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Source: Radiation Research, 168(2) : 143-148

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RR0620.1

RADIATION RESEARCH **168**, 143–148 (2007)
0033-7587/07 $15.00

Determination of a Clinical Value for the Repair Half-Time ($T_{1/2}$) of the Trigeminal Nerve Based on Outcome Data from Gamma Knife Radiosurgery for Facial Pain

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Stieber, V. W., Robbins, M., Balamucki, C., DeGuzman, A., Tatter, S. B., Ekstrand, K. E., McMullen, K. P., Branch, C., Shaw, E. G., Bourland, J. D., Lovato, J., Munley, M. T. and Ellis, T. L. Determination of a Clinical Value for the Repair Half-Time ($T_{1/2}$) of the Trigeminal Nerve Based on Outcome Data from Gamma Knife Radiosurgery for Facial Pain. *Radiat. Res.* 168, 143–148 (2007).

Stereotactic radiosurgery (GKRS) using the Leksell Gamma Knife is a treatment option for patients with trigeminal pain. We analyzed a database of 326 GKRS procedures performed over 4.6 years at three discrete dose levels commonly described in the published literature. Logistic regression was used to model the logit of response as a function of treatment time. The resulting coefficient was converted to an estimated probability of response for the shortest and longest treatment times in clinical practice. The two estimated probabilities were then compared to yield the estimated difference in the biologically effective dose (BED) between the two doses, using a modified linear-quadratic model for stereotactic radiosurgery. This difference was used to back-calculate a clinical value for $T_{1/2}$, resulting in a range of 1.28–1.77 h for $T_{1/2}$. The biological model appeared to accurately predict that, given the doses and treatment times used in general clinical practice, there would be no significant difference in clinical outcome.

INTRODUCTION

Unilateral facial pain limited to the distribution of the trigeminal nerve represents a spectrum of conditions of varying clinical behavior. Idiopathic trigeminal neuralgia (TN), also known as tic douloureux, is characterized by paroxysmal, shock-like pain in one or more of the three trigeminal nerve distributions (*1*). The underlying pathophysiology is usually neural compression by an adjacent artery or, less commonly, a vein (*2*). Root entry zone pathology may be critical to the development of the idiopathic syndrome. Ectopic action potential generation in the sensory root may either trigger or be directly responsible for the painful sensation (*1*). For some patients, TN has accompanying atypical features, such as burning, chronic pain, and/or dull-aching pain. Other patients may have only atypical facial pain without episodic, lancinating type pain. Multiple sclerosis, herpes zoster, and prior trauma or surgery may also result in facial pain (*3*). First-line therapy for idiopathic trigeminal neuralgia is typically medical management with anti-convulsants, and long-term complete relief is often possible (*4, 5*). Eventually the symptoms become refractory to medical management, and some other form of therapy is necessary.

Stereotactic radiosurgery (GKRS) using the Leksell Gamma Knife (LGK) (Elekta Instruments AB, Sweden) is a treatment option for patients with medically refractory facial pain (*6*). The unit uses 201 cobalt sources that target radiation, with an accuracy of ±0.1 mm, onto the trigeminal nerve root entry zone tangential to the brainstem. The results for typical idiopathic TN are quite good (*7, 8*). Complete or partial pain relief is achieved in 57–86% of patients at 1 year with 56% of patients still having complete or partial pain relief at 5 years. Patients with an atypical pain component have a lower rate of achieving pain relief. Ten to 37% of patients develop new or increased subjective facial paresthesia as a result of treatment. A number of radiosurgery treatment-related factors have been evaluated to determine their influence on clinical outcomes. These include radiation dose, length of irradiated nerve, proximity of the isocenter to the brainstem, and the trigeminal nerve-blood vessel relationship (*2, 9–12*). Escalating the treatment dose or treating a longer section of the nerve results in a significantly higher rate of permanent trigeminal nerve dysfunction and no significant increase in duration of pain relief (*9, 12*).

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TABLE 1
Pairwise Comparison of BED Dependent on *t* for Given $T_{½}$ and α/β

$T_{½}$	α/β	*t*	BED	Ratio
0.25	1.5	25.00	3479	
0.25	1.5	60.00	2385	0.69
6.50	1.5	25.00	4831	
6.50	1.5	60.00	4735	0.98
0.25	3	25.00	1782	
0.25	3	60.00	1235	0.69
6.50	3	25.00	2458	
6.50	3	60.00	2410	0.98

Notes. D is fixed at 85 Gy. Abbreviations are defined in the text.

Since the 201 ^{60}Co sources in the GKRS decay with a half-life of 5.26 years, the dose rate is reduced by half and the treatment time is doubled over this period (assuming a constant prescription dose). The biological model developed by Thames and Nilsson for continuous irradiation can be adapted and, taking into account repair and dose rate, may be used to calculate a biologically effective dose (BED) for varying treatment times and prescription doses (*13, 14*). Since dose rate is proportional to treatment time and prescription, this model allows a comparative analysis of treatment outcomes for a heterogeneous patient population. It suggests that over the range of typical treatment times of 25–60 min, the BED could vary by from 2–31% depending on the input values. Since both pain control and the complication rate appear to improve with increasing prescription dose (*9, 10*), the model suggests that clinical outcomes could vary either greatly or not at all over the period of one half-life of cobalt. Table 1 shows, for example, the anticipated changes in BED for a fixed prescription dose of 85 Gy for various values of μ and $T_{1/2}$.

We had at our disposal a database of 326 GKRS procedures performed over 4.6 years between cobalt source replacements (55% of activity remaining). The majority of these procedures were performed using one of three discrete dose levels. We therefore set out to use these data to calculate a clinical $T_{1/2}$ value for the trigeminal nerve.

MATERIALS AND METHODS

This study was approved by the institutional review board prior to any data collection. Between September 1999 and March 2004, 326 GKRS procedures for patients with facial pain were performed at Wake Forest University Baptist Medical Center (WFUBMC) in Winston-Salem, NC. At the time of analysis, charts were unobtainable for 15 patients, and these patients were excluded from data analysis. There were 31 patients who underwent repeat GKRS for recurrent or persistent facial pain. For these patients, only the initial radiosurgical procedure was included in the study. During follow-up review, 41 patients were unreachable by telephone, of which 17 had follow-up data in their charts. Thus the facial pain outcomes of 256 GKRS patients could be analyzed.

After informed consent, all patients were treated in the 201 ^{60}Co source Gamma Knife Stereotactic Radiosurgery unit by a team consisting of a radiation oncologist, a neurosurgeon and a medical physicist. A total of 240 patients were treated in the same fashion: The 50% isodose line was placed tangential to the brainstem, with the isocenter of a 4-mm collimator helmet targeted at the proximal trigeminal nerve root. The radiation dose was prescribed at the 100% isodose line. All dose calculations used the modern 4-mm collimator output factor of 0.87 (*15*). Ninety-six percent of patients received one of three standard doses (80, 85 or 90 Gy); only these 230 patients were included in this analysis.

The long-term follow-up data were obtained through telephone conversations with patients. Patients self-reported pain control data after being asked standard questions about: pain relief after treatment (yes/no), degree of pain relief, time to partial/complete pain relief, pain recurrence, partial/complete pain-free interval, complications (up to four), medication use at 1/2/3/6 months, quality of life improvement (yes/no), and further surgical procedures (yes/no). In accordance with the peer-reviewed literature, pain relief was defined as a complete or >50% response (*7*). The degree of pain relief was recorded in four categories: excellent (complete pain relief with no medication use), good (complete pain relief with medication use), fair (50–99% partial pain relief with or without medication use), and poor (less than 50% pain relief with or without medication use). Self-reported side effects, such as facial numbness, burning and prickling/tingling, were recorded as complications of the GKRS procedure. Medication use was recorded relative to medication use at the time of GKRS with four categories: same, increased, decreased and stopped. All data were recorded into a Microsoft Access database created specifically for the research study.

We had previously performed an analysis of the effect of dose rate on treatment outcome (*16*). In that paper, logistic regression was used to model the logit of response (achieving pain relief as defined above) as a function of treatment time. The resulting coefficient was converted to an estimated probability of response for a treatment time of 25 and 60 min, the shortest and longest times encountered in our series (and in general clinical practice). These estimated probabilities were then compared to yield the estimated difference of BED from 25 to 60 min. This analysis demonstrated no difference in response over this range of treatment times, consistent with the observed clinical outcome. The BED at 60 min was estimated to be 0.91 of the BED at 25 min. When adopting the modification proposed by Guerrero and Li (*17*) that extends the linear-quadratic model for the large fraction doses typically used in stereotactic radiosurgery, the difference becomes even smaller, with the BED at 60 min being 0.94 of the BED at 25 min. This difference is small enough that, in accordance with the clinical outcomes from our patient data set, we should not have been able to detect a clinical difference over that range of treatment times used. We subsequently used the small difference in BED to back-calculate a clinical value for $T_{1/2}$.

For our analysis, we used the biological model developed by Thames and Nilsson for continuous radiation (*13, 14*).

$$\mathrm{BED} = D\left[1 + g \times \frac{D}{\alpha/\beta}\right]$$

with

$$g = \frac{2[\mu t - 1 + e(-\mu t)]}{(\mu t)^2}, \qquad \mu = \frac{\ln 2}{T_{1/2}},$$

where BED is the biologically effective dose, D is the total dose, g is the continuous repair factor, α/β is the ratio of the tissue-specific linear and quadratic survival parameters specific for the linear-quadratic factor (LQF) model (*18*), t is the exposure duration (D/dose rate), μ is the recovery constant, and $T_{1/2}$ is the repair half-time.

For several of these factors, some assumptions had be made since exact human data are not always readily available. The α/β for neural tissue, viewed radiobiologically as a late-responding tissue, is generally thought to be low; most authors believe it ranges between 1.5–3.0. We selected a value of 1.5 for the basis of our calculations, since this lower range was in agreement with most of the available literature (*19*). $T_{1/2}$, the repair half-time, was thought to range from 0.25 h for fast repair to 6.5 h (*20*) for slow repair. We then repeated the calculation adopting the modification proposed by Guerrero and Li (*17*).

RESULTS

Treatment Outcomes

The overall median follow-up interval was 17 months (0.7–59 months). Table 2 and Fig. 1 illustrate the control rates after GKRS for each type of facial pain. Overall, 80% of patients experienced greater than 50% pain relief after GKRS. Fifty-six percent of patients achieved complete pain relief after GKRS, while 24% of patients received partial pain relief. Of these patients, 68% reported that GKRS had improved their quality of life. Overall, pain recurred in 23% of the patients who received initial pain relief. A significant association between the type of facial pain and the pain control rate after GKRS was observed in the study (Pearson; $P < 0.001$).

Table 3 depicts the median time to pain relief and median pain-free interval for both complete and partial pain relief patients. Complete pain relief represents both ''excellent'' and ''good'' facial pain outcomes. Partial pain relief represents the ''fair'' facial pain outcome. In the peer-reviewed literature, ''excellent'', ''good'' and ''fair'' (as we describe them in the Materials and Methods) are collectively defined as a positive outcome (*7*). For the purpose of this study, we therefore defined a ''treatment response'' to include excellent, good and fair pain relief.

Overall, the median time to either complete ($n = 143$) or partial ($n = 61$) pain relief was 4.0 weeks with a range of 0.1–87 weeks and 0.1–28 weeks, respectively. For those patients experiencing any degree of pain relief, there was no significant difference in median time to pain relief or median pain-free interval between any of the pain categories. Overall, the median complete pain-free interval was not reached during the follow-up period in this study.

Effect of Dose Rate and Treatment Time on the Control Rate of Facial Pain

Due to the exponential decay of the 201 ^{60}Co sources on the GKRS unit, the dose rate decreased over time from 3.627 Gy/min (09/07/1999) to 2.001 Gy/min (03/26/2004). Neither dose rate nor treatment time was significantly associated with either the control rate or degree of pain relief. This held true for the overall population of patients as well as for each category of type of pain. Figure 2 shows the relationship of the calculated BED to dose rate for the three most commonly used prescription doses. This suggests that, based on the biological parameters we had chosen, the biological model developed by Thames and Nilsson for continuous irradiation (*14*) appeared to accurately predict that the relative biological efficacy would remain essentially constant for a fixed prescription dose over one half-life, regardless of dose rate. The estimated difference in the BED between treatment times of 25 to 60 min (95% CI) was -11%.

Determination of $T_{1/2}$

We began with the equation for g, the continuous repair factor:

$$g = \frac{2(\mu t - 1 + e^{-\mu t})}{(\mu t)^2}$$

$$g(\mu t)^2 = 2(\mu t - 1 + e^{-\mu t})$$

$$\mu^2 t^2 g = 2\mu t - 2 + 2e^{-\mu t}$$

$$\mu^2 t^2 g - 2\mu t + 2 - 2e^{-\mu t} = 0$$

$$\mu^2 - \frac{2\mu t}{t^2 g} + \frac{(2 - 2e^{-\mu t})}{t^2 g} = 0$$

$$\mu^2 - \frac{2\mu t}{t^2 g} + \frac{(2 - 2e^{-\mu t})}{t^2 g} = 0$$

Then we defined

$$x = \frac{1}{t^2 g}$$

so that we could solve for μ, the recovery constant:

$$\mu^2 - 2\mu t x + x(2 - 2e^{-\mu t}) = 0 \text{ and}$$

$$(\mu - tx)(\mu - tx) = \mu^2 - 2\mu t x + t^2 x^2$$

then

$$t^2 x^2 = x(2 - 2e^{-\mu t})$$

$$t^2 x = (2 - 2e^{-\mu t})$$

$$2e^{-\mu t} = 2 - t^2 x$$

$$e^{-\mu t} = 1 - \frac{t^2 x}{2}$$

$$-\mu t = \ln\left(1 - \frac{t^2 x}{2}\right)$$

$$\mu = \frac{-\ln\left(1 - \frac{t^2 x}{2}\right)}{t}$$

$$\mu = \frac{-\ln\left\{1 - \frac{t^2[1/(t^2 g)]}{2}\right\}}{t}$$

$$\mu = \frac{-\ln\left(1 - \frac{1}{2g}\right)}{t}$$

Since treatment time t was known, this left us to define g to solve for μ. Thames and Nilsson (*14*) define the BED as:

TABLE 2
Facial Pain Control Rates

Type of pain	Facial pain control (%)				
	Pain relief	Excellent	Good	Fair	Poor
Overall (n = 256)	79.7	44.1	11.7	23.8	20.3
Typical TN (n = 172)	90.1	57.0	11.6	21.5	9.9
TN with atypical features (n = 42)	71.4	26.2	11.9	33.3	28.6
Atypical facial pain (n = 20)	60.0	15.0	20.0	25.0	40.0
Symptomatic TN (n = 8)	50.0	12.5	12.5	25.0	50.0
Trigeminal neuropathic pain (n = 8)	37.5	0.0	0.0	37.5	62.5
Postherpetic neuralgia (n = 6)	0.0	0.0	0.0	0.0	100.0

Notes. Excellent: complete pain relief with no medication use. Good: complete pain relief with medication use. Fair: 50–99% partial pain relief with or without medication use. Poor: less than 50% pain relief with or without medication use.

$$\mathrm{BED} = D\left(1 + g\frac{D}{\alpha/\beta}\right)$$

$$\mathrm{BED} = D + g\frac{D^2}{\alpha/\beta}$$

$$\mathrm{BED} - D = g\frac{D^2}{\alpha/\beta}$$

$$\frac{(\mathrm{BED} - D)(\alpha/\beta)}{D^2} = g$$

Since the dose D was also known, we could now—using our initial assumption for α/β—solve for g. This meant that we could now solve (using a simple Microsoft Excel spreadsheet) for μ and hence for $T_{1/2}$:

$$\mu = \frac{\ln 2}{T_{1/2}}$$

$$T_{1/2} = \frac{\ln 2}{\mu}$$

Calculating backwards, this resulted in a value of $T_{1/2}$ = 1.28. This raised the possibility that, at least at the doses used to treat this condition, the trigeminal nerve might respond more like an acutely reacting tissue, in which case an α/β of 10 should be used. We therefore repeated the calculations using this value, arriving at $T_{1/2}$ = 1.31. Since the classic linear-quadratic model applies to fractionated radiotherapy, we repeated the calculation using the modification proposed by Guerrero and Li (*17*) which extends the linear-quadratic model for the large fraction doses typically used in stereotactic radiosurgery, μt becomes ($\mu t + \lambda D$). Using their recommended values of λ = 0.01 and α/β = 3.86, we therefore arrive at a $T_{1/2}$ = 1.76 h. Using our initial value of α/β = 1.5, $T_{1/2}$ = 1.77 h; if we use an α/β of 10, $T_{1/2}$ = 1.77 h. Overall then, the clinically apparent value of $T_{1/2}$ for the trigeminal nerve appears to lie somewhere between 1 and 2 h.

DISCUSSION

Neither declining dose rate nor escalating treatment time was associated with a difference in the rate of facial pain control or degree of pain relief for patients undergoing GKRS. In our analysis, this held true for the overall patient population and for each of the individual types of pain. The statistical analysis of the dose rate accounted for changes in prescription dose over time to prevent prescription dose from being a confounding variable. Furthermore, the previously published treatment time analysis (*16*) accounted for the changes in both dose rate and prescription dose over time, reflecting that treatment time is inversely proportional to the dose rate at isocenter and directly proportional to the prescription dose (treatment time = prescription dose/dose rate at focus). The biological model we describe here also appeared to accurately predict that, given the input param-

TABLE 3
Time to Pain Relief and Length of Pain-Free Interval

Type of pain (n = complete, partial)	Median time to pain relief (weeks)		Median pain-free interval (years)	
	Complete (range)	Partial (range)	Complete (range)	Partial (range)
Overall (n = 143, 61)	4.0 (0.1–87)	4.0 (0.1–28)	1.0 (0.04–4.6)	0.75 (0.04–4.5)
Typical TN (n = 118, 37)	4.0 (0.1–87)	3.5 (0.1–28)	1.25 (0.05–4.6)	0.8 (0.04–4.5)
TN with atypical features (n = 16, 14)	4.0 (0.1–26)	2.0 (0.1–22)	1.0 (0.17–3.0)	0.7 (0.17–3.1)
Atypical facial pain (n = 7, 5)	1.0 (0.1–12)	6.0 (0.1–16)	0.67 (0.04–1.25)	0.8 (0.42–1.5)
Symptomatic TN (n = 2, 2)	5.5 (1–10)	3.5 (1–6)	0.54 (0.083–1.0)	0.42 (0.17–0.67)
Trigeminal neuropathic pain (n = 0, 3)	n/a	4.0 (3.0–12)	n/a	0.6 (0.6–2.25)
Postherpetic neuralgia (n = 0, 0)	n/a	n/a	n/a	n/a

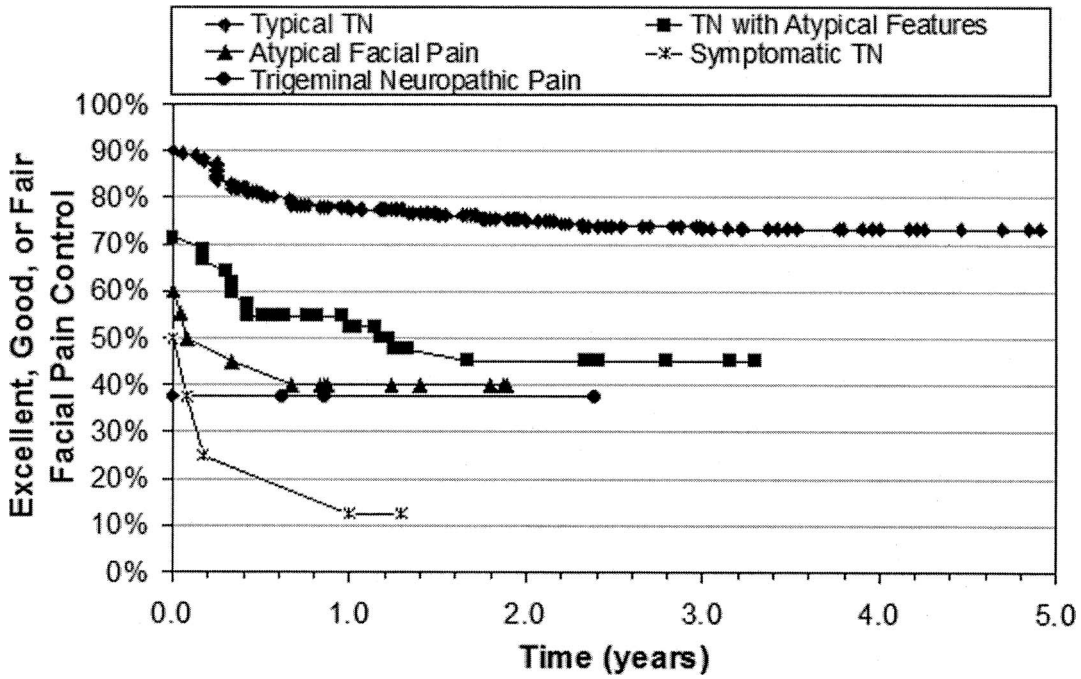

FIG. 1. Facial pain control after Gamma Knife radiosurgery and subsequent recurrence rates.

eters used, there would be no significant difference in clinical outcome. This may be related to the short treatment time relative to $T_{1/2}$.

A biological model exists to support the hypothesis of a dose effect. Kondziolka *et al.* published an animal model of correlative histopathology showing that axonal degeneration occurred at 80 Gy whereas frank necrosis was seen at 100 Gy (*21*). We found that the actuarial control rate varied significantly by dose (data not shown); however, the issue remains contentious because other authors have shown that escalating the treatment dose results in no significant increase in the duration of pain relief (*9, 12*). Using linear analysis of our data (not shown), we have found that the relative risk of numbness for a dose of 90 compared to 80 Gy is 1.34 (range 1.26–1.76, varying by pain type). Furthermore, patients with symptomatic trigeminal neuralgia caused by multiple sclerosis appear to have a much shorter median pain-free interval than those with classic TN, an unexpected finding in the setting of a demyelinating disease, suggesting a multi-factorial pathophysiology. Clearly, further research is required to assess the dose effect since ultimately the model must fit the clinical data and not the other way around.

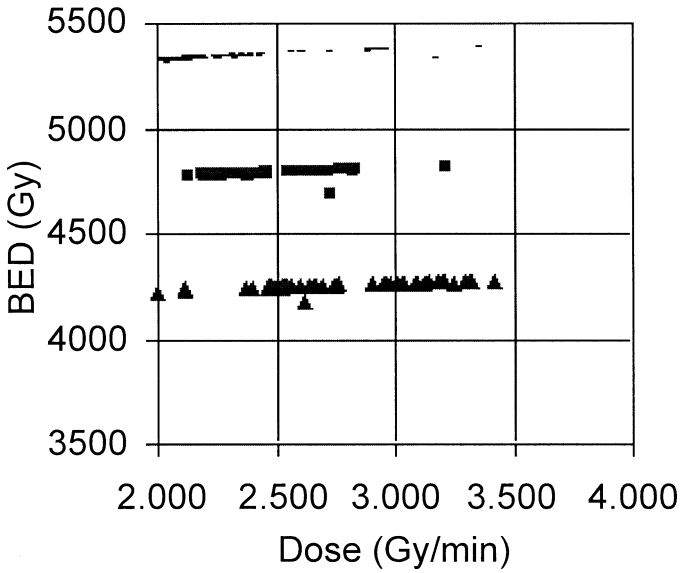

FIG. 2. Relationship of BED to dose rate for the three most commonly used prescription doses. (▲) 80 Gy, (■) 85 Gy, (—) 90 Gy.

A potential source of error in our analysis is the typical cross-sectional diameter of the trigeminal nerve, which is 2–3 mm. The mean deviation between imaging and mechanical measurement on a stereotactic MRI scan may be as high as 1.4 ± 0.5 mm (*22, 23*). The degree of operator error when manually setting the treatment coordinates is not known, but it should be ≤0.5 mm, based on personal experience. The design of the current Leksell Gamma Knife Model "C" eliminates operator error entirely; however, all treatments in this study were performed manually before our institutional upgrade to this model. Thus an estimation of the combined targeting error in any direction based on the above parameters is approximately 3.6 mm, meaning that pain recurrence could be related to a partial miss of the target (i.e. delivery of a sublethal dose), which in turn could artificially affect the relative BED values. Thus the actual BED may be quite different, and the value we have calculated should be interpreted as a clinical value in the context of Gamma Knife radiosurgery.

Another limitation of our study is the definition of re-

sponse in relation to the type of facial pain. A significant association between the type of facial pain and the pain control rate after GKRS was observed in our study (Pearson; $P < 0.001$). However, for those patients experiencing any degree of pain relief, there was no significant difference in median time to pain relief or median pain-free interval between any of the pain categories. For the purpose of this study, we therefore defined a treatment response as excellent, good or fair pain relief, i.e. any pain relief in any pain category. Treatment response was first defined in this manner by the University of Pittsburgh (*7*) and subsequently adopted by the Mayo Clinic (*8*) in their outcome analyses, for better or for worse making this the *de facto* clinical end point. We recognize that different categories of pain likely each have a different underlying pathophysiology. In fact, we may even have treated a small number of patients with true somatoform pain disorder, and we do not know if a placebo effect is even possible, but the fact that some of these patients responded to treatment emphasizes that the pathophysiology of facial pain not classified as classic trigeminal neuralgia deserves further investigation. Correlating the subjective experience of pain with functional and anatomic studies is an area of active research at our institution and other centers (*24, 25*).

ACKNOWLEDGMENT

Funding was provided through a grant awarded by Wake Forest University School of Medicine.

Received: March 14, 2006; accepted: March 15, 2007

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