Gamma Knife stereotactic radiosurgery for idiopathic trigeminal neuralgia

Clinical article

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Object. Trigeminal neuralgia pain causes severe disability. Stereotactic radiosurgery is the least invasive surgical option for patients with trigeminal neuralgia. Since different medical and surgical options have different rates of pain relief and morbidity, it is important to evaluate longer-term outcomes.

Methods. The authors retrospectively reviewed outcomes in 503 medically refractory patients with trigeminal neuralgia who underwent Gamma Knife surgery (GKS). The median patient age was 72 years (range 26–95 years). Prior surgery had failed in 205 patients (43%). The GKS typically was performed using MR imaging guidance, a single 4-mm isocenter, and a maximum dose of 80 Gy.

Results. Patients were evaluated for up to 16 years after GKS; 107 patients had > 5 years of follow-up. Eighty-nine percent of patients achieved initial pain relief that was adequate or better, with or without medications (Barrow Neurological Institute [BNI] Scores I–IIIb). Significant pain relief (BNI Scores I–IIIa) was achieved in 73% at 1 year, 65% at 2 years, and 41% at 5 years. Including Score IIIb (pain adequately controlled with medication), a BNI score of I–IIIb was found in 80% at 1 year, 71% at 3 years, 46% at 5 years, and 30% at 10 years. A faster initial pain response including adequate and some pain relief was seen in patients with trigeminal neuralgia without additional symptoms, patients without prior surgery, and patients with a pain duration of ≤ 3 years. One hundred ninety-three (43%) of 450 patients who achieved initial pain relief reported some recurrent pain 3–144 months after initial relief (median 50 months). Factors associated with earlier pain recurrence that failed to maintain adequate or some pain relief were trigeminal neuralgia with additional symptoms and ≥ 3 prior failed surgical procedures. Fifty-three patients (10.5%) developed new or increased subjective facial paresthesias or numbness and 1 developed deafferentation pain; these symptoms resolved in 17 patients. Those who developed sensory loss had better long-term pain control (78% at 5 years).

Conclusions. Gamma Knife surgery proved to be safe and effective in the treatment of medically refractory trigeminal neuralgia and is of value for initial or recurrent pain management. Despite the goal of minimizing sensory loss with this procedure, some sensory loss may improve long-term outcomes. Pain relapse is amenable to additional GKS or another procedure. (DOI: 10.3171/2009.7JNS09694)

**Key Words**: stereotactic radiosurgery, Gamma Knife, rhizotomy, trigeminal neuralgia

**Abbreviations used in this paper**: BNI = Barrow Neurological Institute; GKS = Gamma Knife surgery; MVD = microvascular decompression; PRGR = percutaneous retrogasserian glycerol rhizotomy; RFL = radiofrequency lesioning.
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Iatropic trigeminal neuralgia; of these, 89 were additional GKS procedures. Forty-two patients did not have follow-up data and were excluded from the analysis. All patients had long-standing pain refractory to medical management with agents such as carbamazepine, phenytoin, baclofen, or gabapentin. In this series, 199 patients were men and 304 were women. The median age was 72 years (range 26–95 years). Prior medical treatment had failed or had been intolerable in all patients. The median symptom duration was 84 months (range 3–444 months). Pain was predominantly distributed in the V2 and V3 distributions of the trigeminal nerve (56%), followed by V3 (15%), V2 (12%), V1 plus V2 (12%), all trigeminal distributions (2.0%), and V1 plus V3 (1%).

One hundred three patients (20.5%) had some sensory disturbance (usually paresthesias) preoperatively, and 3 patients (0.6%) had partial deafferentation pain caused by earlier nerve ablation procedures.

The preoperative characteristics of our patients are summarized in Table 1. Surgery had been performed previously in 215 patients (43%). In this group, multiple surgeries had been performed in 57%. Medical and surgical treatments had failed in the majority of patients. Gamma Knife surgery was the first surgical procedure in 288 patients (57%).

Radiosurgical Technique

Various models of the Gamma Knife (models U, A, B, C, 4C, and Perfexion, Elekta Instruments) were used during this 16-year study. After application of the Leksell Model G stereotactic frame (Elekta Instruments) under local anesthesia, 484 patients underwent stereotactic MR imaging to identify the trigeminal nerve. We used CT scanning in 19 patients who were ineligible for MR imaging. Magnetic resonance imaging was performed using contrast-enhanced, short repetition time sequences, and axial phase volume acquisitions of 512 × 216 matrices divided into 1-mm slices. When the trigeminal nerve was difficult to identify on images (usually because of previous surgery), additional axial long relaxation time MR images were obtained. For CT cisternography, intrathecal contrast was injected via lumbar puncture. A single 4-mm isocenter was used in 498 patients (99%) and two 4-mm isocenters were used in 5 patients (1%). With a single isocenter, the target was 3–8 mm anterior from the junction of the trigeminal nerve and pons. The isocenter was usually located so that the brainstem surface was irradiated at the 20% isodose line or less.

When 2 isocenters were used to create an oval dose plan, a longer nerve segment extending more anteriorly was irradiated. We administered maximum doses of 60 (in 2% of patients), 70 (in 4%), 75 (in 3%), 80 (in 88%), 85 (in 2%), and 90 Gy (in 2% of patients) (Table 1). A team consisting of a neurosurgeon, a radiation oncologist, and a medical physicist performed dose selection and planning.

Follow-Up and Statistical Analysis

This study was approved by the University of Pittsburgh Institutional Review Board. All serial follow-up information was obtained via direct contact with the patient or the referring physicians. We evaluated the degree of pain relief, the latency interval until pain relief, the need for further surgical procedures, the use of medications, and the development of new symptoms or signs. Final outcomes were obtained in all 503 patients by telephone interviews conducted by physicians who were not involved in patient selection or management. To evaluate the effectiveness of GKS, we calculated the time to initial response and the duration of pain relief by using the Kaplan-Meier product-limit method. Pain outcome was scored using the BNI scale.32 We defined BNI Scores I–IIAs as representing significant pain relief and BNI Scores I–IIb as representing adequate pain relief, whereas BNI scores of IV and V were defined as treatment failures. For patients who described facial sensory dysfunction, we also inquired about their quality of life related to trigeminal neuralgia and whether sensory symptoms bothered them.

We also correlated outcomes with various clinical parameters (including sex, age, duration of symptoms, and pain distribution). The preoperative characteristics of our patients are summarized in Table 1. The follow-up analysis was performed using the Kaplan-Meier product-limit method. Pain outcome was scored using the BNI scale.32 We defined BNI Scores I–IIAs as representing significant pain relief and BNI Scores I–IIb as representing adequate pain relief, whereas BNI scores of IV and V were defined as treatment failures. For patients who described facial sensory dysfunction, we also inquired about their quality of life related to trigeminal neuralgia and whether sensory symptoms bothered them.

TABLE 1: Characteristics of 503 patients with trigeminal neuralgia who underwent GKS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
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<tbody>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>304 (60.4)</td>
</tr>
<tr>
<td>male</td>
<td>199 (39.6)</td>
</tr>
<tr>
<td>median age in yrs</td>
<td></td>
</tr>
<tr>
<td>range 26–95 years</td>
<td>72 (26–95)</td>
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<tr>
<td>median duration of symptoms in mos</td>
<td>84 (3–444)</td>
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<tr>
<td>side of pain</td>
<td></td>
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<tr>
<td>rt</td>
<td>295 (58.7)</td>
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<tr>
<td>lt</td>
<td>198 (39.3)</td>
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<tr>
<td>bilat</td>
<td>13 (4)</td>
</tr>
<tr>
<td>dose (Gy)</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>70</td>
<td>19 (3.9)</td>
</tr>
<tr>
<td>75</td>
<td>15 (2.9)</td>
</tr>
<tr>
<td>80</td>
<td>443 (88.1)</td>
</tr>
<tr>
<td>85</td>
<td>9 (1.7)</td>
</tr>
<tr>
<td>90</td>
<td>9 (1.7)</td>
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presence or absence of preoperative sensory dysfunction, presence of additional symptoms, number of previous failed surgical procedures, and maximum dose), using a log-rank test with p < 0.05 set as significant, a stepwise (forward conditional) multivariate analysis, and the Cox proportional hazards model with p < 0.10 set as significant. Outcomes were calculated using actuarial statistics over a 16-year period. The median follow-up duration was 2 years (range 3–156 months).

Results

In this series, 147 patients (29%) required additional surgical procedures for better pain control. Radiosurgery in these patients was considered to have failed (poor outcome), and the results after the additional procedure were excluded from this analysis. Eighty-nine patients (18%) who had repeat GKS, 30 (6%) had a glycerol rhizotomy, 19 (4%) had a microvascular decompression, 6 underwent RFL (1.2%), 2 (0.4%) had balloon microcompression, and 1 (0.2%) had a dorsal root entry zone lesion for anesthesia dolorosa (Table 2).

Time to Initial Response

Four hundred forty-nine patients (89%) responded to GKS after the procedure at a median latency of 1 month. Fifty-four patients (11%) had poor pain relief (BNI Score IV or V) after this procedure. Pain relief was evaluated using the product-limit method of Kaplan and Meier (Fig. 1). The median interval until pain relief (Scores I–IIIb) was 1 month (range 1 day–1 year). Two hundred patients (40%) achieved complete initial pain relief (Score I). Factors associated with earlier initial complete pain relief (Score I), significant pain relief (Scores I–IIIa), and adequate pain relief (Scores I–IIIb) were trigeminal neuralgia without additional symptoms (that is, trigeminal neuralgia Type 1) (score I, p = 0.036, OR 1.7; Scores I–IIIa, p = 0.012, OR 1.3; and Scores I–IIIb, p = 0.014, OR 1.6) (Fig. 2), no prior surgery (Score I, p = 0.050, OR 1.5; Scores I–IIIa, p = 0.018, OR 1.2; and Scores I–IIIb, p = 0.014, OR 1.4) (Fig. 2), and pain for ≤3 years before GKS (Scores I–IIIa, p = 0.011, OR 1.4; and Scores I–IIIb, p = 0.01, OR 1.6). Patients with shorter pain duration before GKS did not achieve a Score I outcome more often (p = 0.098). No other clinical factors were significant in univariate or multivariate testing.

Maintenance of Pain Relief

The duration of pain relief after the initial response was evaluated using the product-limit method of Kaplan and Meier (Fig. 3). The probability of maintaining significant pain relief (BNI Scores I–IIIa) was achieved and maintained in 73% at 1 year, 65% at 2 years, 41% at 5 years, and 26% at 10 years. The probability of maintaining adequate pain relief (Score I, II, IIIa, or IIIb) was achieved and maintained in 80% at 1 year, 71% at 2 years, 46% at 5 years, and 30% at 10 years. At the final evaluation, 330 patients (66%) continued to have pain control (BNI Scores I–IIIb). One hundred forty-four patients (29%) achieved Score I, 11 patients (2%) Score II, 120 patients (24%) Score IIIa, 55 patients (11%) Score IIIb, 126 patients (25%) Score IV, and 47 patients (9%) achieved Score V pain status (Table 2).

Pain eventually recurred in 193 patients. The median time to recurrence in patients who initially had significant relief (BNI Scores I–IIIa) was 48 months (range 3–144 months). An additional surgical procedure was performed in 144 patients, and 96 remained well controlled with medication only.

Factors associated with earlier pain recurrence in those with initial significant relief (BNI Scores I–IIIa) were trigeminal neuralgia with additional symptoms (p = 0.042 [univariate], p = 0.131 [multivariate]; OR 1.2), and patients without any new facial sensory symptoms (p < 0.0001 [uni- and multivariate]; OR 2.9). Factors associated with earlier pain recurrence were age < 65 years (p = 0.022 [univariate], p = 0.024 [multivariate]; OR 1.4), patients with additional symptoms (p = 0.019 [univariate], p = 0.021 [multivariate]; OR 1.4 [Fig. 4]), ≥3 surgeries (p = 0.033 [univariate], p = 0.037 [multivariate]; OR 1.5 [Fig. 4]), and patients without any new facial sensory symptoms (p < 0.0001 [uni- and multivariate]; OR 4.0 [Fig. 5]).

Sensory Dysfunction After GKS

No patient sustained an early complication after GKS. Fifty-three patients (10.5%) later developed increased facial sensory dysfunction such as paresthesias or objective facial sensory loss, which occurred during the first 2 years after radiosurgery. Ten of these patients (19%) had delayed pain recurrence. The 1-, 3-, and 5-year rates for maintenance of sensation in patients who noted sensory

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients (%)</th>
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<tr>
<td>BNI score</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>144 (28.6)</td>
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<tr>
<td>II</td>
<td>11 (2.2)</td>
</tr>
<tr>
<td>IIIa</td>
<td>120 (23.9)</td>
</tr>
<tr>
<td>IIIb</td>
<td>55 (10.9)</td>
</tr>
<tr>
<td>IV</td>
<td>126 (25)</td>
</tr>
<tr>
<td>V</td>
<td>47 (9.3)</td>
</tr>
<tr>
<td>recurrence of pain</td>
<td>193 (42.9)</td>
</tr>
<tr>
<td>median time to pain recurrence in mos (range)</td>
<td>48 (3–144)</td>
</tr>
<tr>
<td>post-GKS sensory dysfunction</td>
<td>53 (10.5)</td>
</tr>
<tr>
<td>deafferentation pain post-GKS</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>additional treatment after GKS</td>
<td>147 (28.6)</td>
</tr>
<tr>
<td>repeat GKS</td>
<td>89 (17.7)</td>
</tr>
<tr>
<td>glycerol rhizotomy</td>
<td>30 (6.0)</td>
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<tr>
<td>microvascular decompression</td>
<td>19 (3.8)</td>
</tr>
<tr>
<td>RFL</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>balloon microcompression</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>dorsal root entry zone lesion</td>
<td>1 (0.19)</td>
</tr>
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</table>
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dysfunction were 96, 82, and 78%, respectively. The 1-, 3-, and 5-year rates for maintenance of significant pain relief (BNI Scores I–IIIa) as well as adequate relief (BNI Scores I–IIIb) in patients who noted sensory dysfunction were 91, 82, and 78%, respectively. We found that patients who developed facial sensory dysfunction had no difference in the maximum dose or number of isocenters compared with the patient group that reported no sensory dysfunction post-GKS (maximum dose, \( p = 0.561 \); and number of isocenters, \( p = 0.392 \)).

We sought to evaluate these 53 patients to obtain their opinion on sensory dysfunction. Thirteen could not be contacted, of whom 5 had died. In 17 patients, the symptoms had resolved (16 described their quality of life to be improved after radiosurgery and 1 not improved due to recurrent pain). Of 23 with persistent sensory dysfunction, 7 described it as not bothersome, 10 as mildly bothersome, 6 as severely bothersome, and 0 as intolerable. Nineteen of these patients said that their quality of life was improved after GKS and that sensory dysfunction was a good tradeoff for pain relief. Four said their quality of life was worse and that this dysfunction was not a good tradeoff.

One patient (0.2%) who already had decreased facial sensation after a prior microvascular decompression, developed deafferentation pain. Eight months after GKS (75 Gy, 2 isocenters) she had increased burning pain and sensory loss. No patient developed a trigeminal motor deficit after GKS or other cranial nerve deficits.

Management and Results of Recurrent Pain

Because of recurrent medically refractory pain, 89 patients underwent a second radiosurgery procedure, of whom 72 were suitable for this analysis. The median interval between procedures was 30 months, and the median follow-up after the repeat procedure was 24 months. The average age was 78 years. The typical maximum dose at the second procedure, targeted just anterior to the first isocenter with some overlap, varied between 60 and 70 Gy. After the second GKS, 68 patients (94%) had pain relief at some time. The actuarial rate for pain control was 90, 73, 63, and 56% at 1, 3, 5, and 10 years, respectively. Eight patients (11%) developed new sensory dysfunction after the second radiosurgery, and in 6 this was permanent.

Discussion

The role of GKS in the management of medically refractory trigeminal neuralgia has evolved. Questions regarding treatment durability, long-term complications, and appropriate patient selection have challenged physicians to place GKS in the context of other therapeutic...
modalities for this disorder.\textsuperscript{33} In this report, we detail our long-term outcomes in a large patient population.

By the end of the 20th century, craniotomy and microvascular decompression emerged as the gold standard for medically refractory trigeminal neuralgia; 64\% of patients had complete relief, which was defined as the absence of lancinating facial pain, or a reduction in pain of at least 98\% without medication (BNI Scores I and II), and 9\% noted partial relief, which was defined as a 75\% reduction in pain with low-dose medication or without medication (BNI Score IIb) 10 years after the procedure.\textsuperscript{1} Unfortunately, many patients with trigeminal neuralgia are poor craniotomy candidates due to advanced age or the presence of medical comorbidities.\textsuperscript{23} Stereotactic radiosurgery is the least invasive modality for such patients.

Optimally, the goal of trigeminal neuralgia surgery is complete elimination of pain and need for medication. To achieve this, there is a balance between surgical risk, maintenance of normal nerve function, and the known rates for pain relief. Not all procedures relieve pain and not all patients can or want to stop medication. For patients in whom at least 1 prior surgery has failed, the expectations for complete relief are reduced. For many patients, pain improvement (not complete relief) can be an acceptable outcome particularly if medication is reduced and daily activities are improved and more comfortable. Unfortunately, since pain can come and go, a patient may report that they have no pain at one assessment (Score I), only to have it recur soon afterward (Score II or worse) but not report it.

Achievement of Pain Relief

Some authors have noted a latency interval to pain relief after radiosurgery of $\sim 1$–2 months.\textsuperscript{11,12,20,39} In the present analysis, we found that 89\% of patients responded to treatment at a median of 1 month. We found that in patients with trigeminal neuralgia, those who underwent GKS as their initial surgical procedure, and those who underwent earlier GKS (< 3 years) after pain onset had faster significant pain relief (Score I–IIa). The median time to complete pain relief (Score I) was 5 months. By 12 months after GKS, 11\% of patients had not achieved maximum relief. Patients who continued to suffer disabling pain required an additional surgical procedure. We advocate repeat GKS only if complete pain relief had been achieved initially, with subsequent recurrence.\textsuperscript{20}

Maintenance of Pain Relief

Our experience indicates that the majority of patients experience lasting, satisfactory pain reduction with few complications after GKS. In this series, 80\% of patients achieved or maintained adequate pain control (BNI Scores I–IIb) at 1 year, 71\% had pain relief at 3 years,
and microvascular decompression for younger patients for whom invasive surgery is suitable. However, the benefit of decompression is reduced when performed a second time, or for recurrent trigeminal neuralgia.

Henson et al. reported a series of 36 patients who underwent PRGR and 63 patients who underwent GKS for trigeminal neuralgia. They found that 86% of patients who underwent PRGR and 92% of patients who underwent GKS achieved a successful treatment outcome, which was defined as BNI Scores I–IIIb (p = 0.49). Fifty-three percent of patients who underwent PRGR and 41% of patients who underwent GKS experienced pain recurrence or no pain relief at a median recurrence time of 5 and 8 months, respectively (p = 0.30). Although PRGR worked faster on average, GKS lasted longer. Menzel et al. reported on 315 patients with trigeminal neuralgia who underwent RFL. At a mean follow-up of 13 years, 20% were pain free and 80% had a recurrence. Five percent of patients developed troublesome dysesthesias. Kanpolat et al. reported on 1600 patients with trigeminal neuralgia who underwent RFL. At a mean 5-year follow-up, 58% were pain free and 42% had a recurrence or the treatment had failed. At an average of 20 years, the pain-free rate decreased to 41%. Other studies have shown that the pain-free rate following RFL varied from 20 to 82% and recurrence or failure varied from 20 to 80%. With RFL, an increased rate of facial sensory dysfunction has been correlated to longer pain relief, but also to dysesthesia. Tatli et al. reported a meta-analysis including MVD and RFL in a total of 28 studies. They concluded that MVD was superior to RFL. Although RFL provided a high rate of initial pain relief, the average pain-free rate was 50.4% at a mean follow-up of 5 years. Thus, radiosurgery appears to have a lower rate of pain relief in longer-term follow-up (5–10 years), but with the lowest morbidity or associated sensory dysfunction. What remains unclear is an assessment of quality of life in the years following any trigeminal neuralgia surgery. Most agree that the 3 key indicators of such quality are pain relief, new sensory symptoms, and medication tolerance if used.

Zakrzewska et al. reported patient satisfaction surveys after MVD or PRGR for trigeminal neuralgia. Response rates were 90% (220 of 245) for those who underwent MVD and 88% (53 of 60) for those who underwent PRGR. Overall satisfaction with their current situation was 89% in patients who underwent MVD and 72% in those who underwent PRGR. Four percent of MVD and 20% of PRGR patients were unsatisfied with the outcome (p < 0.01). Satisfaction was dependent on recurrence and complications or side effects (p < 0.01). For those only undergoing 1 of these procedures, long-term side effects and complications occurred in 24% (30 of 125) in the MVD group and 57% (16 of 28) in the PRGR group, which had some effect on the patients’ quality of life. In the MVD group, the most common complaint was nonspecific headache, whereas in the PRGR group, it was sensory loss.

Impact of Sensory Dysfunction

Postrhizotomy paresthesia or numbness of varying degrees has been observed in 6–70% of patients after thermal rhizotomy, glycerol rhizotomy, or balloon micro-
compression, depending on the technique and the goal of the surgeon. In our study, sensory dysfunction was found in 11%. Only 1 patient (0.19%) developed deafferentation pain. Ten of 53 patients who later developed facial sensory dysfunction had pain recurrence after GKs. The 1-, 3-, and 5-year rates for maintenance of pain relief in patients who later developed facial sensory symptoms were 91, 82, and 78%, respectively. These data suggest that patients who developed facial sensory symptoms had a reduced rate of recurrent pain (p < 0.0001). Pollock et al. reported a significant association between higher radiation dose and increased risk of trigeminal neuropathy; 45% of the patients who had received a maximum dose of 90 Gy reported a trigeminal deficit as opposed to 15% who received less. These authors reported a lower rate of pain recurrence in patients with sensory symptoms (15 vs 41% in those without), but this did not reach significance (p = 0.08).

Consistent with our findings, Brisman alone and with Mooij reported a 5% complication rate in patients who received radiation doses between 70 and 80 Gy. Henson et al. reported that 54% of patients who underwent PRGR and 30% of patients who underwent GKs later developed facial sensory symptoms. A higher morbidity rate was found after PRGR (p = 0.018).

Management of Recurrent Pain

According to this experience, 193 (43%) of 450 patients had pain recurrence after GKs. The time to recurrence varied between 3 and 144 months with a median of 2 years. When a second radiosurgery procedure was performed in 89 patients, the target was just anterior to the first isocenter, with some overlap. The typical second dose was 60, 65, or 70 Gy, which was less than the first dose. Repeat radiosurgery can increase the chance for facial sensory dysfunction, but overall this remained low.

Conclusions

Gamma Knife surgery is safe and effective for trigeminal neuralgia. As the least invasive option, this procedure maintains facial sensation in the vast majority of patients and can be used in all patients regardless of age or medical condition including those on regimens of anticoagulant or antiplatelet agents. In some patients a higher dose, although associated with increased sensory dysfunction, may provide better, sustained outcomes. In patients with recurrent pain, a repeat GKs procedure may reestablish pain control with minimal additional morbidity.

Disclosure

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