Surgical Outcomes of Trigeminal Neuralgia in Patients With Multiple Sclerosis

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BACKGROUND: Trigeminal neuralgia (TN) is relatively frequent in multiple sclerosis (MS) patients and can be extremely disabling. Surgical interventions are less effective for the treatment of MS-related TN compared with classic TN, and higher recurrence rates are observed.

OBJECTIVE: To evaluate initial pain-free response (IPFR), duration of pain-free intervals (PFIs), and factors predictive of outcome in different surgical modalities used to treat MS-related TN.

METHODS: A total of 96 MS patients underwent 277 procedures (range, 1-11 procedures per patient) to treat TN at our institution from 1995 to 2011. Of these, 89 percutaneous retrogasserian glycerol rhizotomies, 82 balloon compressions, 52 stereotactic radiosurgeries, 28 peripheral neurectomies, 15 percutaneous radiofrequency rhizotomies, and 10 microvascular decompressions were performed as upfront or repeat treatments.

RESULTS: Bilateral pain was observed in 10% of patients during the course of disease. During the follow-up period (median, 5.7 years), recurrence of symptoms was seen in 66% of patients, and 181 procedures were performed for symptom recurrence. As an initial procedure, balloon compression had the highest IPFR (95%; $P = .006$) and median PFI (28 months; $P = .05$), followed by percutaneous retrogasserian glycerol rhizotomy (IPFR, 74%, $P = .04$; median PFI, 9 months; $P = .05$). In general, repeat procedures had lower effectiveness compared with initial procedures, with no statistically significant difference seen across the various treatment modalities.

CONCLUSION: Treatment failure occurs in most of the MS-related TN patients independently of the type of treatment. However, balloon compression had the highest rate of IPFR and PFI compared with other modalities in the initial treatment of MS-related TN.

KEY WORDS: Balloon compression, Glycerol rhizotomy, Microvascular decompression, Peripheral neurectomy, Stereotactic radiosurgery

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Trigeminal neuralgia (TN) is a relatively rare condition (3-27 cases/100 000 people) and is defined by paroxysmal electric shocklike painful attacks in 1 or more trigeminal nerve branches.[1-3] Overall, 2% to 8% of TN patients have a history of multiple sclerosis (MS), which is 20-fold higher than in the general population.[1,4-7]

ABBREVIATIONS: BC, balloon compression; **IPFR,** initial pain-free response; **MS,** multiple sclerosis; **MVD,** microvascular decompression; **PFI,** pain-free interval; **PN,** peripheral neurectomy; **PRGR,** percutaneous retrogasserian glycerol rhizotomy; **RFR,** percutaneous radiofrequency rhizotomy; **SRS,** stereotactic radiosurgery; **TN,** trigeminal neuralgia

Although the exact pathophysiology of TN in MS patients is unclear, several mechanisms have been proposed that are based on autopsy, surgical, and radiographic findings. The proposed mechanisms include peripheral demyelination, central plaques, and a mixed peripheral-central mechanism, including dual pathology of inflammatory demyelination resulting from MS plus mechanical demyelination caused by vascular compression.[4,8-15] On the other hand, neuropathic pain syndromes are common complications of MS, affecting >28% of MS patients.[7,16-18] The prevalence of TN in the MS population has been reported to be between 1% and 6.3% and can be extremely disabling for them.[5,6,16,19,20] There is a lifetime risk of 4% for MS patients to have TN, with no significant difference among the different forms of MS.[18]

Treatment of patients with MS-related TN begins with medical therapy. The medications used are the same as those for classic TN with comparable outcomes.[21-23] In terms of surgical treatments, no comprehensive study has evaluated the effectiveness of different surgical modalities in the treatment of MS-related TN.[22] In a few retrospective series with a small number of patients, the results were suboptimal.[22,24] A recently published literature analysis of surgical treatments of MS-related TN failed to show any differences in the short-term results of different procedures.[25] Outcomes of treatment in MS-related TN suggest higher recurrence rates and lower pain-free responses compared with classic TN regardless of treatment modality.[26-33]

In this study, we evaluated outcomes of different interventions for MS-related TN in terms of initial pain-free response (IPFR), pain-free interval (PFI), and complication rate after upfront or repeat procedures. We also evaluated the influence of independent prognostic factors on treatment outcomes. To the best of our knowledge, this is the largest series of surgical outcomes in MS-related TN.

MATERIALS AND METHODS

Study Design

A retrospective review was performed of patients who had a surgical intervention for MS-related TN at the Cleveland Clinic during a 16-year period (1995-2011).

Study Participants and Size

Patients were included in this study if they had a definitive diagnosis of MS, had at least 1 surgical intervention for TN during the study period, and were at least 18 years old. Any other procedures before the study period were also included in the study as long as the patient met the inclusion criteria. Patients were excluded if they had no follow-up after the procedure or had demyelinating plaques on magnetic resonance imaging (MRI) without a definitive diagnosis of MS by a neurologist. A total of 96 patients with 277 procedures were considered for the study. This study was approved by the Cleveland Clinic Institutional Review Board.

Study Setting

A brief description of surgical interventions used follows. Percutaneous balloon compression (BC) was performed under general anesthesia and under guidance of biplanar fluoroscopy (since 1997) by inflating a 4F Fogarty balloon catheter to 0.75 cm^3 for 60 seconds in the Meckel cave. For repeat procedures, the balloon inflation time was often extended by an additional 30 seconds for each previous BC procedure (eg, 120-second compression for the third BC procedure). Percutaneous retrogasserian glycerol rhizotomy (PRGR) was performed under general anesthesia by the injection of 0.5 cm^3 glycerol into the Meckel cave under fluoroscopic guidance. Stereotactic radiosurgery (SRS) was performed with the Gamma Knife model B, C, or 4C or Perfexion (Elekta AB, Stockholm, Sweden) by delivering a prescription dose of 75 to 86 Gy to the proximal trigeminal root. We used root entry zone as the primary target of SRS and more anteriorly in the course of the nerve in cases of redo SRS. Peripheral neurectomy (PN) was performed under general anesthesia with selective cutting of the peripheral branches of the trigeminal nerve. This procedure was performed only in those patients who had significant pain reduction after a nerve block trial in clinic. In a few cases, other methods were used, including microvascular decompression (MVD), percutaneous radiofrequency rhizotomy (RFR), and peripheral nerve stimulation. After the intervention, all patients were followed up for 1 to 2 months at regular intervals by a neurosurgeon and then by a neurologist for their TN and MS.

Variables

Demographic data of the patients, characteristics of the MS and TN, prior medical or surgical treatments for the TN, specifications of each treatment modality, and complications were collected for each patient.

Measurement

Treatment outcomes were defined as IPFR after each procedure (with or without medication) and PFI between procedures and treatment failure or last follow-up in patients who had no failure. We used these 2 measures instead of subjective percentage of pain reduction because we believed that they are probably far less influenced by cognitive factors than the subjective level of pain relief.

Bias

Upfront and repeat procedures were evaluated separately to eliminate the role of prior treatments. We also had selection bias of surgeon preference and expertise in specific treatment modalities. Most of the surgeries were performed by 2 senior authors. G.H.B. performed >130 procedures, including almost all of the BC and SRS procedures and some of the MVDs. J.H.L. performed >120 procedures, including almost all of the PRGRs and neurectomies and some of the MVDs. A few other procedures (20-30 procedures) were performed by other surgeons during the study period.

Statistical Methods

Categorical data were summarized as frequency counts and percentages; measured data were summarized as medians and ranges; and PFI was summarized with the Kaplan-Meier method. The Fisher exact test and χ^2 tests were used for univariable comparisons of IPFR between upfront treatments. The log-rank test was used for comparisons of PFI. Logistic regression models and generalized estimating equations were used for comparisons of IPFR in subsequent treatments to account for patients having multiple procedures. Similarly, the Anderson-Gill model was used for comparisons of PFI. All tests of statistical significance were 2 sided, and all analyses were performed with SAS version 9.2 (SAS Inc, Cary, North Carolina).

RESULTS

Participants

A total of 96 MS patients were treated with 277 surgical and radiosurgical procedures for their TN. The median follow-up after the initial procedure was 5.7 years (range, 2 months-16 years).

Descriptive Data

The majority of patients (60%) were female. The first symptom of MS presented at a median age of 33 years (range, 16-69 years), and the definitive diagnosis of MS was made at a median age of

38 years (range, 17-73 years). The median age at diagnosis of TN was 50 years (range, 28-79 years). The median interval between the first symptoms of MS to diagnosis of TN was 14 years (range, 0-42 years). In 10 patients (11%), TN was the first presentation of MS. The median interval between the definitive diagnosis of MS and diagnosis of TN was 11 years (range, 11 years before to 42 years after MS). In 11 patients, TN was diagnosed before definitive diagnosis of MS. Median Karnofsky Performance Score at the time of the initial intervention was 70 (range, 50-90) and at repeat intervention was 60 (range, 50-90).

MS Characteristics

At the time of initial treatment, 30 patients (31%) had relapsing remitting MS, 22 patients (23%) had primary progressive MS, 31 patients (32%) had secondary progressive MS, and 13 patients (14%) had relapsing progressive MS. During the study period, 4 patients advanced from relapsing remitting MS to secondary progressive (total of 36% secondary progressive). At time of initial treatment, 81 patients (84%) had MS symptoms. Hypoesthesia of the fifth nerve was observed in 5 patients (5%), and other cranial nerve involvement was seen in 24 patients (25%). Brainstem lesions on MRI were reported in 44 patients (47%). In addition, concurrent MS treatment was observed at the time of 151 procedures (55%), including disease-modifying drug in 95 cases (34%), cytotoxic treatment in 19 cases (7%), and steroid treatment in 27 cases (10%). No relationship between type of MS treatment and outcome of TN was observed. During initial treatment, 82 patients (85%) had MS-related disability, which was severe in 42 patients (44%). During repeat treatment, any disability was seen in 95% of cases, with severe disability in 52% (see Table1 for more details).

TABLE 1. Characteristics of Multiple Sclerosis and Trigeminal Neuralgia at the Time of the Initial Procedure and During Follow-up[a]

Factor	During Upfront Treatments, n (%)	During Follow-up, n (%)
MS type		
Relapsing remitting	30 (31)	26 (27)
Primary progressive	22 (23)	22 (23)
Secondary progressive	31 (32)	35 (36)
Relapsing progressive	13 (14)	13 (14)
MS symptoms		
Yes	81 (85)	86 (90)
MS disability		
None	14 (14)	8 (8)
Mild	40 (42)	40 (42)
Severe	42 (44)	48 (50)
TN type		
Typical (purely)	74 (77)	67 (70)
Typical with atypical features	19 (20)	22 (23)
Atypical (purely)	3 (3)	7 (7)
TN location		
Bilateral	4 (4)	10 (10)
Unilateral	92 (96)	86 (90)
V1	1 (1)	1 (1)
V2	19 (20)	13 (14)
V3	34 (35)	27 (28)
V1 + V2	4 (4)	5 (5)
V2 + V3	34 (35)	45 (47)
V1 + V2 + V3	4 (4)	5 (5)

[a]MS, multiple sclerosis; TN, trigeminal neuralgia.

TN Characteristics

At the time of the initial treatment, 74 patients (77%) presented with typical TN, 19 patients (20%) had typical lancinating pain and some atypical constant pain between attacks, and 3 patients (3%) had a purely atypical presentation. Unilateral pain was observed in 92 patients (96%), and 54 patients (56%) had involvement of only 1 trigeminal branch. During the course of the disease and after multiple treatments, an 8% increase was seen in patients having atypical pain (total of 29 patients with atypical features, 30%), a 6% increase in bilateral involvement (total of 10 patients with bilateral pain, 10%), and a 13% increase in multiple branch involvement of the trigeminal nerve (total of 55 patients with multiple branch involvement, 57%). In 20 patients (21%), possible vascular compression was reported on MRI scans (for more details, see Table 1).

Medical Treatment

All patients were initially started on medical treatment as monotherapy or multiple drug regimens. Carbamazepine was the most common medication, used in 75 patients (78%), followed by gabapentin (68 patients, 71%), baclofen (44 patients, 46%), and oxcarbazepine (22 patients, 23%). Initial response to medical treatment with subsequent unresponsiveness was observed in most patients (88 patients, 92%), but 8 patients (8%) were refractory to any medical treatments from the beginning. No correlation between initial response to treatment and better pain control after any specific type of surgery was detected.

Outcome Data

The median time from diagnosis of TN to initial intervention was 2.5 years (range, 0-20 years). Most patients had multiple procedures because of treatment failure as follows: 33 patients (34%) had just 1 procedure, 21 patients (22%) had 2 procedures, 13 patients (14%) had 3 procedures, 15 patients (16%) had 4 procedures, 2 patients (2%) had 5 procedures, 4 patients (4%) had 6 procedures, 3 patients (3%) had 7 procedures, 3 patients (3%) had 9 procedures, and 1 patient each had 10 and 11 procedures (Figure 1). In total, 277 procedures for either initial or repeat treatment were performed. PRGR was the most common intervention (89 procedures, 32%), followed by BC (82 procedures, 30%) and SRS (52 procedures, 19%). As the initial

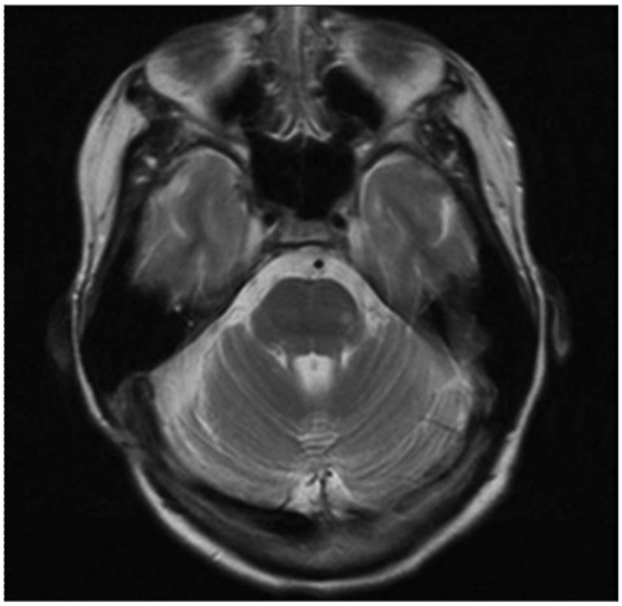

FIGURE 1. *A 63-year-old woman with relapsing remitting multiple sclerosis (MS), first diagnosed with medically refractory, right-sided typical trigeminal neuralgia (TN) treated with microvascular decompression. She came back 4 years later with left-sided TN with atypical features and brainstem plaque on magnetic resonance imaging (current image). Since then, she has been treated with total of 9 procedures for her left-sided TN (stereotactic radiosurgery, 1; percutaneous radiofrequency rhizotomy, 2; balloon compression, 6). The average pain-free interval was 5 months (range, 0-14 months). Such cases show that different forms of TN can occur in MS patients with different responses to treatment.*

intervention, PRGR was the most common (39 patients, 41%), followed by SRS (24 patients, 25%) and BC (19 patients, 20%). For repeat interventions, BC was the most common (63 procedures, 35%), followed by PRGR (50 procedures, 28%) and SRS (28 procedures, 15%).

Balloon Compression

Nineteen patients underwent BC as initial treatment (all with 60-second balloon inflation). IPFR was observed in 18 patients (95%) immediately after the procedure, with 11 (61%) experiencing pain recurrence after an estimated median of 29 months. Temporary numbness was reported in 10 patients (53%). There was 1 complication (5%) resulting in severe numbness, weakness of masticator muscles, and impaired corneal reflex.

In 32 patients, BC was performed 63 times as a repeat treatment (34 of them with 60 seconds, 17 with 90 seconds, 8 with 120 seconds, and 4 with 180 seconds of compression). In 21 patients (22%), >1 BC was performed (2-6 BC procedures per patient). IPFR was reported after 45 repeat BC procedures (71%), which occurred the same day of the procedure in 42 patients and within the first week after surgery in 3 patients. According to the duration of balloon inflation, IPFR occurred in 70% of the 60-second procedures, 67% of the 90-second procedures, 75% of the 120-second procedures, and 100% of the 180-second procedures (P = .38). There were 28 patients who had IPFR who had recurrent pain (62%) after an estimated median of 17 months. Temporary numbness was reported after 18 repeat procedures (29%). Seven patients had a complication after a repeat procedure as follows: carotid-cavernous fistula in 2 patients (both of whom were treated before the implementation of biplane fluoroscopy in 1997), subdural hematoma in 1 patient, and severe numbness of the face in 4 patients (3 with an abnormal corneal reflex and 2 with masticator muscle weakness). Overall, the complication rate of BC with 180 seconds of inflation time was 25% (severe numbness), with 90 seconds of inflation time was 6% (subdural hematoma), and with 60 seconds of inflation time was 15% (all other complications), with no statistically significant differences.

Stereotactic Radiosurgery

Twenty-four patients had SRS as initial treatment (8 with 75 Gy, 13 with 82 Gy, and 3 with 86 Gy). IPFR occurred in 12 patients (50%) after a median of 9 days (range, 1 day-4 months). No significant difference was observed in IPFR with different SRS doses (75-82 Gy). Eight patients (67%) with IPFR recurred after an estimated median of 23 months. No complications were observed after SRS as initial treatment.

In 22 patients, SRS was performed 28 times as a repeat treatment (12 with 75 Gy, 14 with 82 Gy, and 2 with 86 Gy). In 7 patients (7%), SRS was performed more than once (2-3 SRS treatments per patient). IPFR occurred in 17 procedures (61%) after a median of 20 days (range, 1 day-12 months) with no significant difference between different SRS doses. Among the 17 patients who had IPFR with SRS as a repeat treatment modality, recurrence occurred in 9 cases (53%) after an estimated median of 78 months. Complications occurred in 2 patients (7%), both of whom were treated with 75 Gy. The first patient had severe numbness and corneal reflex impairment, and the second patient had severe hyperesthesia after treatment. Of note, of all patients who had SRS treatment as a repeat procedure, IPFR was 87% in patients who had a prior SRS as an initial treatment, whereas IPFR was 50% in patients who had other initial treatment modalities, although this difference was statistically nonsignificant. The recurrence rate was similar in both the initial and repeat SRS groups (57% and 60%, respectively). No significant complications were reported in patients who had >1 SRS treatment.

Percutaneous Retrogasserian Glycerol Rhizotomy

Thirty-nine patients had PRGR as an initial treatment. IPFR was observed in 29 patients (74%) after PRGR, which occurred the same day of the procedure in 27 patients and within the next 2 weeks in 2 patients. Among the 29 patients with IPFR, recurrence occurred in 20 patients (69%) after an estimated median of 28 months. Temporary numbness occurred after 4 procedures (10%), and 1 patient (3%) had severe numbness with impaired corneal reflex.

PRGR was performed 50 times as a repeat treatment in 31 patients. Twenty-four patients (25%) had > 1 PRGR (2-6 PRGR treatments per patient). IPFR was observed after 35 procedures (70%). In 29 patients, IPFR happened the same day of the procedure and within the next month in 6 patients. Among the 50 repeat PRGR procedures, recurrence occurred after 33 procedures (66%) within a median of 12 months. Temporary numbness occurred after 9 procedures (18%). Complications occurred after 3 procedures (6%), which consisted of bacterial meningitis in 1 patient, chemical meningitis in 1 patient, and MS exacerbation in 1 patient.

Other Procedures

We performed PN in 2 patients as an initial treatment and 26 PNs in 12 patients as repeat treatments. In 9 patients (9%), >1 PN was performed (2-5 PN procedures per patient). IPFR was reported in 1 of the initial (50%) and 21 of the repeat PN procedures (81%), all on the same day as surgery. Recurrence occurred in the only patient with upfront PN, who had IPFR after 24 months, and in 14 cases of repeat PN (67%) after an estimated median of 12 months. Two complications of severe numbness were observed after PN.

Fifteen RFR procedures were performed, 7 as an initial treatment and 8 as a repeat procedure, in 6 patients. IPFR occurred the same day as surgery in 86% and 75% of patients, respectively. All patients who initially benefited for RFR recurred, with a median time to recurrence of 5 months with upfront treatment and 9 months with repeat treatment.

MVD was also performed in patients with possible vascular compression on preoperative imaging as initial treatment (5 patients) or repeat treatment (5 patients). IPFR was observed the same day as surgery in 2 patients (40%) who had MVD as an upfront treatment and in 4 patients (80%) who had MVD as a repeat treatment. One patient with IPFR after MVD as initial treatment recurred after 10 months, and all patients who had MVD as repeat treatment recurred after a median of 17 months. Complications included 1 case of bacterial meningitis (20%) after upfront MVD and 1 case of cerebrospinal fluid rhinorrhea (20%) after MVD as repeat treatment. Finally, we had 1 case of peripheral nerve stimulation as a repeat treatment for a patient experiencing insufficient pain control.

Main Results

Treatment failure of initial procedures (no IPFR or recurrence after IPFR) occurred after 12 BC (63%), 30 PRGR (77%), 20 SRS (83%), 4 MVD (80%), and all RFR and PN (100%) procedures. Median PFI was 29 months after BC procedures, 9 months after PRGR procedures, 4 months after SRS, and 1 month after all other procedures combined, which was statistically significant between BC and PRGR with other treatments (P = .05). In repeat procedures, treatment failure occurred in 47 BC (78%), 37 PRGR (77%), 20 SRS (71%), 19 PN (73%), and all MVD and RFR (100%) cases. Median PFI was 8 months after BC procedures, 9 months after PRGR procedures, 7 months after SRS, and 9 months after all other procedures (P = .19). Kaplan-Meier curves are shown in Figure 2. BC and PRGR tended to have shorter PFI when used as repeat therapies than when used upfront (P = .01 in both cases). In contrast, SRS as a secondary treatment trended toward a longer PFI than when used as upfront treatment (P = .11). In 4 of 11 patients with repeat SRS who had >1 year PFI, redo SRS had been performed after failure of prior SRS treatments. Median PFI in this group (redo SRS) was 36 months compared with 5 months in those who had redo SRS after other procedures, although this difference was statistically nonsignificant. Further intergroup comparison is detailed in Table 2.

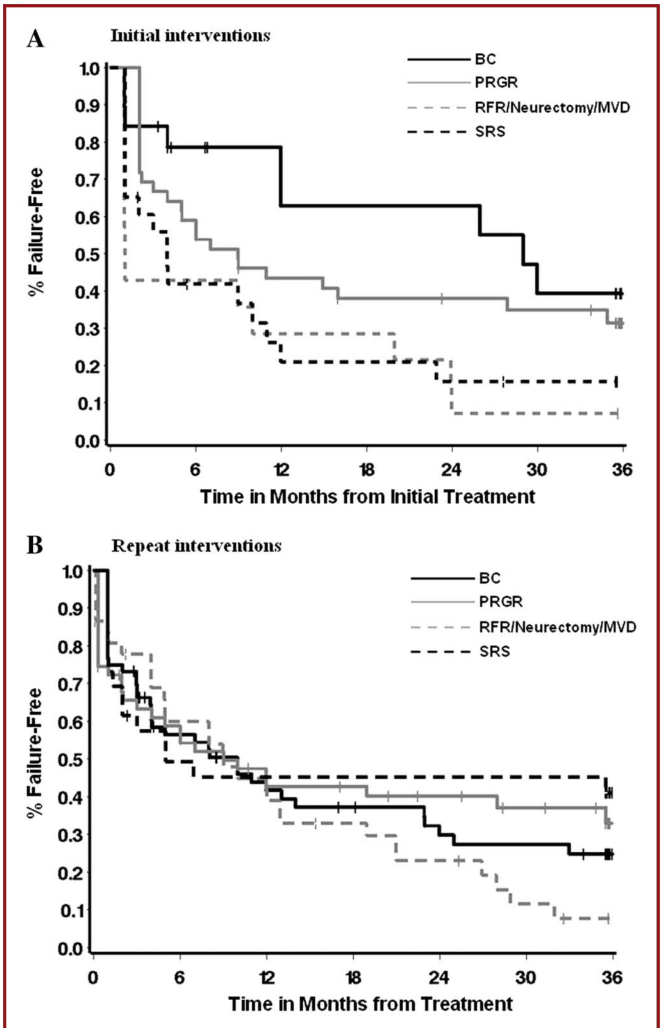

FIGURE 2. *Kaplan-Meier curve of pain-free interval after initial (**A**) and repeat (**B**) procedures in different treatment modalities. BC, balloon compression; MVD, microvascular decompression; PRGR, percutaneous retrogasserian glycerol rhizotomy; RFR, percutaneous radiofrequency rhizotomy; SRS, stereotactic radiosurgery.*

TABLE 2. Actuarial PFI in Different Procedures Separating Upfront and Repeat Treatments[a]

Factor	6-mo PFI, n (%)	1-y PFI, n (%)	2-y PFI, n (%)	3-y PFI, n (%)	5-y PFI, n (%)
BC					
Upfront treatment	12 (75)	10 (71)	8 (57)	5 (36)	3 (21)
Repeat treatments	27 (50)	20 (38)	14 (27)	10 (20)	5 (10)
PRGR					
Upfront treatment	24 (62)	17 (45)	13 (35)	10 (29)	5 (15)
Repeat treatments	27 (57)	20 (44)	14 (33)	10 (26)	3 (8)
SRS					
Upfront treatment	9 (41)	6 (27)	4 (18)	3 (14)	1 (5)
Repeat treatments	13 (50)	11 (44)	11 (44)	11 (44)	8 (33)
RFR					
Upfront treatment	3 (43)	2 (29)	1 (11)	0	0
Repeat treatments	4 (50)	3 (43)	1 (11)	0	0
PN					
Upfront treatment	1 (50)	1 (50)	1 (50)	0	0
Repeat treatments	14 (64)	9 (41)	3 (14)	0	0
MVD					
Upfront treatment	2 (40)	1 (20)	1 (20%)	1 (20)	1 (20)
Repeat treatments	2 (40)	2 (40)	2 (40%)	0	0

[a]BC, balloon compression; MVD, microvascular decompression; PFI, pain-free interval; PN, peripheral neurectomy; PRGR, percutaneous retrogasserian glycerol rhizotomy; RFR, percutaneous radiofrequency rhizotomy; SRS, stereotactic radiosurgery.

Other Analyses

Significant predictors of IPFR after initial treatment were treatment type and concurrent MS symptoms. In terms of treatment types, BC (odd ratio, 22.5; 95% confidence interval, 2.5-201.9; $P = .006$) and PRGR (odd ratio, 3.3; 95% confidence interval, 1.1-10.3; $P = .04$) had significantly better IPFR than other modalities when performed as initial treatments. In addition, having no concurrent symptoms of MS at the time of the procedure (odd ratio, 9.3; 95% confidence interval, 1.1-78.8; $P = .04$) also had a significant impact on IPFR in upfront procedures. No treatment modalities were statistically predictive of higher IPFR after repeat treatment. Notably, higher age at the time of initial treatment was the only significant predictor of treatment failure after repeat procedures ($P = .03$).

DISCUSSION

Key Results

MS-related TN is classified as symptomatic TN and is assumed to be etiologically different from classic TN[11] despite often presenting with typical symptoms like classic TN.[3,24,34] In addition, there is no difference in distribution of pain between classic and MS-related TN.[3] Although still controversial, numerous retrospective studies have noted that MS-related TN tends to present at younger ages compared with classic TN (48 years vs 57 years, respectively),[3,5,6,35] is more often bilateral (11% vs 32%),[3-6,32,36,37] may have trigeminal sensory deficits in 13% to 37%[3,5,37] and has more frequent (30%) atypical constant pain between TN attacks.[37] The average time between MS onset and TN was reported as 5 to 12 years,[4-6] but TN can occur as the presenting symptom of MS in up to 14% of patients.[4,5] Late onset of MS (≥ 37 years of age) has been reported as a risk factor of MS-related TN.[5,18] In our series of 96 patients, the median age of MS onset was 33 years, the median age of definite MS diagnosis was 38 years, TN was diagnosed almost 12 years later (median age at TN diagnosis, 50 years), and TN was the presenting symptom of MS in 11% of patients, which correlates well with the prior study. In addition, we observed 78% of typical presentation of trigeminal pain, 5% of sensory deficit, 19% of pain between attacks, and 56% of single branch involvement at the time of initial presentation of TN. Our data also showed evolution of TN symptoms during the follow-up period (median follow-up, 5.7 years). For example, bilateral pain was observed in 4% of patients at first presentation, but during the follow-up, this number increased to 10% of patients. In addition, we had more atypical features in trigeminal pain during follow-up (33%) compared with the time of diagnosis (25%), as well as more multiple-branch involvement during the course of disease (57% vs 44%, respectively). PFI was evaluated in our study for each procedure. For initial treatments, we had better results with BC (median PFI, 29 months) compared with SRS ($P = .05$) and RFR ($P = .01$). In general, repeat BC and PRGR procedures had relatively shorter PFI compared with the initial treatments ($P = .001$ in both cases).

Interpretation

Surgical treatment is indicated in cases of medically refractory TN with or without MS.[22,38] The best surgical modalities should have a high IPFR, a long PFI, and a low complication rate. For example, MVD is the preferred first-line surgical treatment for classic TN,[39] with an IPFR of 82% to 96% and a 10-years pain-free rate of 65% to 70%.[40-42] However, it is not considered a first-line option for MS-related TN[43] except for selected cases with a high likelihood of vascular compression based on preoperative MRI.[29] Although IPFR have been shown to be relatively acceptable (74%-90%) in some small series of MS-related TN, 40% to 50% of the patients recurred after a follow-up of 1 to 2 years,[28,29,33] which is much lower than the 10-year pain-free response of 65% to 70% in classic TN. In our institution, MVD is rarely performed for MS-related TN and is reserved for rare cases with high probability of vascular compression and no brainstem plaque on MRI on the same side as the TN symptoms. Compared with other series, our results demonstrated even lower IPFR and higher recurrence rates after MVD for treatment of MS-related TN, confirming the secondary role of MVD for this disease (more details are provided in Table 3).

Another commonly used treatment of TN is SRS. Results of SRS for classic TN include an IPFR of 60% to 95% (after a median delay of 10-30 days) with >50% pain-free rate after 5 years.[48-51] In 3 small series of patients (<40 patients each) with MS-related TN treated with SRS, IPFR ranged from 56% to 89%, which is

TABLE 3. Review of Surgical Outcomes in Different Surgical Procedures in Patients With Multiple Sclerosis-Related Trigeminal Neuralgia[a]

Author, Year	MS-Related TN Procedures, n	Procedure Type	IPFR, %	Recurrence, %[b] (Estimated Median Time to Recurrence, mo)	Median Follow-up (Range), mo	Complications, %
Kondziolka et al,[26] 1994	53	PRGR	75	30 (17)[c]	36 (6-122)	18
Pickett et al,[31] 2005	54	PRGR	78	59 (7)	86 (2-151)	20
Mallory et al,[44] 2012	67	PRGR	75	54	28[c]	3
Current series (upfront procedure)	39	PRGR	74	69 (28)	69 (2-192)	3
Current series (repeat procedure)	50	PRGR	70	66 (35)		6
Rogers et al,[45] 2002	15	SRS	80	33 (18)[c]	17[c] (6-38)	0
Zorro et al,[32] 2009	37	SRS	62	37 (74)	56 (6-174)	5
Current series (upfront procedure)	24	SRS	50	67 (23)	69 (2-192)	0
Current series (repeat procedure)	28	SRS	61	53 (78)		7
Montano et al,[46] 2012	21	BC	81	57 (14)	48 (16-108)	0
Mallory et al,[44] 2012	69	BC	65	64	18[c]	12
Current series (upfront procedure)	19	BC	95	61 (29)	69 (2-192)	5
Current series (repeat procedure)	63	BC	71	62 (17)		11
Broggi et al,[28] 2000	10	MVD	90	40	24[c] (12-39)	
Sandell et al,[33] 2010	19	MVD	74		55 (17-99)	16
Current series (upfront procedure)	5	MVD	40	50 (10)	69 (2-192)	20
Current series (repeat procedure)	5	MVD	80	100 (17)		20
Kanpolat et al,[27] 2000	17	RFR	94	29 (25)[c]	60[c] (6-141)	0
Berk et al,[47] 2003	13	RFR	100	50	52[c] (24-84)	0
Current series (upfront procedure)	7	RFR	86	100 (5)	69 (2-192)	0
Current series (repeat procedure)	8	RFR	75	100 (9)		0
Current series (upfront procedure)	2	PN	50	100 (24)	69 (2-192)	0
Current series (repeat procedure)	26	PN	80	67 (12)		8

[a]BC, balloon compression; IPFR, initial pain-free response; MS, multiple sclerosis; MVD, microvascular decompression; PN, peripheral neurectomy; PRGR, percutaneous retrogasserian glycerol rhizotomy; RFR, percutaneous radiofrequency rhizotomy; SRS, stereotactic radiosurgery; TN, trigeminal neuralgia.
[b]After initial pain-free response.
[c]Mean.

comparable to classic TN. However, 5-year pain-free rates were only 20%, which is much lower than for classic TN patients.[32,45,50] In our study, which included 52 patients treated with SRS, we likewise found lower IPFR (50% as initial treatment, 61% as a repeat treatment) and higher recurrence rates (67% and 53%, respectively) compared with the historical control of classic TN. We also had a median delay of 20 days until IPFR was observed after SRS.

Two treatment modalities have targeted the gasserian ganglion, both of which are routinely used for MS patients in our institution. PRGR has been used widely for classic TN with IPFR of 79% to 92% and 50% pain-free after 4 years.[52-55] In 3 small series of MS-related TN patients (n = 67, 54, and 53), these results consist of an acceptable IPFR (75%-78%). However, a high recurrence rate (30%-59%) was observed at 7 to 17 months after the procedure, which is shorter compared with non-MS patients.[26,31,44] Of 89 PRGR procedures, we observed an IPGR of 74% for initial and 70% for repeat treatments. Almost two-thirds of patients had recurrence after either initial or repeat procedures, which is higher compared with the previously mentioned historical controls of classic TN. BC has been used for classic TN with an IPFR of 85% to 100% and long-term pain-free rate of 35% to 76%.[56-58] In 2 series of MS-related TN patients (n = 69 and 21), IPFR occurred in 65% to 81% of patients, with recurrences occurring in 57% to 64% of patients.[44,46] Our results for upfront BC procedures show a 95% IPFR and a 61% recurrence rate (71% and 62% for repeat treatment, respectively) in 82 BC treatments. Despite having a good IPFR, recurrence rate looks higher than the historical control of classic TN.

RFR is another method of treatment in TN patients. In classic TN, IPFR after RFR has been reported to be between 97% and 100% with 50% recurrence at the long-term follow-up.[59-61] In 2 small series of 17 and 13 patients with MS-related TN, IPFR and recurrence rate were reported to be almost the same as for classic TN.[27,47] Of 15 patients with MS-related TN treated with RFR in our series, IPFR was 86% for initial and 75% for repeat treatments. The recurrence rate was 100% for both initial and repeat treatments, which is much higher than the historical controls of classic TN, as mentioned above. Finally, although PN can be used to treat TN, it is no longer commonly used to treat classic TN. In older series of PN for classic TN, the IPFR was reported as 80% to 100% with a recurrence rate of 25% to 42% after 2 years.[62,63] We were unable to find any series in the literature that specifically evaluated PN in MS-related TN patients, but in our series of 28 PN procedures, the IPFR was 50% for initial and 80% for repeat treatments. The recurrence rate was 100% after initial and 67% after repeat treatments, which is relatively higher than previously mentioned historical controls of classic TN (Table 3).

Generalizability

It is difficult to draw definitive conclusions in comparisons of treatment modalities because studies of MS-related TN treatments are limited by small sample sizes and multiple confounding factors. However, it is reasonable to conclude that response to treatment is generally lower and recurrence rates are higher in MS-related TN patients compared with classic TN with all treatment modalities. In our study, BC (P = .006) and PRGR (P = .04) had significantly better IPFR as initial treatments in multivariate analysis. In repeat procedures, we did not find any difference between treatment modalities, and all procedures had comparable IPFRs. This similarity may be explained by selection bias in patients receiving repeat treatments. As shown, some patients had multiple treatments with the same procedure because of satisfactory IPFR (or PFI) from their prior experiences with the same procedure. Hence, repeat treatments were individualized for each patient on the basis of the efficacy of each treatment in any individual patient. Patients treated with SRS as a secondary treatment tended to have somewhat longer PFI compared with patients in whom it was used as upfront treatment (P = .11). This can be seen in the 7 patients who had $>$ 1 SRS treatment. Results of redo SRS compared with repeat SRS after other procedures showed relatively higher IPFR (87% vs 50%) and PFI (36 vs 5 months). In a few, small retrospective series of classic TN, it has been shown that redo SRS may have similar[64] or even better outcomes, especially in those patients who had good initial response to SRS.[65] Although a cumulative dose-response relationship has been shown after repeat SRS, there is currently no consensus about the recommended prescription dose for redo SRS.[64-66] In 1 series of SRS for MS-related TN, all 5 patients with redo SRS had some pain relief with no medication in 3 patients.[45] Our results suggest that redo SRS after failure of the initial SRS may have better short-term and long-term pain control for MS-related TN compared with the initial SRS; however, these results would have to be replicated in large studies.

Finally, in terms of complication rates, no significant difference was shown between different treatment modalities in our series, and no mortality related to these procedures was reported.

Limitations

Given the lack of known superior treatments for MS-related TN and the retrospective design of this study, the study was limited by selection bias. Specifically, we did follow any specific protocol in selecting a specific intervention as the initial or repeat treatment modality for MS-related TN. For initial treatments, decisions were based on the general medical condition of the patient (eg, high risk for general anesthesia), MS-related neurological disabilities, surgeon expertise in a specific treatment modality, and patient preference. For repeat treatment, patient satisfaction from prior procedures was an additional factor that affected treatment selection besides those factors in initial treatment selection.

Another limitation was that dedicated MRI sequences to detect vascular compression were not available for all patients. Although this may have affected treatment recommendations, it was not the only factor used in recommending a particular modality, as discussed.

Finally, not enough patients were available for certain interventions such as MVD, RFR, and neurectomy to evaluate them separately. As a group, we found that they were not as effective as other treatments; however, they would have to be studied individually with higher numbers to further evaluate their effectiveness.

CONCLUSION

Surgical outcomes for treatment of MS-related TN have lower IPFR and PFI rates compared with historical surgical outcomes for treatment of classic TN. As the initial treatment of MS-related TN, percutaneous procedures targeting the gasserian ganglion (BC and PRGR) had the best IPFR and PFI rates compared with other treatment modalities. For repeat treatment of MS-related TN, no significant difference was found between procedures. Hence, we recommend individualizing repeat treatments on the basis of the efficacy of prior procedures.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

In 2008 the American Academy of Neurology and the European Federation of Neurological Societies produced joint guidelines on the management of trigeminal neuralgia. One of the key questions was: "Which surgical techniques should be used in patients with multiple sclerosis?" In the conclusions, the sad answer to this question was that the available evidence was insufficient to support or refute the effectiveness of the surgical management of trigeminal neuralgia in patients with multiple sclerosis, with any kind of surgical method. A major complaint of the guidelines' authors was the lack of studies using different types of intervention to allow a direct, head-to-head, comparison.

The article by Barnett et al. is, by far, the largest study in these patients and, using measures that are less influenced by cognitive factors than the mere pain reduction compares several surgical methods. Hence eventually the guidelines' authors can smile. The comparison between balloon, glycerol, and gamma knife was supported by high numbers, and it is certainly interesting to readers to know that a nowadays popular procedure such as gamma knife did not yield great results. Unfortunately the number of patients that underwent microvascular decompression was too low to allow meaningful comparisons. But I am confident that this kind of intervention, given the suggested role of neurovascular compression in the pathophysiology of trigeminal neuralgia associated with multiple sclerosis, will be properly targeted in the future.

This article will undoubtedly help clinical decision-making and be a useful reference for the next studies.

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CME QUESTIONS:

1. What is the lifetime incidence of trigeminal neuralgia in patients with Multiple sclerosis?
   A. 4%
   B. 8%
   C. 12%
   D. 16%
   E. 20%
2. What is the most common clinical characteristic of trigeminal neuralgia in multiple sclerosis patients?
   A. Bilateral facial pain
   B. Otalgia
   C. Excess lacrimation
   D. Atypical facial pain
   E. Lancinating pain
3. In patients with multiple sclerosis and medication refractory trigeminal neuralgia, what treatment modality has the best pain-free response?
   A. Percutaneous balloon compression
   B. Percutaneous retro-gasserian glycerol rhizotomy
   C. Stereotactic radiosurgery
   D. Microvascular decompression of trigeminal nerve
   E. Percutanous radiofrequency rhizotomy