

## **The effect of Hyperbaric Oxygen Therapy combined with Hair transplantation surgery for the treatment of alopecia**

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#These authors contributed equally to this study.

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### **Author's contribution statement**

Zhi-Qi Hu and Yong Miao designed experiments; Zhe-Xiang Fan and Yuyang Gan carried out experiments; Qian Qu and Jin Wang analyzed experimental results; Lunan Yang researched related literature; Zhe-Xiang Fan wrote the manuscript; Bingcheng and Ruosi Chen made important revisions to the paper; Zhi-Qi Hu and Yong Miao approved final version.

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### **Short running head: HBOT combined with hair transplantation**

#### **Abstract**

**Background:** Transplanted hair follicles suffer from various injury, which are difficult to prevent. Hyperbaric Oxygen Therapy (HBOT) was reported to be an excellent procedure to promote capillary regeneration and reduce ischemia-reperfusion injury.

**AIM:** To evaluate the clinical efficacy of HBOT as an adjuvant therapy for hair transplantation surgery.

**Methods:** 34 patients with II-IV alopecia were divided into the control group and HBOT group randomly. The control group were treated with routine FUE procedure, while HBOT group combined with HBOT. Patients were treated with 100% oxygen under 2.0 atmospheres absolute pressure for 60 minutes through a facemask during HBOT and take the therapy daily for 7 days continuously after operation. Satisfaction and clinical improvement were evaluated at the fourth week and the sixth month postoperatively.

**RESULT:** Itching and folliculitis was significantly decreased in HBOT group (11.8% versus 35.3%). In addition, HBOT resulted in a lower postoperative shedding rate ( $27.6 \pm 2.6\%$  versus  $69.1 \pm 2.4\%$ ), nevertheless, the survival rate at 9 months showed no significant difference between HBOT ( $96.9 \pm 0.5\%$ ) and control ( $93.8 \pm 0.6\%$ ). The early postoperative satisfaction in control group was much lower than HBOT group (52.9% versus 88.2%), whereas all patients showed satisfaction with the final result.

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**CONSULSION:** HBOT is able to minimize the postsurgical follicle shedding and lead to less folliculitis and itching, which provides evidence for HBOT to act as an adjuvant therapy for hair transplantation surgery.

**Keywords:** Hyperbaric Oxygen Therapy; Hair transplantation; alopecia

## INTRODUCTION

Alopecia is a worldwide problem caused by miscellaneous reasons, affecting people of different ages and causing mental and psychosocial barriers to patients, some of whom become afflicted with depression<sup>[1]</sup>. Autologous hair transplantation is the gold standard for the treatment of alopecia with high patient satisfaction postoperatively<sup>[2]; 3]</sup>. More and more surgeons prefer follicular unit extraction (FUE) technique to follicular unit transplantation (FUT) technique, as the former has the advantages of a less invasive procedure, unnoticeable scar, rapid recovery and wider donor graft sources<sup>[4]</sup>. However, most of the transplanted hair follicles have a shedding period which affects the postoperative appearance and requires 6-month recovery period. The mechanism involved in the shedding period may be related to ischemia-reperfusion and lack of nutrition<sup>[5]</sup>. It also reported that some patients have postoperative complications, such as folliculitis and scalp necrosis<sup>[6]; 7]</sup>. Therefore, we urgently need improved effective treatments for alopecia.

HBOT, which involves breathing 100% oxygen at higher atmospheric pressures to increase the oxygen levels of plasma and tissue, has been used in the medical field for hundreds of years<sup>[8]</sup>. Recently, HBOT gained widespread clinical attention. It is proved to exhibit merits of anti-hypoxia and anti-infection, promoting capillary regeneration and reducing ischemia-reperfusion injury<sup>[9]; 10]</sup>. Furthermore, it's reported that HBOT can prevent necrosis or decrease necrotic tissue size, which laid foundation for further investigation<sup>[11]</sup>. Thus, the strong foundation of knowledge underpinning HBOT as a new adjuvant strategy for many diseases, such as paraplegia secondary to spinal cord injury, compromised graft or flap transplantation<sup>[12]; 13]</sup>.

Until now, there are few reports exploring the clinical efficacy of the integrated therapy of

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hair transplantation and HBOT. Therefore, our study aimed to evaluate the therapeutic efficacy of HBOT as an auxiliary therapy of traditional hair transplantation.

## **PATIENTS AND METHODS**

34 patients (19 males and 15 females) with AGA were enrolled prospectively from March 2018 to August 2018 at the Plastic and Aesthetic Department in Hospital. This study was approved by the ethics committee of the hospital and college, and conducted in accordance with Declaration of Helsinki. Written informed consent was obtained from all participants. They were clinically examined to exclude concomitant dermatological or psychological disorders, which would influence hair transplantation. Patients with Chronic obstructive pulmonary disease hypoventilation, epilepsy, eustachian tube dysfunction, claustrophobia, eye surgeries, a history of spontaneous pneumothorax, upper respiratory infections or severe sinus infections were excluded. Patients were randomly divided into control group (n = 17) and HBOT group (n = 17). The study was conducted by comparing one patient with another. After local anesthesia with 1% lidocaine containing 1:100000 adrenaline, hair follicles were obtained from the occipital scalp with a 1.0 mm punch respectively. Hair follicles were placed in cool Ringer's lactate before transplantation. Follicle units were transplanted in the receptor region of the scalp. For Hyperbaric oxygen therapy, patients breathed 100% oxygen under 2.0 atmospheres absolute pressure for 60 minutes through a facemask inside a hyperbaric chamber, finally decompressed at a constant speed to the normal pressure. HBOT was performed once a day, beginning from the first day postoperatively to the seventh day. Photography and dermoscopy assessment were performed before surgery and at 1, 3, 5, 7 days and 2, 4, 8, 16, 24 weeks, 9 months after surgery. We marked five areas of 1 cm<sup>2</sup> randomly in the recipient zone before transplantation. Dermoscopy assessment were performed with five marked areas of 1 cm<sup>2</sup> randomly by a blinded dermatologist. The number of red marked areas compared with normal skin was calculated at one month. Then, the hair follicle number in the marked area was counted under dermoscopy 7 days (number 7 days), 1 month and 9 months (number 24 weeks) after the operation. The survival rate was calculated by the following formula: survival rate = (average of number 9 months /average of Number 7 days) × 100%. Postoperative shedding rates was calculated by the following formula: survival rate = (average of number 1 month /average of Number 7 days) × 100%. The number of patients

suffered from infection, itching or folliculitis was recorded, the complication rate (people with visual disturbance; barotrauma; oxygen toxicity with respect to HBOT; infection, itching or folliculitis ;any other adverse events.) was calculated by the following fomula: complication rate = (number suffered from complication)/total number of patients  $\times$  100%. Postoperative satisfaction status was categorized as very unsatisfied, unsatisfied, satisfied and very satisfied, the satisfaction rate was calculated by the following fomula: postoperative satisfaction rate = (number satisfied + number very satisfied)/total number of patients  $\times$  100%.

### Statistical analysis

Quantifiable data was described in the form of  $M \pm SD$  and enumerate data was described in the form of rate. Univariate analysis was conducted by t-test and  $\chi^2$  test.  $P < 0.05$  was considered to be statistically significant.

### Result

A total of 34 AGA patients (19 males) were included in this study. The median age was 26.8 in control group and 27.4 years in HBOT group (Table 1). The mean number of transplanted hair follicles in control group and HBOT group were  $2668.5 \pm 125.6$  and  $2578.4 \pm 112.9$ , respectively (Table 1). Although previous studies have reported visual disturbance, barotrauma, oxygen toxicity and other complications, no severe adverse effects were observed or reported by patients in our study<sup>[14; 15]</sup>. At one month, the recipient site of control group was redder than normal skin, but the recipient site of HBOT group is not significantly different from normal skin. The number of red marked areas in control group was more than that in HBOT (Fig. 1 the redness of recipient site, which was assessed by dermoscopy,  $p < 0.05$ ). Two weeks later, some of the transplanted hair follicles in both groups shed. At one month after surgery, HBOT led to a lower postoperative shedding rate compared to the control group (Table. 1 and Fig. 2, 27.6% in HBOT versus 69.1% in control group,  $p < 0.05$ ). The patients suffered from mild itching and folliculitis was significantly decreased in HBOT group (Table 1, 11.8% in HBOT versus 35.3% in control group). Furthermore, the early postoperative satisfaction (assessed at one month after surgery) in control group was much lower than HBOT group (Table 1, 52.9% in control group versus 88.2% in HBOT,  $p < 0.05$ ). The survival rate at 9 months showed no significant difference between control group ( $93.8 \pm 0.6\%$ ) and

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HBOT group (96.9±0.5%). All patients showed satisfaction with the final results when followed up 9 months postoperatively.

## DISCUSSION

HBOT was first used in the treatment of decompression sickness<sup>[16]</sup>. With the development of technology, more and more functions of HBOT have been confirmed, and its application fields have become more and more extensive. In previous work, the clinical advantages of HBOT as a therapeutic method were proved in the treatment of several neurological disorders, chronic wound, auditory ailments<sup>[10; 11; 17]</sup>. In this study, we demonstrated that the integrated therapy of hair transplantation and HBOT can reduce the postoperative shedding rate of transplanted hair follicles and effectively overcome side effects of itching and folliculitis.

With the improvement of hair transplantation technology, besides the density and survival rate of transplanted hair follicles, more and more attentions have been paid on postoperative recovery period. The transplanted hair follicles will undergo a shedding period and there is currently no effective preventive treatment<sup>[2]</sup>. In this study, we found that hyperbaric oxygen can reduce the shedding rate of transplanted HFs. This may be related to three reasons. First of all, in the early postoperative stage, due to the injury induced by surgery, the recipient site and the transplanted HFs suffered from ischemia, lack of oxygen, where many normal metabolic activities in the cell are blocked, and mitochondria cannot maintain their structural integrity<sup>[18]</sup>. At the same time, a large number of metabolites accumulate in the cells, which will lead damage the cells. HBOT can directly increase the partial pressure of oxygen and increase resistance to ischemia through improved tissue oxygenation, provide oxygen for normal metabolic activities<sup>[19]</sup>. Furthermore, HBOT could improve the expression of VEGF, which can promote the synthesis of nitric oxide (NO), and NO has the effect of vasodilation, thereby further increasing the partial pressure of oxygen in the recipient areas<sup>[20; 21]</sup>.

Secondly, due to ischemia, transplanted hair follicles can only obtain limited nutrients and growth factors from the surrounding tissue fluid, resulting in malnutrition of most hair follicles<sup>[5]</sup>, eventually leading to shedding. Then we observed that most of the transplanted HFs in the control group fell off, which is the same as the previous research. HBOT could

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enhance collagen synthesis and deposition, improve the expression of VEGF, which stimulate angiogenesis<sup>[22]</sup>. Earlier and better blood vessel formation can lead to better oxygen and nutrient delivery, reduce damage to transplanted HFs.

Thirdly, when the blood supply to the HFs gradually recovers, it is accompanied with the generation of reactive oxygen species, which can damage DNA double strands and cell membranes through lipid peroxidation, then cause cell death<sup>[18]</sup>. At the same time, the adhesion and infiltration of neutrophils and the contraction of microvessels will occur<sup>[12]</sup>. Hair follicles are damaged and the hair follicles undergo reperfusion injury. However, damage induced by reactive oxygen species, neutrophil adhesion/infiltration and microvascular vasoconstriction can also be reversed or limited by HBOT<sup>[23; 24]</sup>. Moreover, HBOT could enhance release of TGFβ1, which up-regulated bcl-2, inhibited the apoptosis of fibroblasts, and TNF-α expression, so that reduced reperfusion injury<sup>[19]</sup>. As a result of these, HBOT may be an adjuvant therapy to improve the postoperative shedding (assessed at one month after surgery).

In addition, hair transplantation may lead to some postoperative complications, such as folliculitis and itching<sup>[7]</sup>. Folliculitis and itching were also observed in our research, but we observed that the incidence of itching and folliculitis was much lower in the HBOT group. This may be related to the anti-infective ability of HBOT. Folliculitis and itching may be related to infection (local tissue hypoxia may lead to wound infection), and HBOT can enhance the function of neutrophils and lymphocytes, thereby enhancing the body's natural immune response<sup>[25]</sup>. Besides, although PGs has immunosuppressive effects, HBOT can significantly reduce the production of prostaglandins (PGs)<sup>[19]</sup>. Reducing PGs synthesis may play an important role in the anti-inflammatory effects of HBOT and may ultimately enhance the general immune system. HBOT can also enhance the proliferation of fibroblast, accelerate wound healing, decrease the incidence of infection.

Previous studies have confirmed the safety of HBOT and patients in the HBOT group had no complications during treatment<sup>[26; 27]</sup>. The total cost of HBOT for each patient is cheap, which is less than 80 dollars. Hyperbaric oxygen is beginning from the first day postoperatively in a special hyperbaric oxygen center, with special medical staff for relevant care. But we need to closely observe changes in the patient's condition and detect all vital signs. We carefully

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excluded patients with hyperbaric oxygen contraindications before the start of the study, which further ensures safety.

As can be deduced from the results, integrated therapy of HBOT with hair transplantation reducing the shedding of transplanted hair follicles and overcoming side effects of itching and folliculitis, which is also safe and economical. Although the survival rate at 9 months showed no significant difference in two groups, lower shedding rates and complication rates ultimately lead to higher early postoperative satisfaction in HBOT group. Futuristic and comprehensive work need to be done on larger number of patients and dissect the mechanism and molecular events underlying the catagen loss.

### **Conclusion**

This study clearly demonstrated beneficial effect impact of integrated therapy of HBOT with hair transplantation. HBOT is beneficial in reducing the shedding of transplanted hair follicles, early recovery of the skin, lead to less folliculitis and itching, and faster display of postoperative results.

### **Data Availability Statement**

All data generated or analyzed during this study are included in this article.

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#### **Table 1 Comparison of control group and HBOT groups.**

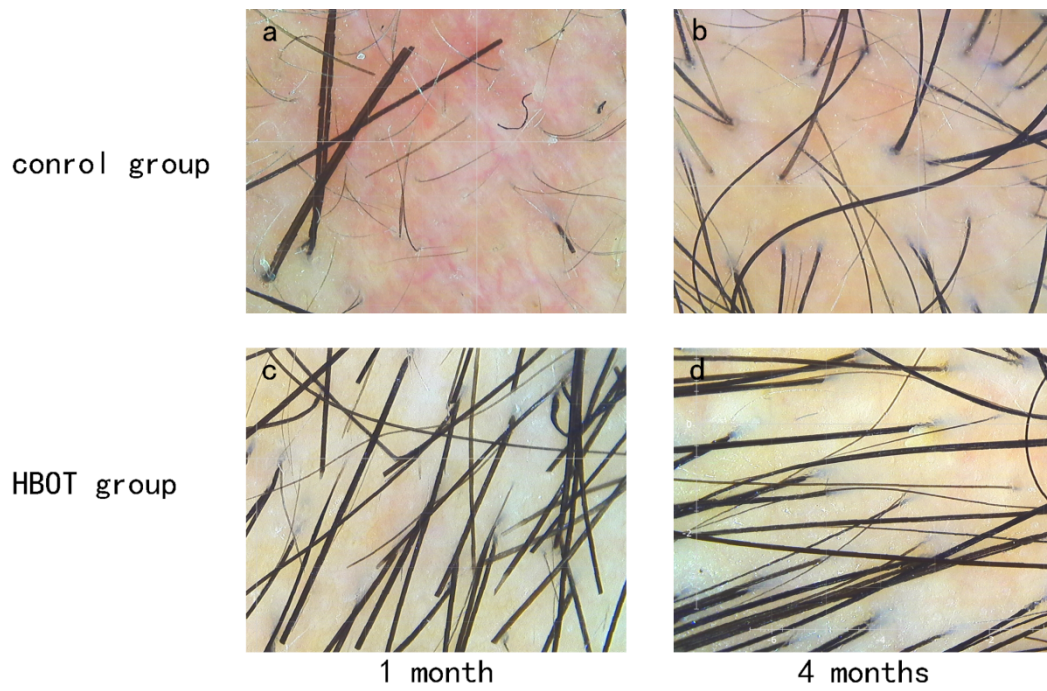
**Figure. 1 Dermoscopic photographs of control (a-b) and HBOT groups (c-d).** HBOT led to a lower postoperative shedding rate compared to the control group at one month after surgery (a, c) . At one month, the recipient site of control group was redder than normal skin, but the recipient site of HBOT group is not significantly different from normal skin(a-d). Recipient site 1 month after transplantation (a, c), and 4 months after transplantation (b, d).

**Figure. 2 Comparison of cosmetic outcome between control (a-d) and HBOT groups (e-h).** HBOT led to a lower postoperative shedding rate compared to the control group at one month after surgery. All patients in the two groups showed satisfied cosmetic results at 9 months after the surgery. Recipient site before transplantation (a, e), 1 day after

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transplantation (b, f), and 1 month after transplantation (c, g) and 9 months after transplantation (d, h).

Table 1 - Comparison of control group and HBOT group							
	Median age of patients	Mean number of transplanted hair follicles (p<0.05)	Postoperative shedding rate (p<0.05)	Itching &Folliculitis	Early postoperative satisfaction	Survival rate (p>0.05)	Number of red marked areas(p<0.05)
Control	26.8	2668.5±125.6	69.1±2.4%	35.3%	52.9%	93.8±0.6%	3.5±0.3%
HBOT	27.4	2578.4±112.9	27.6±2.6%	11.8%	88.2%	96.9±0.5%	0.4±0.2%



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