Effectiveness and Safety Evaluation of Microresection of Vestibular Schwannoma After Gamma Knife Treatment

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Research Article

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Abstract

PURPOSE

We aimed to explored the influence of preoperative gamma knife treatment on the clinical effect of microsurgical resection of vestibular schwannoma.

METHODS

The patients who underwent vestibular schwannoma resection in our hospital between November 2010 and December 2019 were retrospectively collected. According to retrospectively collected data, the patients who met the inclusion and exclusion criteria were defined as group A. The 1:3 ratio design was adopted in this study to select the group B that was not subjected to gamma knife treatment in the same period. The pre/postoperative clinical manifestations, neurological function grade, postoperative complications, tumor recurrence and increase were collected and compared between the two groups.

RESULTS

There were 40 patients in group A and 120 patients in group B. At the last follow-up, the number of patients with poor facial nerve function was 15 (39.5%) in group A and 25 (21.2%) in group B ($P = 0.025$). In group A and group B, disequilibrium occurred in 14 patients and 17 patients respectively after operation ($P=0.003$). 7 patients caught the pulmonary infection in group A and 3 patients had a pulmonary infection in group B ($P=0.03$) after operation.

CONCLUSIONS

when a patient with vestibular schwannoma undergoes microsurgical surgery, the preoperative history of gamma knife treatment will make a recovery from postoperative facial paralysis difficult for the patients, making them more prone to suffer from postoperative disequilibrium and postoperative pulmonary infection.

Introduction

Vestibular schwannoma (VS), also known as acoustic neuroma (AN), is a histopathologically benign tumor arising from Schwann cells surrounding the vestibular nerve[1]. VS has an incidence of around 1/100,000 person-years[2]. Following technological advancements such as magnetic resonance imaging, the incidence of VS has been on the rise[3]. If left untreated, 36-69%[4–8] tumors continue to grow, eventually affecting the nerve function.

The earliest treatment for VS is surgical resection. With the development of VS microoperation, the living qualities of patients after tumor resection has greatly improved[9]. At present, microsurgical resection is the primary management choice for patients with VS[10]. However, it is an invasive method whose main disadvantages include the possibility of injuries and a long postoperative recovery time. In 1969, VS gamma knife[11], a noninvasive method was proposed for the first time for the treatment of small and medium-sized VS. On the one hand, this allowed for maximized preservation of nerve function in VS, i.e., facial preservation of 87-96% and useful hearing preservation of 49- 78%[12–14], while on the other hand, the tumor control rate reached 85.7-92%[10, 13, 14]. However, quite a few cases of VS still continue to progress, calling for microsurgical excision as indispensable further intervention. Herein, we aimed to explore the influence of preoperative gamma knife treatment on the clinical effect of microsurgical resection of vestibular schwannoma by evaluating the effect of microsurgical resection of vestibular schwannoma with or without preoperative gamma knife treatment.

Materials And Methods

Patients

A total of 928 patients who underwent VS resection in the Department of Neurosurgery, West China Hospital, Sichuan University between November 2010 and December 2019 were enrolled in the study. According to retrospectively collected data, the patients who met the inclusion and exclusion criteria were defined as group A. Inclusion criteria were the following: patients who underwent ipsilateral gamma knife treatment before microsurgical resection for VS. Exclusion criteria referred to patients: 1) with tumors in other parts of the brain; 2) with type II neurofibromatosis; 3) with a preoperative history of surgical resection of vestibular schwannoma; 4) with a preoperative history of other intracranial tumors; 5) with craniocerebral trauma; 6) absent in the follow-up process. The 1:3 ratio design was-adopted in this study to select the group B that was not subjected to gamma knife treatment in the same period based on several critical features such as the operation date, follow-up time, age, gender, tumor location, tumor stage, cystic or solid, preoperative facial nerve function, and preoperative related symptoms. This study was approved by the West China Hospital Ethics Committee, written informed consent was exempt for the present study as a retrospective clinical study.

Surgical Technique

The indications for surgery in group A were sustained tumor enlargement or progression of neurological symptoms. The surgical procedures were all performed by two senior neurosurgeons (YueKang Zhang and Xuhui Hui). All patients were placed in a lateral position, and A retro-sigmoid approach was used for all patients. In order to reduce the adhesion between tumor and surrounding tissues, intracapsular resection was carried out for larger tumors. All internal auditory canals were removed by an emery drill. Under the premise of protecting facial nerve function, the tumor was removed to the maximum extent. When electrophysiological monitoring was performed during the operation, the trigeminal nerve, the facial nerve, and the auditory nerve were protected as much as possible.

Follow-up and outcome assessment

All patients underwent three-dimensional enhanced MRI of the head within one month and every year after the operation. According to the postoperative MRI review, the tumor resection rate and tumor recurrence or enlargement were judged. The extent of tumor resection was classified as total, near-total, partial, and subtotal[15]. Tumor occurrence or enlargement was defined as a ≥2mm increase in any tumor diameter in 3 planes. A cystic tumor was defined as a tumor with a cystic portion greater than 50% in volume. The House-Brackmann (HB) scale[16] was used to evaluate the facial nerve function, where HB score ≤ 2 points, was defined as good, and >2, as bad. Koos grade[17] was utilized for the classification of VS. By querying objective case records and asking patients about their subjective feelings, we retrospectively collected some information about patients such as age, gender, the size and location of the tumor, cystic or solid of the tumor, the date of gamma knife operation and surgical resection, and pre/postoperative clinical findings (including headache, disequilibrium, tinnitus, dizziness, and Trigeminal neuropathy), facial nerve function during the different phases: before operation and one week after the operation and a long term after the operation (at least one year), postoperative complications, resection range, postoperative pathological results, and postoperative hospital stay. Eventual recurrence or enlargement and eventual deaths related to surgeries were all recorded. Patients were followed up more than 18 mouths through outpatient review and telephone follow-up.

Statistical analysis

SPSS software version 25.0 (IBM Corp., Armonk, New York, USA) was used for data analysis. Descriptive statistics were used to summarize patient characteristics and clinical features; classified variables are described by percentages, and continuous variables are described by mean ± standard deviation or median (range). Categorical variables were compared with the Chi-squared test and Fisher's exact probability test. Continuous variables were compared with Independent-Samples T-Test or rank-sum test. During this analysis process, all statistical tests were 2-sided, and P-value < 0.05 was considered as statistically significant.

Results

Baseline characteristics

Careful inquiry revealed 40 out of the 928 patients with vestibular schwannomas who met the inclusion and exclusion criteria and were included in group A. According to the 1:3 ratio design principle, 120 patients who underwent MS alone in the same period were randomly enrolled in group B. As shown in Table 1, among the 40 patients in group A, 19 were males, and 21 were females, with a mean age of 49.4 years old. In group B, there were 56 male and 64 female patients with a mean age of 50.9 years old. In group A, the median time from the last follow-up to operation was 64 months (range, 18-127 months). In group B, it was 58 months (range, 18-126 months). According to the Koos grade, in group A, six patients (15%) had grade II tumor, 19 patients (47.5%) had grade III tumor, and 15 patients (37.5%) had grade IV tumor vs. 12 patients with (10%) grade II tumor, 46 (38.3%) with grade III tumor and 62 (51.7%) with grade IV tumor in group B. There was no grade I tumor in any of the groups. In group A, there were 15 (37.5%) cystic tumors in group A and 36 (30%) cystic tumors in group B. There was no significant difference in age, gender, tumor location, cystic or solid, tumor Koos grade, and average follow-up time between the two groups.

Table 1
Preoperative patient general information

Variables	Group A(n=40)	Group B(n=120)	P value
Age (year)	49.4 ±13.1	50.9±12.2	0.504
Sex			0.927
male	19(47.5%)	56(46.7%)	
famle	21(52.5%)	64(53.3%)	
Side of VS			0.855
left	20(50%)	58(48.3%)	
right	20(50%)	62(51.7%)	
Koos grade			
I	0	0	
II	6(15%)	12(10%)	
III	19(47.5%)	46(38.3%)	
IV	15(37.5%)	62(51.7%)	
HB grade			
1	29(72.5%)	100(83.3%)	
2	6(15%)	13(10.8%)	
3	1(2.5%)	3(2.5%)	
4	4(10%)	1(0.8%)	
5	0	3(2.5%)	
6	0	0	
cystic or solid			0.378
solid	25(62.5%)	84(70%)	
cystic	15(37.5%)	36(30%)	
Median time between Gamma Knife and operation(month)	17.5(1-96)		
Median follow-up time(month)	64(18-127)	58(18-126)	0.208

Preoperative neurological symptoms

Table 2 shows the neurological function in group A and group B before microsurgery. Vertigo was the most common symptom before operation. In group A, 12 (42.9%) patients suffered from dizziness vs. 46 (38.3%) patients in group B. In group A, there were 35 patients (87.5%) with good facial nerve function and 5 patients (12.5%) with bad facial nerve function; in group B, there were 113 patients (94.2%) with good facial nerve function and seven patients (5.8%) with bad facial nerve function. Nine patients (22.5%) in group A and 41 patients (34. 1%) in group B had trigeminal neuropathy. In group A, 17 patients (42.5%) suffered from headaches before the operation, 15 patients (37.5%) experienced disequilibrium before the operation, and 15 patients (37.5%) had tinnitus before operation. In group B, 45patients (37.5%) suffered from headaches before the operation, 30 patients (25%) experienced disequilibrium before the operation, and 45 patients (37.5%) had tinnitus before operation. The neurological symptoms above revealed no significant difference ($P>0.05$).

Table 2
Comparison of preoperative characteristics of patients between two groups

Variables	Group A (n=40)	Group B (n=120)	P value
Koos grade			0.120[a]
1-3	25(62.5%)	58(48.3%)	
4	15(37.5%)	62(51.7%)	
HB grade			
1-2	35(87.5%)	113(94.2%)	0.177[b]
3-6	5(12.5%)	7(5.8%)	
Headache			0.574[a]
Yes	17(42.5%)	45(37.5%)	
No	23(57.5%)	75(62.5%)	
Disequilibrium			0.128[a]
Yes	15(37.5%)	30(25.0%)	
No	25(62.5%)	90(75.0%)	
Tinnitus			1.000[a]
Yes	15(37.5%)	45(37.5%)	
No	25(62.5%)	75(62.5%)	
Dizziness			0.342[a]
Yes	12(42.9%)	46(38.3%)	
No	28(57.1%)	74(61.7%)	
Trigeminal neuropathy			0.168[a]
Yes	9(22.5%)	41(34.1%)	
No	31(77.5%)	79(65.9%)	

[a] is for Chi-square test, [b] is for Fisher's exact test.

Postoperative neurological symptoms

Table 3 shows the different performances of the neurological function in group A and group B after the operation. After we evaluated the facial nerve function of all patients after operation within one week, we found that in group A the number of patients with poor facial nerve function increased by 9 (22.5%) compared with that before operation; in group B, it similarly increased by 18 (32.6%), and there were no significant differences among the groups. At the last follow-up, the number of patients with poor facial nerve function in group A continued to increase by 1, reaching 15 (39.5%) compared with one week after the operation. However, the number of patients with poor facial nerve function in group B decreased by 21 and reached 25 (21.2%) compared with one week after operation (P = 0.025). In terms of the last follow-up, there were 14 patients (36.8%) with disequilibrium after operation in group A vs. 17 patients (14.4%) with disequilibrium after operation in group B (P=0.003). There was no significant difference in other postoperative symptoms between the two groups.

Table 3
Comparison of postoperative characteristics and clinical symptoms at the last follow-up between two groups

Variables	Group A: n (%)	Group B: n (%)	P value
HB grade within one week after operation			0.706[a]
1-2	26(65.0%)	74(61.6%)	
3-6	14(35.0%)	46(38.4%)	
HB grade at the last follow-up			0.025[a]
1-2	23(60.5%)	93(78.8%)	
3-6	15 (39.5%)	25(21.2%)	
resection range			0.058[b]
Total	33(82.5%)	112(93.3%)	
Residual	7(17.5%)	8(6.7%)	
Complications			0.027[a]
Yes	9(22.5%)	11(9.2%)	
No	31(77.5%)	109(90.8%)	
Postoperative hospital stay			0.286 [a]
≤8 days	24(60%)	83(69.2%)	
>8 days	16(40%)	37(30.8%)	
Recurrence or enlargement			0.573[b]
Yes	0	4(3.4%)	
No	38	114(96.6%)	
Headache			0.868[a]
Yes	6 (15.8%)	20 (17.0%)	
No	32(84.2%)	98 (83.0%)	
Disequilibrium			0.003[a]
Yes	14(36.8%)	17(14.4%)	
No	24(63.2%)	101(85.6%)	

[a] is for Chi-square test, [b] is for Fisher’s exact test.

Variables	Group A: n (%)	Group B: n (%)	P value
Tinnitus			0.433[a]
Yes	7(18.4%)	29(24.6%)	
No	31(81.6%)	89(75.4%)	
Dizziness			0.053[a]
Yes	5(13.2%)	34(28.8%)	
No	33(86.8%)	84(71.2%)	
Trigeminal neuropathy			0.165[a]
Yes	5(13.2%)	28(23.7%)	
No	33(86.8%)	90(76.3%)	
Deaths related to surgeries	1(2.5%)	1(0.8%)	0.439[b]

[a] is for Chi-square test, [b] is for Fisher's exact test.

Postoperative complications

Table 4 shows the detailed information related to complications in this study. In group A, seven patients caught the pulmonary infection after operation; 1 patient developed a pulmonary infection and CSF leakage at the same time after operation; another one had surgical site infection, and one more patient suffered from intracranial infection. However, in group B, five patients suffered from intracranial infection; 3 patients had a pulmonary infection; 1 patient simultaneously developed a pulmonary infection and intracranial infection; 1 patient developed CSF leakage; 1 patient developed severe hydrocephalus; 1 patient developed subcutaneous hydrops, and one patient developed an intracranial hematoma. The postoperative complications in the two groups were respectively compared. The postoperative pulmonary infection rate in group A was significantly higher than that in group B (P=0.03). There was no significant difference in other complications.

Table 4
Comparison of postoperative complications between two groups

Variables	Group A (n)	Group B (n)	P value
Pulmonary infection	7(17.5%)	3(2.5%)	0.03
Intracranial infection	1(2.5%)	5(4.2%)	1.0
Surgical site infection	1(2.5%)	0	0.25
CSF leakage	1(2.5%)	1(0.8%)	0.43
Severe hydrocephalus	0	1(0.8%)	1.0
Subcutaneous hydrops	0	1(0.8%)	1.0
Intracranial hematoma	0	1(0.8%)	1.0
We use fisher's exact test			

Table5. **Literature review: microresection of vestibular schwannoma after gamma knife**

Author/Date of Publication	number of cases(n)	Mean tumor size before surgery cm^3/ cm	Tumor control rate (%)/follow-up time	HB1-2 Facial nerve function retention rate (%)	Complication rate (%)
Lee H.2017	6	2.9 cm	100%/12m	33.3%	17%
Lee C.2014	13	6.5cm^3	92.3%/36m	46.2%	0%
Basant K.2019	16	3.4cm	100%/50m	56.2%	-
Limb C.2005	8	2.6cm	-	37.5%	37.5%
Shuto T.2008	12	6.9cm^3	91.7%/21.5m	41.6%	-
This study	40	3.03cm	100%/64m	59.5%	22.5%

Postoperative tumor control

In our study, there were 33 patients (82.5%) with total tumor resection in group A and 112 patients (93.3%) in group B, 1 patient (2.5%) with near-total resection in group A and 4 patients (3.3%) in group B, 2 patients (5%) with partial resection in group A and 3 patients (2.5%) in group B, and 4 patients (10%) with subtotal resection in group A and 1 patient (0.8%) in group B. As of June 2020, no patients in group A experienced tumor recurrence or increase during the follow-up; however, in group B, 4 patients (4.3%) were found to have tumor recurrence or increase at 5th month, 24th month, 29th month and 95th month after the operation. There was no significant difference in tumor resection rate between the two groups, nor in tumor recurrence and increase between the two groups.

Postoperative patient outcomes

Postoperative pathology indicated that both groups of patients had benign schwannomas, and no malignant schwannomas were found. The follow-up revealed that 4 patients died where 2 deaths were directly related to the operation, and the other 2 patients died of a cerebrovascular accident 3 and 6 years later after the operation. One patient in group A died of complications; he suffered from coughing weakness after the operation, which caused pulmonary infection and eventually death one month after the operation. One patient in group B developed both pulmonary infection and internal infection and died one month after the operation. There was no significant difference in operation-related deaths between the two groups (P=0.439).

Discussion

Previous studies have reported that the incidence of final tumor enlargement after gamma knife surgery is about 2%-9%[18–20]; however, as only about 26% of these patients choose surgical resection[21], such cases are rare. Nonetheless, with the extended follow-up, the number of patients who failed gamma knife treatment may continue to increase. Significant adhesions, thickening, and fibrosis have been reported during surgery for VS after gamma knife treatment [22, 23], which is similar to our findings. Nevertheless, there are only a few studies on the effect of preoperative gamma knife therapy on VS resection's clinical efficacy and safety. Recent studies on the efficacy of microsurgical resection of VS after gamma knife (**Table 5**[23–27]) included a small number of cases, with a maximum of 16 cases[27]. To the best of our knowledge, the current study has the largest number of cases to date. Lee *et al*[26] included 13 patients in their study, some of whom underwent gamma knife and craniotomy prior to microsurgical resection of VS, and even some of them were NF-2. As these factors may have interfered with the final results compared with the study, which enrolled patients with VS who only underwent gamma knife before surgery[28], these factors were excluded from the present study.

Facial paralysis is one of the most serious diseases because the loss of facial expression is a physically and mentally debilitating condition[29]. Protecting facial nerve function is the basic goal of the treatment of vestibular schwannoma and also the key factor affecting the treatment decision[24, 30]. In their study, Gerganov *et al*[28] found that the long-term facial nerve function retention rate in patients with no preoperative gamma knife was better than in patients with preoperative gamma knife, which is consistent with our findings. This could be explained by the following: 1) microsurgical resection was more likely to cause facial nerve injury in group A; 2) postoperative facial nerve function was more difficult to recover in group A. The main cause of postoperative facial paralysis is the direct intraoperative injury to the facial nerve[31]. In this study, there was no significant difference in facial nerve function between the two groups one week after surgery, indicating that a preoperative gamma knife does not make facial nerve more likely to be intraoperatively injured. Previous studies with long-term follow-up of facial nerve function after VS surgery[32, 33] showed that worse early postoperative facial nerve function of patients, and within the last follow-up after surgery, patients would experience A long recovery period of facial nerve function. However, during follow-up, we found that patients in group A did not experience a recovery period of neurological function (**Figure 1**). The House Ear Clinic (Los Angeles, California) reported that once the facial nerve has been radiated, the regeneration potential is diminished, and the recovery from microsurgical trauma is not as robust[22]. The results of our clinical study confirmed the validity of their theory. Therefore, it is more important to protect the nerve during surgical resection of patients with a preoperative history of gamma knife treatment. Advanced microsurgical techniques and neurophysiological monitoring have been reported to be effective for intraoperative protection of the facial nerve [34].

In this study, the incidence of postoperative disequilibrium in patients with a preoperative history of gamma-knife was significantly higher compared to patients without preoperative gamma-knife treatment, which might be due to the following reasons: 1) the vestibular nerve is involved in the regulation of the balance in human body[35]; it adheres to the tumor and is vulnerable to damage by gamma knife. The recovery ability of the vestibular nerve is weakened after microresection. 2) After gamma knife treatment, vestibular schwannoma strongly adheres to the cerebellum, and the cerebellum can be easily damaged during operation. Disequilibrium is one of the most significant factors that can negatively affect the daily life of patients[36]. The early postoperative period is critical for appropriate treatment to alleviate postoperative symptoms[37]. Therefore, we believe that after the resection of vestibular schwannoma with a preoperative gamma knife, attention should be paid to whether the patients experience disequilibrium in the early postoperative period, which should be actively managed via the implementation of effective measures. A previous prospective randomized clinical study suggests that specific exercises with visual biofeedback improve vestibulospinal compensation and balance function in patients after vestibular schwannoma microsurgical removal[38], which could serve as an effective way to treat disequilibrium.

As shown in **Table 6**, the postoperative control rate of tumors after surgical resection for patients with preoperative history of gamma-knife treatment was as high as 91.7-100% in previous studies. In this study, the tumor control rate in patients from group A reached 100% during the mean follow-up time of 52 months, possibly because 82.5% of patients underwent total tumor resection, which was far higher compared to previous studies[25, 26]. Currently, there is still controversy about whether VS should be completely excised. Gerganov *et al*[28] suggested that every VS should be completely excised, especially in those patients with a previous history of gamma knife therapy. Gurge's preferred option is to protect neurologic function versus complete resection of the tumor, as residual tumors can then be treated with stereotactic radiation therapy[39]. In the present study, seven patients in group A did not have total resection of the tumor; however, their tumor did not increase during long-term follow-up. Therefore, we believe that when the total resection of the tumor is difficult for a patient with a history of gamma knife surgery, total resection is not necessary.

Lee *et al*[23] suggested that gamma knife treatment before microdissection may increase the probability of postoperative complications, which is in line with our results. We found that the incidence of postoperative pulmonary infection in group A was higher than that in group B, which may be due to the following: 1) prolonged operation time tends to increase the probability of pulmonary infection after craniocerebral surgery[40]. A previous study has reported that the average operation time of vestibular schwannoma patients with gamma knife treatment history takes 95 minutes longer[24]. 2) Because of the severe adhesion between tumor and nerve after gamma knife operation, the posterior cranial nerve can be easily damaged during operation, which might be associated with the occurrence of postoperative pulmonary infection[41]. The meticulous surgical technique helps surgeons to avoid unnecessary nerve injury and prolongation of surgery duration.

Limitation

There are some limitations in the present study. First, this is a single-center retrospective study. Surgical technique and management of patients vary among hospitals. Second, there is a lack of quantitative indicators used to describe the degree of tumor adhesion. Finally, in the process of retrospective follow-up, some data were missing, such as hearing test results. The conclusion of this study needs to be further verified via multi-center research with a larger sample size and more detailed data.

Conclusion

When a patient with vestibular schwannoma undergoes microsurgical surgery, the preoperative history of gamma knife treatment will make a recovery from postoperative facial paralysis difficult for the patients, making them more prone to suffer from postoperative disequilibrium and postoperative pulmonary infection.

Declarations

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Conflict of Interests

The authors declare no conflict of interests.

Disclosures

None.

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Figures

Figure 1. Recovery of facial nerve function after operation

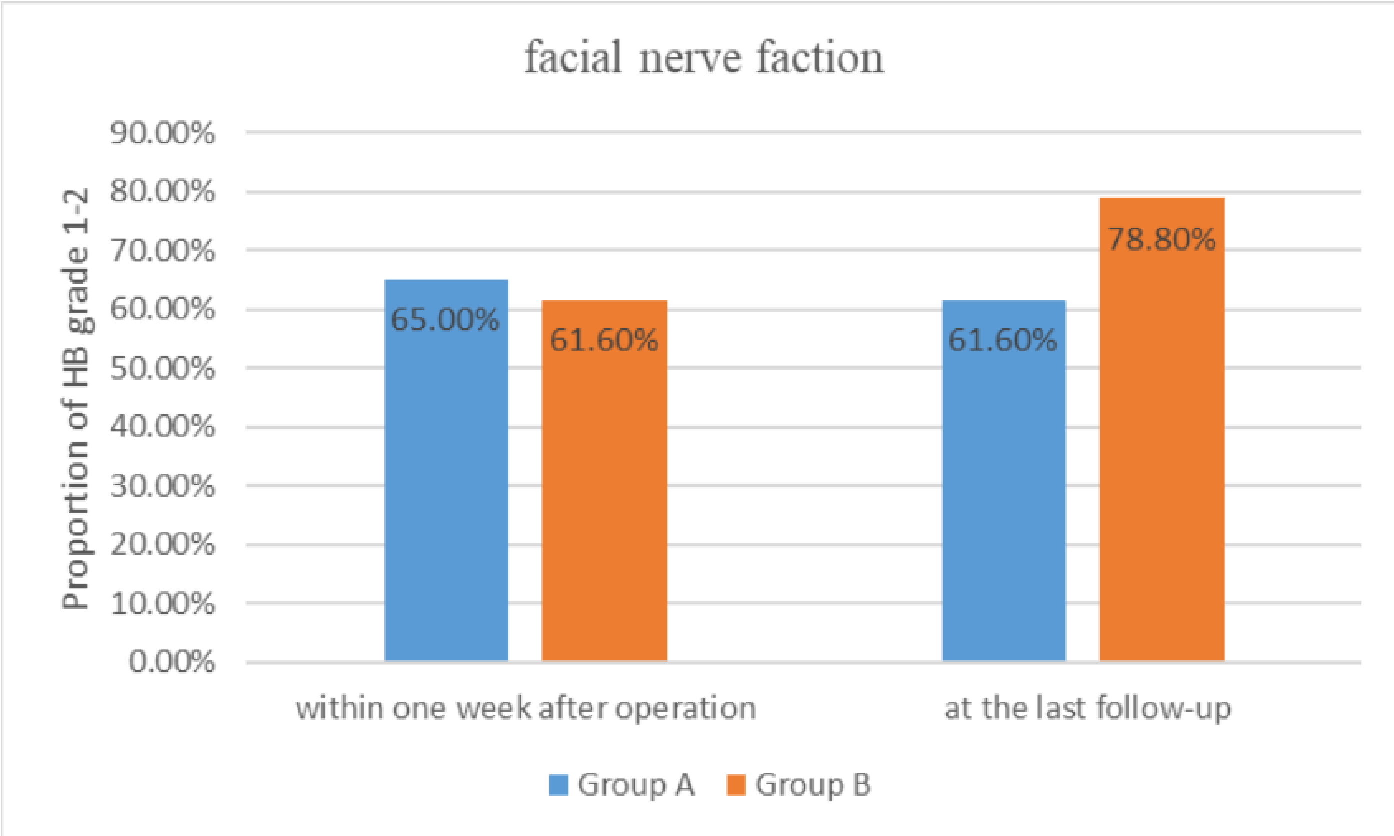

Figure 1

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