Evaluation of vision-related quality of life with autologous internal limiting membrane transplantation for refractory macular hole.

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Research article

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Abstract

Background: To evaluate the vision-related quality of life of vitrectomy combined with autologous internal limiting membrane(ILM) transplantation for refractory macular hole. **Methods:** A prospective and nonrandomized clinical study was carried out. There were forty eyes with refractory macular hole included and all eyes received 23G vitrectomy and ILM peeling with autologous ILM transplantation. Preoperative and postoperative basic conditions were recorded, including best corrected visual acuity (BCVA), intraocular pressure, central retinal thickness (CRT) measurement by Optical coherence tomography (OCT) examination, macular hole index (MHI) and operative complications. The Chinese version of visual-related quality of life scale -25 (CVRQoL-25) was used to evaluate the visual related quality of life of patients after operation. The correlation between the quality of life and the postoperative visual acuity and the size of the macular hole before operation was tested by Spearman rank correlation test. **Results:** All patients were followed up for three months after surgery, and 38 patients achieved anatomical closure. The mean postoperative logMAR BCVA was 1.09 ± 0.33 , which has significantly improved than that before operation ($P=0.000$). The vision-related quality of life of patients after surgery was closely related to the macular hole index ($r=0.375$, $P=0.017$), but was negatively correlated with the best corrected visual acuity before and after surgery ($r=-0.495$, $P=0.001$; $r=-0.760$, $P=0.000$). It was also found that the vision-related quality of life of patients positively correlated with the postoperative CRT ($r=0.414$, $P=0.008$). **Conclusions:** The anatomical structure of refractory macular hole patients with ILM peeling combined with autologous ILM transplantation was largely reduced, and the visual acuity of the patients improved significantly. Meanwhile, the vision-related quality of life was significantly improved after surgery. **Trial Registration:** ChiCTR-INR-16008660, date of registration: 2016/06/17

Background

Macular hole refers to the continuous interruption of the retinal neuroepithelial layer in the macula zone, which causes metamorphopsia and decreased vision. Presently, macular hole is generally treated with vitrectomy combined with internal limiting membrane (ILM) peeling [1]. However, for patients with complex traumatic macular holes, large macular holes (diameter > 600um), high myopia macular holes with retinal detachment and other refractory macular holes, simple ILM peeling may be difficult to achieve stage I rupture closure and the postoperative visual function improvement is limited [2]. In view of the above refractory macular holes, De Novelli FJ et al. have found that the methods of ILM tamponade, inverted ILM flap and autologous ILM transplantation have relatively better effect on hole closure [3]. Our previous study have reported a new surgical technique of non-inverted pedicle ILM transposition for the treatment of eyes with large macular hole [4]. Our findings indicate that the non-inverted pedicle ILM transposition results in a high incidence of anatomic closure with good visual outcome for the treatment of large macular hole. But for patients with refractory macular holes, the vision-related quality of life was not just about the closure rate of macular hole, it was about visual activity and visual quality such as contrast sensitivity. Many researches have reported that the tiled transplantation ILM pedicle flap technique is more advantageous than inverted ILM flap technique, because the microenvironment of

former is more similar to the normal physiological conditions, for example, the MHs directly contact the same surface of the ILM the same as normal physiological conditions[5,6]. Our results also indicated that the visual acuity increased with autologous ILM transplantation, but the vision-related quality of life was not evaluated. In this study, patients with refractory macular hole including macular hole with large diameter, high-myopia macular hole and secondary macular hole were treated with vitrectomy of ILM peeling combined with autologous ILM transplantation. Chinese version vision-related quality of life-25 (CVRQoL-25) chart was used to evaluate the effect of the operation on visual function improvement of patients.

Methods

This was a prospective and nonrandomized clinical study in the First Affiliated Hospital of Nanjing Medical University. This study was performed following the guidelines of the Declaration of Helsinki and Tokyo for humans, and approved by Ethic Committee of First Affiliated Hospital of Nanjing Medical University (Approved number: 2017-SR-223). Forty patients with refractory macular hole were enrolled in this research from January 2017 to December 2018. Among them, 25 patients with large diameter macular hole ($>600\mu\text{m}$), 12 patients with high-myopia macular hole, and 3 patients with secondary traumatic macular hole. There were 17 male (17 eyes) and 23 female (23 eyes). The average age of patients was 57.6 ± 7.8 year. All patients received visual examination of best corrected visual acuity (BCVA), slit-lamp examination, ophthalmoscopy examination after mydriasis, A/B ultrasound examination, eye-ground photography stack examination and spectral-domain optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec Inc, Dublin, CA) examination before and after operation. The visual examination was conducted by Snellen visual chart, and the results were converted into logarithm vision with the angle of minimum resolution (log MAR). After OCT scan for the macular region, central retinal thickness (CRT), the base diameter and the minimum diameter for macular hole were measured, and the macular hole indexes (MHI) were calculated afterwards. MHI equals to the ratio of the edge thickness of hole and the diameter of the hole base.

All the patients were conducted with 23G vitrectomy with ILM peeling combined with autologous ILM transplantation successfully. The surgical method was as follows: three channels through pars plana corporis ciliaris were established, and the vitreous body was excised. Indocyanine green staining was performed for 15 seconds. Afterwards, intraocular forceps were used to tear the inner limiting membrane within the range of 1 papillary diameter (PD) in the macular area and a pedicle attached to the superior temporal retina was left. The free temporal edge of the ILM was grasped and the whole pedicle ILM was rotated till the nasal part of ILM fully cover the MH. Cover the ILM directly on the macular hole in the former direction as a non-inverted way. A little DK-Line Perfluorodecalin was injected to fix the ILM to avoid floating and moving. Then the Perfluorodecalin was sucked out after fluid-air exchange. At the same time, the peeling ILM was fixed in macular region. Finally the vitreous chamber was filled with silicone oil. The patient maintained a prone position after surgery. Phacoemulsification combined with vitrectomy can be performed on 36 patients with cataract.

All the patients were followed up for at least 3 months after surgery. The parameters mainly included postoperative BCVA, intraocular pressure (IOP), post-mydriasis funduscopy, and OCT examination for closure of the macular hole. Besides, the evaluation of Chinese version vision-related quality of life-25 questionnaire (VFQ-25, CVRQoL-25) was performed to investigate the influence of transplantation of ILM on vision-related life quality of the patients with refractory macular hole.

CVRQoL-25 questionnaire was composed of 12 dimensions and in total of 26 items [7]. The 12 dimensions as follows: "holistic health conditions", "general vision", "ophthalmodynia", "close-range activity", "remote activity", "drive", "surrounding vision", "colour vision", "limitation of social role", "degree of dependence", "social function" and "mental health conditions". There are six grades of A, B, C, D, E and F for each dimension, and the first five are scoring 100, 75, 50, 25 and 0 respectively, while F is deemed as "no response". The higher the score, the better the survival quality of the project. No corresponding situation was regarded as deficiency, and was not counted into the final score statistics. For example, if the colour perception dimension is missing, the general score is conducted with the average value of other dimensions except from color vision dimension.

SPSS 17.0 statistical software was used for statistical analysis. The measurement data was expressed as mean $\pm$ standard deviation and the counting data were expressed as rate (%). Descriptive statistics and independent-sample t-test were used to compare measurement data and Spearman rank correlation analysis was used to compare the correlations between parameters. $P < 0.05$ was used for statistically significance.

Results

After 3 months follow-up, 38 patients with macular hole were anatomically closed and the hole closure rate was 95.0%. The 2 unclosed eyes had significantly MHI improvement (0.64 to 0.93 and 0.39 to 0.78, respectively). The preoperative logMAR BCVA was 1.52 ± 0.29 and MHI was 0.51 ± 0.18 . After three months of surgery the logMAR BCVA was 1.09 ± 0.33 and the CRT was $160.05\mu\text{m} \pm 14.88\mu\text{m}$. The overall average value of CVRQoL-25 before surgery and 3 months after surgery were 57.28 ± 6.63 and 71.50 ± 8.81 , respectively (Table 1). The Independent t-test result showed that postoperative visual acuity was significantly improved ($t=6.234$, $p=0.000$). Mean general score of CVRQoL-25 was also increased ($t=8.162$, $p=0.000$).

Spearman rank correlation analysis showed that the postoperative CVRQoL-25 was negatively correlated with preoperative logMAR BCVA ($r=-0.495$, $P=0.001$) (Fig1) and postoperative logMAR BCVA ($r=-0.760$, $P=0.000$) (Fig2). It was also positively correlated with preoperative MHI ($r=0.375$, $P=0.017$) (Fig3), and postoperative CRT ($r=0.414$, $P=0.008$) (Fig4).

Discussion

The ILM peeling combined with non-inverted pedicle autologous ILM transplantation is a new option to treat refractory macular hole. In recent years, Ding C et al. have indicated that this method can significantly increase the closure rate of macular hole [8]. However, only clinical anatomical reduction of macular hole cannot completely reflect the visual functional recovery of patients. Therefore, the improvement of visual acuity and patients' subjective sensation of life quality after surgery are also the key factors to evaluate the success of surgery. In this research, CVRQoL-25 scores and recovery status of macular holes were assessed, which to evaluate the efficacy of ILM peeling combined with transplantation on refractory macular hole, and to provide a new direction for the prognosis assessment of such diseases.

Many studies have reported changes in the severity of metamorphopsia were significantly relevant to changes in the VFQ-25 composite score, but changes in other variables were not, including BCVA and contrast sensitivity (CS) in MH and ERM [9,10]. The latest study indicated that the visual function and VR-QOL were significantly improved after successful macular hole surgery [11]. In our research, we found that CVRQoL-25 was negatively correlated with pre- and post-operative logMAR BCVA. In addition, the postoperative logMAR BCVA was also significantly improved. Single ILM peeling for refractory macular hole might be ineffective for anatomical reduction owing to the complicated pathological structure and (or) complications (such as choroidal atrophy, retinoschisis, traumatic choroidal rupture, etc.) for refractory macular hole. In recent years, ILM flap surgery or autologous ILM transplantation has been increasingly applied to refractory macular hole treatment. In 2010, Michalewsk et al. first reported the ILM flap surgery and compared the surgical curative effect with traditional surgery on treating large-diameter MH with more than 400 μm [12]. Their results showed that the ILM flap surgery group had higher MH closure rate and had better vision prognosis compared with the traditional surgery group. Compared with ILM flap, the autologous ILM transplantation has a wider range of applications, especially in patients with macular hole not closed after the first ILM peeling and ILM flap surgery can not be performed. Morizane et al. [13] used this method to treat 10 patients with refractory MH, of which 9 patients had MH closure and postoperative visual acuity was significantly improved. About 80% of patients had visual acuity improved by more than 0.2. This research found that 38 of the 40 patients achieved anatomical reduction of MH successfully, and the anatomical reduction rate was 95%. And the postoperative visual acuity of the patients was significantly improved, which is consistent with the conclusions in the early previous study. We also found that the vision-related quality of life of patients was closely associated with the patients' visual acuity. The surgery improved the patients visual acuity, meantime, greatly improved the patients' quality of life.

Macular hole index is commonly used to assess deformation degree of macular hole. The larger of the macular hole index, the smaller preoperative deformation of macular hole is, of which suggesting that postoperative visual recovery could be better. Kusuvara et al. [14] showed that MHI was closely related to postoperative BCVA. The visual prognosis of $\text{MHI} > 0.5$ group was significantly better than that of $\text{MHI} < 0.5$ group. In this study, we found that patients' vision-related quality of life was positively correlated with preoperative MHI, and the larger the MHI, the higher the patients' postoperative visual vision-related quality of life is. Therefore, it is believed that the MHI of macular hole can affect vision-related quality of

life of patients to a certain extent. And MHI can also be used as a prognostic indicator for refractory macular hole.

The thickness of macula fovea of patients that accepted autologous ILM transplantation was evaluated by OCT examination. The results indicated that the postoperative CRT value was positively correlated with postoperative score of patients' visual quality. It is suggested that the increase of postoperative CRT thickness causes improvement of visual quality of patients. Recent studies have demonstrated that during macular hole closure, the Müller cells and other glial cells proliferate and close holes in form of bridge-like proliferation to repair damaged photoreceptor cells, leading to recovery of morphology of macula central fovea [15]. Some other researches suggesting that the closure of macular hole is due to the removal of traction from photoreceptor cells by surgery, so that the cells can be repositioned to achieve the purpose of closing the macular hole [16]. In this study, the ILM was implanted as a scaffold above the macular hole, and the photoreceptors were repositioned by the proliferation of glial cells to promote the repairment of the retinal neuroepithelial layer, thus promoting macular hole healing. In addition, some studies suggest that the transplanted ILM can reconstruct the lacuna between the retinal neuroepithelial layer and the pigment epithelial layer, which improve the pump function of the pigment epithelial cells, and promote the healing of the macular hole [17].

Conclusions

In conclusion, ILM peeling combined with autologous ILM transplantation could relieve the traction of macular holes, and provide a support for proliferation of Müller cells and help to restore function of photoreceptor cells, which significantly increases patients visual acuity and improves patient's visual-related quality of life. It is a preferable way to treat refractory macular hole by combination of ILM peeling and autologous ILM transplantation. However, the disadvantage of this study is lack of observation of large scale clinical trials at presently. In addition, further researches are needed to get to know the prognosis of ILM transplantation and damage of surgery on retina to evaluate its clinical efficacy.

Abbreviations

ILM: internal limiting membrane; BCVA: best corrected visual acuity; CRT: central retinal thickness; OCT: Optical coherence tomography; MHI: macular hole index; CVRQoL-25: Chinese version of visual-related quality of life scale -25; IOP: intraocular pressure.

Declarations

Ethics approval and consent to participate

The study was approved by Ethic Committee of First Affiliated Hospital of Nanjing Medical University (Approved number: 2017-SR-223) and was conducted in accordance with the Declaration of Helsinki and Tokyo for humans. Written informed consent was obtained from all enrolled participants.

Consent for publication

We obtained written informed consent for publication from the patients related to details and images.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

Conceptualization of the study: DQY, WWZ, QHL. Data acquisition and analysis: DQY, STY, PX, QHL. Manuscript preparation: DQY, WWZ, QHL. All authors have read and approved the manuscript for publication.

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References

- [1] Chatziralli IP, Theodossiadis PG, Steel DHW. Internal limiting membrane peeling in macular hole surgery; why, when, and how? *Retina*. 2018;38(5):870-82.
- [2] Pires J, Nadal J, Gomes NL. Internal limiting membrane translocation for refractory macular holes. *Br J Ophthalmol*. 2017;101(3):377-82.
- [3] De Novelli FJ, Preti RC, Ribeiro Monteiro ML, Pelayes DE, Junqueira Nóbrega M, Takahashi WY. Autologous Internal Limiting Membrane Fragment Transplantation for Large, Chronic, and Refractory Macular Holes. *Ophthalmic Res*. 2015;55(1):45-52.
- [4] Hu Z, Ye X, Lv X, Liang K, Zhang W, Chen X, Cao E, Gu X, Liu Q, Xie P. Non-inverted pedicle internal limiting membrane transposition for large macular holes. *Eye (Lond)*. 2018;32(9):1512-18.

- [5] Wang LP, Sun WT, Lei CL, Deng J. Clinical outcomes with large macular holes using the tiled transplantation internal limiting membrane pedicle flap technique. *Int J Ophthalmol*. 2019;12(2):246-51.
- [6] Takai Y, Tanito M, Sugihara K, Ohira A. The Role of Single-Layered Flap in Temporal Inverted Internal Limiting Membrane Flap Technique for Macular Holes: Pros and Cons. *J Ophthalmol*. 2019;2019:5737083.
- [7] Huang J, Liu XL. Development and Evaluation of Chinese Version Vision-related Quality of Life Questionnaire-25. *Chin J Optom Ophthalmol Vis Sci*. 2016;18(11):660-4.
- [8] Ding C, Li S, Zeng J. Autologous Neurosensory Retinal Transplantation for Unclosed and Large Macular Holes. *Ophthalmic Res*. 2019;61(2):88-93.
- [9] Okamoto F, Okamoto Y, Fukuda S, Hiraoka T, Oshika T. Vision-related quality of life and visual function after vitrectomy for various vitreoretinal disorders. *Invest Ophthalmol Vis Sci*. 2010;51(2):744-51.
- [10] Fukuda S, Okamoto F, Yuasa M, Kunikata T, Okamoto Y, Hiraoka T, Oshika T. Vision-related quality of life and visual function in patients undergoing vitrectomy, gas tamponade and cataract surgery for macular hole. *Br J Ophthalmol*. 2009;93(12):1595-9.
- [11] Wang Y, Liang X, Gao M, Liu J, Liu L, Liu W. Vision-related quality of life after pars plana vitrectomy with or without combined cataract surgery for idiopathic macular hole patients. *Int Ophthalmol*. 2019 May 29. [Epub ahead of print]
- [12] Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. *Ophthalmology*. 2010;117(10):2018-25.
- [13] Morizane Y, Shiraga F, Kimura S, Hosokawa M, Shiode Y, Kawata T, Hosogi M, Shirakata Y, Okanouchi T. Autologous transplantation of the internal limiting membrane for refractory macular holes. *Am J Ophthalmol*. 2014;157(4):861-869.e1.
- [14] Kusahara S, Teraoka Escaño MF, Fujii S, Nakanishi Y, Tamura Y, Nagai A, Yamamoto H, Tsukahara Y, Negi A. Prediction of postoperative visual outcome based on hole configuration by optical coherence tomography in eyes with idiopathic macular holes. *Am J Ophthalmol*. 2004;138(5):709-16.
- [15] Bringmann A, Pannicke T, Grosche J, Francke M, Wiedemann P, Skatchkov SN, Osborne NN, Reichenbach A. Müller cells in the healthy and diseased retina. *Prog Retin Eye Res*. 2006;25(4):397-424.
- [16] Hangai M, Ojima Y, Gotoh N, Inoue R, Yasuno Y, Makita S, Yamanari M, Yatagai T, Kita M, Yoshimura N. Three-dimensional imaging of macular holes with high-speed optical coherence tomography. *Ophthalmology*. 2007;114(4):763-73.
- [17] Alkabes M, Mateo C. Macular buckle technique in myopic traction maculopathy: a 16-year review of the literature and a comparison with vitreous surgery. *Graefes Arch Clin Exp Ophthalmol*.

Table 1

Table 1. Comparison of the visual acuity, MHI, CRT and CVRQoL-25 scores before and after surgery.

Index	ILM peeling combined with autologous ILM transplantation			
	Preoperative	3months Postoperative	t	P
LogMAR BCVA	1.52±0.29	1.09±0.33	6.234	0.000
MHI	0.51±0.18			
CRT		160.05±14.88		
CVRQoL-25 grade	57.27±6.63	71.50±8.81	-8.162	0.000

Figures

Figure 1

The correlation between postoperative CVRQoL-25 and preoperative logMAR BCVA.

Figure 2

The correlation between postoperative CVRQoL-25 and postoperative logMAR BCVA.

Figure 3

The correlation between postoperative CVRQoL-25 and preoperative MHI.

Figure 4

The correlation between postoperative CVRQoL-25 and postoperative CRT.

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