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Evaluation of Some Modalities of Therapy in Idiopathic Trigeminal Neuralgia

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Abstract The first-line management for idiopathic trigeminal neuralgia (ITN) is medical therapy. The effectiveness of medications typically wanes over time,so we need to evaluate other modality of therapy. Objective: To compare pharmacotherapy versus Gamma knife radiotherapy (GKRS) in relief of pain in patients with idiopathic trigeminal neuralgia (ITN). Methods: the study included sixty eight patients with idiopathic trigeminal neuralgia. They were assessed by Barrow Neurological Institute (BNI) pain intensity scale. They were classified into two groups: Group I: 34 patients, were treated by GKRS and were chosen from Gamma knife center in Nasser institute hospital. They were 19(55.9%) male and 15 (44.1%) female with ages ranged from 40-59 years (Mean±SD was 49.5±6.1). They were assessed by BNI scale before and immediately after GKRS, One month and three months after GKRS treatment. Group II: 34 patients, were chosen from neurology department Zagazig University Hospitals. They were 19 (55.9%) male and 15 (44.1%) female with ages ranged from 40-60 years (Mean±SD was 49.0±6.95). They were assessed by BNI scale before and one week after pharmacotherapy, One month and three months after pharmacotherapy. Results: There was no statistically significant difference between the two groups regarding pain intensity before GKRS or pharmacotherapy (p=0.33) while one week after pharmacotherapy ten (29.4%) patients showed statistically significant improvement of pain.After one month, group I showed statistical significant better outcome (41.2%) than group II (8.8%). BNI score three months after managements was highly statisticallly significant better (32.4%) among group I than group II (p=0.001). Most of group I (82.4%) had good overall outcome while 50% of group II had fair outcome and26.5% had good outcome.Conclusion: medical management of ITN had an initial good results in improving pain intensity which begins to wane over one month and the effect of GKRS begins to appear. The effect of GKRS on ITN pain is still evolving through three months follow up.

Keywords: *idiopathic trigeminal neuralgia, pharmacotherapy, Gamma knife radiotherapy*

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1. Introduction

Trigeminal neuralgia (TN) is pain in one or more of the trigeminal nerve distribution in one side of the face. The pain is characterized by paroxysmal attacks in electric trigger areas that when stimulated brings on this classic type of pain. The condition is associated with periods of remission and exacerbation [1]. Most trigeminal neuralgia is idiopathic, but a small percentage is due to secondary causes as brain tumors or multiple sclerosis [2]. The first-line management for idiopathic trigeminal neuralgia (ITN) is medical therapy. Typical initial oral agents include carbamazepine, oxcarbazepine, gabapentin, phenytoin and baclofen, used alone or in combination. The effectiveness of medications typically wanes over time despite increasing doses, with many patients not able to tolerate side effects [3]. Gamma knife radiosurgery (GKRS) was first used by Leksell (1971) to treat ITN. GKRS is based on closed-cranial irradiation of intracranial targets using multiple photon beams after localization of the target(s) in stereotactic space. [4]. Unlike the surgical alternatives GKRS can be offered to every patient and is performed on an outpatient basis in addition to the relatively low incidence of procedure related complications [5].

2. Subjects and Methods

This study was conducted on 68 patients with idiopathic trigeminal neuralgia which were classified into two groups: Group I: 34 patients, were chosen from Gamma knife center in Nasser institute hospital. They were 19(55.9%) male and 15(44.1%) female with ages ranged from 40-59 years (Mean±SD was 49.5±6.1). Group II: 34 patients, were chosen from neurology department Zagazig University Hospitals. They were 19 (55.9%) male and 15 (44.1%) female with ages ranged from 40-60 years (Mean±SD was 49.0±6.95). The study was done during the period from January 2015 to December 2016. Informed consent was obtained from every participant.

Patients were selected according to the following criteria:

***Inclusion criteria*:**

1. Idiopathic trigeminal neuralgia confirmed clinically [6] and by brain magnetic resonance imaging (MRI).
2. Both sexes with ages ranged between 40-60 years.

***Exclusion criteria*:**

1. Secondary causes of trigeminal neuralgia as compression of the trigeminal nerve e.g tumors or other structural abnormalities such as arteriovenous malformations, or multiple sclerosis (MS).
2. Patients with system failure as renal, respiratory, liver failure or with malignancy.
3. Diabetic patients.
4. Patients with pacemakers, defibrillators or other implanted electronic devices cannot be scanned using magnetic resonance imaging (MRI)
5. pregnant patient or suspected that she may be pregnant as GKRS radiation exposure during pregnancy may lead to birth defects.

All patients were subjected to the following:

1- Complete history taking and thorough complete general and neurological examination.
2- Laboratory investigations to exclude secondary causes of TN
3- MRI brain was performed using a (GE 1.5 Tesla magnet) MRI machine. For all patients axial T2 FLAIR, axial or coronal T2W, axial or sagittal T1W. Slice thickness was 1.6 mm with zero space.
4- Barrow Neurological Institute (BNI) pain intensity scale [7]. This scales describes the level of medication usage. This scale classifies pain into the following grades:

I. No trigeminal neuralgia pain, requires no medication
II. Occasional pain, requires no medication
IIIa. Pain, requires no continued medication
IIIb. Some pain, controlled adequately with medication
IV. Pain improved, but not adequately controlled with medication
V. Continued severe pain without relief.

The trigeminal pain in all patients was assessed by BNI before and after intervention.

2.1. Gamma Knife Technique for Group I

The patients in this group were chosen from gamma knife center in Nasser Institute Hospital, with the previous criteria and free of pharmacotherapy at least one week before the start of gamma knife radiotherapy. Gamma knife radiosurgery was performed in all patients using the Leksell gamma unit (model C; Elekta Instruments, Stockholm, Sweden). This version of gamma knife has 201 Co-60 sources and an Automatic Positioning System (APS). A Leksell G stereotactic frame (Elekta Instruments AB) was used. The treatment planning was done using GammaPlan® version 9 developed by Elekta Instruments Inc. It would seem that the desirable dose is between 70 and 90 Gy but there is no clear cut evidence to support either dose in view of variations in other parameters such as shot location, previous treatment and the use of plugs [8]. Patients were followed up by Clinical assessment of pain using BNI pain intensity scale. The scale will be done as follow: Before, Immediately after, One month after, and three months after gamma knife session.

2.2. Medical Treatment for Group II

The patients of group II were subjected to The protocol therapy [9] which were used as monotherapy or polytherapy according to the condition:

1) Carbamazepine(CBZ) 300-1000 mg begin with small doses, depending on tolerability, retard version useful at night.
2) Oxcarbazepine 300-1200 mg is better tolerated than carbamazepine, and can be used four times a day.
3) Gabapentin 200-900 mg.
4) Baclofen 50-80 mg begin very slowly, frequent dosage.
5) Lamotrigine 200-400 mg Initially very slow escalation. Can be used in combination with CBZ.

• Pain will be assessed by BNI pain intensity scale. This scale has been applied as follow: Before, One week after, One month after, and three months after medical treatment

We considered pain outcome after three months as: [10] - Good outcome = BNI score I and II and IIIa - Fair outcome = BNI score IIIb - Bad outcome = BNI score IV and V.

2.3. Statistical Analysis

The data were tabulated and statistically analyzed using Statistical package of social science (SPSS) Version 14.0.0 software package. Level of significance: the threshold of significance is fixed at 5% level (P value).P value of > 0.05 indicates non-significant results.P value of ≤ 0.05 indicates significant results.P value of ≤0.001 indicates highly significant results. The smaller the p value obtained the more significant are the results.

3. Results

Descriptive data of the studied groups showed no statistically significant difference between the two groups regarding age, gender, pain side or distribution of pain (Table 1). Table 2 described Barrow Neurological Institute (BNI) score before, immediately after GKRS and one week after medical treatment, one month and three months after GKRS and medical treatment as there was no statistically significant difference between the two groups regarding pain intensity before GKRS or medical treatment. While group II showed statistical significant improvement one week after pharmacotherapy (p=0.01). But group I showed statistical significant better outcome than group II after one month of treatment (p=0.009). Three months after treatment, group I showed highly statistical significant better outcome than group II. This difference was highly statistically significant (p=0.001). Barrow neurological institute (BNI) score during the study period among group I (Table 3) showed progressive pain improvement among group I as measured by Barrow neurological institute (BNI) scale during the study period and this difference was highly statistically significant (p=0.001).

Table 4 studied Barrow Neurological Institute (BNI) score during the study period among group II, we found progressive pain improvement among group II as measured by Barrow neurological institute (BNI) scale

during the study period and this difference was highly statistically significant till one week after medical treatment (p=0.05) and statistically significant at one month without any patient had BNI score I or II through group II study. Table 5 showed overall outcome in both groups and demonstrated that most of patients of group I (82.4%) had good outcome while half of the patients of group II (50%) had fair outcome.

Table 1. descriptive data of the studied groups

	Group I	Group II	P value
Age(years) range	40-59	40-60	
M±SD	49±6.1	49±6.95	0.71
Gender(no,%) male female	19 (55.9) 15 (44.1)	19 (55.9) 15 (44.1)	1.0
Pain side(no,%)right left	24 (70.6) 10 (29.4)	24 (70.6) 10 (29.4)	1.0
Trigeminal branch distribution(no-%) V1 V2 V3 V2 +V3 V1 + V2 V1 +V2 +V3	 2 (5.9) 12 (35.3) 6 (17.6) 12 (35.3) 1 (2.9) 1 (2.9)	 4 (11.8) 7 (20.6) 2 (5.9) 16 (47.1) 3 (8.8) 2 (5.9)	0.31

Table 2. Barrow Neurological Institute (BNI) score before, immediately after GKRS and one week after medical treatment, one month and three months after GKRS and medical treatment

BNI score	Group I (no-%)	Group II (no-%)	P value
before therapy: IV V	 20(58.8) 14(41.2)	 16(47.1) 18(52.9)	0.33
immediately after GKRS and one week after medical treatment: III b IV V	 1(2.9) 23(67.6) 10(29.4)	 10(29.4) 18(52.9) 6(17.6)	0.01
one month after GKRS and medical treatment: III a III b IV V	 14(41.2) 15(44.1) 4(11.8) 1(2.9)	 3(8.8) 17(50.0) 11(32.4) 3(8.8)	0.009
three month after GKRS and medical treatment: I II III a III b IV V	 11(32.4) 7(20.6) 10(29.4) 3(8.8) 3(8.8) 0(0.0)	 0(0.0) 0(0.0) 8(23.5) 15(44.1) 8(23.5) 3(8.8)	0.001

Table 3. Barrow neurological institute (BNI) score during the study period among group I

BNI score	**Before GKRS** (no-%)	immediately after GKRS (no-%)	one month after GKRS(no-%)	three months after GKRS (no-%)	P Value
I	0(0.0)	0(0.0)	0(0.0)	11(32.4)	0.001
II	0(0.0)	0(0.0)	0(0.0)	7(20.6)	0.001
IIIa	0(0.0)	0(0.0)	14(41.2)	10(29.4)	0.001
IIIb	0(0.0)	1(9.1)	15(44.1)	3(8.8)	0.001
IV	20(58.8)	23(67.6)	4(11.8)	3(8.8)	0.001
V	14(41.2)	10(29.4)	1(2.9)	0(0.0)	0.001

Table 4. Barrow Neurological Institute (BNI) score during the study period among group II

BNI score	**Before medical treatment**(no-%)	**One week medical treatment**(no-%)	**One month medical treatment**(no-%)	**Three months medical treatment**(no-%)	P value
I	0(0.0)	0(0.0)	0(0.0)	0(0.0)	-----
II	0(0.0)	0(0.0)	0(0.0)	0(0.0)	---
IIIa	0(0.0)	0(0.0)	3(8.8)	8(23.5)	0.05
IIIb	0(0.0)	10(29.40	17(50.0)	15(44.1)	0.001
IV	16(47.1)	18(52.9)	11(32.4)	8(23.5)	0.001
V	18(52.9)	6(17.6)	3(8.8)	3(8.8)	0.001

Table 5. overall outcome in both groups

outcome	groupI(no-%)	groupII(no-%)
Good	28 (82.4)	9 (26.5)
Fair	3 (8.8)	17 (50.0)
Bad	3 (8.8)	8 (23.5)

4. Discussion

We found that ITN was more frequent in right side (70.6%) than left side (29.4%) in both groups.

This observation was in agreement with other studies which reported that right side ITN was more frequent: [11,12,13] However in other study, Dellaretti et al. 2008 [14] found the left side ITN was 52.6% and right side was 47.4 %.

We found higher pain distribution in V2 and V3 (41.1%) among all patients without a significant difference between both groups. This goes in hand with Dusan Urgosik et al. 2005 [15], Chuan-Fu Huang et al. 2008 [12] and Kondziolka et al. 2010 [16] who found higher pain distribution in V2 and V3: 36.5%, 64%, 56.3% respectively. Neto et al. 2005 [17] reported that smaller size of foramen rotundum and foramen ovale on the right side in their study accounted for the higher incidence of right V2 and V3 pain distribution. While Bennetto et al. 2007 [18] and Dellaretti et al. 2008 [14] found higher pain distribution in ITN patients was in V2: 35% and 32.9% respectively.

The effectiveness of medications in idiopathic trigeminal neuralgia typically wanes over time despite increasing doses, with many patients not able to tolerate side effects, If this fails further developments in neurosurgical and radiosurgical techniques have provided effective treatments with increasingly wider margins of safety [3].

We found only one patient (2.9%) showed immediate improvement in pain score (BNI score IIIb) after GKRS, This is in agreement with other studies which reported no marked immediate improvement after GKRS [14,19,20]. While one week after medical treatment, we found ten patients (29.4%) showed improvement in pain score (BNI score IIIb), with highly statistically significant difference, so the medical treatment showed faster pain relief effect because less time to reach the therapeutic level of the drug. This was in agreement with the finding of Cruccu et al. 2008 [9] who found pain improvement in 58 % of the patients through one week following medical therapy.

One month following GKRS: pain score improvement was noticed: 14 patients (41.2%) changed from score IV and V to score IIIa and 15 patients (44.1%) changed from score IV and V to score IIIb. While in medically treated patients: improvement was as follow: 17 patients (50%) changed from score V to score IIIb, and three patients (8.8%) changed from score IV to score IIIa. This better response to GKRS was highly statistically significant. This finding is consistent with other studies [13,14,21,22,23].

The latency period was defined by these studies as it is the period between Gamma knife radiosurgery and state of pain improvement. This period is needed by Gamma knife radiosurgery to make DNA necrosis in the nerve and beginning its effect [21]. The effectiveness of medical therapy typically wanes over time despite increasing doses, with many patients not able to tolerate side effects [3].

GKRS treated patients showed pain score improvement: 32.4% had BNI score I and 20.6% had BNI score II three months following GKRS while no patients had BNI score I or II in medically treated Group. This difference between both modalities of therapy showed higher statistically significance. This continuous significant improvement of pain among GKRS treated group has been reported by other studies [13,23]. As with the time, Gamma Knife radiation progressively distorts the DNA mapping of the cells of abnormal tissue and make them unable to divid.

Conclusively, our results demonstrated progressive pain improvement among GKRS treated group during the study period as immediately after GKRS 9.1% of the patients had BNI score IIIb. One month follow up, 44.1% of the patients had score IIIb and 41.2% had score IIIa. Three months follow up, 20.6% had BNI score II and 32% had score I.

Regarding medically treated group (group II) progressive pain improvement has been demonstrated as one week after treatment 29.4 % ot the patients had BNI score IIIb. At one month follow up, 50 % of the patients had score IIIb and 8.8% of them had BNI score IIIa.

The overall outcome among group I after three months was 82.4 % of the patients had good outcome, 8.8 % of the patients had fair outcome and 8.8 % of the patients had bad outcome. These results are in agreement with Dellaretti et al. 2008 [14], Little et al. 2008 [24], Hayashi et al. 2009 [21] who found their patients good outcome were 83.1%, 83 % and 83 respectively. On the contrary, Sheehan et al. 2005 [25] found that only 44% of their patients treated by GKRS had good outcome. The differences which had been recorded in results of the previous studies regarding GKRS outcome can be attributed to different treatment techniques as the maximum dose of GKRS, target localization and also to different period of follow up that may reach up to 36 month in some of them [26].

The overall outcome among group II after three months was 26.5 % of the patients had good outcome, 50 % had fair outcome and 23.5% of them had bad outcome. The results of the present study were in line with those of Cruccu et al. 2008 [9], Oomens and Forouzanfar. 2015 [27]. On the other hand, the results of the present study were not in line with those yielded by Sato et al.2004 [28] who studied the effect of CBZ in 50 patients with ITN and they concluded that 45 patients (90%) of them became pain free.

The differences in the results in various studies may be due to different treatment protocols, doses of used drugs and differences in the lengths of the follow-up periods [29].

5. Conclusion

- Medical management of ITN (monotherapy or polytherapy) had an intial good results in improving pain intensity as measured by BNI score in comparison with GKRS.
- Through one month, the effect of medical treatment began to wane and the effect of GKRS bagin to appear on ITN patients.
- The effect of GKRS on ITN pain was still evolving through three months follow up while medical treatment typically decreased.
- In those with ITN whom treated by GKRS 82.4 % of patients had overall good outcome

While 26.5% of pharmacotherapy treated group had overall good outcome. Based on our results and previous studies GKRS is a good choice therapeutic option for use with patients who have ITN.

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