Treatment of primary trigeminal neuralgia: A comparative study of microvascular decompression surgery and stereotactic gamma knife radiosurgery

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ABSTRACT

Objectives: To compare the clinical efficacy of microvascular decompression surgery (MVD) and gamma knife radiosurgery (GKR) as a treatment for patients with primary trigeminal neuralgia (TN) and evaluate the outcome regarding pain relief, recurrence, and complications with both modalities of treatment. 3738

Patients and Methods: A randomized prospective study conducted in SaadAlwitry Neurosciences Hospital, Baghdad, Iraq. Eighty-four patients with TN from January 2016 to January 2018, 45 patients had GKR while 39 patients treated with MVD. The pain evaluated pre- and post-operatively using the Barrow Neurological Institute Pain Intensity scale (BNIPI), visual analog scale (VAS) and Brief Pain Inventory Facial (BPI-Facial) scoring systems. In GKR procedure, the trigeminal root entry zone targeted with a radiation dose of 80 Gy. MVD was performed using retro-sigmoid approach. Follow-up period was two years.

Results: Both groups showed a considerable decrease in BNIPI scores and VAS scores in the postoperative two years follow-up compared with the preoperative scores with a *P*-value <0.01. However, pain relief rate was significantly higher in the MVD group (92.3%) compared to that of GKR groups (73.3%) with a *P* value of 0.02. Postoperative VAS scores of the MVD group were remarkably lower as compared with those treated with GKR during the same postoperative time . (*P*=0.01).

Conclusion: GKR and MVD offered safe and efficient treatment options. MVD remains the standard surgical method of treatment for patients with TN with better pain relief rate, lesser pain recurrence rate and faster response than GKR.

Keywords: Gamma knife radiosurgery, Microvascular decompression surgery, Stereotactic radiosurgery, Trigeminal neuralgia.

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Introduction

TN, also known as tic douloureux, is a disorder characterized by recurrent unilateral brief, electric, shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve, often triggered by innocuous trigeminal tactile stimuli.[1] It may develop without apparent cause (classic or typical TN) or may be a result of another diagnosed disorder (secondary or symptomatic TN).[2,3,4]

In this study, we tried to evaluate the clinical outcome for patients with TN in whom they did not respond well to conventional medical therapy. The patients divided randomly into two groups to compare the therapeutic effect of both available treatment modalities namely the Microvascular Decompression Surgery (MVD) and the Gamma Knife Radiosurgery (GKR).

Patients and Methods:

This study is a randomized prospective of 84 patients with TN followed from January 2016 to January 2018 in SaadAlwitry Neurosciences Hospital, Baghdad, Iraq.

We applied demographic analysis concerning age, gender, and clinical presentation. This analysis also included a description of the pain distribution within trigeminal nerve branches and different pain intensity scales/scores. The criteria for patients selection were:

1. All patients with TN referred by a neurologist to neuroscience hospital/ surgery department to receive surgical treatment.
2. Patients had high BNIPI scale[5] (BNIPI IV and BNIPI V).
3. Only primary TN included in this study.
4. All patients did not respond to adequate trial of medical treatment.
5. None of the patients received prior surgical or radiosurgical treatment.

All the patients were informed about all the details within each treatment procedure and were allowed to choose their own treatment between GKR and MVD.

All the patients submitted a written consent prior to going into surgery or radiosurgery and all of the selected patients were informed about this study and written consent was taken from them for general publication purposes.

We used the BNIPI also used as an initial assessment step in patient's evaluation. The BPI-Facial[5] range used to evaluate multiple dimensions of pain in patients with TN. VAS[5] was also implemented to all patients to assess general pain relief. Postoperative complications for both procedures were also recorded in this study.

We apply treatment procedure of GKR using Gamma Knife Perfexion, Elekta. One isocentre of 4 mm away from the brainstem targeting trigeminal nerve entry zone via a 4 mm collimator window with selected collimator blocking of the nearby brain stem. The target dose was 80 Gy. The brainstem dose was <10 Gy.

MVD was carried out by retro-sigmoid craniotomy. Park Bench position was used with the head turned toward the contra lateral side. The vessels separated from the trigeminal nerve with Teflon.

Patients follow-up:

analyses. In this study, we assumed statistical significance as *P*<0.05.

Results:

Eighty-four patients diagnosed with TN. Forty- five patients (39 with typical TN, and 6 with atypical TN) managed with GKR and thirty-nine patients (35 with typical TN, and 4 with atypical TN) treated with MVD. The GKR group consisted of 15 males (33.33%) and 30 females (66.67%) with age ranging from 25-81 years (mean age ± standard deviation = 54.13± 16.01). The mean duration of pain in the GKR patients was 6.38±2.95 years. The MVD group included 9 males (23.08%) and 30 females (76.92%) with age ranging from 22-78 years (mean age ± standard deviation = 44.92 ± 14.79). The mean duration of pain in the MVD patients was 10.93±7.25 years The age difference between the two group was not significant (*P* = 0.062) while there was a considerable difference in the patient's gender (females are more affected in both groups with *P* = 0.013).

Distribution of pain:

Both groups showed no involvement of V1 branch of the trigeminal nerve but showed the highest affection with the combined V2 and V3 branches of the trigeminal nerve (40% in GKR group and 61.54% in MVD group). The variation between the pain distribution between the two groups was not significant (*P* = 0.418). Most of the patients were complaining from right sided pain (80% in GKR group and 84.62% in the MVD group) with three patients experienced bilateral distribution over V1 and V2 branches of the trigeminal nerve (6.67% in the GKR group). This difference was not significant (*P* = 0.473).

The facial numbness presented in both groups; nine patients (20%) experienced facial anesthesia in the GKR group. The MVD group also showed nine patients (21.43%) presented with associated facial numbness.

The vessel involved in the MVD group:

Patients assessed immediately following treatment to evaluate the post- operative complications.

We carried out regular three months intervals of assessment using BNIPI and VAS scores for two years and we calculated the Mean Change Score. This Score includes the raw and percentage change score for each of the three domains of the BPI-Facial score: pain intensity, composite general interference, and the composite facial interference. For each patient, we calculated the raw change score by subtracting the follow-up score from his/her baseline score. Whenever the result was a positive number, this reflects a decline in the pain intensity and interference while an adverse effect corresponds to a worsening in the patient condition and interference. We calculated the percentage change by dividing the raw change score by the baseline score.

Patient Global Impression of Change (PGIC):[5]

In the final assessment, we used the PGIC as one method assessing success or failure of the two surgical procedures. The PGIC is a 7-point Likert scale of overall change in which we ask the patients to choose one of seven descriptors that best describes how their symptoms have improved or worsened. The seven options are as follows:

1. Very much improved 2. Much improved 3. Minimally improved 4. No change 5. Minimally worse 6. Much worse 7. Very much worse

Procedure failure:

Procedure failure was estimated based on one of the following:

1. BNIPI score of IV or V.
2. PGIC of a worse condition/no change
3. Negative raw and percentage change.

Statistical analysis:

The independent samples t-test used to analyze the continuous data. Microsoft Excel 2013 was used for data input, calculation and utilized for performing

Pre- and post-operative pain assessment with BNIPI and VAS scores:

BNIPI score distribution preoperatively was similar between GKR and MVD groups (*P*-value = 0.136 which represents non-significant sample variation). VAS score distribution was also similar between the two groups with *P*-value =0.437 (non-significant sample variation). The detailed distribution of both preoperative BNIPI and VAS scores shown in table 1.

In 24 patients (61.54%) the trigeminal nerve compressed by the superior cerebellar artery (SCA) while in nine patients (23.08%) compressed by both SCA and anterior inferior cerebellar artery (AICA). Venous compression by the superior petrosal vein (Dandy's vein) found in six patients (15.38%). When no vascular impingement was found, we performed longitudinal incisions in the neural sheath of the trigeminal nerve.We could not identify the compressing vessel in the GKR group by MRI.

Table 1. Initial pain assessment with BNI and VAS scale.

	GKR	%	MVD	%	Total	%	*P*-value
BNIPI IV	27	60	15	38.46	42	50	0.136
BNIPI V	18	40	24	61.54	42	50	
VAS mean	8.47		8.54		8.5		0.437
ST Deviation	1.187		1.198		1.171		

Postoperatively, both samples that received treatment by GKR and MVD showed significant improvement in BNIPI scores compared with their respective preoperative BNIPI scores (*P*<0.01). The total number of patients with TN who received GKR and had pain relief (BNIPI score I-III) was 33 out of 45 (73.3%) after two years of follow-up while the total number of patients with TN who received MVD and attained pain relief was 36 out of 39 (92.3%). There was a noticeable difference in the total remission rates (73.3% for GKR compared to 92.3% for MVD) with *P*-value= 0.02 (table 2).

The postoperative VAS scores mean for GKR and MVD were significantly lowered as compared with their respective preoperative VAS scores (*P* <0.01). However, MVD group shows a significantly better decrease in the VAS score compared to that of GKR group at different points (*P*≤0.01) (table 2).

Table 2. Therapeutic effect of GKR and MVD after two years of follow-up.

	BNIPII	BNIPI II	BNIPI III	BNIPI IV	BNIPI V	*p*-value
Pre-GKR	-	-	-	27	18	
Post-GKR	9	9	15	12	0	< 0.01*
Pre-MVD	-	-	-	15	24	
Post-MVD	24	3	9	3	0	< 0.01**
Post-GKR						0.02***

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Post-MVD						
***Comparison of BNI of GKR before and after treatment.** ****Comparison of BNI of MVD before and after treatment.** *****Comparison of BNI treated by GKS and MVD after two years of follow-up.**						

	GKR	**MVD**	
VAS mean	3.67	1.53	<0.01*
ST Deviation	2.71	1.89	<0.01**
Post-GKR **Post-MVD**			0.01***
***Comparison of VAS of GKR before and after treatment.** ****Comparison of VAS of MVD before and after treatment.** *****Comparison of VAS treated by GKS and MVD after two years of follow-up.**			

deviation = 7.07 ±0.85to 3.21 ± 2.01 in GKR group and from mean ± standard deviation = 6.08 ± 1.5 to 1.57 ± 1.03 in the MVD group). However, there was a remarkable difference in all categories of the BPI-Facial score favoring MVD over GKR (table 3).

Pre and postoperative pain assessment with BPI-Facial and PGIC scores:

Both groups showed a significant decrease in all three categories of the BPI-Facial scale. The highest noticed reduction in the interference with facial specific activities category (from mean ± standard

Table 3. Pre/Post-operative pain assessment with BPI-Facial scale.

	Pain intensity mean ±STDev.	**Interference with general activities ±STDev.**	**Interference with face specific activities ±STDev.**
Pre - GKR	4.63 ± 1.36	4.58 ± 1.36	7.07 ±0.85
Post – GKR	3.08 ± 2.14	2.82 ± 1.48	3.21 ± 2.01
	P= 0.012	*P*<0.01	*P*<0.01
Pre – MVD	4.58 ± 1.69	4.85 ± 1.75	6.08 ± 1.5
Post – MVD	1.33 ± 1.61	1.18 ± 0.58	1.57 ± 1.03

	P =0.011	*P*<0.01	*P*<0.01
GKR/MVD	*P* =0.01	*P*<0.01	*P*<0.01

In the MVD group, the results were better with the highest percentage of patients described their PGIC being "Very much improved" and "Much improved" equally, reaching about 46%. Only three patients (8%) described PGIC of "No change"(table 4).

We calculated the patients PGIC after two years of post-surgical procedure follow-up in each group. The highest results in the GKR group was "Much improved" reaching to 40% while about 7% of patients described a PGIC of "No change" and about 7% of patients described a PGIC of "Minimally worse."

Table 4. A post-operative PGIC score of MVD and GKR groups.

	Very Much Improved	Much improved	Minimally improved	No change	Minimally worse
GKR	9	18	12	3	3
%	20	40	26.67	6.67	6.67
MVD	18	18	0	3	0
%	46.15	46.15	0	7.69	0

We found that the raw change score (subtracting the follow-up score from baseline score in each category of the BPI-Facial score) and the percentage change was more in patients who described their PGIC of "Very much improved" in both groups (table 5).

Table 5. Detailed PGIC scale with Raw and Percentage change.

PGIC	**GKR**					
	Pain intensity		Interference with general activities		Interference with facial specific activities	
	Raw change	**Percentage change**	**Raw change**	**Percentage change**	**Raw change**	**Percentage change**
Very much improved	4.5 ± 1.15	100 ± 0	3.62 ± 1.95	74.27 ± 17.29	5.81 ± 0.08	79.39 ± 8.66
Much improved	1.42±1.07	32.28±21.76	1.62±1.22	34.06±13.75	4.38±1.01	66.2±13.03
Minimally improved	0.25±2.01	0.12±45.92	089±1.16	18.04±25.05	3.07±1.54	40.71±22.41
No change	1.5±0	20±0	3.14±0	53.66±0	1.86±0	30.95±0
Minimally worse	-1.25±0	-25±0	-0.86±0	-17.14±0	0	0
Much	-	-	-	-	-	-

worse						
Very much worse	-	-	-	-	-	-
MVD						
Very much improved	3.29±0.99	88.70±10.07	3.95±1.84	83.72±9.65	5.12±1.40	88.05±5.07
Much improved	3.33±1.40	70.24±10.23	3.67±1.99	68.73±12.05	4.05±1.53	65.25±10.48
Minimally improved	-	-	-	-	-	-
No change	1.50±0	19.35±0	2±0	46.67±0	3.57±0	48.08±0
Minimally worse	-	-	-	-	-	-
Much worse	-	-	-	-	-	-
Very much worse	-	-	-	-	-	-

significance seems to be decreasing over time (*P*-value increases over time).

Postoperative complications and hospital stay:

There was no postoperative hospital stay for GKR group. The average hospital stay for MVD group was five ± 1.79 days ranging from 3 to 10 days.

There was no corneal numbness, eye problem, diplopia nor a hearing problem in both groups. For the MVD group, there wasn't any symptoms or signs for bacterial or aseptic meningitis, but there was a local wound infection in six patients (15.38%) which were treated by simple conservative measurement by meticulous dressing and oral antibiotics.

Three patients (7.69%) in the MVD group suffered from postoperative transient ataxia that lasted for one week. However, this was not significant when compared to the GKR group who did not show any

Postoperative pain remission rate:

Both samples showed pain relief over time. The GKR group showed pain remission rate of 27% during the first postoperative week compared to 69% in the MVD group. The mentioned two rates revealed a significant difference between the two groups ($P<0.05$).

After three months, GKR group showed increased pain remission rate reaching 46.67% but still significantly different from the pain remission rate of MVD which was 76.92% ($P<0.05$).

The pain remission rate continues to rise in both GKR and MVD groups within six months (66.67% and 84.62% respectively, with $P<0.05$). We noticed that within two years after the operation, the pain remission rates peaked reaching 73.33% in GKR and 92.31% in MVD group with P = 0.021. Although the remission rates were significantly different in both groups, the higher rate reaching to about 6:1.[8] Loeser J. performed a clinical study to document the distribution of pain in patients with TN in which it shows that the higher percentage of trigeminal nerve division involvement was about 31% of patients over the V2 and V3 divisions. About 18% of patients with pain over V1, 2 and three divisions. Isolated V2 division pain of TN was reaching to about 17%, isolated V3 involvement was about 15%, and isolated V1 division pain of TN was infrequent reaching to 3% only.[9] Those can consolidate our study in which the highest involvement was with the combined V2 and V3 divisions of the trigeminal nerve reaching to about 50%. Combined V1, 2, three divisions involvement of the TN was reaching to about 14%. Isolated involvement of V3 division was the highest percentage among isolated division involvement achieving to about 21.4%. Separate V2 affection was 11% with no participation of V1 division in both groups.

Some studies suggested that bilateral involvement is present in only 3- 5% of patients, although no patient has bilateral tic pain during one episode.[9,10] In a retrospective study by Pollack and colleagues, patients that presented with bilateral TN were more commonly females.[11] All mentioned findings support our research since only one female patient from our sample (3.57%) suffered from the bilateral involvement of the trigeminal nerve over V1, two divisions of the trigeminal nerve.

About 83% of patients with primary TN reported to have vascular compromise of the trigeminal nerve, with 63.8−80% of such vessels found to be SCA and 9−35% being veins.[12,13,14,15,16] Approximately 84.62% of patients in our study who underwent MVD showed that the trigeminal nerve compressed by patient with cerebellar signs (*P* = 0.168). Three patients in the GKR group (6.67%) showed symptoms and signs of anesthesia Dolorosa (*P* = 0.167) when compared to the MVD group with no patients with this complication. Both GKR and MVD groups developed paresthesia (26.67% for GKR and 23.08% for MVD groups) and dysesthesia (26.67% for GKR and 7.67% for MVD groups) within the trigeminal nerve divisions with no significant differences in both procedures (*P*=0.417 and 0.095 respectively).

Discussion:

In our prospective study, the findings showed that both MVD and GKR procedures were safe and effective. Both are recommended as a first-line surgical treatment for patients with TN and can be recommended as an adjunctive line of therapy as well.

In a similar retrospective study by Dai Z. and colleagues, TN showed a slight female predominance (44.5% of the study samples were males, and 55.4% were females).[6] In our study, we noticed that our patients express a much higher female predominance reaching to about 71% compared to about 29% of male dominance. However, another reported series showed that there is a variation of female: male ratio from 2:1 to 4:3, which can support our study. [7] The mean age ± standard deviation that reported in the mentioned study was 63 ± 10.7 years in the GKR group and 58 ± 11.6 years with the highest age group was 60-70 years reaching to about 40% of the total sample.[6] In our study, it seems that the mean age ± standard deviation is less for both groups (54.13 ± 16.01 in the GKR group and 44.92 ± 14.79) with the highest percentage of patients (53%) being in a younger age group (< 50 years).

In the previous study, the incidence of TN was 4-5 per 100,000 population involving mainly the right side more often than the left side at a ratio about 3:2 in which supports our study but with a much possible that missed additional compression of the trigeminal nerve by the trigeminal vein (which compresses the posterior and inferior aspect of the nerve) is the cause. This vein usually drains into the superior petrosal sinus and may be missed if only microscope used because of obstruction of the view by a prominent ridge of the petrous bone. It is wise to use the endoscope to look 360° around the nerve roots and look at the nerve entrance to the Meckel's cave.[27] Our study showed that MVD is a safe procedure as a surgical treatment for patients with TN with minimum complications. Our patients did not express any facial paralysis nor hearing loss. Apfelbaum study showed that the rate of moderate to severe facial weakness reached about 0.5% in which 14 patients had hearing loss (nine of them had a permanent hearing loss).[13] Our study sample was much smaller than the mentioned study, so, it is also possible that with such a low incidence of this complication cannot be assessed accurately in our research. Dai Z and colleagues showed that their MVD group developed postoperative herpes zoster around the mouth (15 of 87 patients in their MVD group). It was attributed to reactivation of latent herpes zoster in the trigeminal nerve after treatment with MVD.[6] In our study, MVD group did not show this complication. It may be due to our sample size. In a consecutive series of 559 patients treated with MVD between November 1975 and June 2009, only three deaths occurred due to cerebellar hemorrhagic infarction.[28] No mortality occurred in our study, and we believe that this potentially lethal complication prevented by avoiding veins sacrificed during surgery. In the same mentioned series, occasionally, some patients experienced non-painful, twinge-like cerebellar arteries and about 15.38% of patients showed that the compression of the trigeminal nerve was via veins.

Two studies showed that patients with TN who were treated by MVD expressed excellent results with up to 98% of patients reporting immediate pain relief and more than 85% and 80% of patients pain-free without medication at the 5 and nine years follow-up, respectively.[17,18]

Other previous studies showed that the success rate of MVD for the treatment of TN ranged from 75-100%.[19,20,21,22]

In our study, patients showed spectacular results with more than 93% success rate within six months of follow-up. Theoretically, patients should express immediate pain relief following MVD. However, only 69% showed immediate pain relief within the first postoperative week, and it took one month to reach about 77% success rate. We believe that this delayed response was due to the long-term vascular compression, which might result in demyelination of the trigeminal nerve. It is possible that a longer disease history and a higher VAS score of the patient before the treatment results in a more resistant/refractory patient to this modality of treatment.

Only three of the thirty-nine patients who treated with MVD (about 7.7%) experienced pain recurrence within two years of follow-up. Dai Z and colleagues supported our study showing that 6.9% of patients showed pain recurrence six months following surgery.[6] Other studies suggested that the pain recurrence rate in patients with TN treated by MVD was from 1-19.4%.[23,24,25,26] Potential factors that may lead to pain recurrence include new compression site over the trigeminal nerve, misplacement of the Teflon patch, and formation of granulation tissue/adhesions around the Teflon patch and the trigeminal nerve. It is also supported by a survey by Tayler, Kabara, et al. who conducted a study to examine the difference between 70 Gy and 90 Gy effect on patients receiving GKR for TN. He noticed that patients receiving 90 Gy experienced the shortest duration of pain relief, the highest pain remission rate (93.2%), and the lowest pain recurrence rate (11.9%).[34] Other studies anticipated more postoperative complications with a dose more than or equal to 90 Gy.[35,36]

In Douglas Kondziolka et al. study no patient had nausea or headache after stereotactic radiosurgery, and no patient developed new neurological deficits or systemic complications.[37] This study supports ours concerning the mentioned complications. In the same cited research, about 10% of patients had new or increased trigeminal paresthesia or numbness following radiosurgery [37] Our study reveals similar but slightly higher results with new paresthesia within the trigeminal nerve divisions of 27%. Both Douglas Kondziolka et al. and our study reported no case complicated by anesthesia Dolorosa since it is an infrequent complication. Our GKR group did not develop any loss of corneal reflex compared to Dai Z and colleagues study (25%).[6] The BPI-Facial is a reliable multidimensional tool that consists of 18 questions. It measures three domains of pain: pain intensity, interference with general activities of daily living and face-specific pain interference. This scale conducted a study done by Sandhu S. et al. in a study using the BPI–Facial to measure the minimum clinically significant difference (MCSD).[38] In our study, initial BPI-Facial scale and PGIC calculated, but we did not estimate MCSD because MCSD mainly used for a more complex form of pain assessment in patients with TN and it is not applicable in feeling in the face that often described as *zippy* sensation. This sensation was frequent, self-limiting and does not indicate a potential return of pain.[28] Our study supported by this since transient facial numbness/dysesthesia developed in our MVD group reaching 23%. Transient dizziness, disequilibrium, and ataxia in the mentioned series was 3.6% which support our study (7.7%) but at a lower rate.[28]

Many studies reported that GKR is an alternative modality of treatment for patients with TN with a pain relief rate 57-60%.[29,30,31,32] In their research, Dai Z, and colleagues suggested even a higher pain relief rate (>80%) at the end of the first year follow-up.[6] In our study, patients responded very well to GKR as a treatment for TN with a pain relief rate of 73.33% which is supported by the mentioned studies. However, we noticed a higher success rate in Dai Z et al. review. We saw that they perform GKR procedure with two isocentres, where one target was the nearby Gasserian ganglion, and the other one was about 2-4 mm away from the brainstem, via a 4 mm collimator targeted the trigeminal root entry zone.[33] In our study, we aimed the trigeminal root entry zone only in the GKR procedure. Pain recurrence in our study can also be explained possibly by insufficient damage to the trigeminal nerve with the current radiation dose, newly formed collateral electrical disturbances or stimulation by local inflammation.

In our study, GKR group responded slower than MVD group to the surgical treatment. The response rate was about 27-46.67% during the first three month of follow-up, and it increases gradually reaching a steady level at the 1st and 2nd years of follow-up. It can also be attributed to lower radiation dose (80 Gy) when compared to other studies. Also this study (out of our objectives). Additionally, MCSD needs a larger sample and detailed statistical calculations.

Conclusion:

Both GKR and MVD are effective and safe surgical treatment for patients with TN. However, patients treated with MVD had superior pain relief rate and lesser pain recurrence compared to those treated with GKR. However, the most critical determinant of outcome and morbidity is a careful patient selection.

Morbidity and mortality are rare complications when the procedure performed by an experienced surgeon. Patients treated with GKR response was somehow slower; we believed that optimal target selection and radiation dose played a significant role in this subject.

Although MVD remains the golden treatment in patients with TN, stereotactic radiosurgery is an effective alternative treatment for those with a high-risk group to undergo general anesthesia and withstand a craniotomy procedure or those who are unwilling to be treated by MVD. We believe that GKR can be offered to patients with TN who failed MVD procedure.

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