

SURGICAL ASPECT of FACIAL NERVE DISORDERS

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Surgical Aspect of Facial Nerve Disorders

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Guest Editors: Sertac Yetiser, Peter S. Roland, and Nebil Goksu



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Editorial

Surgical Aspect of Facial Nerve Disorders

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Facial expression is the essential complementary of the verbal communication between humans. “Face is a window to the heart.” An ancient proverb tells us the importance of facial expression more than anything. When harmonic and symmetric movement of both sides of the face has lost, one is unable to express his emotion by distorted facial movement. This person becomes unwilling to communicate, hides himself, and escapes from social events. It is a collapsing life for patients not being able to cope with physical and psychological consequences of a facial paralysis.

Facial nerve is one of the unique cranial nerves innervating several tiny muscles and maybe the original one traveling through a long bony tunnel. These particular features make this nerve more vulnerable to different injuries than others resulting in obvious involvement of several agonist and antagonist muscles. An injury which may not be so harmful for others may cause a long-term bothersome problem by entrapment of axonal conduction. Thereafter critical questions directed by the patients are as follows: Is the facial function expected to recover soon, to what extent, and when? The primary problem facing the clinician is to distinguish the patients who will recover spontaneously or with medication from those who will not.

Facial nerve dysfunction can be seen in a sudden or gradual manner. However, investigation of possible underlying causes as well as a prognostic evaluation is necessary. For more chronic problems, a multidisciplinary team work provides better solutions for the relief of symptoms. Protection of eye, prevention or treatment of synkinesis, and

resolution of psychological problems are best handled with collaboration between specific experts. As a summary, acute facial nerve dysfunction, chronic facial nerve problems, and its several presentations can be managed by medical and surgical ways. However, there will always be a new approach to this old problem.

Restoration of functional integrity of the diseased facial nerve has been subject of studies for decades. This special issue about facial nerve problems, probably, will not be the last one. However, prognosis of facial nerve injury, selection of good candidates for surgery, decision making and timing, as well as the type of approach always need new updates and renewals. This special issue will give some insight to this problem and promote a discussion of some different aspects of the facial paralysis.

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Clinical Study

The Dehiscent Facial Nerve Canal

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Accidental injury to the facial nerve where the bony canal defects are present may result with facial nerve dysfunction during otological surgery. Therefore, it is critical to know the incidence and the type of facial nerve dehiscences in the presence of normal development of the facial canal. The aim of this study is to review the site and the type of such bony defects in 144 patients operated for facial paralysis, myringoplasty, stapedotomy, middle ear exploration for sudden hearing loss, and so forth, other than chronic suppurative otitis media with or without cholesteatoma, middle ear tumors, and anomaly. Correlation of intraoperative findings with preoperative computerized tomography was also analyzed in 35 patients. Conclusively, one out of every 10 surgical cases may have dehiscence of the facial canal which has to be always borne in mind during surgical manipulation of the middle ear. Computerized tomography has some limitations to evaluate the dehiscent facial canal due to high false negative and positive rates.

1. Introduction

Facial nerve is the most vulnerable structure in the middle ear during otological surgery. Accidental injury may result with facial nerve dysfunction if the surgeon may not pay enough attention to the site where the bony defects are frequently expected to present. Baxter found that 57% of people have dehiscence of the facial canal in the oval niche [1]. Takahashi and Sando have reviewed 160 temporal bones from 129 individuals and have reported facial canal dehiscences in 74% of them, the most frequent site being at the oval window with a length of 0.4–2.64 mm [2]. Moreano et al. have reviewed 1000 temporal bones and have found 56% incidence of at least one facial canal dehiscence with 76.3% prevalence of bilaterality [3]. The incidence of multiple dehiscences along the course of the fallopian canal in the same temporal bone is much higher in specimens of newborns and young children [4]. Comparative studies of histopathological incidence of facial canal dehiscence are a few. Nomiya et al. have compared 133 temporal bones from 84 otosclerosis cases with 102 normal temporal bones from 70 subjects and have found that the incidence in otosclerosis (49.6%) was lower than normal controls (65.7%) [5]. Di Martino et al. have compared the actual clinical findings

in 357 operated cases with 300 temporal bones and have reported fallopian canal dehiscence in 6.4% of the operations and 29.3% of the autopsies [6].

The issue of facial canal anomalies in clinical setting rises some important questions to be solved particularly in medical centers where the training of otologic surgery has routinely been made. The aim of this study is to review the site and the type of such bony defects and variations of the facial canal in patients operated for facial paralysis, myringoplasty, stapedotomy, middle ear exploration for sudden hearing loss, and so forth other than chronic suppurative otitis media with or without cholesteatoma, middle ear tumor, and anomaly.

2. Subjects and Methods

Patients who have been operated for otological reasons other than chronic otitis media with or without cholesteatoma in last 4 years were included for the study. Patients' charts, clinical notes, and operation reports were reviewed. Otoscopic findings, type of surgery used, the presence and absence of cholesteatoma, and other intraoperative findings related to the facial nerve were systematically documented. Presence of active or chronic infection with discharging ear,

cholesteatoma, middle ear tumors, and middle ear anomaly were the main items for exclusion criteria to rule out the possible erosive effect.

144 patients who have been operated for ear problems in last 4 years were enrolled for the study (48 women, 96 men) with ages ranging from 8 to 66. Of those, 92 were tympanoplasty with or without mastoidectomy, 28 were stapes surgery for otosclerosis, 8 were ossiculoplasty for traumatic injury, 11 were exploration of the middle ear for gradual or sudden hearing loss, and 5 were subtotal facial nerve decompression due to severe paralysis resistive to medical therapy.

Dehiscence of the facial canal was classified in 5 basic groups.

- (1) If the dehiscence is before the coq, it is classified as *Geniculate ganglion dehiscence*.
- (2) If the dehiscence is between the second genu and the coq, it is classified as *tympanic or horizontal segment dehiscence*.
- (3) If the dehiscence is located in the second genu very close to the lateral semicircular canal, it is classified as *dehiscence at the second genu*.
- (4) If the dehiscence is protruding over the oval window only, it is classified as *dehiscence of oval window niche*.
- (5) If the dehiscence is after the lower level of the oval window at the mastoid or vertical segment, it is classified as *vertical segment dehiscence*.

On the other hand, in an attempt to qualify the wider dehiscence, if the dehiscence is wide enough extending to both horizontal segment and the second genu, it is classified as *second genu + horizontal segment dehiscence*, and if the dehiscence is extending between the second genu and the inferior level of the oval window, it is classified as *second genu + vertical segment dehiscence*.

Results were also compared with preoperative CT findings in 35 cases only since the preoperative CT was not routine. Thus, it was available only in 25.9% of operated cases (144/35). Fine axial cuts of each CT have been reviewed by an expertise radiologist. If there is a dehiscence, the site has been described as Group-I, no dehiscent; Group-II, suspicious dehiscent; in other words, it is hard to tell whether there is a bony defect around the nerve or not; and Group-III, positive dehiscent.

3. Results

13 referred ears with tympanic membrane perforation were reoperation due to previous failure. Otherwise all were primary surgery. Intraoperatively, 16 ears (11%) demonstrated an exposed facial nerve. Of those, 5 were at the level of second genu, 4 were at the horizontal segment, 3 were at the level of oval window niche, 3 were at the second genu and horizontal segment, and 1 was at second genu and vertical segment. None of the patients in this series had an isolated geniculate ganglion or vertical segment dehiscence. Of the 16 patients with facial canal defect, 4 were stapes surgery (28/4;

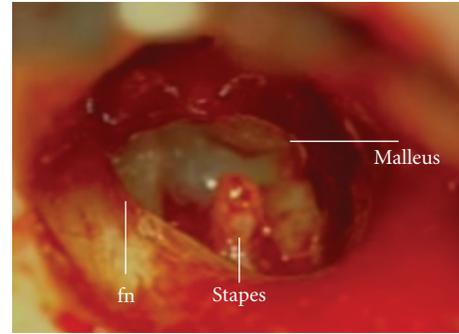


FIGURE 1: Right ear: middle ear of the patient with incus dislocation after head trauma. Defective facial canal is marked (fn: facial nerve).

TABLE 1: Demographic data of the patients with dehiscent facial nerve canal.

Ear surgery	No. of patients	No. of dehiscent canal	%
Tympanoplasty	92	11	11.9
Stapedotomy	28	4	14.2
FN decompression	5	—	—
Ossiculoplasty	8	1	12.5
ME exploration	11	—	—
TOTAL	144	16	11

14.2%), 11 were tympanoplasty surgery (92/11; 11,9%), and 1 was middle ear exploration due conductive hearing loss (8/1; 12,5%). This patient had incus dislocation after head trauma without temporal bone fracture (Figure 1). One patient with otosclerosis had completely exposed facial nerve with abnormal course anterior to the stapes (Figures 2(a), 2(b), 3(a), and 3(b)). Four cases demonstrated facial paresis after surgery with minimal cosmetic problem and recovery was uneventful without any intervention in 2 weeks. Demographic data of the patients are presented in Table 1.

CT findings have been reported as follows: 19 of 35 cases had no dehiscence (Group-I), it was not certain in 2 (Group-II), and 14 patients had bony defect (Group-III) (Figure 4). Three patients from Group-I and one patient from Group-II had facial canal defect intraoperatively (false negatives according to CT, 21/4: %19). 13 of 16 cases with intraoperative facial canal dehiscence have been referred to tomography preoperatively. Of those, 9 temporal bone CTs which described dehiscent facial canal preoperatively were correlated with the intraoperative findings. 4 patients did not disclose any facial canal defect (false positive according to CT, 13/4: %30.7).

4. Discussion

The facial canal is shaped during enchondral ossification of the otic capsule in fetal life. However, it is not completely dependent to the ossification process [7]. Abnormal course of the facial canal is expected in malformed temporal bones and the nerve can be exposed [8]. But, the fibrous layers surrounding the facial nerve seem to be responsible

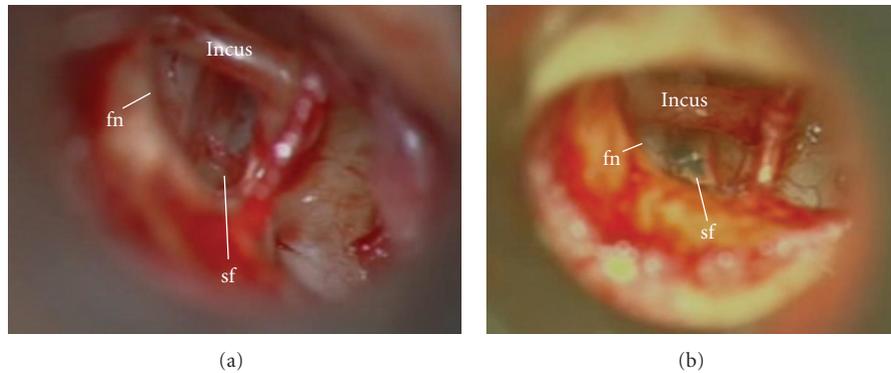


FIGURE 2: (a) Right ear: middle ear of the patient with otosclerosis. Note the capillary vessel over the facial nerve. (b) Footplate was perforated for insertion of the prosthesis (sf: stapes footplate; fn: facial nerve).

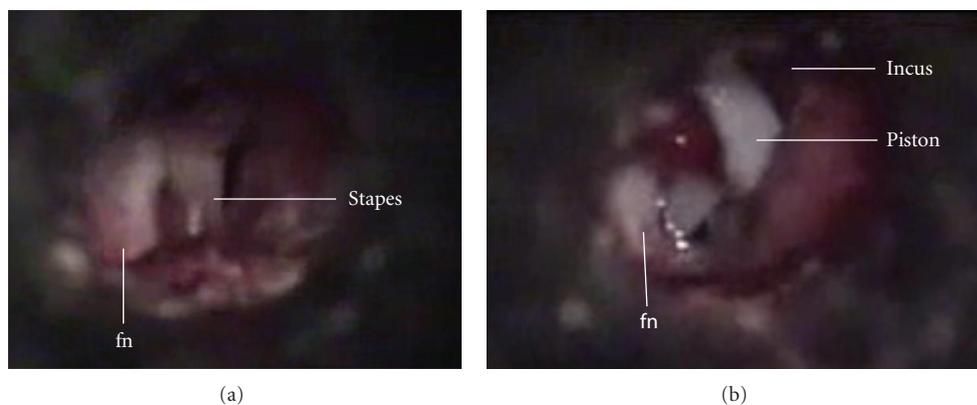


FIGURE 3: (a) Left ear: middle ear of the patient with otosclerosis. The facial nerve is completely exposed and located anterior to the stapes. (b) The same patient after prosthesis placement (fn: facial nerve).

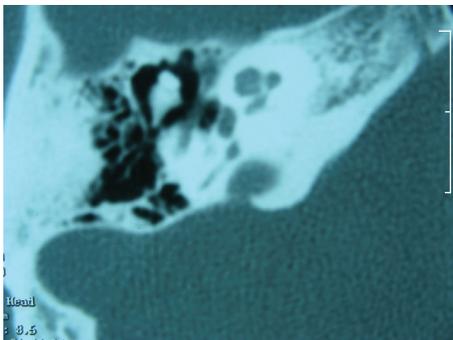


FIGURE 4: Axial computerized tomography of the patient with otosclerosis. Note that facial nerve is dehiscence at the level of second turn and oval niche.

for the final architecture of the facial canal. Therefore, from clinical aspects, it is critical to know the incidence and the type of facial nerve dehiscences in the presence of normal development of the facial canal. The highest incidence of exposed facial nerve has been reported to be 30–35% during surgery for middle ear cholesteatoma [9–11]. Majority of those were found to be in revised cases and at

the tympanic segment since it was in the way of extension of the cholesteatoma [12–15]. However, it is difficult to estimate the real number of developmental ones from those due to erosive defect. Patients with tumors, developmental anomalies (atresia), and chronic discharging ears with or without cholesteatoma have been excluded in our series.

It is important to know the nature of such defects to understand the possible underlying mechanism of facial paralysis due to chronic otitis media since a congenital dehiscence or bony defect exposes the nerve to the inflammatory effect of suppuration. Pensak et al. have reviewed 250 consecutive operative cases of chronic otitis media with 54% revision surgeries and have found that an exposed facial nerve was present in 38% of the cases, and of these, 77% of cases had cholesteatoma [16]. Savic and Djeric. have analyzed 64 cases with facial paralysis due to chronic otitis media and reported that the bone destruction of the facial canal is an associated finding in 75% of cases. Tympanic segment was the most common site of involvement (77.2%) which has been stated by the authors that the main reason for this occurrence is the dehiscence facial canal or very thin canal wall most frequently found at this part exposing the nerve to the inflammation [17]. Yetiser et al. have found 83.3% dehiscence facial canal in patients facial paralysis due to chronic otitis

media with the most common sites being at second genu and horizontal portions [18]. It is likely true that the bony dehiscence over the nerve is responsible for the extent of the inflammation.

The main group in this series contains patients with otosclerosis. The incidence has been reported to as high as 11.4%–19% [19, 20]. Middle ear has several traps for new beginners to otologic surgery. It is sometimes difficult to identify the facial nerve covered by a thick mucosal layer only. The frequency of iatrogenic injury to the facial nerve has declined with the advent of microsurgical techniques. However, dehiscence at the vestibular surface of the facial canal is usually out of the surgeon's point of view and may be open to an accidental injury. Choung et al. have demonstrated that surgical dehiscence of the facial canal presented in 43% of cases while 73% of those responded to electrical stimulation which indicated an increased vulnerability to trauma and termed this condition as "electrical dehiscence" [21]. Routine monitorization of the facial nerve during surgery of chronic otitis media has been found to be effective and necessary [16, 21].

A high-resolution CT scanning frequently discloses a dehiscence of the bony canal of the facial nerve. However, minor bony defects may stay undetected because of multiplanar and tortuous route of the facial canal. Multiple planes of view are necessary for an optimal image of the canal [22, 23]. Fuse et al. have found that computerized tomography coincided with surgical findings in 75% of cases with 66% sensitivity and 84% specificity [24]. Geniculate ganglion region is particularly important when middle fossa approach is planned. Isaacson and Vrabec have found dehiscent ganglion in 14.5% of 278 cases evaluated by CT scan [25]. Conclusively, one out of every 10 surgical cases may have dehiscence of the facial canal which has to be always borne in mind during surgical manipulation of the middle ear. Computerized tomography has some limitations to evaluate the dehiscent facial canal due to high false negative and positive rates.

Disclosure

This study was not presented in any meeting before or submitted for publication to another journal.

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Research Article

Schwann Cell Metabolic Activity in Various Short-Term Holding Conditions: Implications for Improved Nerve Graft Viability

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Strategies for improvement of nerve regeneration and optimal conditions to prevent Schwann cell (SC) loss within a nerve transplant procedure are critical. The purpose of this study was to examine SC viability, which plays an important role in peripheral nerve regeneration, under various incubation conditions up to three hours. To address this issue, Schwann cell metabolic activity was determined using different independent test methods. The following experimental conditions were compared: SCs prepared from nerves were incubated in (1) isotonic saline solution (2) Dulbecco's modified Eagles medium as used for cell culturing, (3) Hannover bioreactor medium, and (4) Leibovitz's medium. SC metabolic activity of excised rat sciatic nerve was determined at 4°C, 18°C, and 37°C over 3 hrs. The results indicate that SC activity was optimized by the usage of Leibovitz's medium or HBRM at 37°C. Greater SC viability at the time of surgical nerve grafting could contribute to improved axonal regeneration and remyelination after nerve transplantation, and thus more successful functional recovery.

1. Introduction

Axonal regeneration and remyelination after peripheral nerve injury can be robust with significant functional recovery in contrast to the central nervous system where long white matter tract regeneration is absent or minimal [1]. After peripheral nerve transection, for example, after tumor resection, Wallerian degeneration characterized by macrophage infiltration, axonal membrane digestion, and retraction and proliferation of SCs occurs in the distal nerve segment [2]. The detached SCs from the degenerating axons upregulate the expression of nerve growth factor (NGF) and its low-affinity receptor p75NGFR [3]. For a period of time these SCs are activated [4] and provide trophic support for regeneration. Regeneration occurs from the proximal stump by axonal sprouting and elongation and continues into the distal stump or nerve transplant [5]. The status of a nerve transplant is critical for successful nerve regeneration.

While nerve regeneration through Schwann-cell-enriched basal lamina tubes can reestablish connections with peripheral targets such as skin and muscle, a number of issues, such as navigation of axons across a complex nerve

injury site where scarring can occur and appropriate targeting to peripheral end structures are major clinical concerns [6]. Although local endogenous SCs play an important role in regeneration of peripheral nerve, transplantation of additional Schwann cells into a lesion site was shown to assist this regenerative process [7, 8]. Nerve repair combined with transplantation of myelin-forming cell is a relatively simple, rapid, and efficient means of peripheral nerve repair [9]. Moreover, functional nerve regeneration requires not only axonal sprouting and elongation, but also remyelination and appropriate ion channel deployment at the node of Ranvier [8, 9]. The combination of surgical nerve repair and transplantation of peripheral myelin-forming cells has been shown to enhance axonal regeneration and remyelinate demyelinated fibers in experimental models [10] and is currently being investigated in clinical studies [7, 11].

In nerve defect injuries treated with autologous nerve transplantation, the nerve fibers within the transplant contain a high number of Schwann cells which are indirectly transplanted; the viability and activity of these indirectly engrafted Schwann cells may be critical to optimize success

of the nerve graft. The importance of the Schwann cells and their basal lamina for axonal regeneration is well established [4, 10, 12]. Loss of viable Schwann cells in a nerve graft results in a reduced neurotrophic support with an attendant reduction in regeneration [13, 14]. Thus, the holding conditions for nerve segments removed for nerve grafting are critical for both SC preservation and potential success of the graft. In the present study, we compared various holding conditions including temperature and medium for short-term preservation (up to 3 hours) followed by determination of Schwann cell viability assessed by two independent test methods after dissociation of excised nerve segments as used for nerve transplantation.

2. Materials and Methods

2.1. Isolation and Cultivation of Schwann Cells. Experiments were performed in accordance with the German Animal welfare guidelines for the care and use of laboratory animals. The Hannover Medical School and the Nds. Landesamt für Verbraucherschutz und Lebensmittelsicherheit approved all animal protocols. For preparation of adult Schwann cells, adult male Sprague-Dawley rats were deeply anesthetized and sciatic nerves were removed. The sciatic nerves were desheathed, minced, and washed with 10 mL serum-free DMEM low glucose (1 g/L) with L-Glutamine (PAA, Pasching Austria), transferred to a 15 mL tube (TPP, Europe, Switzerland) and washed by centrifugation. For enzymatic dissociation, 15 mg lyophilized Collagenases A and D (Roche, Mannheim, Germany) were dissolved in 10 mL serum-free DMEM; the nerve tissue was incubated at 37°C and 5% CO₂ for 20 min followed by trituration through a fire-polished siliconized pasteur pipette and washed for three times with DMEM containing 10% FCS. The cells were resuspended and either seeded onto two 25 cm² cell culture flasks (TPP, Europe, Switzerland) coated with Laminin (Engelbreth-Holm-Swarm murine sarcoma basement membrane, Sigma-Aldrich, Steinheim, Germany) for immunocytochemical characterization or plated onto 96-well plates for cell viability assay. The viability of Schwann cells was measured before and after incubation for 1 hr, 2 hrs, and 3 hrs in selected media (see below) at 4°C, 37°C, and 18°C (Figure 1).

2.2. Characterization and Quantification of Schwann Cells by Immune Fluorescence. The purity of the prepared Schwann cells was determined by indirect immunofluorescence staining for Schwann cell characteristic marker anti-S100 (polyclonal Rabbit, Dako, Glostrup, Denmark) and visualized with secondary antibody Alexa Fluor 546 (secondary antibody, donkey anti-rabbit, Invitrogen, Karlsruhe, Germany). Nuclei were counterstained with DAPI (Vector Laboratories, CA, USA). Quantification of purity was obtained by counting immunopositive S100 cells in ratio to the number of nuclei. Schwann cell purity was >95% (data not shown).

2.3. Measurement of Metabolic Activity. Viability of Schwann cells of sciatic nerves after incubation in selected media was measured by the CellTiter-Blue (CTB) Cell Viability Assay

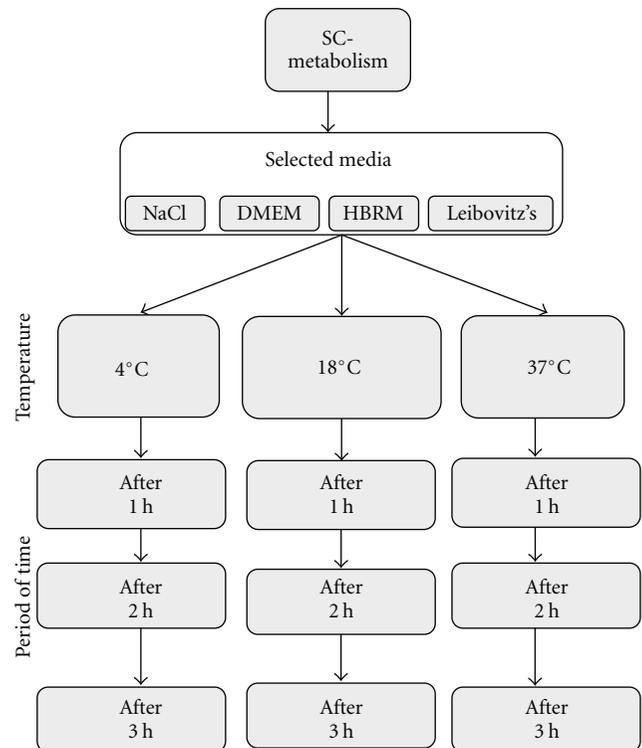


FIGURE 1: Conditions for testing the metabolic activity of Schwann cells in vitro after incubation in selected media including saline, DMEM with 10% FCS, HBRM, and Leibovitz's medium. Sciatic nerves were incubated in these selected media at 4°C, a room temperature 18°C and 37°C. For each temperature condition, Schwann cell metabolism was determined after 1 hrs, 2 hrs, and 3 hrs.

(Promega, Madison, WI, USA), the CellTiter 96 Aqueous Nonradioactive Cell Proliferation Assay (Promega, Madison, WI, USA), which indicates cell viability on the basis of cell metabolism. The CTB assay uses the capacity of viable cells reducing the dye resazurin to resorufin, which emits fluorescence at 590 nm. The intensity of fluorescence is proportional to the number of viable cells. As second independent test to verify results, the CellTiter 96 Aqueous Assay contains a tetrazolium compound (MTS; [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt]) and PMS (phenazine methosulfate) as an electron coupling reagent. Viable cells reduce the MTS reagent into formazan. The absorbance of formazan can be measured at 490 nm and the quantity of absorbance is directly proportional to the number of viable cells.

Selected media for storage were (1) isotonic sodium chloride (NaCl 0.9%, Deltaselect GmbH, Dreieich), (2) DMEM low glucose (1 g/L) supplemented with L-Glutamine (PAA, Pasching, Austria) and 10% FCS (fetal calf serum, Biochrom AG, Berlin, Germany) and 1% Penicillin/Streptomycin (Biochrom AG, Berlin, Germany), (3) Hannover bioreactor medium (HBRM; consisting out of 1000 mL DMEM-F12 (Biochrom AG Berlin, Germany), 10 mL/insulin-transferrin

selenium-A supplement (Gibco), 456 IU Prednisolone, 400 IU Insulin 108 mg/mL Glucagon, 10 μ L Soludecortin (10 mg/mL), 5 mL Amphomonal (Biochrom AG, Berlin, Germany), 20 mL HEPES (Biochrom AG, Berlin, Germany), 50 mg Hyaluronic acid (Sigma Aldrich, Germany), 5 mg/L Penicillin/Streptomycin (Biochrom AG, Berlin, Germany) and (4) Leibovitz's medium (L-15 medium with L-Glutamine mit 25 mM Hepes, PAA, Pasching, Austria). After incubation, Schwann cells were seeded onto 96-well plates (Nunc, NY, USA) with 5000 Schwann cells/well. After 1 hr, 2 hrs, and 3 hrs, 20 μ L of the CTB-reagent was added to the dissociated cells and measurements were performed after incubation according to the suppliers' specifications. All measurements were repeated at three independent times. The background fluorescence or absorbance of microtiter plates with tested medium and lacking cells was subtracted from these data.

2.4. Statistics. All statistical analysis of data was performed using SigmaStat software (SPSS, Chicago, IL, USA). All data were evaluated using one-way ANOVA and post hoc analysis using the Student-Newman-Keuls method. All data are expressed as means \pm SE.

3. Results

Standardized 2 cm segments of rat sciatic nerve were removed and Schwann cells were prepared for culture. Schwann cell viability was determined after incubation in either saline, DMEM, HBRM, or Leibovitz's solution ($n = 3$ per group) for 0 hr, 1 hrs, 2 hrs, and 3 hrs. For each medium condition and time point, metabolic activity was studied at three separate temperatures: 4°C, room temperature 18°C, and 37°C (Figure 1). Cell viability was determined by two independent methods: the CTB and MTS test.

3.1. Metabolic Activity of Schwann Cells at 4°C. Metabolic activity was studied upon dissociation of the Schwann cells of rat sciatic nerves after incubation in the selected four media conditions and measured by CTB (Figure 2 for line chart and Figure 3 for bar chart). Schwann cell metabolic activity incubated at 4°C (Figure 2(a) and Figure 3(a), resp.) was decreased at 1 hr and remained decreased in the 2 hrs and 3 hrs groups. In general, at 4°C the metabolic activity was the lowest for the DMEM condition. Thus, Schwann cell metabolic activity in culture was reduced with time with all three media significantly. The cell viability was more than reduced to half within the first hour in all four experimental groups. The greatest Schwann cell viability in this set of experiments at 4°C could be observed in saline where cell metabolic activity was significantly higher than in DMEM and HBRM. The lowest viability was obtained at 4°C in DMEM with about 70% reduction in metabolic activity within the first hour followed by a reduction, nearly complete loss of metabolic activity, of 99.7% to 0.3% after 3 hours. Cell viability was examined by MTS.

3.2. Metabolic Activity of Schwann Cells at Room Temperature. At room temperature (Figure 2(b) and Figure 3(b), resp.), metabolic activity of cultured Schwann cells determined by CTB decreased for the DMEM and HBRM conditions, nominally was unchanged for the Leibovitz's medium and marginally increased in saline over time (Figures 2(b) and 3(b)). The reduction in metabolic activity was observed in DMEM with most loss of cell viability within the first hour of more than 90%. An increase of cell metabolic activity (132%) with incubation in saline occurred within the first 2 hours of cell activity followed by a continued reduction of approximately 10% within the third hour. The poorest conditions were obtained at room temperature with DMEM. Thus, the best Schwann cell activity at room temperature could be seen in the saline group over the three-hour period with increase of cell metabolism.

3.3. Metabolic Activity for Schwann Cells Incubated at 37°C. Metabolic activity for Schwann cells incubated at 37°C and measured by CTB increased for those incubated in HBRM, Leibovitz and saline (Figure 2(c) and Figure 3(c), respectively). Activity of Schwann cells in HBRM increased nearly 4-fold within the first hour followed by a slight reduction at the 2-hour time point, but still showing an increase in cell metabolism of 318% at the 3-hour time point. Incubation in Leibovitz's medium showed a similar 4-fold increase of Schwann cell metabolism within the first hour followed by continued decrease within the next 2 hours of observation period. After the three-hour period, there is still an increase of activity of 100% noticeable. Schwann cells metabolism after incubation in saline showed a 3-fold increase within the first hour resulting in an increase of activity of 120% after 3 hours. Schwann metabolism preincubated in DMEM did not show an increase in metabolic activity. The increase in metabolic activity for these HBRM, saline, and Leibovitz's medium peaked at 1 hr after nerve incubation at 37°C. Metabolic activity was reduced for all three conditions at 2 hrs and 3 hrs, but remained higher than at 0 hr. For nerves, the metabolic activity remained continuously high when incubated with HBRM at 2 and 3 hrs, indicating a broader time window for postincubation Schwann cell metabolic activity than the other 3 media.

3.4. Metabolic Activity of Schwann Cells Measured by MTS at 4°C, Room Temperature, and 37°C. Additionally, Schwann cell metabolism was also assessed as absorbance measured with MTS at 4°C (Figure 4(a)), room temperature (Figure 4(b)), and at 37°C (Figure 4(c)) incubated in the described media. At 4°C, all conditions resulted after 3 hours in massive reduction of cell viability. At room temperature, incubation in HBRM and DMEM showed slightly better results than NaCl and Leibovitz. Optimal cell viability with increase of Schwann cell metabolism can be seen after incubation in HBRM at 37°C as observed by determination of cell viability by reducing resazurin to resofurin with CTB in Figure 2.

Thus, Schwann cell metabolic activity over time in culture from ex vivo nerves incubated in one of four media was generally reduced at 4°C and room temperature incubation

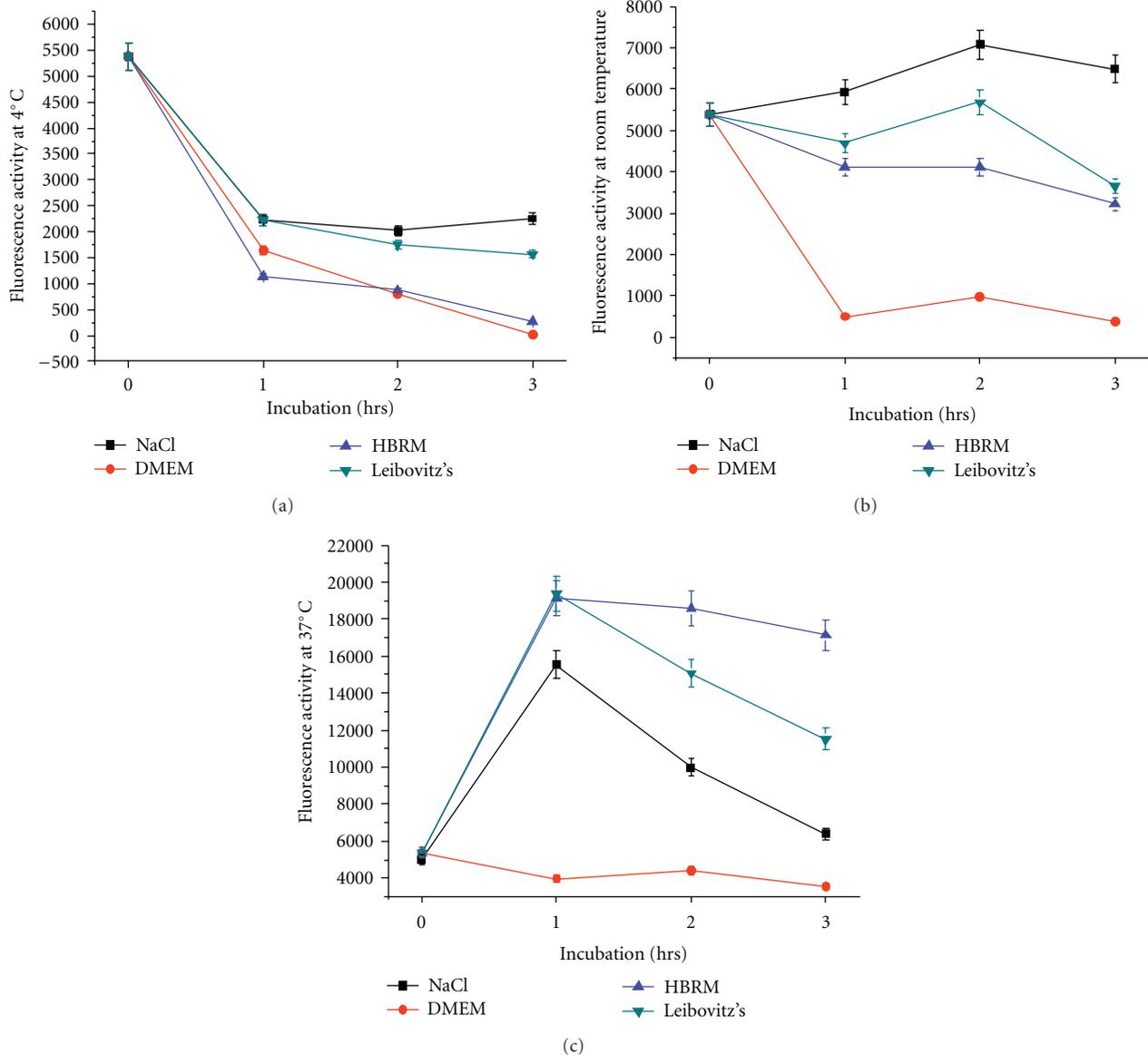


FIGURE 2: This Figure and respectively, Figure 3: Schwann cell metabolism indicated as fluorescence activity at 4°C (a), room temperature (b), and at 37°C (in (c)) incubated in the described media. Cell viability was measured by reduction of resazurin to resofurin by CellTiter-Blue (CTB) Cell Viability Assay. Most reduced cell viability was observed after 3-hour incubation of Schwann cells in DMEM at 4°C. Optimal cell viability with increase of Schwann cell metabolism can be seen after incubation in HBRM at 37°C. $P < 0.05$.

temperatures over a time window for three hours as measured by CTB and MTS independently. Most reduction in cell viability was observed within the first hour of incubation in both tests of more than 50% in all media at 4°C. For incubation at 37°C, Schwann cell metabolic activity was increased for nerve segments incubated in HBRM, Leibovitz, and saline over the observation period of three hours. But, there was no increase at 37°C in Schwann cell metabolic activity incubated in DMEM. While Schwann cell metabolic activity peaked at the 1 hr nerve incubation time point and declined for Leibovitz's and saline, the activity remained high even at the 2- and 3-hour time points. Most reduced cell viability was observed after 3-hour incubation of Schwann

cells in DMEM at 4°C. Optimal cell viability with increase of Schwann cell metabolism can be seen after incubation in HBRM at 37°C. This could be verified by the results obtained with the MTS at 37°C.

4. Discussion

In this study, we demonstrated that Schwann cell metabolic activity is dependent on several factors including temperature, holding media, incubation, and holding time. The greatest increase in metabolic activity of all these groups was observed at 37°C over a period of three hours. Here, a significant increase in metabolic activity could be observed in

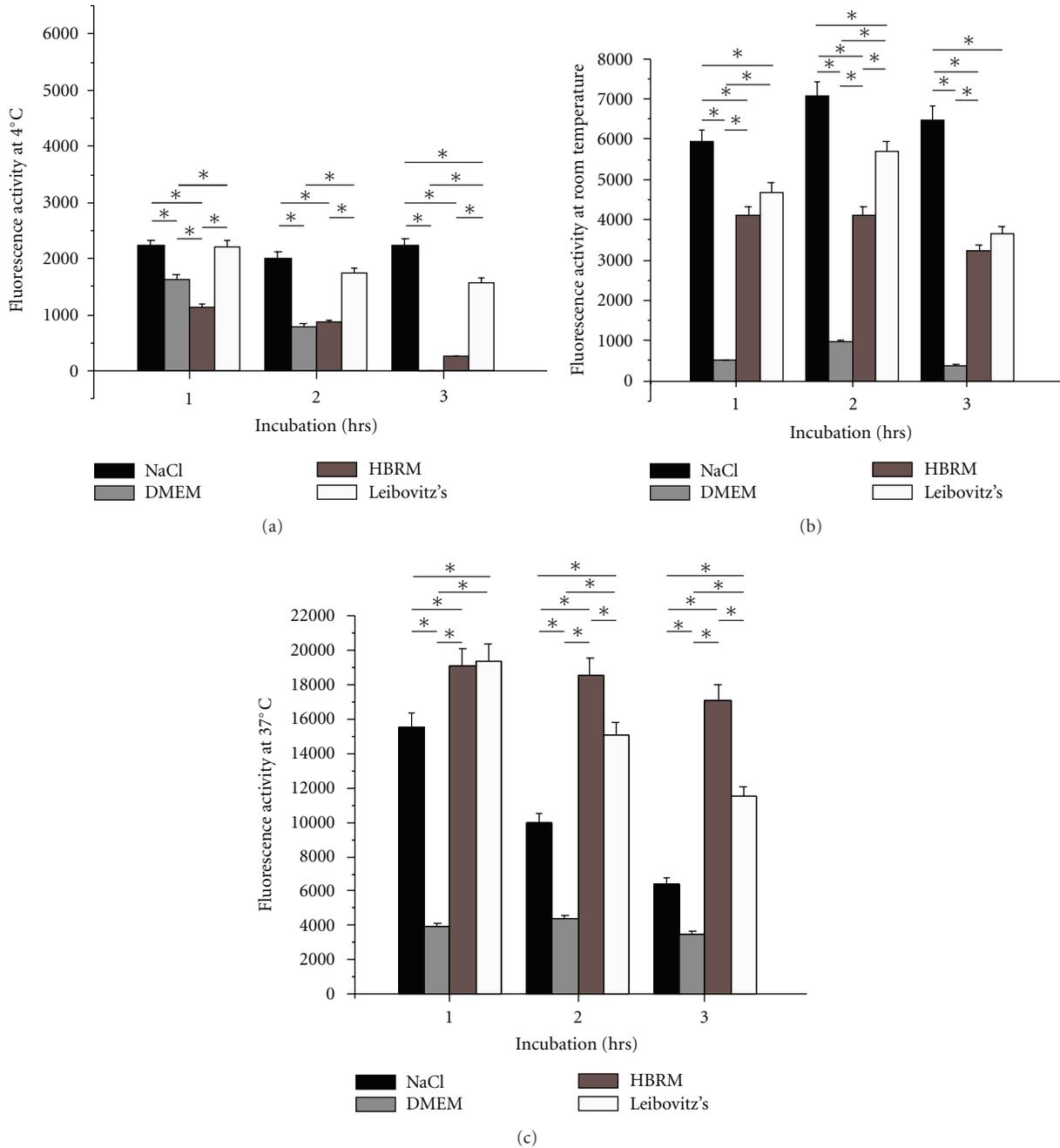


FIGURE 3

Leibovitz's medium and HBRM with a 3-fold increase after incubation of 3 hours in HBRM. Saline resulted in moderate increase of 120% in comparison to the other groups at 37°C.

Observing just 1 hour of incubation period at 37°C, best results were observed in correspondence to 3 three hours in saline, Leibovitz's medium, and HBRM with maximum activity with a 4-fold increase after 1 hour in both conditions. Most decrease in cell metabolic activity was observed at nerves incubated at 4°C in all 4 experimental groups. Cell metabolism was reduced to half after 3 hours in the saline

group and was close to zero metabolic activity in the DMEM group. The DMEM group resulted in all three temperature conditions in most reduction in cell metabolism activity. It is important to point out that our data demonstrated that incubation in the commonly used, the culture medium of Schwann consisting of DMEM with 10% serum did not result at any time point, and temperature in an increase, but instead in a significant decrease in cell metabolism activity within the three hour observation period. Thus, DMEM is suboptimal as a medium for preservation of Schwann cell metabolism and alternatives should be considered.

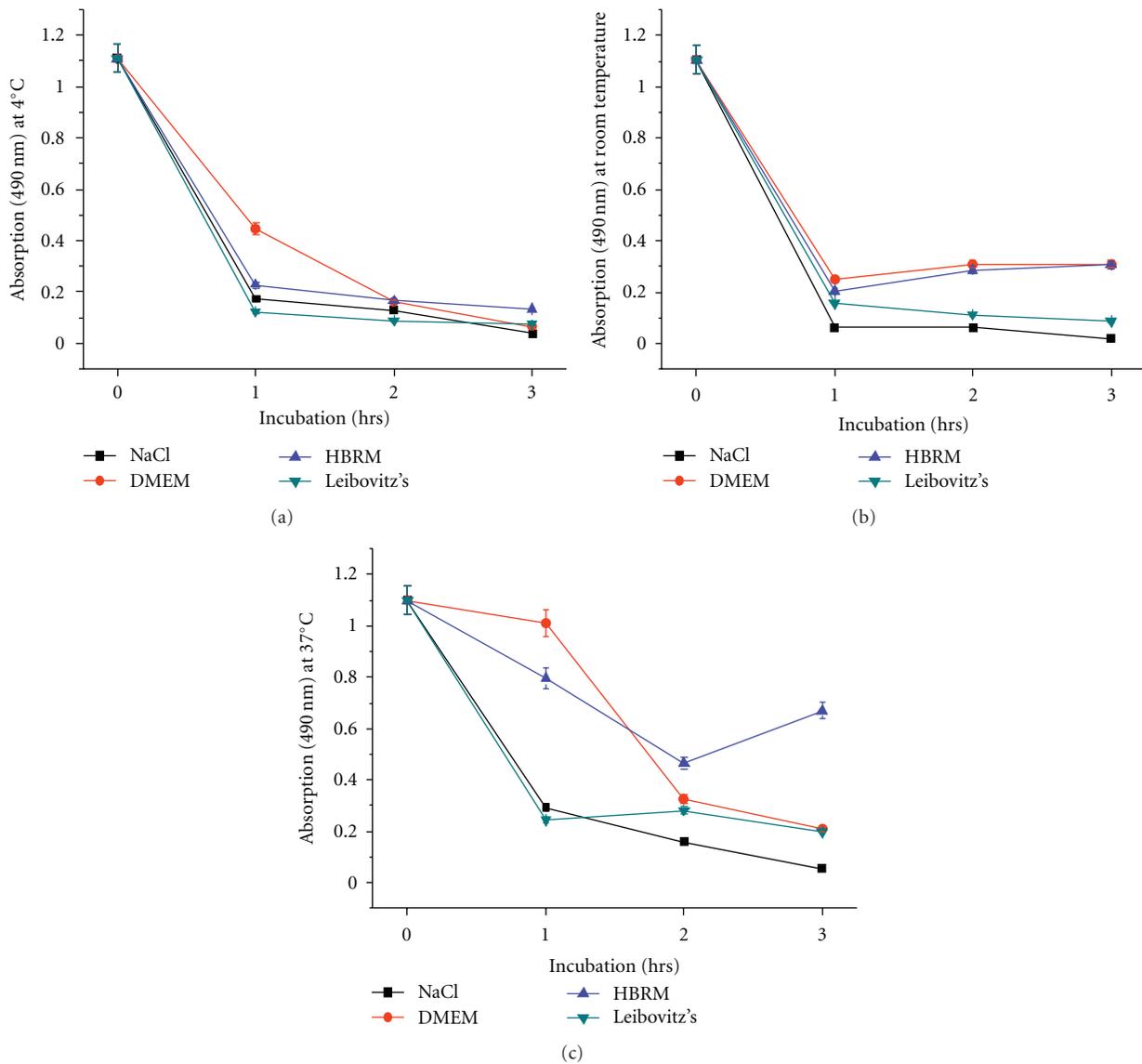


FIGURE 4: Schwann cell metabolism indicated as absorbance measured with MTS at 4°C (a), room temperature (b), and at 37°C (c) incubated in the described media. At 4°C all conditions resulted after 3 hours in massive reduction of cell viability. At room temperature incubation in HBRM and DMEM showed slightly better results than NaCl and Leibovitz's. Optimal cell viability with increase of Schwann cell metabolism can be seen after incubation in HBRM at 37°C as observed by independent determination of cell viability by CTB in Figure 2. $P < 0.05$.

Schwann cells play an important role in peripheral nerve regeneration; and poor survival of Schwann cells is thought to influence the outcome of nerve transplantation [15]. Reduced number of Schwann cells after suboptimal storage conditions of donor nerve removed for autologous cell transplantation, for example, in traumatic nerve defect injuries or after wide tumor resection, could lead to a reduction in growth factor production, less axonal guidance of elongating axons resulting in increased sprouting, and failure to connect to peripheral targets or even painful neuroma formation [11].

For improvement of peripheral nerve regeneration, it was shown that additional transplantation of Schwann cells leads to more directed growth of regenerating axons and

a significant better functional result with a greater nerve conduction velocity after crush lesion and after microsurgical repair [8–10]. The survival of Schwann cells could be experimentally improved by overexpression of polysialic acid [15] or addition of FK506 [16, 17]. Moreover, pre-degeneration of nerve grafts resulted in improvement of nerve regeneration based on the activation of Schwann cells [17–20]. The efficacy of 2–7 days of 14-day pre-degeneration in DMEM of rat Schwann cell culture was described in a recent study by Kraus et al. (2010) [21].

Moreover, further experimental studies demonstrated the importance of seeded Schwann cells to improve the efficacy of acellular nerve grafts [22] or artificial nerve guidance channels [23, 24] to improve effectiveness of nerve

repair. Addition of Schwann cells to muscle as nerve guidance in peripheral nerve defect injuries resulted in significant better functional and histological results than without cell supplement indicating the important role of Schwann cells for enhancement of axonal regeneration and remyelination after injury. Schwann cell-seeded bioartificial nerve conduits are subjects of several ongoing studies to improve functional results after nerve repair and to bridge extended nerve defects [24, 25]. Thus, incubation for optimal Schwann cell metabolic activity of donor nerve or of Schwann cell suspension for direct transplantation is essential and underlines the importance of our presented data. To verify our observed results, we performed independent test methods including using the CTB and MTS assay for comparison of cell metabolism according to previous reports [26, 27]. We archived similar results with all test methods demonstrating optimal cell viability of Schwann cell metabolism after 3-hour incubation in HBRM at 37°C.

In contrast to previous reports, we directly investigated Schwann cell viability which has a critical influence on the histological and functional results after nerve repair and nerve transplants after dissociation in a short period of time of three hours which is clinical relevant. Previous reports examined Schwann cell proliferation after 2 days and 3 days of culture [28]. Here, progressive increase of proliferation over 3 days could be observed. Successful storage of peripheral nerve before transplantation after this time could be demonstrated in an experimental study in rats by using polyphenol to reduce oxidative stress [29]. In this study, nerve segments were kept for up to 30 days in polyphenol solution followed by determination of nerve viability by calcein-AM/ethidium homodimer staining. In another study, storage in polyphenol solution was compared to conventional University of Wisconsin solution for long-term peripheral nerve banking [30].

5. Conclusion

The results demonstrated the enhancement of Schwann cell metabolism and optimal Schwann cell viability after incubation at 37°C with usage of either Leibovitz or HBRM up to three hours. The commonly used saline solution at room temperature demonstrated a slight increase in cell metabolism at 37°C. To obtain optimal results after nerve transplantation, removed nerves should be stored in the described conditions with usage of Leibovitz's medium or HBRM in 37°C upon transplantation. Additional experimental studies will determine if the presented results in vitro could be confirmed in vivo. With regard to clinical application, increased SC viability in autologous nerve transplants could result in enhanced axonal regeneration and remyelination leading to improved functional outcome after nerve grafting.

Abbreviations

SC: Schwann cell
 HBRM: Hannover bioreactor medium
 CTB: Cell Titer-Blue Cell Viability Assay
 DAPI: 4',6-diamidino-2-phenylindol

DMEM: Dulbecco's modified Eagles' medium
 EDTA: Ethylenediamine tetraacetic acid
 FCS: Fetal calf serum
 HEPES: 2-(4-(2-Hydroxyethyl)-1-piperazinyl)-ethansulfonsäure
 MTS: Tetrazolium salt ([3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt])
 NaCl 0.9%: Isotonic 0.9% sodium chloride
 NGF: Nerve growth factor
 PBS: Phosphate buffered saline solution
 PMS: Phenazine methosulfate
 p75NGFR: Low affinity nerve growth factor receptor
 RT: Room temperature (18°C).

Acknowledgments

The authors thank Sabrina Jahn and Andrea Lazarides for their excellent technical assistance.

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Clinical Study

Prognostic Value of Facial Nerve Antidromic Evoked Potentials in Bell Palsy: A Preliminary Study

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To analyze the value of facial nerve antidromic evoked potentials (FNAEPs) in predicting recovery from Bell palsy. *Study Design.* Retrospective study using electrodiagnostic data and medical chart review. *Methods.* A series of 46 patients with unilateral Bell palsy treated were included. According to taste test, 26 cases were associated with taste disorder (Group 1) and 20 cases were not (Group 2). Facial function was established clinically by the Stennert system after monthly follow-up. The result was evaluated with clinical recovery rate (CRR) and FNAEP. FNAEPs were recorded at the posterior wall of the external auditory meatus of both sides. *Results.* Mean CRR of Group 1 and Group 2 was 61.63% and 75.50%. We discovered a statistical difference between two groups and also in the amplitude difference (AD) of FNAEP. Mean \pm SD of AD was $-6.96\% \pm 12.66\%$ in patients with excellent result, $-27.67\% \pm 27.70\%$ with good result, and $-66.05\% \pm 31.76\%$ with poor result. *Conclusions.* FNAEP should be monitored in patients with intratemporal facial palsy at the early stage. FNAEP at posterior wall of external auditory meatus was sensitive to detect signs of taste disorder. There was close relativity between FNAEPs and facial nerve recovery.

1. Introduction

Bell palsy is a neuropathy of the peripheral seventh cranial nerve, usually resulting from traumatic, compressive, infective, inflammatory, or metabolic abnormalities. However, in many cases no etiology is identified, and the eventual diagnosis is idiopathic [1]. Its annual incidence was from 0.011% to 0.040% [2]. For many patients, the questions that whether their facial function will return to normal one day and how long this is going to take are mostly concerned about. Evaluation of the prognosis of Bell palsy is useful for counseling of patients and guiding further management. Since 1970s, prognostication has been based mainly on various electrophysiologic tests [3–10], such as electromyography (EMG), electroneurography (ENoG), maximal nerve excitability testing, and facial motor nerve conduction (MNC) testing. However, the electrophysiologic tests above are facial nerve orthodromic evoked potentials. Abnormal findings from these tests are obtained after the degeneration-process extends to the extratemporal segment of the facial

nerve with 1- to 2-week delay [11]. Decompression surgery cannot play a part in retrieve and prevent degeneration after most of facial nerve function has already degenerated. Therefore, if we want to detect nerve degeneration and to predict facial function recovery during its early stages, it is necessary to use a test that can diagnose degeneration within 1 week after the onset of paralysis.

The facial nerve antidromic evoked potentials (FNAEP) was first described by Bumm et al. in 1974 [12]. It is the only one method to represent the intratemporal facial nerve function [13]. It has the possibility to diagnose nerve degeneration during the early stage of paralysis. Nakatani et al. [14] had used FNAEP to value the prognosis of facial paralysis. However, the correlativity of intra- or extra-temporal facial nerve was not pointed out, and the quantitative analysis was not obtained. The purpose of this study was to evaluate the prognostic use of FNAEP quantitatively within three days in a successive series of patients with Bell palsy associated with or without taste disorder at a university-based center.

TABLE 1: Stennert system.

Facial paralysis symptoms	Evaluating standard	Secondary damage	Evaluating standard
Static state		Hyperacusis	Yes
Bilateral palpebral fissure difference	≥3 mm	Taste disorder	Yes
Lower eyelid ectropion	Yes	Joint movement: Amount, eyes, nasolabial fold, mouth and cheek	
Nasolabial fold loss	Yes		
Ptosis of labial angle	≥3 mm	Two among the above	Yes
Movement		Three among the above	Yes
Frown	No	Blink (secondary spasm)	Yes
Palpebral fissure could not close:		Contracture	Yes
Sleeping	Yes	Tear secretion:	
Maximum stimulation	Yes	Palpebral fissure static ≥70%	Yes
Grin: upper and lower canines	Not visible	<70%	Yes
Upper lateral incisors	Not visible	0%	Yes
Whistle: distance between philtrum and mouth corner on diseased side more than that on healthy side	>50%	Tear	Yes
Facial paralysis index		Secondary damage index	

2. Patients and Methods

2.1. Populations. From January to December 2010, there were 46 patients with unilateral Bell palsy in a single center (Department of Oral and Maxillofacial Surgery, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine). Out of the patients, 23 were male and 23 were female. Ages ranged from 19 to 66 years (mean, 43.5 yrs). The duration from onset to treatment was from 1 to 3 days (mean, 2.9 d). The right side was involved in 24 patients, and the left was in 22 patients. The etiology was idiopathic. The patients were divided into two groups: 26 patients with taste disorder (Group 1) and 20 patients without taste disorder (Group 2). Interventions given to the patients were local physical therapy and pharmacotherapy, such as high-dose prednisone within 3 days after onset, besides methylcobalamin and vasodilators in 1 month after onset. Forty-three patients (93.5%) were followed up with the average follow-up period of 4.8 months (ranged from 1 to 9 months).

2.2. Clinical Evaluation of Facial Nerve Function. The initial and final facial nerve function was reported using the Stennert system [15] (Table 1). Each indicator was scored 10. The score ranged from 0 to 200. Clinical recovery rate

(CRR) = $(200 - \text{follow-up score})/200 \times 100\%$. The recovery outcomes of facial nerve function was graded as follow: excellent (CRR ≥80%), good ($50\% \leq \text{CRR} < 80\%$), and poor (CRR <50%).

2.3. FNAEP Evaluation of the Facial Nerve Function. The FNAEP device (Viking Quset, Nicolet Corp, USA) includes bipolar stimulators, discoid electrodes, needle electrodes, and monitor. The patients were examined by FNAEP for the first presentation at the clinic. Before the test, the cerumen of external auditory canal was cleared and the degrease cream was embrocated at the external auditory canal and the earlobe. Ground wire was connected on a wrist. Two discoid electrodes with a little conductive paste were located at the posterior wall of the external auditory canal (recording electrode) and the earlobe (reference electrode), respectively (Figure 1). FNAEP was performed first on the asymptomatic side and then repeated on the symptomatic side. The superficial projection of the homolateral stylomastoid foramen was stimulated by the bipolar stimulator with band-pass filtering of 2–10000 Hz and stimulus intensity of 30 mA. The results of both sides were recorded (Figure 2). The amplitude difference (AD) and latency difference (LD) between symptomatic side and asymptomatic side were calculated according to the following formula:

$$AD = \frac{(\text{amplitude of symptomatic side} - \text{amplitude of asymptomatic side})}{\text{amplitude of asymptomatic side}} \times 100\%,$$

$$LD = \frac{(\text{latency of symptomatic side} - \text{latency of asymptomatic side})}{\text{latency of asymptomatic side}} \times 100\%.$$
(1)

2.4. Statistical Analysis. Statistical analysis of the data, presented as means ± SD, was performed using SAS 8.1

software. The difference between "Group 1" and "Group 2" was analyzed. Significance was established when probability

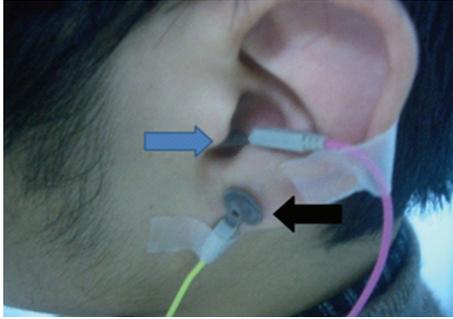


FIGURE 1: The recording electrode of the posterior wall of the external auditory canal (blue arrow) and the reference electrode of posterior wall of the earlobe (black arrow).

was $P < 0.01$. Statistical difference was established when probability was $0.01 < P < 0.05$. No statistical difference was established when probability was $P > 0.05$.

3. Results

3.1. Clinical Facial Nerve Function. During the period of follow-up, the mean CRR was $61.63\% \pm 18.90\%$ (ranged from 30% to 90%) in Group 1. There were 6 cases (26.09%) with excellent result, 12 cases (52.13%) with good result, and 5 cases (21.74%) with poor result. In Group 2, the mean CRR was 75.50% (ranged from 50% to 100%). There were 12 (60%) cases with excellent result, 8 cases (40%) with good result, and no cases with poor result (Figure 3). There was a statistical difference between the two groups ($P = 0.0189 < 0.05$).

3.2. FNAEP Results. The mean of AD of Group 1 and Group 2 were -33.88% and 5.47% . There was a significant difference between them ($P < 0.01$). For the patients with excellent result, mean \pm SD of AD and LD were $-6.96\% \pm 12.66\%$ and $0.54\% \pm 7.23\%$. For the patients with good result, mean \pm SD of AD and LD were $-27.67\% \pm 27.70\%$ and $12.11\% \pm 7.23\%$. For the patients with poor result, mean \pm SD of AD and LD were $-66.05\% \pm 31.76\%$ and $23.36\% \pm 1.61\%$ (Figure 4). There was a significant difference of AD between the “excellent” group and the “poor” group ($P = 0.0014 < 0.01$), and there were statistical differences between the “excellent” group and the “good” group ($P = 0.010 < 0.05$) and between the “good” group and the “poor” group ($P = 0.0287 < 0.05$). There was a statistical difference of LD between the “excellent” group and the “poor” group ($P = 0.0124 < 0.05$), and there was a significant difference between the “excellent” group and the “good” group ($P = 0.0041 < 0.01$) and no significant difference between the “good” group and the “poor” group ($P = 0.2041 > 0.05$).

4. Discussion

The majority of the drug treatments for Bell palsy at the early stage are effective. Nevertheless, those patients who are not completely improved by medication deserved facial

nerve decompression surgery. Accordingly, for almost all the patients, the questions that whether their facial function will return to normal and the facial nerve decompression surgery is necessary or not and when to take are mostly concerned about. Evaluation of the prognosis of Bell palsy is useful for counseling of patients and guiding further management. Although electrical tests were already introduced to predict the prognosis of Bell palsy in the 1970s, they were still controversial. As the facial nerve is stimulated out of the temporal bone in these tests, the evaluation of nerve function is limited to the extratemporal facial nerve. There is general agreement that abnormal findings from these tests are obtained after the degeneration process extends to the extratemporal segment of the facial nerve with 1-week delay [3–10]. We are not able to obtain information about facial nerve damage in the temporal bone at the early stage of facial palsy with extratemporal electrodiagnostic tests, such as MNC, EMG, and ENoG. Decompression surgery cannot play a part in retrieve and prevent degeneration after most of the nerve function has already degenerated. To raise therapeutic effect, we should precisely evaluate the poor outcome that patients who suffered from Bell palsy are possible to gain before completion of facial nerve degeneration. With regards to this, it is necessary to use a test that can diagnose degeneration within 1 week after the onset of paralysis.

The FNAEP is the only method of monitoring a nerve action potential, among all the electrodiagnostic tests of the facial nerve [3–10]. Other than traditional electrophysiological testing, FNAEP stimulated the extratemporal segment of facial nerve and was recorded at the intratemporal segment. If the lesion occurred, its amplitude would cause abnormal changes, which provided strong evidence of intratemporal location [16]. The waveform of this potential reaction was more constant and had obvious time locked relationship with the stimulus. Tashima et al. [17] reported that the recorder located at the posterior wall of external auditory meatus could represent the vertical portion of facial nerve, and the characteristic waveform of the FNAEP was also revealed in animal experiments.

Taste disorder in facial paralysis implies the lesion of vertical portion of facial nerve intratemporally. In this study, the duration from onset to test was from 1 to 3 days, and the mean of AD of Group 1 and Group 2 were -33.88% and 5.47% . There was a significant difference between them. Also, there was a statistical difference of CRR between two groups. Significant abnormal of AD of FNAEP was correlative with taste disorder. It was confirmed that FNAEP can prompt facial nerve damage in the temporal bone, and recorder at the posterior wall of external auditory meatus was appropriate. With the preliminary assessment, we found that the relativity between FNAEP amplitude and the clinical results was closer than that between latency and the clinical results, and the symptom of taste disorder would occur if AD of FNAEP was lower than -30% . It was important to evaluate the nerve function of intratemporal segment at the early stage. FNAEP was the best choice to evaluate and predict the facial nerve function at the early stage.

Herzon et al. [18] never applied FNAEP to evaluate prognosis of facial paralysis. Comparison of FNAEP between

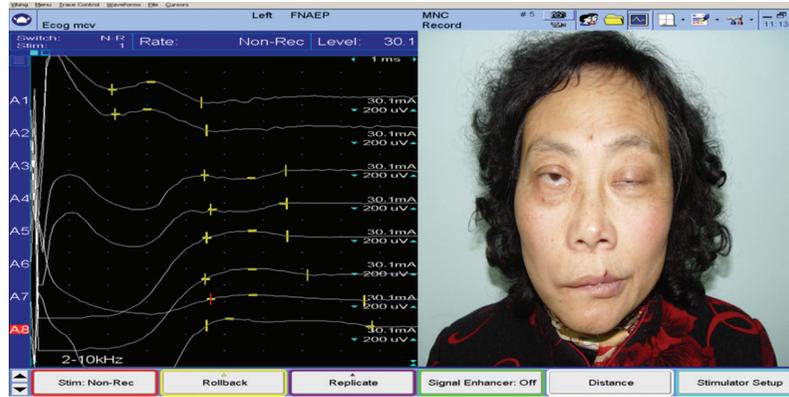


FIGURE 2: The waveform of FNAEP. A1–A4 show the recorders of asymptomatic side; A5–A8, which amplitude decreased (arrow), show the recorders of symptomatic side.

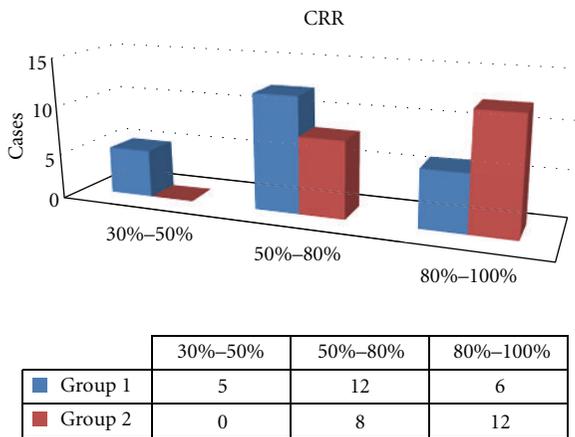


FIGURE 3: The CRR in the group with taste disorder and the group without taste disorder.

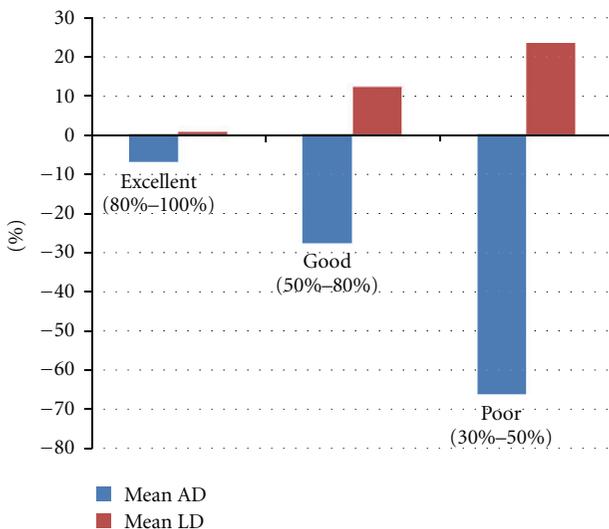


FIGURE 4: Mean AD and LD in the groups with excellent, good, and poor clinical results.

symptomatic side and asymptomatic side showed that the clinical results were good when only amplitude was temporarily discrete, and the results were poor while amplitude obviously reduced. However, Herzon failed to obtain quantitative analysis. According to our quantitative analysis, it was preliminary considered that when AD between symptomatic side and asymptomatic side was ranged from 0 to -20% , the predicted result was excellent; when it was ranged from -20% to -50% , the predicted result was good and when it was ranged from -50% to -100% , the predicted result was poor; facial nerve decompression may be considered.

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Clinical Study

Total Facial Nerve Decompression for Severe Traumatic Facial Nerve Paralysis: A Review of 10 Cases

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Management of traumatic facial nerve disorders is challenging. Facial nerve decompression is indicated if 90–95% loss of function is seen at the very early period on ENoG or if there is axonal degeneration on EMG lately with no sign of recovery. Middle cranial or translabyrinthine approach is selected depending on hearing. The aim of this study is to present retrospective review of 10 patients with sudden onset complete facial paralysis after trauma who underwent total facial nerve decompression. Operation time after injury is ranging between 16 and 105 days. Excitation threshold, supramaximal stimulation, and amplitude on the paralytic side were worse than at least 85% of the healthy side. Six of 11 patients had HBG-II, one patient had HBG-I, 3 patients had HBG-III, and one patient had HBG-IV recovery. Stretch, compression injuries with disruption of the endoneurial tubules undetectable at the time of surgery and lack of timely decompression may be associated with suboptimal results in our series.

1. Introduction

Indication and timing of the facial nerve decompression for facial paralysis and the anatomical extent of decompression has been a subject of controversy for years. Studies indicate that the number of surgical interventions has decreased over decades. In an analysis of large volume of published data between 1966 and 1999 regarding the management of facial nerve injury due to temporal bone trauma, Chang and Cass have reported that the patients with normal facial nerve function after injury regardless of progression, those with presentation of incomplete paralysis with no progression to complete paralysis, and those with less than 95% degeneration on ENoG at initial admission usually do not require surgical intervention. However, they have also reported that no data were available to provide information on exactly how much the return of function will be for the remaining patients who presumably have poorer prognosis [1]. Brodie and Thompson have reviewed 58 facial nerve injuries and reported that all patients with incomplete paralysis in the beginning recovered and 8 of 9 patients with delayed and 3 of 5 patients with sudden onset facial paralysis recovered after surgical decompression. But 2 of those (40%) patients with immediate-onset complete paralysis presented poor prognosis

[2]. McKennan and Chole have compared recovery of patients with delayed and immediate-onset traumatic facial paralysis and have found that recovery is likely to occur in 94% of delayed-onset facial paralysis without surgical intervention [3]. Darrouzet et al. have reported that 49 of 50 medically treated patients based on clinical and electrophysiological assessment experienced normal or near-normal facial function recovery. They have reported that of the 65 surgically treated patients 52 had immediate paralysis and at 2 years after surgery, 93.8% had a grade-I–III recovery [4].

However, the issue of late exploratory surgery for those who do not experience adequate recovery of facial function also has many unclear points. Ulug and Ulubil have reviewed 10 patients with immediate-onset facial paralysis associated with temporal bone fracture who underwent surgical intervention ranging between 14 and 75 days after injury. They have reported HB-I recovery in 5 and HB-II recovery in 4 patients regardless of timing of surgery [5]. Quaranta et al. have studied 13 patients who underwent late decompression surgery for facial nerve paralysis due to temporal bone fracture and reported HB-I and II recovery in 78% of patients [6]. Sanus et al. have reviewed 25 patients with delayed traumatic facial nerve paralysis without temporal bone fracture who have worsening of facial function to complete paralysis. Of

TABLE 1: Intraoperative findings of facial nerve (TA: traffic accident, LF: longitudinal fracture, TL: translabyrinthine, MCF: middle cranial fossa, FD: falling down, HMT: heavy metal hit, Exp: explosion, FB: falling from bicycle, FT: falling from truck, RE: right ear, and LE: left ear).

No	Cause	Site	Type of fracture	Operation	Facial nerve
(1)	TA	RE	LF	TL	Labyrinth filled with fibrous tissue
(2)	TA	RE	LF	MCF	Compression of genu with bony fragment
(3)	FD	LE	LF	MCF	Hyperemia and edema of geniculate ggl.
(4)	FD	LE	LF	MCF	Edema, granulation tissue
(5)	HMH	RE	LF	MCF	Hyperemia of geniculate ganglion
(6)	Exp	LE	TF	TL	Extensive edema, granulation tissue of the vertical segment
(7)	FB	RE	LF	MCF	Granulation tissue, fibrosis
(8)	FT	Bilat	Bilat LF	MCF (RE)	Fractured fragments
(9)	TA	RE	TF	MCF	Granulation tissue throughout the vertical segment of the nerve
(10)	TA	LE	LF	MCF	Granulation tissue

those, 13 patients underwent surgical decompression, whereas 12 patients were managed medically depending on clinical and electrophysiological findings, and complete or near complete recovery was found in 66.6% and 76.9% of patients in medically and surgically treated groups, respectively [7].

The aim of this study is to present retrospective review of 10 patients with complete facial paralysis after trauma who underwent total facial nerve decompression.

2. Material and Methods

Retrospective chart review of 10 patients who have undergone total facial nerve decompression due to severe traumatic facial paralysis between 2002 and 2010 were included. All patients had computerized tomography at the earliest. All patients had immediate-onset facial paralysis. House-Brackmann (HB) grading system was used to evaluate the function of the facial nerve [8]. Electromyography or electroneurography, if possible, was taken from the patients with facial paralysis. Excitation threshold, latency, and amplitude of orbicularis oculi muscle were used to compare normal and paralytic side during electroneurography. 9 patients are male, 1 patient is female with ages ranging from 20 to 53. 1 patient had bilateral and 9 patients had unilateral temporal bone fracture (5 right, 4 left). 2 patients had multiple and transverse, 1 patient had mixed (both parallel and perpendicular to the long axis

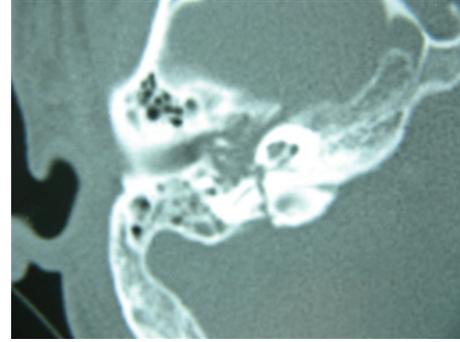


FIGURE 1: Transverse fracture of the temporal bone involving the midportion of the vertical segment is seen as an axial cut of the right temporal bone.

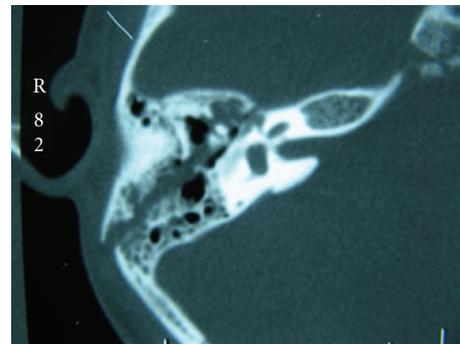


FIGURE 2: Longitudinal fracture of the temporal bone involving the perigeniculate region is seen as an axial cut of the right temporal bone.

of the petrous bone), and 7 patients had longitudinal fracture (Table 1, Figures 1 and 2).

Surgical technique: for patients with no hearing loss, transmastoid middle fossa combined approach was made with a postauricular skin incision at the mastoid apex going upward to the top of the auricle, 1.5–2 cm posterior and parallel to the postauricular sulcus. At 1 cm above the auricle, the incision was turned to the anterior for 3 cm, then following the temporalis hairy line, it was extended superiorly about 4 cm and then it was turned posteriorly for about 4 cm resembling “a reversed question mark.” Opposite to the skin incision (posteriorly based skin flap) an anteriorly based temporalis muscle flap incision was made for two-layer closure with inversely based opposing flaps at the end of surgery. After standard mastoidectomy and decompression of the facial nerve from digastric ridge to the second genu, a standard posterior tympanotomy was made, incudostapedial articulation was separated, and the incus was removed. Then the surgery was proceeded after drilling out the bone from tympanic side by decompressing the facial nerve anterior to the lateral semicircular canal from second genu to the geniculate ganglion beneath the malleus. At the level of head of malleus, 4 × 5 mm bone was removed from tegmen tympani to expose the dura to provide a landmark from middle fossa side. One cm above the mastoidectomy cavity, a 4 × 5 craniotomy

parallel to the zygomatic route with the 2/3 rd of the base located anteriorly was made. Dura was retracted, bony opening landmark was located, and the facial nerve was decompressed from geniculate ganglion to the IAC. Dura over the IAC was cut to release some CSF. After total decompression, the sheath was cut along the nerve, steroid soaked gel foams was placed over the nerve, a piece of muscle was secured with fibrin glue over the IAC, and incus was articulated between the malleus and head of stapes in its original position and secured with glue. If the incus was dislocated or eroded lenticular process due to trauma, a partial prosthesis was placed between the ear drum and stapes. The wound closure was completed in a standard way.

For patients with total hearing loss, translabyrinthine approach was made with a skin incision from mastoid apex to the scalp going posterior for 5-6 cm; then the incision was turned to superior for 6 cm; then it was turned anterior again, toward the top of auricle parallel to the lower incision. Temporalis muscle incision followed the skin incision, and standard translabyrinthine approach was completed by decompressing the facial nerve totally from stylomastoid foramen to the IAC. After steroid moistened gel foam placement over the nerve, the cavity is filled with fat tissue and fixed with fibrin glue to prevent CSF leakage.

3. Results

The type of trauma was as follows: falling from high in 2 patients, falling from bicycle in 1 patient, falling from behind a moving truck in 1 patient, traffic-car accident in 4 patients, strike of a flying heavy metal in dockyard in 1 patient, and explosion in 1 patient (Table 1). Facial nerve was totally exposed via middle fossa and transmastoid combined approach in 9 patients to preserve hearing and via translabyrinthine approach in 2 patients with total hearing loss due to transverse temporal bone fracture. One patient injured by explosion also had multiple fracture of the auditory canal and had canal wall down mastoidectomy during facial decompression. None of the patients had normal hearing before the surgery. Two patients had total hearing loss and 8 patients had conductive hearing loss. Out of 8 patients, 3 had profound (average air conduction between 62 and 55 dB), 2 had moderate (average air conduction between 55 and 30 dB), and 3 had mild (average air conduction between 30 and 20 dB) hearing loss.

Intraoperative pathology of the facial nerve was as follows: the integrity of the nerve was not interrupted as seen during surgery. Hematoma, multiple bone chips compression, granulation tissue, and edema were the main findings as summarized on Table 1. Extensive fibrosis around facial nerve was evident in patients with transverse fracture. Operation time after injury is ranging between 25 and 105 days (Table 2). Followup after surgery is ranging from 6 months to 3.5 years. Five patients had late EMG with axonal degeneration and 5 patients had electroneurography. None of the patients had voluntary motor unite action potential before the surgery. Excitation threshold, supramaximal stimulation, and amplitude on the paralytic side were worse than %85 of

the healthy side in one patient and worse than 90% in the others. Two patients were judged as HBG-5 dysfunction before the surgery had total axonal degeneration at late EMG. During followup, all patients with MCF approach had audiogram. Electrophysiological evaluation was performed every 6 months. Three patients had partial prosthesis over the stapes, and 6 patients had incus relocation during surgery. One month after surgery average conductive hearing loss was 30 dB on the operated side, and 3 months after surgery patients had 22 dB average conductive hearing loss. No serious complication, including neurosensorial hearing loss and meningitis, was seen. Only one patient had normal facial function during followup. Six of 11 patients had HBG-II, and 3 patients had HBG-III (Table 2).

4. Discussion

Electrical conduction may continue up to 72 hours to the muscles at the distal part of the injured nerve before a severe axonal block takes place. Facial nerve decompression and exploration are indicated if 90–95% loss of function is seen at the very early period on ENoG or if there is axonal degeneration on EMG lately with no sign of recovery. The latter is generally due to compression, edema, or intraneural hemorrhage without neural injury and usually does not necessitate surgery. However, early electrophysiological workout or even to evaluate the patient's voluntary facial movement is not possible often times in majority of patients with cranial trauma due to poor general condition at the emergency rooms and during intensive care period. Tests are neglected and treatment is delayed. The timing of surgical intervention is more than 30 days in 6 patients in this study. Priority of surgical intervention was modified due to multiple organ failures or the facial function was not properly evaluated because of loss of consciousness in these patients.

Electroneurography performed in a few days after trauma is valuable to differentiate the severity of injury which will eventually result with HBG-1/II or HBG-VI. But it does not provide any information about the level of injury between HBG-II and VI. Therefore EMG is also valuable for the followup in the late period. However, predictive value of evoked EMG for traumatic facial paralysis has been found questionable in some studies. Sillman et al. have compared prognostic value of evoked EMG in 62 idiopathic and 29 traumatic facial paralysis. Of those 9 cases with idiopathic and 12 cases with traumatic facial paralysis underwent total nerve decompression as determined by maximal decline of compound muscle action potential (CAP). Among patients who did not undergo surgical decompression, incomplete clinical recovery was not associated with CAP decline of greater than 90% for traumatic paralysis [9]. Coker et al. have proposed that excitation threshold below 3.5 mA on the paralytic side is a worse prognostic sign [10].

The incidence of temporal bone trauma and associated facial nerve injury has increased in recent decades together with the increasing traffic and population [11]. Management of traumatic facial nerve disorders is challenging. The type of injury, sudden or delayed-onset, complete or partial paralysis, localization of the injury, and severity of conduction

TABLE 2: Electrophysiology, surgical timing and the results of facial decompression (Mo: month, OOC: orbicularis oculi, mV: microvolt, mA: milliampere, SMS: supramaximal stimulation, amp: amplitude, ET: excitation threshold, RE: right ear, LE: left ear, and MUP: motor unite potential).

No	EMG/ENoG	Loss %	Timing	Preop grade	Postop grade
(1)	Total axonal degeneration	—	1 mo	6	2
(2)	Total axonal degeneration	—	1.5 mo	5	2
(3)	Total axonal degeneration	—	2 mo	5	1
(4)	OOC; SMS RE; 25, LE; 100 mA ET RE; 17, LE; 2.1 mA No voluntary MUP	89%	1.5 mo	6	2
(5)	OOC; amp RE; 0.2, LE; 2 mV No voluntary MUP	90%	2 mo	6	3
(6)	OOC; amp RE; 2.3, LE; 0.2 mV No voluntary MUP	91%	25 days	6	2
(7)	OOC; amp RE; 0.3, LE; 2.8 mV ET RE; 44, LE; 6.4 mA No voluntary MUP	85%	1 mo	6	2
(8)	OOC; amp LE; 2.5, RE; 0.2 mV No voluntary MUP	92%	1 mo	6	2
(9)	Total axonal degeneration	—	3.5 mo	6	3
(10)	Total axonal degeneration	—	2 mo	6	3

block based on the electrophysiological tests are the main determinants of the prognosis. Cranial injury may or may not be with temporal bone fracture and it is difficult to tell that in which type of fracture, the axis has greatest risk to intervene with the course of the nerve. Coker et al. have reported that 14 of 18 patients with temporal bone fracture who needed to have facial nerve exploration had longitudinal fracture [10]. Ulug and Ulubil have reported that 7 of 11 fractures in their surgical treatment series were of longitudinal type [5]. Majority of the patients in our series had longitudinal fracture which was associated with the involvement of the fallopian canal in the perigeniculate region. Labyrinthine segment is the most delicate and narrow part of the facial nerve. Degenerative and fibrotic changes after severe injury affect this region more than any part of the facial nerve. Felix et al. have examined facial nerve segments removed from 12 patients with persisting facial paralysis following temporal bone fracture and found that traumatic injury involving the geniculate ganglion presented profound retrograde degeneration through the labyrinthine and distal meatal segments of the facial nerve even though the fracture line was involving the horizontal segment only [12]. Hematoma, multiple bone chips compression, and edema were the main findings in our patients as seen in Table 1. Extensive fibrosis around facial nerve was evident in patients with transverse fracture. However, the integrity of the nerve was not interrupted as seen during surgery except in one patient with gunshot wounding who has grafting with greater auricular nerve.

Middle cranial or translabyrinthine approach is planned for total nerve exploration depending on hearing. Horizontal segment and geniculate ganglion can be exposed via transmastoid transsattal approach [13–15]. However, superior canal and its ampulla limit the exposure to the labyrinthine segment from transmastoid approach. Nyberg and Fisch, and

later on Graham and Kemink, described transmastoid and middle fossa combined total facial nerve exploration in patients with recurrent facial paralysis [16]. Total facial nerve decompression instead of limited segmental access to the blocked motor fibers is preferred in our series. This approach provides inspection of the facial nerve in every segment from brainstem to the parotid [17, 18]. We always attempt to do posterior tympanotomy to inspect the middle ear and prefer to remove incus before decompressing the horizontal segment to avoid the vibratory hazardous effect of the drill to the ossicular chain. The incus is later secured in its original position with some bone cement and fibrin glue. Mild conductive hearing loss was restored within 3 months after surgery and none of the patients with middle fossa approach had severe conductive or neurosensorial hearing loss.

The rate of recovery within HBG I-II after total facial nerve exploration in our short series is 70% (10/7). Stretch, compression injuries with disruption of the endoneurial tubules undetectable at the time of surgery may be associated with suboptimal results in our series. One other possible explanation would be the lack of timely decompression of the facial canal in some of them.

Disclosure

This study was not presented in any meeting before or submitted for publication to another journal. However, some of the cases in this series are presented before [11].

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Review Article

Clinical Outcomes of Gamma Knife Radiosurgery in the Treatment of Patients with Trigeminal Neuralgia

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Since its introduction by Leksell, Gamma Knife radiosurgery (GKRS) has become increasingly popular as a management approach for patients diagnosed with trigeminal neuralgia (TN). For this reason, we performed a modern review of the literature analyzing the efficacy of GKRS in the treatment of patients who suffer from TN. For patients with medically refractory forms of the condition, GKRS has proven to be an effective initial and repeat treatment option. Cumulative research suggests that patients treated a single time with GKRS exhibit similar levels of facial pain control when compared to patients treated multiple times with GKRS. However, patients treated on multiple occasions with GKRS are more likely to experience facial numbness and other facial sensory changes when compared to patients treated once with GKRS. Although numerous articles have reported MVD to be superior to GKRS in achieving facial pain relief, the findings of these comparison studies are weakened by the vast differences in patient age and comorbidities between the two studied groups and cannot be considered conclusive. Questions remain regarding optimal GKRS dosing and targeting strategies, which warrants further investigation into this controversial matter.

1. Introduction

Trigeminal neuralgia (TN) is a disorder of cranial nerve (CN) V that results in severe episodes of shock-like or lancinating pain in one or more of its three divisions (V1–V3). TN can be classified into two categories based on etiology: classical and symptomatic [1]. Idiopathic TN and cases due to vascular compression of CN V are categorized as classical TN [1]. Patients diagnosed with symptomatic TN experience trigeminal-related facial pain secondary to a brain tumor, skull deformity, or multiple sclerosis (MS) [1]. Evidence suggests that the majority of cases of TN are the consequence of focal compression of the entry zone of the root of the trigeminal nerve [2], while only 2% of cases are observed in patients diagnosed with MS [3]. Other than excruciating facial pain, there are no other direct medical symptoms

associated with TN, and the condition does not decrease life expectancy. However, many patients with TN struggle with accomplishing tasks that affect quality of life, which is how this disorder elicits a negative impact on the social and mental wellness of the patients who suffer from this illness.

Following the diagnosis of TN, pharmacotherapy is often the initial management approach in achieving facial pain control. However, many patients experience only limited relief from medication or are unable to endure the side effects of the prescribed drugs, and in turn seek neurosurgical intervention. Currently, surgical approaches include microvascular decompression (MVD) or a number of techniques that target the trigeminal ganglion or root which involve the destruction or blockage of portions of those anatomical structures [1, 2]. Although the neurosurgical modalities are preferred in many clinical situations and have proven to be

effective in achieving initial pain control, they are known to come with a variety of complications, and facial pain recurrence is likely [4].

Stereotactic radiosurgery (SRS) has proven to be an effective management approach for patients with medically [5] and surgically [6] refractory TN as a primary and repeat treatment modality. The use of radiosurgery in the treatment of TN dates back to Sweden in the 1950's, where Professor Lars Leksell performed radiogangliotomies directed at the gasserian ganglion [7]. Since the time of Leksell, advancements in radiosurgery and imaging technologies has led to the increasing popularity of SRS as a treatment option for patients with TN. One form of SRS that can be delivered to a patient is through a machine called the Gamma Knife (GK). The GK device is a cobalt-60-based machine, with 201 separate 4 to 18 mm collimator openings, that emits multiple gamma rays that converge on a target specified by computer planning. For specific medication intolerable patient subsets, Gamma Knife radiosurgery (GKRS) can be used as an initial management approach, or as a secondary management approach following radiosurgery or one or more of the various surgical modalities. As the evidence examining the role of GKRS in the management of patients with TN is increasing, it is of utmost importance for physicians to understand the criteria associated with GKRS, so that the optimal course of treatment for their patients can be prescribed.

An evidence-based review on the evaluation and treatment of TN by Gronseth et al. [8] found Level C evidence indicating that gasserian ganglion percutaneous techniques, GKRS, and MVD may be considered for facial pain management for medically refractory patients. However, questions remain regarding optimal treatment modalities in specific patient subsets. For this reason, the goal of this paper is to provide a modern review of the literature thoroughly analyzing the efficacy of GKRS in the treatment of patients with TN, as well as evaluating the treatment planning and methods associated with this evolving modality.

2. Review of Gamma Knife Radiosurgery for Trigeminal Neuralgia

2.1. Literature Search Strategy. To identify contemporary studies assessing the clinical outcomes of patients treated with GKRS for TN, a PubMed search from 2006 to April 2011 was performed. Keywords for search included "Gamma Knife OR Gamma Knife radiosurgery OR stereotactic radiosurgery trigeminal neuralgia OR *tic douloureux*." Studies analyzed in this review included retrospective cohort studies and prospective cohort studies with ≥ 5 evaluated patients. Studies published only in abstract form and studies published in a language other than English were excluded from our analysis. Due to our broad search strategy and the vast amount of world literature, references from existing review articles were also selected and analyzed for study inclusion eligibility.

2.2. Clinical Outcomes of Patients Undergoing a Single Gamma Knife Treatment. We reviewed a total of 19 studies

[4, 5, 9–25] analyzing the efficacy of patients with TN who were treated once with GKRS (Table 1). Thirteen of the 19 evaluated studies [4, 5, 9–19] utilized the Barrow Neurological Institute (BNI) pain intensity scale [26] as a measurement of response to treatment (See Section 3). One of the studies [18] included patients diagnosed with atypical TN. Of these 13 studies, only two [9, 13] analyzed patients treated with GKRS as an initial management approach. With a median followup of 31 months, Sheehan et al. [9] classified 87% of patients in BNI class I-IIIb, while Chen et al. [13] classified 91% of patients in BNI class I-IIIb (median followup = 15 months). Chen et al. [13] also reported that five of the 44 patients (11%) treated with GKRS developed hypoesthesia following the procedure.

The other 11 BNI pain intensity scale studies we reviewed included patients where previous surgical procedures were performed in a fraction of patients [4, 5, 10–12, 15–19] or all patients [14]. Of the 10 studies where previous surgical procedures were performed in a fraction of patients, nine reported outcomes in terms of categorizing patients in BNI class I-IIIb [4, 5, 10–12, 15–18]. Specifically, Riesenburger et al. [10] classified 58.6% of patients in BNI class I-IIIb (median followup = 48 months), Kondziolka et al. [5] classified 71% of patients in BNI class I-IIIb at three years, Dhople et al. [18] classified 72% of patients in BNI class I-IIIb (median followup = 29 months), Han et al. [11] classified 76.7% of patients in BNI class I-IIIb (mean followup = 58 months), Dhople et al. [17] classified 81% of patients in BNI class I-IIIb (median followup = 5.6 years), Matsuda et al. [16] classified 82% of patients in BNI class I-IIIb (median followup = 37 months), Little et al. [15] classified 83% of patients in BNI class I-IIIb (median followup = 6.3 years), Dellaretti et al. [4] classified 89.5% of patients in BNI class I-IIIb (mean followup = 20.3 months), and Park and Hwang [12] classified 94% of patients in BNI class I-IIIb with a minimum followup of 3 years. Pan et al. [19] reported clinical outcomes with respect to BNI class I, which contained only 5.7% of patients. The study that evaluated GKRS where previous surgical procedures were performed in 100% of patients classified 85% of patients in BNI class I-IIIb, with a median followup of 36 months [14].

We also reviewed two studies that used the excellent-good-fair-poor (EGFP) categorical scale to assess patient outcomes [20, 21] (See Section 3). Azar et al. [21] treated 30 patients with TN with GKRS at Iran Gamma Knife Center between 2006 and 2007. The authors reported that 40% of patients had an excellent outcome, 10% of patients had a good outcome, 33% of patients had a fair outcome, and 17% of patients had a poor outcome following the procedure. Approximately 13% of patients reported facial numbness related to GKRS. Sekula et al. [20] analyzed 29 consecutive patients who underwent MVD after failed GKRS. After surgery, 15 patients (54%) reported an excellent outcome, one patient (4%) reported a good outcome, two patients (7%) reported a fair outcome, and 10 patients (36%) reported a poor outcome. The complications from MVD included facial numbness in six patients (21%), dysesthesias in three patients (11%), and delayed facial palsy in one patient (4%).

TABLE 1: Clinical outcomes of patients undergoing a single Gamma Knife treatment.

Author (year)	Clinical evaluation method	GKRS max dose (Gy)	Study endpoints	Results
Sheehan et al. [9] (2010)	BNI	Median: 84	Patients with vessel impingement	59%
			Pain relief in patients with or w/o vascular impingement	$P = NS$
			BNI score I	57%
			BNI score II	17%
			BNI score III	13%
			BNI score IV	10%
Chen et al. [13] (2010)	BNI	90	BNI score V	2%
			BNI score I	43%
			BNI score I–IIIb	91%
Riesenburger et al. [10] (2010)	BNI	Median: 80	Patients with hypoesthesia	11%
			BNI score I	32.1%
			BNI score II	3.8%
			BNI score IIIa	1.9%
			BNI score IIIb	20.8%
			BNI score IV	41.5%
Kondziolka et al. [5] (2010)	BNI	60–90	Patients with facial numbness	36%
			1-y BNI score I–IIIb	80%
			3-y BNI score I–IIIb	71%
			5-y BNI score I–IIIb	46%
			10-y BNI score I–IIIb	30%
Dhople et al. [18] (2007)	BNI	Median: 75	Patients with facial numbness or paresthesia	10.5%
			BNI score I	22%
			BNI score II	6%
			BNI score III	44%
Han et al. [11] (2009)	BNI	Mean: 79.7	Patients with trigeminal dysfunction	19%
			BNI score I–IIIb	76.7%
			Patients with pain recurrence	52.2%
Dhople et al. [17] (2009)	BNI	Median: 75	Patients with radiation-induced cranial neuropathy	15%
			1-y actuarial rate of freedom from treatment failure	60%
			3-y actuarial rate of freedom from treatment failure	41%
			5-y actuarial rate of freedom from treatment failure	34%
			7-y actuarial rate of freedom from treatment failure	22%
			Superior response duration in patients w/o prior surgery	$P < 0.02$
Matsuda et al. [16] (2010)	BNI	80–90	Patients with facial numbness	6%
			BNI score I–IIIb	82%
Little et al. [15] (2008)	BNI	70–90	Patients with trigeminal nerve dysfunction	41.3%
			7-y GKRS initial treatment pain-free rate	45%
			7-y GKRS secondary treatment pain-free rate	10%
			Patients with bothersome facial numbness	5%

TABLE 1: Continued.

Author (year)	Clinical evaluation method	GKRS max dose (Gy)	Study endpoints	Results
Dellaretti et al. [4] (2008)	BNI	Mean: 85.1	1-y complete pain relief rate	83.1%
			2-y complete pain relief rate	70.9%
			3-y complete pain relief rate	62.5%
			Superior pain relief in patients w/o prior surgery	$P < 0.05$
			Patients with trigeminal dysfunction	21%
Park and Hwang [12] (2011)	BNI	80–90	BNI score I	17.6%
			BNI score II	17.6%
			BNI score IIIa	41.2%
			BNI score IIIb	17.6%
			BNI score V	5.9%
			Patients with trigeminal nerve dysfunction	23.5%
Pan et al. [19] (2010)	BNI	80	BNI score I	5.7%
			Patients with pain recurrence	44.2%
			Patients with facial numbness	9.6%
Kano et al. [14] (2010)	BNI	60–90	1-y BNI score I	26%
			1-y BNI score 1-IIIb	85%
			Patients with trigeminal sensory loss or paresthesia	9.3%
Azar et al. [21] (2009)	EGFP	90	Excellent outcome	40%
			Good outcome	10%
			Fair outcome	33%
			Poor outcome	17%
			Patients with facial numbness	13%
Sekula et al.* [20] (2010)	EGFP	NR	Excellent outcome	54%
			Good outcome	4%
			Fair outcome	7%
			Poor outcome	36%
			Patients with facial numbness	21%
			Patients with dysesthesias	11%
Régis et al. [22] (2006)		Median: 85	Patients with complete pain relief	83%
			Patients with facial numbness	6%
			Patients with hypesthesia	4%
Knafo et al. [23] (2009)		80	Patients with complete pain relief	32.6%
			Patients with significant pain relief	77.6%
			Patients with sensory side effects	14.9%
Longhi et al. [24] (2007)		75–95	Patients pain-free w/o medication	61%
			Patients pain-free with medication	29%
			Patients with no pain relief	10%
			Patients with side effects	9%
Kang et al. [25] (2008)		Mean: 84.3	Patients with complete pain relief	29.9%
			Patients with pain improvement	49.4%
			Patients with side effects	15.6%

BNI: Barrow Neurological Institute; EGFP: excellent-good-fair-poor; GKRS: Gamma Knife radiosurgery; MVD: microvascular decompression; NR: not reported; NS: nonsignificant.

*Study includes patients treated with MVD after failed GKRS.

Four of the 19 studies we evaluated [22–25] used other methodologies in determining the effectiveness of GKRS. In a prospective controlled trial, Régis et al. [22] analyzed 100 patients with TN treated with GKRS and reported that 83 patients (83%) were completely pain free, 58 of which (58%) discontinued all medication following the procedure (minimum followup = 12 months). Ten patients (10%) experienced radiation-induced complications, which included facial paresthesia or hypesthesia. Knafo et al. [23] performed a study investigating the short-term efficacy of GKRS in 67 patients with medically refractory TN. The authors performed followup assessments at 2, 4, and 6 months. Overall, 77.6% of patients witnessed some degree of pain relief, with 32.6% of those patients becoming completely pain free. Of the 67 patients, 10 (14.9%) experienced complications from the procedure, which included hypoesthesia and paresthesia. Longhi et al. [24] treated 160 patients with TN with GKRS (mean followup = 37.4 months). Sixty eight patients (42.5%) underwent prior invasive treatments. In clinical analysis, it was found that 61% of patients were pain free without medication, 29% of patients were pain free with medication, and 10% of patients did not respond to GKRS. The observed side effects were paresthesia (6.25%) and hypoesthesia (2.5%). Kang et al. [25] treated 77 patients with idiopathic TN with GKRS. Thirty eight patients (49.4%) exhibited some level of pain improvement following GK treatment, with 23 of those patients (29.9%) reporting a pain-free outcome. Twelve patients (15.6%) experienced complications, which were reported to be mild facial sensory changes and mild facial nerve dysfunction.

2.3. Clinical Outcomes of Patients Undergoing Multiple Gamma Knife Treatments. As GKRS has proven to be an effective initial treatment for TN, numerous reports have been published analyzing patients treated on multiple occasions (>1) with GKRS. We reviewed six studies evaluating patients treated more than once with GKRS [27–32] (Table 2). Of these six articles, two [29, 32] utilized the BNI pain intensity scale [26]. Gellner et al. [32] evaluated 21 patients treated on two occasions with GKRS. Ten patients (48%) had undergone previous surgical procedures. Sixteen patients (76.2%) exhibited compelling improvements and were placed in BNI class I-II. Huang et al. [29] analyzed 65 medically refractory patients with TN who were treated with GKRS as a second treatment modality. Of these 65 patients, 30 (46%) had undergone GKRS as an initial management approach. The authors placed 22 patients (34%) in BNI class I, 11 patients (17%) in BNI class II, four patients (6%) in BNI class IIIa, and five patients (8%) in BNI class IIIb. Overall, with a median followup of 64 months, 65% of patients reported successful results in terms of pain control rates.

A total of three of the six reviewed studies evaluated patients using the EGFP categorical scale [28, 30, 31]. Aubuchon et al. [31] analyzed 37 patients treated a second time with GKRS for recurrent TN and reported that 17 patients (46%) achieved excellent pain relief, nine patients (24%) achieved good pain relief, five patients (14%) achieved fair pain relief, and six patients (16%) achieved poor pain relief. However, the authors concluded that 57% of patients

experienced some form of trigeminal dysfunction following repeat radiosurgery. Similar to the results reported by Aubuchon et al. [31], Huang et al. [28] treated 28 patients with repeat GKRS and reported that 12 patients (43%) exhibited excellent pain relief, five patients (18%) exhibited good pain relief, and two patients (7%) exhibited fair pain relief. In addition, the authors found a statistically significant ($P = 0.047$) correlation between cumulative radiation doses >115 Gy and facial numbness. In a separate study, Huang et al. [30] evaluated the efficacy of MVD following failed repeat GKRS. Specifically, a total of eight patients underwent MVD a mean of 7.6 months following repeat GKRS. Of the eight patients, seven (87.5%) were completely pain free at a mean of 21 months following neurosurgery. This data supports the use of MVD if multiple GK procedures are deemed ineffective.

Kimball et al. [27] treated 53 patients with repeat GKRS and analyzed the patients not lost during followup using the Marseille scale [22], which categorizes patients into one of five classes, with a higher class statistically indicating a worse prognosis for the patient. With a mean followup of 42 months, 20 patients (43.5%) were categorized in Marseille class I-II, six patients (13%) were categorized in Marseille class III-IV, and 20 patients (43.5%) were categorized in Marseille class V. The authors also reported a statistically significant ($P = 0.047$) correlation between facial numbness and superior long-term pain relief. A total of 22 patients (48%) experienced trigeminal dysfunction of any kind, while 21 patients (46%) experienced numbness in the face.

2.4. Clinical Outcomes of Patients Undergoing Single versus Multiple Gamma Knife Treatments. Since GKRS can be performed as both initial and salvage treatment options for patients who suffer from TN, its efficacy has been compared in patients who undergo one versus multiple radiosurgery procedures. We reviewed eight studies to further examine this matter [3, 33–39] (Table 3). Four of the eight studies utilized the BNI pain intensity scale [26] to evaluate patient outcomes [3, 33–35]. Verheul et al. [33] performed 450 GK procedures in 365 patients. With a median followup of 28 months, it was reported that 75%, 60%, and 58% of patients with idiopathic TN had BNI scores of I–IIIb at 1, 3, and 5 years, respectively. The 1-, 3-, and 5-year-BNI scores of I–IIIb in patients with MS-related TN were 56%, 30%, and 20%, respectively. The authors concluded that repeat GKRS exhibited similar success rates when compared to the initial procedure. Similar to Verheul et al. [33], Park et al. [34] did not find differences in terms of time to initial response, time to pain recurrence, and overall pain relief when comparing patients who underwent one versus two GK treatments. However, it was observed that patients who received two GK treatments were more likely to have facial sensory changes when compared to patients treated a single time with radiosurgery. Little et al. [35] performed a study where 79 patients with typical TN were treated with GKRS as a salvage procedure. Twenty-one patients (27%) underwent GKRS as an initial modality. Approximately five

TABLE 2: Clinical outcomes of patients undergoing multiple Gamma Knife treatments.

Author (year)	Clinical evaluation method	GKRS max retreatment dose (Gy)	Study endpoints	Results
Gellner et al. [32] (2008)	BNI	Mean: 74.3	BNI score I	47.6%
			BNI score II	28.6%
			BNI score III	23.8%
Huang et al. [29] (2010)	BNI	Mean: 49	BNI score I	34%
			BNI score II	17%
			BNI score IIIa	6%
			BNI score IIIb	8%
			1-y pain control rate	74%
			2-y pain control rate	71%
			3-y pain control rate	66%
			Facial numbness	17%
Aubuchon et al. [31] (2010)	EGFP	Mean: 84.4	Excellent pain relief	46%
			Good pain relief	24%
			Fair pain relief	14%
			Poor pain relief	16%
			Trigeminal nerve dysfunction	57%
Huang et al. [28] (2006)	EGFP	Mean: 52	Excellent pain relief	43%
			Good pain relief	18%
			Fair pain relief	7%
			Facial numbness	36%
Kimball et al. [27] (2010)	Marseille	70	Marseille class I-II	43.5%
			Marseille class III-IV	13%
			Marseille class V	43.5%
			Facial numbness	46%

BNI: Barrow Neurological Institute; EGFP: excellent-good-fair-poor; GKRS: Gamma Knife radiosurgery.

years following salvage GKRS, the authors reported that 50% of patients experienced pain relief and 20% of those patients were completely pain free. In addition, a statistically significant ($P = 0.029$) correlation between GKRS failure and prior MVD was found. Zorro et al. [3] treated 37 patients (78% had failed prior surgery) with MS-related TN with GKRS. Nine patients (24%) underwent GKRS as their first procedure. The reported 1, 3, and 5 year BNI scores of I–IIIb were 82.6%, 73.9%, and 54%, respectively.

The other four studies we reviewed utilized the EGFP categorical scale as a measurement of response to treatment [36–39]. Two of the evaluated studies [36, 37] were conducted by Fountas et al. and analyzed patients treated with GKRS for idiopathic TN based on whether or not they had undergone previous surgical or radiosurgical procedures for facial pain control. One of the studies evaluated 106 patients (19 previous radiosurgery procedures) and concluded that the treatment group without a previous history of surgical or radiosurgical procedures exhibited superior clinical outcomes, with 1-year and 2-year complete pain relief rates of 82.5% and 78%, respectively [36]. The 1-year and 2-year complete pain relief rate in the patient group with a history of surgical or radiosurgical procedures was 69.4% and 63.5%, respectively [36]. As expected, similar results were found

in the other study by Fountas et al. [37]; however, no prior radiosurgical procedures were performed in the patient group with a history of prior procedures. Huang et al. [38] conducted a study where 89 patients with idiopathic TN were treated with GKRS as an initial management approach, 20 of which underwent a subsequent GKRS procedure for facial pain recurrence. Following the initial radiosurgical procedure, 50 patients (56%) had an excellent response, 12 patients (13.5%) had a good response, and 7 patients (7.9%) had a fair response. Following the second radiosurgical procedure, 11 patients (55%) had an excellent response and one patient (5%) had a good response. In a separate study, Huang et al. [39] assessed 21 patients with benign tumor-related TN who were treated with GKRS as an initial or repeat procedure. Following the initial GK procedure to the tumor, 12 patients (57%) had an excellent response and 1 patient (5%) had a good response. A total of eight patients were treated with a subsequent GKRS procedure targeted at the ipsilateral trigeminal root or ganglion due to facial pain recurrence. Following the second radiosurgical procedure, the authors reported four patients (50%) with an excellent response.

2.5. Comparison Studies. We identified six studies comparing patients treated with GKRS with patients treated with one

TABLE 3: Clinical outcomes of patients undergoing single versus multiple Gamma Knife treatments.

Author (year)	Clinical evaluation method	GKRS max dose (Gy)	Study endpoints	Results
Verheul et al. [33] (2010)	BNI	1st treatment: 80 2nd treatment: 80	BNI scores of I–IIIb at 1-y for idiopathic TN	75%
			BNI scores of I–IIIb at 3-y for idiopathic TN	60%
			BNI scores of I–IIIb at 5-y for idiopathic TN	58%
			BNI scores of I–IIIb at 1-y for MS-related TN	56%
			BNI scores of I–IIIb at 3-y for MS-related TN	30%
			BNI scores of I–IIIb at 5-y for MS-related TN	20%
			5-y idiopathic retreatment pain relief rate	75%
			5-y MS retreatment pain relief rate	46%
Park et al. [34] (2011)	BNI	1st treatment mean: 82.4 ± 6.25 2nd treatment mean: 81 ± 4.89	Pain outcome in primary versus secondary GKRS	<i>P</i> = NS
			Primary GKRS facial numbness	21%
			Secondary GKRS facial numbness	45.8%
Little et al. [35] (2009)	BNI	1st treatment: 80 2nd treatment: 40–50	BNI score of I–III at 1-y	75%
			Patients requiring additional surgery	41%
			Patients with mild facial numbness	76%
			Patients with bothersome facial numbness	8%
			Patients with eye symptoms	12%
Zorro et al. [3] (2009)	BNI	Median: 80	BNI scores of I–IIIb at 1-y	82.6%
			BNI scores of I–IIIb at 3-y	73.9%
			BNI scores of I–IIIb at 5-y	54%
			Patients with facial sensory dysfunction	5.4%
Fountas et al. [36] (2007)	EGFP	Median: 80	1-y no previous treatment excellent outcome rate	82.5%
			1-y previous treatment excellent outcome rate	69.4%
			2-y no previous treatment excellent outcome rate	78%
			2-y previous treatment excellent outcome rate	63.5%
			No previous treatment paresthesia rate	15.8%
Fountas et al. [37] (2006)	EGFP	Median: 80	Previous treatment paresthesia rate	16.3%
			1-y no previous treatment excellent outcome rate	80.8%
			1-y previous treatment excellent outcome rate	69.2%
			2-y no previous treatment excellent outcome rate	64%
			2-y previous treatment excellent outcome rate	11.5%
Huang et al. [38] (2008)	EGFP	1st treatment mean: 79 2nd treatment mean: 52	No previous treatment facial numbness rate	17.3%
			Previous treatment facial numbness rate	16%
			1st treatment excellent outcome rate	56%
			1st treatment good outcome rate	13.5%
			1st treatment fair outcome rate	7.9%
Huang et al. [39] (2008)	EGFP	Mean: 60.7	2nd treatment excellent outcome rate	55%
			2nd treatment good outcome rate	5%
			Facial numbness associated with repeat GKRS	<i>P</i> = 0.007
Huang et al. [39] (2008)	EGFP	Mean: 60.7	Excellent outcome rate after GKRS to the tumor	57%
			Excellent outcome rate after GKRS to CN V	50%

BNI: Barrow Neurological Institute; CN: cranial nerve; EGFP: excellent-good-fair-poor; GKRS: Gamma Knife radiosurgery; NS: nonsignificant.

TABLE 4: Comparison studies.

Author, surgery type (year)	GKRS max dose (Gy)	Study endpoints	Surgery	GKRS	<i>P</i> value
Linskey et al. [2], MVD (2008)	80–90	Initial actuarial pain-free rate	100%	78%	0.0002*
		2-y actuarial pain-free rate	88%	50%	
		5-y actuarial pain-free rate	80%	33%	
Brisman [40], MVD (2007)	75	12-mo complete pain relief rate	68%	58%	0.089*
		18-mo complete pain relief rate	68%	24%	
		Patients requiring retreatment	4.2%	18%	
Oh et al. [41], MVD (2008)	Mean: 77.8	BNI Grade I-II classification	63%	56%	NR
		Patients with pain recurrence	11.1%	11.1%	NR
Aryan et al. [42], MVD (2006)	90	TN complexity grade	3	5.8	<0.001
		Average response following treatment	3.4	2.4	0.017
		Patient satisfaction	8.7	6.4	0.02
Pollock and Schoeberl [43], PFE (2010)	Median: 85	1-y pain-free rate	84%	66%	0.003*
		4-y pain-free rate	77%	56%	
		Retreatment rate	15%	35%	
Pollock and Stein** [44], PFE (2010)	Median: 76.1	Patients treated with additional surgery	22%	48%	0.02

BNI: Barrow Neurological Institute; GKRS: Gamma Knife radiosurgery; MVD: microvascular decompression; NR: not reported; NS: nonsignificant; PFE: posterior fossa exploration; TN = trigeminal neuralgia.

**P* value indicates overall pain-free levels.

**Data includes patients treated with ≥ 3 prior operations.

of the various surgical modalities [2, 40–44] (Table 4). The authors of this review acknowledge the importance of percutaneous techniques in the management of TN; however, our modern literature search predominantly yielded comparison studies analyzing the efficacy of MVD when compared to GKRS. Specifically, four of the six studies [2, 40–42] analyzed patients treated with GKRS against patients treated with MVD. Linskey et al. [2] prospectively evaluated a total of 80 patients with typical TN. No previous procedures were performed on the patients constituting this study. Specifically, 36 were treated with MVD (45%), while 44 were treated with GKRS (55%). The MVD treatment arm statistically differed from the GKRS treatment arm with respect to age (median of 54 versus 74 years), preoperative symptom duration (median of 2.6 versus 7.5 years), and the presence of major comorbidities (2.8 versus 58.3%). The mean followup time was determined to be 3.4 ± 2.1 years. The authors reported that patients treated with MVD exhibited superior levels of initial (100%), 2 year (88%), and 5 year (80%) actuarial pain-free rates when compared to the patients treated with GKRS (78, 50, and 33%, resp.), with a *P* value of 0.0002. In addition to increased levels of patient satisfaction, as reported by required patient surveys, the MVD treatment group also had a decreased level of permanent mild (5.6%) and severe sensory loss (0%) when compared to the GKRS treatment group (6.8% and 2.3%, resp.). Two patients (5.6%) in the MVD group experienced permanent mild paresthesias or numbness, one (2.8%) patient experienced a cerebrospinal fluid leak from the wound, and one patient (2.8%) experienced hearing loss and diplopia. Three patients (6.8%) in the GKRS group experi-

enced permanent mild paresthesias or numbness, one patient (2.3%) experienced a more permanent sensory numbness, and one patient (2.3%) experienced a transient headache and nausea following the GK procedure.

Brisman [40] compared 24 patients treated with MVD with 61 patients treated with GKRS. All patients were diagnosed with typical TN and did not undergo previous GK or MVD procedures. It was reported that patients treated with MVD exhibited superior levels of complete pain relief at 12 (68%) and 18 months (68%) when compared to the GKRS group, who's complete pain relief rate was 58% at 12 months and 24% at 18 months (*P* = 0.089). The treatment arms did not statistically differ in terms of $\geq 90\%$ pain relief at 12 and 18 months. No permanent complications were observed. This study could be criticized due to the large difference in the number of patients constituting the two treatment arms.

Oh et al. [41] evaluated a total of 45 elderly patients (>65 years of age) diagnosed with idiopathic TN who were treated with either MVD (27 patients) or GKRS (18 patients). It was reported that three MVD patients (11%) and three GK patients (17%) underwent previous percutaneous procedures. The mean followup period was reported to be 35.9 months for the MVD group and 33.1 months for the GKRS group. According to the BNI pain intensity scale [26], the MVD group had a superior prognosis, with 17 patients (63%) classified in BNI class I-II compared with the 10 patients (56%) in the GKRS group classified in BNI class I-II. The two groups did not differ in terms of pain recurrence during followup. The observed complications following MVD included constant headache in 11 patients (40.7%), facial paresthesia in five patients (18.5%), paresthesia of the

tongue in two patients (7.4%), infection at the site of incision in one patient (3.7%), an acute subdural hemorrhage in one patient (3.7%), temporary hearing loss in one patient (3.7%), and otitis media with cerebrospinal leakage in one patient (3.7%). Two patients (11%) in the GKRS group experienced paresthesia.

Aryan et al. [42] compared the clinical outcomes of 19 patients treated with MVD with 15 patients treated with GKRS. Patients diagnosed with symptomatic TN were excluded from this study. Nine GK patients (60%) and four MVD patients (21%) underwent previous surgical procedures. The treatment arms statistically differed ($P = 0.0005$) with respect to mean patient age, with the mean age of the GKRS group exceeding the MVD group by 13 years (74 versus 61 years). The median followup was determined to be 17 months. The authors determined clinical results by using the EGFP categorical scale. In addition, patient satisfaction was graded on a scale of 1 (unsatisfied) to 10 (completely satisfied). It was reported that the mean TN complexity grade was statistically different ($P < 0.001$) between the treatment arms (GK = 5.8; MVD = 3). The average response following the procedure was determined to be 3.4 for the MVD group and 2.4 for the GKRS group ($P = 0.017$). Also, it was found that the satisfaction score for the MVD group was superior to the GKRS group (8.7 versus 6.4), with a P value of 0.02. The authors reported a statistically significant correlation between TN complexity grade and clinical response ($P < 0.001$), as well as TN complexity grade and patient satisfaction ($P < 0.001$).

To date, no randomized trials have been conducted analyzing the outcomes of patients with TN who are treated with MVD compared to GKRS. In a large review on TN management, Zakrzewska and Linskey [45] found evidence that MVD is an effective treatment for long-term facial pain relief but comes with an increased risk of ipsilateral hearing loss. In addition, the authors concluded that single-dose SRS is an effective treatment for long-term facial pain relief but puts patients at risk for facial numbness or facial paresthesias. Investigation into this matter in the form of a randomized controlled trial would provide the best evidence in terms of facial pain relief and procedure-related complications.

In addition, we reviewed two studies comparing patients treated with GKRS with patients treated with posterior fossa exploration (PFE) [43, 44], both of which were conducted by Pollock and colleagues at the Mayo Clinic College of Medicine. One of the studies [43] was a specific prospective comparison of 91 patients treated with PFE and 49 patients treated with GKRS for idiopathic TN as an initial management approach. The treatment arms statistically differed in terms of age (GKRS = 67.1 years; PFE = 58.2 years), with a P value < 0.001 . The median followup time was 38 months. It was reported that patients treated with PFE were more likely to be pain free and off medications at 1 year (84%) and 4 years (77%) when compared to the GKRS group (66 and 56%, resp.) ($P = 0.003$). Retreatment for recurrent facial pain was performed in 15% of the patients in the PFE treatment arm and 35% of patients in the GKRS treatment arm ($P = 0.009$). Also, it was found that nonbothersome facial numbness occurred more frequently in the GKRS group

($P = 0.04$). An additional study from the Mayo Clinic evaluated patients with recurrent TN who underwent 3 or more surgical procedures [44]. The authors reported that patients treated with PFE exhibited superior levels of complete pain relief at 3 years of followup when compared to patients treated with GKRS, balloon compression, and glycerol rhizotomy ($P < 0.01$) and underwent additional surgery for recurrent facial pain less often when compared to patients treated with the other modalities ($P = 0.02$). Clinical outcomes did not differ between patients treated with GKRS and patients treated with the percutaneous techniques.

3. Treatment Planning and Methods

3.1. Types of Radiosurgery. SRS can be performed by a variety of tools, which include GKRS, CyberKnife technology, and linear accelerator (LINAC)-based treatment. Our analysis yielded one study whose primary endpoint was to devise a method using CyberKnife treatment planning that would mimic the dosimetric characteristics of the GK treatment plan in five patients undergoing radiosurgery for TN [46]. The position of the trigeminal nerve was determined using computed tomography cisternography. Both the isodose lines and critical structures were identified using the GKRS treatment plan and were transferred to the CyberKnife treatment planning system. It was reported that the average length of the trigeminal nerve receiving a dose of 60 Gy was 4.5 mm for the GK, 4.5 mm for the nonisocentric CyberKnife, and 4.4 mm for the isocentric CyberKnife. The authors found it more difficult to minimize the dose to critical structures when using CyberKnife technology. Also, the dose falloff of GKRS was found to be steeper when compared to CyberKnife technology due to, what the authors hypothesized, the large number of gamma rays produced which converge on the focal point with precision.

As previously mentioned, the GK machine's primary functional unit is cobalt-60, which is used to emit photon energy through 201 separate 4 to 18 mm collimator openings that converge on a target specified by a treatment planning system. Balamucki et al. [47] performed a study examining if the half life of cobalt (5.26 years) relates to the outcomes for patients being treated for TN with GKRS. The authors collected data on 239 GKRS procedures performed at their institution between 1999 and 2004. Patient surveys were used to measure responses to radiosurgery. With the followup time ranging from one to six months, it was reported that 80% of patients experienced some degree of pain relief and that 56% of those patients were pain free. The authors concluded that clinical outcomes remained consistent during the first half life of cobalt-60.

3.2. Dosing. An area of controversy in the treatment of patients with TN is defining the optimal maximum radiosurgery dose that can be delivered to specific patient subsets. We analyzed five studies whose primary endpoint was to assess GKRS-dosing efficacy [48–52]. Kim et al. [48] utilized the BNI pain intensity scale [26] to assess 66 TN patients treated with a GK maximum dose of 80 Gy and 44 TN

patients treated with a GK dose of 85 Gy. Although the two groups did not statistically differ in terms of facial pain relief and procedure-related complications, the authors did report that patients treated with a GK dose of 85 Gy experienced a more rapid response to treatment when compared to the patients treated with a GK dose of 80 Gy. Arai et al. [50] analyzed 165 patients with TN treated with a GKRS dose of 80 Gy. Specifically, the authors divided the patients into two groups, which differed in the radiation dose rate received (low-dose rate = 1.21–2.05 Gy/min; high-dose rate = 2.06–3.74 Gy/min). Using the BNI pain intensity scale [26] as a clinical evaluation method, it was reported that the low-dose-rate group and the high-dose-rate group did not statistically differ in terms of initial pain relief, maintenance of pain relief, and clinical complications.

Massager et al. [49] divided 358 patients with TN into three treatment groups. Patients in group one were treated with a GK dose <90 Gy with no beam channel plugging, patients in group two were treated with a GK dose equal to 90 Gy with no beam channel plugging, and patients in group three were treated with a GK dose equal to 90 Gy with beam channel plugging. Although the trend did not reach full statistical significance ($P = 0.054$), patients in group three exhibited the highest level of pain relief, while patients in group one exhibited the lowest level of pain relief. The authors also observed that the three groups statistically differed ($P < 0.0001$) in terms of trigeminal nerve dysfunction, with patients in group three experiencing the highest rate of mild and bothersome complications and patients in group one experiencing the lowest rate of mild and bothersome complications. Similar to the results of Massager et al. [49], Morbidini-Gaffney et al. [52] reported positive outcomes in patients treated with GK doses >85 Gy. The authors also found that patients treated with two isocenters were more likely to have superior BNI pain intensity scale [26] scores during their course of followup when compared to patients treated with a single isocenter.

Dvorak et al. [51] analyzed GKRS retreatment doses in 28 patients. The median initial dose was 80 Gy, and the median retreatment dose was 45 Gy. Although the authors did not report any predictors in terms of facial pain control and patient morbidity, they did compare the results of their study with seven published retreatment articles and found that successful levels of pain control (>50%) were significantly correlated with cumulative GKRS doses >130 Gy, as well as new trigeminal nerve dysfunction (>20%).

3.3. Targeting. In addition to dose selection efficacy in select patient cohorts, the radiosurgical target of CN V is another subject matter that requires further clinical investigation. We reviewed three studies [53–55] analyzing specific GKRS targeting methods in the treatment of TN and one study [56] that examined the accuracy of GKRS to its image-guided target. Matsuda et al. [53] compared patients treated with GKRS targeted at the dorsal root entry zone (59 patients) with patients whose radiosurgical target was the retrogasserian zone of the trigeminal nerve (41 patients). With a median followup of 30 months, the dorsal root entry target group

TABLE 5: Barrow Neurological Institute pain intensity scale [26].

<i>BNI Class I</i>	No trigeminal pain; no medication
<i>BNI Class II</i>	Some trigeminal pain; no medication
<i>BNI Class IIIa</i>	No trigeminal pain; managed with medication
<i>BNI Class IIIb</i>	Persistent trigeminal pain; managed with medication
<i>BNI Class IV</i>	Some trigeminal pain; not adequately managed with medication
<i>BNI Class V</i>	Severe pain or treatment failure

exhibited statistically superior levels of initial complete pain remission ($P = 0.003$) and experienced less complications than the retrogasserian zone group ($P = 0.009$). Chen et al. [54] also reported positive results with the dorsal root entry zone-targeting approach, with a success rate of 82.8% and a complication rate of 15%. Park et al. [55] compared the dorsal root entry zone and retrogasserian zone-targeting methods in the treatment of 39 patients with medically refractory TN. The authors reported that the two treatment arms did not statistically differ in treatment success (BNI class I-IIIb) with respect to the BNI pain intensity scale [26]. However, patients treated with the retrogasserian zone-targeting method experienced a substantially shorter time of response to GKRS than patients treated with the dorsal root entry zone-targeting method ($P = 0.044$). Although the two groups did not statistically differ with regard to treatment-related morbidities, it was found that the patients whose targeting approach was the dorsal root entry zone experienced a greater amount of bothersome complications than the retrogasserian zone group.

Massager et al. [56] analyzed the targeting accuracy of GKRS in 65 patients treated for TN whose six month followup MRI showed focal contrast enhancement of the trigeminal nerve. The authors found that the median deviation of the coordinates between the intended radiosurgical target and the center of contrast enhancement was 0.91 mm in Euclidean space. The median radiation dose fitting into the contrast enhancement region was determined to be 77 ± 8.7 Gy. This small deviation from the GKRS target explains the high accuracy and precise nature of the machine.

3.4. Measurements of Response to Treatment. The two most common methods of measuring patient outcomes from GKRS in the management of TN are the Barrow Neurological Institute pain intensity scale [26] (Table 5) and the excellent-good-fair-poor (EGFP) categorical scale (Table 6). The BNI pain intensity scale divides patients into one of five classes, with a higher class indicating a worse prognosis for the patient. Patients in BNI class I experience no trigeminal pain and do not require medication. Patients in BNI class II experience occasional trigeminal pain but do not require

TABLE 6: Excellent-good-fair-poor categorical scale.

<i>Excellent</i>
Complete pain relief without medication
<i>Good</i>
Complete pain relief with medication
<i>Fair</i>
>50% pain relief
<i>Poor</i>
<50% pain relief

medication. Patients in BNI class IIIa do not experience trigeminal pain but require the use of medication. Patients in BNI class IIIb experience some trigeminal pain that can be satisfactorily managed with medication. Patients in BNI class IV experience some trigeminal pain that is not satisfactorily managed with medication. Patients in BNI class V do not experience a reduction in pain. The EGFP method categorizes patients into one of four groups. “Excellent” outcomes are defined as complete pain relief without the need of medication. “Good” outcomes are defined as complete pain relief with the need of medication. “Fair” outcomes are defined as a >50% pain relief rate. “Poor” outcomes are defined as a <50% pain relief rate or treatment failure.

4. Conclusions

For patients with medically refractory forms of TN, GKRS has proven to be an effective initial and repeat treatment option. Cumulative research suggests that patients treated a single time with GKRS exhibit similar levels of facial pain control when compared to patients treated multiple times with GKRS. However, patients treated on multiple occasions with GKRS are more likely to experience facial numbness and other facial sensory changes when compared to patients treated once with GKRS. Although numerous articles have reported MVD to be superior to GKRS in achieving facial pain relief, the findings of these comparison studies are weakened by the vast differences in patient age and comorbidities between the two studied groups and cannot be considered conclusive. Further evidence in the form of a Phase III-randomized trial is needed to confirm the clinical outcomes of patients treated with either modality. Questions remain regarding optimal GKRS dosing and targeting strategies, which warrants further investigation into this controversial matter.

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