the use of peripheral trigger-site deactivation surgery for the treatment of migraine headache. Our study demonstrates that a single surgical intervention is more cost-effective over the course of a patient's lifetime than repeated lower cost botulinum toxin type A injections.

CONCLUSIONS

Peripheral trigger site deactivation surgery is more effective and less costly than botulinum toxin type A injections, and is the most cost-effective treatment for refractory migraine headaches requiring treatment for greater than 6.75 years. The cumulative costs and decreased benefits associated with botulinum toxin type A injections accrued over a patient's lifetime make this treatment modality significantly less cost-effective than migraine surgery. Peripheral trigger site deactivation surgery should be offered to patients who suffer from refractory migraine headaches who are deemed appropriate operative candidates.

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