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ARTICLE

Gamma knife radiosurgery for trigeminal neuralgia: first case series from Latin America

Radiocirurgia por gamma knife para tratamento da neuralgia do trigêmeo: primeira série de casos na América Latina

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ABSTRACT

Gamma Knife® radiosurgery (GKRS) for trigeminal neuralgia is an effective treatment with at least a 50% reduction of pain in 75-95% of patients. **Objective:** To present the first series of patients treated for trigeminal neuralgia using GKRS in Latin America. **Methods:** Retrospective analysis. Analysis consisted of time to improvement of symptoms, best Barrow Neurological Institute scale (BNI) score after procedure, time without pain, time to recurrence and post-procedural hypoesthesia. **Results:** Nineteen cases of classical trigeminal neuralgia were analyzed and three cases of symptomatic trigeminal neuralgia were described. Mean time from symptom onset to radiosurgery was 99.6 months, and 78.9% of patients had undergone invasive procedures before treatment. Patients were followed for a mean of 21.7 months. BNI I was achieved in 36.8%, IIIa in 21.1%, IIIb in 21.1%, IV in 5.3% and V in 15.7%. New hypoesthesia developed in 12.1% patients, which was associated with achieving BNI I after the procedure ($p < 0.05$). Time from diagnosis to GKRS was higher in patients who failed to achieve BNI I (143 vs. 76 months). The distance from the root entry zone in patients who achieved BNI I was greater than patients who did not (1.94 vs. 1.14 mm). Mean distance from the root entry zone in patients with new hypoesthesia was 2.85 mm vs. 1.06 mm ($p = 0.06$). **Conclusion:** Clinical response to GKRS is related to the time between diagnosis and procedure, thus its indication should be considered early in the management of these patients.

Keywords: Trigeminal neuralgia; radiosurgery; neuropathic pain

RESUMO

A radiocirurgia por Gamma Knife (GKRS) para neuralgia do trigêmeo é um tratamento comprovado, com redução de pelo menos 50% da dor em 75-95% dos casos. **Objetivo:** Apresentar a primeira série de pacientes tratados por neuralgia do trigêmeo com GKRS na America Latina. **Métodos:** Análise retrospectiva. A análise consistiu no tempo até melhora do sintoma, melhor escala do *Barrow Neurological Institute* (BNI) depois do procedimento, tempo sem dor, tempo até recorrência e hipoestesia pós-procedimento. **Resultados:** Dezenove casos de neuralgia do trigêmeo clássica foram analisados e três casos de neuralgia do trigêmeo sintomática foram descritos. Tempo médio entre começo dos sintomas e GKRS foi de 99,6 meses e 78,9% dos pacientes já tinham sido submetidos a procedimento invasivo prévio. O tempo de acompanhamento médio foi de 21,7 meses. BNI I foi conseguido em 36,8%, IIIa em 21,1%, IIIb em 21,1%, IV em 5,3% e V em 15,7%. Nova hipoestesia apareceu em 12,1% dos casos, o que foi associado a conseguir BNI I pós-procedimento ($p < 0,05$). Tempo desde o diagnóstico até GKRS foi maior em pacientes que não conseguiram BNI I (143 vs. 76 meses). Distância da zona de entrada do nervo em pacientes que conseguiram BNI I foi maior (1,94 vs. 1,14mm). Distância do zona de entrada do nervo em pacientes com nova hipoestesia foi de 2,85mm vs. 1,06mm ($p = 0,06$) Conclusão: A resposta à GKRS está relacionada ao tempo entre diagnóstico e procedimento, pelo que a indicação de GKRS deve ser considerada cedo no tratamento desses pacientes.

Palavras-chave: Neuralgia do trigêmeo; radiocirurgia; neuralgia

Trigeminal neuralgia is a disease characterized by facial pain in the somatosensory distribution of the trigeminal nerve. Typically, pain is described as shock-like, with spells of ultra-short duration, triggered by specific actions, such as teeth brushing, eating, speaking or even touching the affected area. Its incidence varies from 4.3 to 27 new cases per 100,000

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people per year[1,2,3], and a lifetime prevalence of 0.16–0.3%, according to population-based studies[2,3,4].

Non-pharmacological treatments for trigeminal neuralgia, such as percutaneous radiofrequency rhizotomy, percutaneous balloon compression, microvascular decompression, and stereotactic radiosurgery with either linear accelerator, Gamma Knife® or CyberKnife®, are effective treatments for trigeminal neuralgia. For Gamma Knife radiosurgery (GKRS), published series have revealed a benefit of at least a 50% reduction of pain in 75% to 95% of patients[5,6,7,8,9,10,11,12,13,14,15,16,17,18,19], with relapse of pain in 34–73% of patients, after a mean time of 2–4.2 years[16,17,18,19]. Maximal doses prescribed to the trigeminal nerve range from 70 to 90 Gy, although in the repeat setting, doses as low as 45 Gy have been found to yield a clinical response[20]. Thus far, the majority of the data regarding GKRS comes from United States and Europe, as access to GKRS in developing countries is still very limited.

Our objective was to present the first series of patients treated with GKRS for trigeminal neuralgia in Latin America with at least six months of follow-up.

METHODS

Patients who underwent GKRS for trigeminal neuralgia between October, 2012 and December, 2017 at the Neurological Institute of Curitiba, Brazil, were included in the study. The preprocedural diagnosis, demographic characteristics, such as sex and age at time of the procedure were obtained, as well as previous treatments, pretreatment hypoesthesia, time from symptom onset to GKRS, side and affected trigeminal branch(es) and the presence of arterial neurovascular conflict on magnetic resonance imaging. Facial pain was evaluated using the Barrow Neurological Institute Scale (BNI), which classifies pain in six grades: I: no pain, no medication; II: occasional pain without medications; IIIa: no pain, continued medications; IIIb: persistent pain, controlled with medications; IV: some pain, not controlled with medications; V: severe pain, no pain relief[18]. The BNI was recorded before the radiosurgical procedure, as well as during routine follow up. A post-procedural BNI of I, II and IIIa were considered a good response.

The procedure was performed using the Gamma Knife Perfexion equipment (Elekta, Sweden). A single shot was used in all patients. The distance between the 50% isodose line and the root entry zone (REZ) of the trigeminal nerve, prescription dose at 50% of isodose and brainstem dose in 10 mm^3 were also considered for analysis.

Follow-up analysis evaluated the time to improvement of symptoms, best BNI after the procedure, time without pain (if applicable), time to recurrence and post-procedural hypoesthesia. Information was mostly obtained from the last available follow-up on the electronic medical record; however, when the patient was followed in another centre, information was obtained via telephone.

Institutional review board approval was obtained from our institution's review committee and the need to obtain a consent form was waived.

For statistical analysis, Student's t-test was used to compare continuous variables, and a two-tailed Fisher's exact test was used for categorical data. A p-value < 0.05 was considered as significant.

RESULTS

Twenty-five patients underwent radiosurgery for trigeminal neuralgia at our centre during the study period. From these, 22 had a diagnosis of classical trigeminal neuralgia, and three of symptomatic trigeminal neuralgia, being one with multiple sclerosis, one with osteogenesis imperfecta type III and one with a petrous meningioma in contact with the trigeminal nerve. In three cases of classical trigeminal neuralgia, the last follow-up on the electronic medical record was less than six months, and contact with the patient was not achieved and they were, therefore, excluded from the analysis.

Classical trigeminal neuralgia

Nineteen cases of classical trigeminal neuralgia were included in the analysis (Table 1). There were eight women and 11 men in our series. The mean age at treatment was 68.5 years (range 44–95 years). All cases were unilateral, with 12 cases affecting the left trigeminal nerve. Seven cases (36.8%) had involvement of one branch of the trigeminal nerve, in eight cases (42.1%) two branches were involved, and the remaining four (21.1%) had involvement of the three branches of the trigeminal nerve. In 15 patients (78.9%), an arterial vascular conflict with the nerve was found on magnetic resonance imaging (two patients with a megadolichobasilar artery conflict). The mean time from symptom onset to radiosurgery was 99.6 months (range 24–456 months). Fifteen patients (78.9%) had already undergone some type of invasive procedure before radiosurgical treatment, with nine patients (47.4%) having some degree of hypoesthesia before radiosurgery.

Procedural data

The mean dose to the nerve was 86.5 Gy (range 80-90 Gy). The mean distance between the 50% isodose curve and the brainstem was 1.44 mm (range 0–4.5 mm) (Figure). In 10 patients, the shot was positioned in the REZ, with the 50% isodose curve partially involving the pons. The mean dose in 10 mm^3 of the brainstem was 47.45 Gy (range 9–61 Gy). In cases when the shot was positioned on the REZ, the mean dose was 49.7 Gy (range 40–61 Gy) vs. 19.9 Gy in the other cases (range 9-36 Gy).

Table 1. Preprocedural characteristics and procedural data of patients with classical trigeminal neuralgia.

N	Age	Sex	Side	Prior Treatment	Diagnosis-to-GK Time (months)	NVC	Trigeminal Branch Affected	Previous Hypoesthesia	GK		
									Distance from 50% isodose curve to REZ (mm)	Dose (Gy)	Brainstem Dose in 10 mm³
1	48	F	R	MVD	96	Yes	V2 + V3	Yes	2.2	42.5	17.2
2	44	M	R	No	24	Yes	V2 + V3	No	4.3	42.5	18.2
3	77	F	R	No	72	Yes	V1 + V2	No	3.4	42.5	15.4
4	95	F	L	No	456	No	V3	Yes	2.6	42.5	19.8
5	48	M	L	No	36	No	V1	No	4	35	9.0
6	67	M	L	PBC	180	Yes	V1 + V2 + V3	Yes	3.7	42.5	17.8
7	56	F	L	PBC + 2 RF	72	Yes	V2 + V3	No	4	43.8	20.4
8	63	F	R	No	24	No	V1 + V2 + V3	No	0.9	45	36.0
9	85	F	L	RF	24	No	V2	No	0	45	56
10	76	M	L	2 RF	148	Yes	V1 + V2 + V3	Yes	0	45	61
11	77	M	L	MVD + PBC + RF	180	Yes	V2 + V3	Yes	0	40	50
12	51	M	L	MVD + PBC	120	Yes	V1 + V2 + V3	Yes	0	45	55
13	87	M	L	PBC + 3 RF	144	Yes	V2 + V3	Yes	0	45	45
14	67	M	R	2 PBC	132	Yes (Basilar)	V1 + V2	Yes	0	45	42
15	78	F	R	PBC	48	Yes	V3	No	2.2	45	25
16	54	M	L	2 PBC	84	Yes (Basilar)	V2	Yes	0	40	55
17	85	M	R	No	120	Yes	V1	No	0	45	46
18	63	M	L	MVD	108	Yes	V2 + V3	No	0	45	47
19	81	F	R	PBC + RF	180	Yes	V3	No	0	45	40

F: female; M: male; R: right; L: left; MVD: microvascular decompression; PBC: percutaneous balloon compression; RF: radiofrequency trigeminal rhizotomy; GK: Gamma Knife; NVC: neurovascular conflict; V1: ophthalmic branch of the trigeminal nerve; V2: maxillary branch of the trigeminal nerve; V3: mandibular branch of the trigeminal nerve; REZ: root entry zone; Gy: gray; BNI: Barrow Neurological Institute Scale.

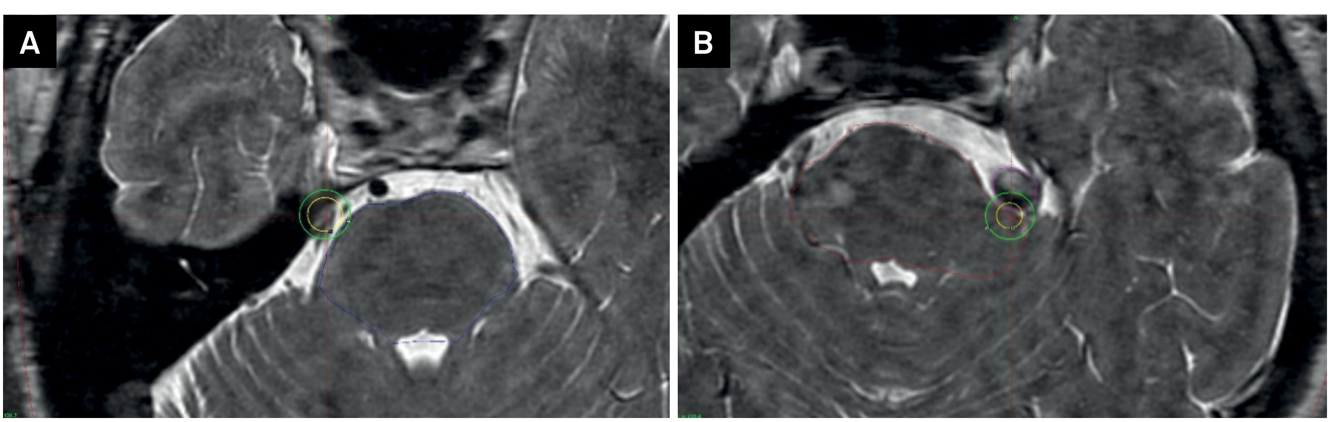

Figure. Radiosurgical planning for trigeminal neuralgia. A: Planning for a right V2 and V3 trigeminal neuralgia with distance between the 50% isodose line and the root entry zone of 4.3 mm. B: Planning for a left V2 trigeminal neuralgia the 50% isodose line on the root entry zone. A megadolichobasilar artery distorting the nerve can also be seen.

Follow-up results

Patients were evaluated for a mean follow-up of 21.7 months (range 6–66 months). All patients had a score of BNI V before treatment (Table 2).

At the last follow-up, a good response was achieved in 57.9%, with the best clinical outcome registered as BNI I in seven patients (36.8%), BNI IIIa in four patients (21.1%), BNI IIIb in four patients (21.1%), BNI IV in one patient (5.3%) and,

Table 2. Outcomes of patients who underwent Gamma Knife radiosurgery for classical trigeminal neuralgia.

N	Last Follow-up					
	Months after GK	BNI before treatment	Best BNI after treatment	Time to best BNI (months)	Duration of best BNI response (months)	Postprocedural hypoesthesia
1	66	V	I	1.5	73	Yes
2	55	V	I	11	10	Yes
3	32	V	IIIb	1	17	No
4	31	V	IIIa	1.5	14	Yes
5	31	V	V	-	-	No
6	30	V	IIIb	2	26	Yes
7	27	V	I	2.5	18	Yes
8	22	V	I	12	4	Yes
9	20	V	IIIa	3	14	No
10	17	V	I	2.5	9,5	Yes
11	16	V	IIIb	2	Not recalled	Yes
12	11	V	V	-	-	Yes
13	10	V	IV	1	Not recalled	Yes
14	10	V	IIIb	3	Not recalled	No
15	9	V	I	4	4	Yes
16	7	V	IIIa	3	4	Yes
17	6	V	I	1	5	No
18	6	V	V	-	-	No
19	6	V	IIIa	3	2	No

GK: Gamma Knife; BNI: Barrow Neurological Institute Scale.

in three patients (15.7%), there was no improvement after the procedure (BNI V).

The time from diagnosis to GKRS was longer in patients who failed to achieve BNI I (143 vs. 76 months, $p = 0.15$). In patients where the pain improved (BNI I-IIIa), the mean time to best BNI was 3.86 months (range 1–12 months), and they sustained that response for a mean period of 14.4 months (range 2-66 months). In patients who achieved BNI I, the clinical response was sustained for a longer period (mean 17.6 months).

In patients without neurovascular conflict, a good response was achieved in 75% (3/4 patients), BNI I was achieved in one patient, BNI IIIa in two patients, and one patient did not improve (BNI V). For cases with neurovascular conflict, a good response was obtained in 53.3% (8/15 patients), BNI I was achieved in six patients, BNI IIIa in two, IIIb in four, BNI IV in one, and two patients did not improve. On the other hand, six out of seven patients who achieved BNI I (85.7%) had an arterial neurovascular conflict, compared with nine out of 12 patients (75%) in the group who did not ($p = 1.0$).

The distance between the 50% isodose and REZ in patients who achieved BNI I was greater than in patients who had poorer BNI scores (1.94 vs. 1.14 mm, $p = 0.34$). In patients on whom the shot was positioned in the REZ (10 patients), a good response was found in 50%, with the best BNI achieved being I in two patients, IIIa in three patients, IIIb in two patients, IV in one patient, and V in two patients. Patients with a more peripheral shot had a good response in 66.7%, with BNI I in five patients, IIIa in one patient, IIIb in two patients and V in one patient ($p = 0.65$).

Twelve patients had hypoesthesia on their last follow-up, which appeared after radiosurgery in four patients (12.1%). One patient who had hypoesthesia before radiosurgery improved during follow-up. All four patients with new hypoesthesia after GKRS achieved BNI I in a mean time of nine months (range 4-18 months). The occurrence of new hypoesthesia was directly associated with achieving BNI I after the procedure ($p < 0.05$). The mean distance from the REZ in patients with new hypoesthesia was 2.85 mm vs. 1.06 mm ($p = 0.06$). The mean dose delivered in patients with new hypoesthesia was 44 Gy (vs. 43 Gy for the rest), and the mean brainstem dose in $10mm^3$ was 24.9 Gy vs. 49.7 Gy ($p = 0.15$). There were no other side effects or complications associated with the procedure.

Symptomatic trigeminal neuralgia

Three treated patients had symptomatic trigeminal neuralgia and were, therefore, excluded from the statistical analysis. Their information is shown below:

Patient 1: A 40-year-old man with a prior diagnosis of multiple sclerosis, and a 60-month history of right V2 and V3 trigeminal neuralgia, BNI V. The patient underwent GKRS using a single shot with 42.5 Gy at 50% isodose, 2.2 mm from the REZ. The patient experienced early improvement, achieving BNI I for 35 months. No hypoesthesia occurred during a follow-up of 41 months.

Patient 2: A 30-year-old woman with a diagnosis of osteogenesis imperfecta type III. The patient developed a left V3 trigeminal neuralgia 49 months prior to GKRS, and had already undergone two percutaneous balloon compressions, but remained BNI V. The patient underwent treatment with 45 Gy at 50% isodose (maximum dose 90 Gy), 2.8 mm from the REZ. She achieved BNI I after four months, maintaining that response for eight months, as well as developing post-treatment hypoesthesia.

Patient 3: An 82-year-old woman with a small petrous apex meningioma in mild contact with the trigeminal nerve. Due to her clinical condition, she was not suitable for surgical resection of the tumor and was, therefore, treated with GKRS. Eighteen months after radiosurgery, she developed a left V2 and V3 trigeminal neuralgia, so a new radiosurgical procedure, focusing on the nerve, was planned six months after symptom onset. A dose of 42.5 Gy was delivered at 50% of the isodose (maximum dose 85 Gy), achieving immediate improvement of the pain, and remaining BNI I for nine months. The patient developed paroxysmal hypoesthesia after radiosurgery

DISCUSSION

GKRS has been proposed as a major treatment for refractory cases of trigeminal neuralgia for the last 30 years. Experimental studies of the trigeminal nerve after stereotactic radiosurgery have shown changes in the nerve, mostly related to axonal degeneration and edema, which are supposedly related to the axonal nerve block, decreasing paroxysms and pain[21]. Blocking sodium channels is probably the most important functional change related to clinical improvement[22,23]. In most American centers, this is the procedure of choice in patients with trigeminal neuralgia who cannot undergo surgical microvascular decompression[24,25].

Kondziolka et al.[5] proposed that the dorsal REZ is more radiosensitive than more distal portions of the nerve (transition between more radiosensitive oligodendrocytes and more resistant Schwann cells). This finding was supported by data from Columbia University, which demonstrated improved pain outcomes in patients with greater volumes of brainstem receiving a dose of 15 Gy[26]. Alternatively, others have proposed the pars triangularis as an optimal location for the isocenter, because the increasing caliber of the nerve at this point allows a larger anatomic target and the distal location along the nerve, yields a lower brainstem dose[27]. Multiple series have supported the observation that placement of the radiosurgical isocenter at the pars triangularis yields a lower rate of trigeminal nerve dysfunction and equivalent pain relief to more proximal isocenter locations[8,27]. Our series failed to show a significant association between distance from the REZ and clinical outcomes, but a tendency toward a greater distance from the REZ was seen in patients with a good response (1.94 vs. 1.14 mm).

The presence of neurovascular compression does not seem to predict the response to GKRS, but an association between the isocenter and site of compression has been described[28]. Our series also failed to find an association between the neurovascular conflict and clinical response; nevertheless, most patients who achieved BNI I had an arterial conflict. Of the patients with dolichobasilar neurovascular conflict, one achieved BNI IIIa and the other IIIb.

Hypoesthesia is the most common complication of the procedure, occurring in 6–42% of patients[19,29,30,31,32,33,34,35], with the location isocenter along the trigeminal nerve associated with the development of this side effect[8]. Overall, our series showed 63% of hypoesthesia on follow-up, but most patients (8/12) already had hypoesthesia before radiosurgery, due to previous procedures. Post-radiosurgical hypoesthesia has been advocated as the most significant factor predicting treatment efficacy, with the pons maximum dose, REZ dose, and dose at the petrous dura not directly affecting efficacy[16,35,36]. Likewise, we found a significant relationship between the presence of new hypoesthesia and the probability of achieving BNI I, without a difference in REZ distance, dose delivered to brainstem or other anatomical variables. A tendency toward a greater distance from the REZ (2.85 mm vs. 1.45 mm), as well as a lower mean dose delivered to the brainstem (24.9 Gy vs. 35.3 Gy) was also found. Of note, the four patients with new hypoesthesia did not report it as being bothersome, or interfering with daily activities in any way.

There is a history of other invasive treatments that have been associated with a decreased response to GKRS[26], so this may be a factor to account for our results, which were within the range of what has been published, but on the lower end of the spectrum. Moreover, early radiosurgical treatment, specifically within five years of symptom onset has been associated with more favorable outcomes[32,37]. Given the socioeconomic characteristics of our country, access to Gamma Knife radiosurgery is still very limited, which, due to the lack of awareness of some physicians, who care for these patients, of the local availability of this treatment modality, may have contributed to a longer interval between the onset of symptoms and radiosurgical treatment. In our series, the mean time between diagnosis and treatment was 118 months, which would explain our lower response rate when compared with other series (57.9% of good response), even though we were still able to detect a difference between the mean time and the clinical response (76 months for good response vs. 143 months for poor response).

Even though we present a small number of patients, to our knowledge, this is the first report of GKRS for trigeminal neuralgia from South America. Our center began offering

GKRS in 2012 and, since then, only 25 patients with trigeminal neuralgia have been treated, with an increasing number of patients each year (one in 2012, one in 2013, two in 2014, five in 2015, five in 2016, 11 in 2017). We hope that more studies coming from developing countries will help to increase access to this modality for a wider population.

In conclusion, GKRS is a safe and feasible treatment for trigeminal neuralgia. As the clinical response is related to the time between diagnosis and procedure, its indication should be considered early in the management of these patients. Even in our small sample, the appearance of hypoesthesia after radiosurgery was associated with a better clinical response.

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