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The Relation of pain Value and Touch Threshold of patient with Trigeminal Neuralgia-The effect of Gamma knife Stereotactic Radiosurgery

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Abstract

Trigeminal neuralgia (TN) is a chronic neuropathic pain disorder that makes daily life difficult. Recently, gamma knife surgery (GKS) has been employed for treating intractable pain control such as trigeminal neuralgia (TN) or cancer pain. Nine patients (4 males and 5 females) with TN of second branch were investigated in this study. All patients (mean age: 66.7±7.5) were irradiated a maximum dose of 90 Gy at retro Gasserian after the target area were coordinated with magnetic resonance imaging (MRI) and computed tomography (CT). They were asked symptom, medical history and what induces the pain attack. We also assessed visual analog scale (VAS) of pain, presence or absence of allodynia, cold sensation dullness and touch threshold on the lateral of nasal wing using Semmes-Weinstein monofilaments before and 1, 3, 6, and 12 months after GKS. The relation of the pain value and touch threshold were estimated. There were two kinds of pain character, like an electric shock (5 patients) and like prickling (4 patients). The mean±SD of pain VAS value was 8.5±1.4 and touch threshold on disease side (6.0±2.8 gf/mm^2) was significant higher than the healthy side (3.7±1.3 gf/mm^2) at first visiting (paired t-test; $P<0.05$). All patients experienced asignificant pain reduction without side affections within 6 month after GKS. Allodynia, facial paresthesia or cold sensation dullness occurred before GKS disappeared within 3 touch threshold. These results suggest that GKS is safe and effective method to let a pain and dysesthesia due to TN disappear. There are individual differences in these effect after treatment.

Keywords: Gamma Knife Surgery, Trigeminal Neuralgia, Pain, Touch threshold, Allodynia

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Introduction

Trigerminal neuralgia (TN) consists of brief and severe paroxysms of pain in the facial distribution of the trigeminal nerve, which is often triggered by facial movements or stimulation on the face such as washing face. For treatment of TN, pharmacological approaches such as carbamazepine are selected as a first line therapy[1]. Then if the medication is not effective, percutaneous nerve blocking or microvascular decompression can be considered. However, it is thought of poor long-term outcome of nerve blocking and possibility of side effects such as facial numbness, moreover, general anesthesia for invasive procedures is not suitable for elderly patients. Therefore, development of novel methods for treatment of trigeminal neuralgia is demanded. Thus recent advances in radiosurgical methodology have provided Gamma knife surgery (GKS) for the refractory cases of trigeminal neuralgia which is ineffective with classical treatment modalities [2,3,4].Gamma knife treatment is one of radisurgical therapy and is minimally invasivetechnique[5]. It has been widely used in neurosurgical operations to treat several diseases including brain cavernoma[6], cerebral arteriovenous malformation[7], schwannoma[8] and metastatic brain tumor [9] from malignant melanoma[10] or breast cancer [11]. After its introduction in

Japan during 1990s, it has been actively applied especially in intractable pain cases[12], such as trigeminal neuralgia[13,14,15], cancer pain[16] and thalamic pain symdrome[17].

Root entry zone (REZ: 2-4 mm distal of the trigeminal nerve entrance to brainstem) was targeted for treatment of trigeminal neuralgia with Gamma knife irradiation[18]. However, since this zone is near brainstem, sensory paralysis is easy to occur. Therefore we used a 90 Gy dose to retro Gasserian zone (to the notch between petrous bone and trigeminal nerve), which provides high efficiency. The previous reports has showed that stereotactic radiosurgery is well tolerated, but that is associated with a low risk of significant numbness and dysesthesias[19]. We actually think that any treatment includes a side effect. And there is no report which is described the measured value of touch sensation and pain, allodynia, cold sensation dullness before and after GKS. Moreover, the treatment for TN was included the insurance adaptation in Japan from 2015.

In this study, we investigated the pain value and other sensation before and after GKSfor trigeminal neuralgia to assess the safety and efficiency of this treatment.

Patients and Methods

Patients

All patients gave informed consent in writing to participate in the study and to publish anonymized results.

The subjects in this study were 9 patients (4 males and 5 females) who were treated at neurological center of Tokyo Women`s Medical University with Gamma knife radiosurgery, and their age ranged from 60 to 82 years old (mean age: 66.7±7.5). Four patients firstly visited each dental clinic for the pain on the face. One of them received pulpectomy treatment 15 years ago and extraction the same teeth 7 years ago. Another received pulpectomy 5 years ago. The others were done tooth extraction 5, 1 years ago, respectively. But pain was not relieved, so these patients were diagnosed as trigeminal neuralgia. In the rest 5 patients visited internal medicine physician for facial pain and were diagnosed as trigeminal neuralgia. Thus all patients were diagnosed as trigeminal neuralgia before applying to our clinics and were treated with medication such as clonazepam, prednizolon or carbamazepine. Three patients received nerve blocking more (Table1).

Patients number	age	sex	Medication	Types of pain	Medical history	
					Dental treatment	Medical treatment
1	72	M	clonazepan	prickling	none	nerve blocking
2	61	F	carbamazepin	prickling	pelpectomy	none
3	72	F	carbamazepin	prickling	pelpectomy + extraction	nerve blocking
4	61	F	prednizolon	electric shock	none	none
5	60	M	carbamazepin	electric shock	none	nerve blocking
6	67	M	carbamazepin	electric shock	none	none
7	60	F	carbamazepin	electric shock	extraction	none
8	82	F	carbamazepin	electric shock	none	none
9	65	M	carbamazepin	prickling	extraction	none

Table1: Patient's background. Patient's age, sex, medication, pain's type and medical history as background

Their pain did not go out with medicine for long time or blocking, so GKS was finally applied to the patients. But the medication wascontinued after GKS and the dose diminished in parallel with the pain decrease.

Anamnesis

Same examiner performed all anamnesis and examinations of sensation before and 1,3, 6, and 12 months after GKS. Each patient was examined in a private room and it took 60 minutes for anamnesis time. In the anamnesis of the patients, we asked what induces the attack of trigeminal neuralgia in daily life, or how weather and how situation do.

Examination of sensation

Only one dentist performed all examination of sensation. Visual Analog Scale (VAS) as an objective method was used for the degree of the pain[20]. We showed each patient the figure which a line of 10 cm (the left edge: 0 - non pain, the right edge: 10 –most terrible pain) was described and had them check how much the degree of the current pain was. The lengths from the left edge to the participant's check point were assumed the evaluation of their pain.

Touch threshold was examined on the lateral part of nasal wing of both sides with closed eye condition using Semmes-Weinstein monofilaments (North Coast Medical, Inc.). The filaments for measuring touch threshold were touched to skin in a 90 degree position, then were pressed until bending and kept about 1.5 seconds at the state. This examination was started from healthy side with weakest filament marking (shortened FM hereafter) (2.52 gf/mm^2) and then the intensity was gradually increased. Touching by each FM was performed 3 times to the same place, the intensity recognized more than twice was accepted as the threshold of the day. The

intensity of the FM were converted to pressure value (gf/mm2) from the values reported by Bell-Krotoski[21]. These touch thresholds were compared with the disease side and healthy side. At the same time, they were asked if they got allodynia or not. Moreover, the correlation between the rate of the touch threshold on the disease side for one on the healthy side and pain VAS value before and 1 month after GKS was statistically analyzed.

After examination of the touch threshold, the patients were given 3 minutes of rest, and then the examination of cold sensation was performed with closed eye. A cotton ball soaked in 70% ethanol was touched to 3 cm line along the zygoma from the lateral part of nasal wing. Touching of cotton ball was performed twice on the same parallel areas of both sides. Then they were asked whether there is the difference of cold sensation between disease side and healthy side.

Gamma knife irradiation

In neurological center of our institution, a local anesthesia was done at fixative part of Leksell frame, and the patient head was fixed with a position, at which the frame slope is in parallel to running of trigeminal nerve. After installing the frame, 0.5 mm MRI axial slices (3D heavily T2W1 (SSFP: TOSHIBA)) and 1.0 mm CT axial slices (bone image) to correct the distorted MRI images were taken and transferred to Gamma knife specific computer. A specific treatment planning software (Gamma Plan: ELEKTA Instrument AB) was used to correctly mark radiation planned retro Gasserian area (to the notch between petrous bone and trigeminal nerve) on the images. (Fig.1)

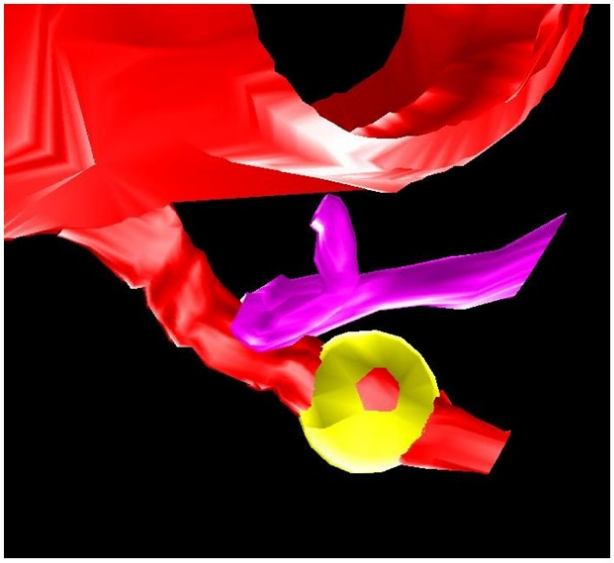

Figure 1: Gamma planning image, showing the target for trigeminal neuralgia. The relationship between trigeminal neuron, blood vessel and brainstem was displayed by 3D image. The target area of 4 mm diameter covers trigeminal neuron on the retro gasserian. (yellow: target area, red: trigeminal neuron and brainstem)

The numerical values of 3 dimensional axes of coordinates were input into ModelC-APS (automatic positioning system: ELEKTA Instrument AB). Then 90 Gy of irradiation was applied on the retro Gasserian area.

Statistical analysis

The differences between the touch threshold on the disease side and on the healthy side before and 1 month after GKS were analyzed by a paired t-test using SPSS ver.23 (IBM Inc, New York, USA).

The correlation between the rate of the touch threshold on the disease side for one on the health side and pain value of before and 1 month after GKS was statistically analyzed by Pearson's correlation test using SPSS ver.23. $P < 0.05$ was considered significant.

Results

Nine patients contracting trigeminal neuralgia on the second branch (right side 4, left side 5) were taken part in this study. All patients have felt the pain on the location including the lateral part of nasal wing. The factors to cause an attack of trigeminal neuralgia were eating, talking, face moving, face washing or hair washing. Moreover, it was easy to induce an attack when they were tense or tired, and it was strong windy, cold, rainy or humid day (Table 2). Six patients also received hypnotics or anxiolytics due to sleep disorder. The pain property was described two types, one was pain like an electric shock from nasal wing on the face to head through sagittal direction and the other was pain like prickling. The former was found in 5patients and the latter was in 4 patients.

Factors	the number of patients
Eating	5
Talking	3
Face washing	3
Hair washing	3
Moving face	2
Tense	1
Tired	1
Strong windy day	1
Cold day	4
Rainy day	1
Humid day	1

multiple responses

Table 2: The factors to cause an attack of trigeminal neuralgia. Patients were permitted multiple responses.

Before GKS, pain VAS value was 8.5±1.4 (average±SD) and allodynia in 2 patients and cold sensation dullness in 3 patients were recognized at disease side (table 3). In the examination of touch threshold, same threshold at both sides was recognized in a patient and hypersensitivity of disease side in 1 patient were detected. Seven patients showed touch sensation dullness on the disease side compared with healthy side. The mean±SD of touch threshold on the disease side was 6.0±2.8 gf / mm^2 and one on the healty side was 3.7±1.3 gf / mm^2 at first visiting. The touch threshold on the disease side showed significant higher than one on the healthy side (paired t-test; P<0.05) (Fig.2).

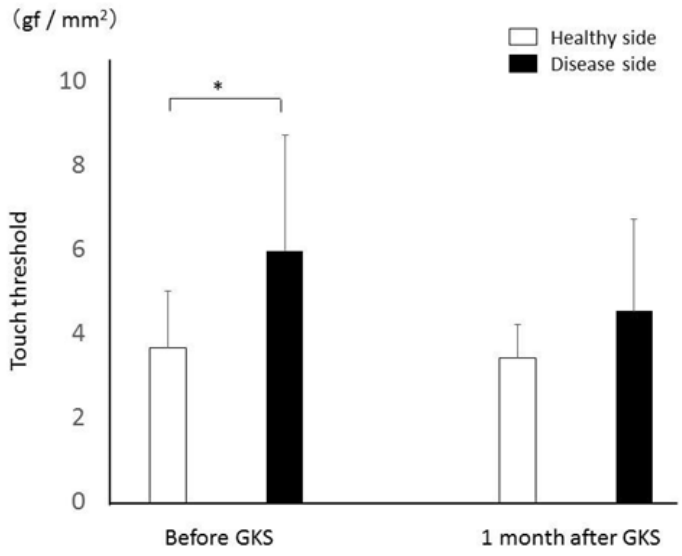

Figure 2: Comparison with the touch threshold of disease side and normal side before and 1 month after GKS. Each vertical bar represents the mean ± SD. *p < 0.05

Pain at the area of the frame fixation disappeared within 10 days after application of GKS, however, some attack of trigeminal neuralgia have been observed still.

At 1 month after GKS, the mean of pain VAS value was 3.2±1.2 (average±SD) (table 3). Although the intensity of the pain was diminished in the all patients, pain value did not decrease to zero level. Allodynia disappeared at this time, but cold sensation dullness in a patient and amblyaphia in 5 patients on the disease side were observed (Table 3, 4). There was significant difference between the touch threshold on the disease side (4.6±2.2 gf / mm^2) and one on the healthy side (3.4±0.8 gf / mm^2) (Fig.2).

At 3 months after GKS, uncomfortable feeling as well as rare attacks in 2 patients were detected. The pain in 7 patients completely disappeared (table 3). Allodynia, cold sensation dullness or amblyaphia was not recognized at this time (Table 3, 4). Seven patients without pain were recommended to decrease their medication in case of no attack. Three patients of them stopped their medication after followup of 6 month, and no trouble was seen. At regular follow-up of 6 month and 12 month, the pain VAS values were zero in all cases, and allodynia, cold sensation dullness and touch sensation dullness also were not recognized (Table 3, 4).

Patients number	VAS value				
	After irradiation				
	before	1 month	3 month	6 month	12 month
1	(8)	(3)	0	0	0
2	5.5	3.3	0	0	0
3	[9.8]	3	1	0	0
4	9	4.2	0	0	0
5	(9.5)	1	0	0	0
6	[9.7]	2	0	0	0
7	(9.5)	4	2	0	0
8	8	3.5	0	0	0
9	7.8	5	0	0	0

○: cold sensation dullness □: allodynia

Table3: Pain value (VAS) before and after GKS.Patient's age, sex and medication as background and pain value of before and 1,3,6,12 months after GKS.(○:cold dullness, □: allodynia)

Patients number	Disease side	Touch threshold (gf / mm^2)							
		before		after 1 month		3 month		6 and 12month	
		R	L	R	L	R	L	R	L
1	R	9.49	6.30	9.49	4.23	4.23	4.23	4.23	4.23
2	R	4.23	2.52	2.52	2.52	2.52	2.52	2.52	2.52
3	R	3.22	3.22	6.30	4.23	4.23	4.23	3.22	3.22
4	L	2.52	3.22	2.52	3.22	2.52	2.52	2.52	2.52
5	L	4.23	9.49	4.23	4.23	4.23	4.23	4.23	4.23
6	L	3.22	6.30	3.22	4.23	3.22	3.22	3.22	3.22
7	R	4.23	6.30	4.23	4.23	4.23	4.23	4.23	4.23
8	L	2.52	4.23	2.52	2.52	2.52	2.52	2.52	2.52
9	L	3.22	9.49	3.22	4.23	3.22	3.22	3.22	3.22

R:right, L:left

Table4: Touch threshold on both side before and after GKS. Disease side of patients and touch threshold (gf / mm^2)on the both side before and1,3,6,12 month after GKS. (R: right, L: left)

Five patients stopped use of the medication after follow-up of 12 month. Only 1 patient continued to use the drug due to worry of attack but actually absence of any pain. As shown in table 3, there were two kinds of types for decreasing pain value, quickly and slowly.

Though a patient did not have the abnormality at the regular follow-up time, the patient got recurrences on the 4 and 7 months after GKS. The patient was prescribed analgesic for 2 weeks, and there was not the symptom in particular until the next follow-up. In addition, even if the touch threshold of both sides were the same value at follow-up, three patients told us that there seemed to be numbness on the disease side.

There is no correlation between the rate of the touch threshold on the disease side for one on the normal side and pain value of before and 1 month after GKS (Pearson'scorrelation coefficient: before GKS r=-0.285, after GKS r=0.05) (Fig.3).

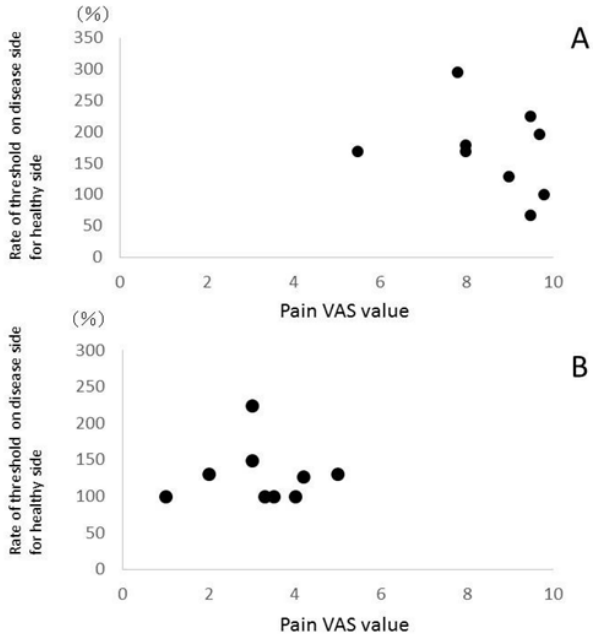

Figure 3: The correlation between growth rate of touch threshold and pain value.Growth rate showed rate of touch threshold on the disease side for one on the normal side. (A: before GKS, B: 1 month after GKS)

Discussion

Despite pharmacology approach is first selected for trigeminal neuralgia, for those patients who did not respond medication therapy, next step of treatment protocol should be decided by doctor and patient[14,15]. One of treatment methods in the current study, GKS was first described by Leksell in 1953, and was started as an application of low dose irradiation of Gamma beam to trigeminal nerve ganglion for trigeminal neuralgia pain at the time[22]. Since decades have passed after onset of its application for trigeminal neuralgia, good outcome has been obtained without a significant side effect. It has been now an established method of the therapy for trigeminal neuralgia[23]. The treatment is not an invasive technique, most patients easily select this treatment mode.

Trigeminal neuralgia is an intractable disease with symptoms of repeated sudden attacks of stabbing like sharp pain on the facial distribution of the trigeminal nerve. Nine patients were recognized pain at the location including the lateral of nasal wing. Moreover, the character of pain was like an electrical shock or prickling. Pain value at the first examination was pretty high, which have been suggested that the pain of the trigeminal neuralgia was quite strong.

The origin of trigeminal neuralgia is considered as a morphological problem due to very close running of the vessel with the nerve. And pain attacks are precipitated at eating, washing face, tooth brushing, or conversation and is easy to occur on a rainy, cold or humid day regardless of their medical history. Even feeling of wind in the face and turning of the head downwards resulted in appearance of attacks. These actions are essential elements of the daily life and difficult to avoid. All patients don't know when the attack occurs.

Therefore they have to spend eating soft foods, hesitating from conversation and laughing because of worry for recurrence attack, which induce insufficient sleeping in night and becoming in a depressed state. Thus continuance of pain in the patients with trigeminal neuralgia should also be discussed as a triggering factor for attack in dental and medical field. The results also indicated that an appropriate diagnosis is most important to be treated as trigeminal neuralgia early.

High pain VAS value, high touch threshold, allodynia and cold sensation dullness was recognized at first examination. These results suggest that the strong pain might affect not only cold sensation related C fiver nerve transmitting pain but also β fiber nerve transmitting touch sensation. The pain value in all cases decreased at 1 month after GKS. However, cold sensation dullness

in one patient and high touch threshold in 5 patients were observed. In these results there was no significant difference between touch thresholds on the healthy side and disease side. Seven patients showed complete pain relief at 3 months after GKS and the others also relief at 6 months after GKS. Allodynia, cold sensation or touch dullness was not recognized after 3 months. All patients had a much better facial expression and cheerful daily life as compared with the pre-treatment times. Our results indicated that allodynia and cold sensation or touch dullness occurs only in case of strong pain, and they disappears when pain value approaches zero. It was thought that these paresthesias were linked to the strength of the pain regardless of medical history or medication. However, there was no significant correlation between pain values and the rate of the touch threshold on the disease side for one on the healthy side. These various levels might be attributed to individual differences. And we doesn't definitely know their progress after 12 months of GKS, because there was no next appointment. That is a limitation in our study.

We got a successful result from Gamma knife radiosurgery to retro Gasserian zone for trigeminal neuralgia without sensation dullness or eyeball dry feeling within 12 months of regular follow-up. However, mechanism of the Gamma knife irradiation treatment still remains unknown.

In rat experiments, Gamma knife (GK) irradiation at the injured nerves facilitates regeneration and re-myelination. When GK-induced alleviation of allodynia was initially detected, the expression of glial cell line-derived neurotrophic factor (GDNF), a potent analgesic factor, was significantly increased by GK irradiation[24]. Kipnis has reported that low dose of Gamma irradiation has been demonstrated to induce T cell proliferation and thus play a role in repair of damaged nerve or spinal cord[25]. On the other hand, it has been reported that application of 100 or more of GK irradiation in rats resulted in vascular changes such as hyperplasia of endothelial cells as well as thickening of vessels. These animals showed edema, bleeding and necrosis within 3 months[26,27,28]. That will mean that these dose is too strong for rat experiment. Although many studies has been reported for influence of GK irradiation on the cells, these researches are not likely to be a base for mechanism of pain relief.

Several hypotheses including constriction of vessel accompanied to trigeminal neuralgia, inhibition of nerve excitability or transmission, and induction of intrinsic opioids upon application of GK irradiation can be considered for mechanism of pain relief. Basic researches should be performed to clarify these possibilities. Based on accumulation of the information from basic as well as clinical researches in this field, cases of atypical trigeminal neuralgia or cases with previous microvascular decompression history, which could possibly have a benefit with modified application of this method.

Niranjan A et al, reported that GKS is associated with 60-90% rate of pain relief in patients with refractory trigeminal neuralgia[29]. We also obtained an affective results from GKS for trigeminal neuralgia. On the other side, Pollock BE reported that there were some side effects such as recurrence of pain and mild trigeminal sensory after GKS[30]. One person of our patient certainly temporarily accepted a recurrence, however, the patient did not have the sunk expression to be before GKS. And the attack did not occur by analgesic medication for 2 weeks. In this study, we recognized for the first time that even if patients felt numbness on disease side compared with healthy side, the touch threshold on both side were the same vale. Therefore, finally Gamma knife treatment may provide a great contribution in the clinics as an epoch-making method.

Conclusion

The pain value of trigeminal neuralgia was very severe, which induced allodynia, cold sensation dullness and touch dullness. The touch threshold on the disease side showed significant higher than one on the healthy side before treatment. However, there is no correlation between the rate of the touch threshold on the disease side for one on the normal side and pain value of before GKS. Then after the trigeminal neuralgia was treated by GKS, the severe pain went out and the dysesthesia also disappeared regardless of medical history or medication.

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