ONLINE FIRST

CASE REPORT

Effect of Hyperbaric Oxygen Therapy Dose on Post-Replantation of the Distal Phalanx of Digiti II Manus Sinistra

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ABSTRACT

Finger replantation in adults requires a more extended healing period and is at risk of failure. Giving hyperbaric oxygen therapy (HBOT) at the correct dose can speed healing, reducing the risk of failure. A case involved a 32-year-old woman after replantation of the distal phalanx of digiti II manus sinistra of the patient who experienced cyanosis and necrosis. This report analyzes the relationship between HBOT dose and accelerated stimulation of growth factors that can improve the wound healing process.

Replantation refers to the reconnection of an amputated body part to its anatomical structure to restore the function of the injured part. The outcome depends on the dose of HBOT, the patient's intrinsic factors, and the nature of the injury. Giving HBOT once a day, in this case, was not effective because the patient's fingertips became more cyanotic, and necrosis increased. Providing the correct dose of HBOT twice a day accelerates overcoming hypoxia. It helps successfully heal wounds through angiogenesis, collagen formation, and epithelialization, so new tissue growth is expected to accelerate.

KEYWORDS: HBOT dose, Post-replantation, Wound healing, Angiogenesis, Collagen formation, Epithelialization, Growth factors

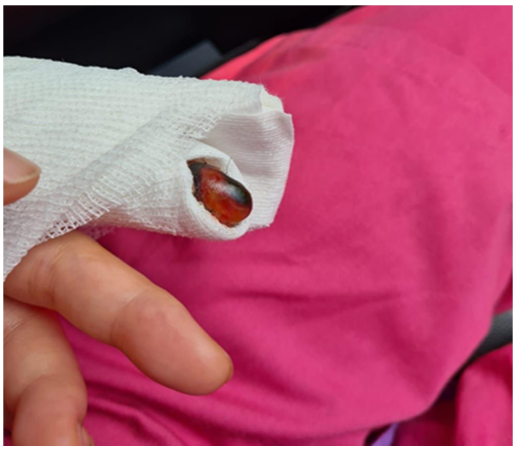
INTRODUCTION

Replantation is an action that reunites all tissue and bones wholly severed. This procedure is performed using microvascular techniques in a process called revascularization. Upper and lower extremity amputation risks causing physical disability and can cause psychological burdens. Amputations can occur due to vascular disorders, trauma, cancer, infection, or congenital abnormalities. Research states that the most common cause of someone losing a limb is due to complications from diabetes, peripheral vascular disease (PVD), and further trauma[1].
Replantation aims to return the amputated part to its anatomical location, maintaining function and appearance. Factors that influence finger replantation failure include an increase in the number of damaged fingers, long duration of surgery, total avulsion, current smoking, diabetes, hypertension, procedural difficulty score, and the occurrence of postoperative complications [2].
Hyperbaric oxygen therapy (HBOT) refers to inhaling pure oxygen in a closed, high-pressure chamber at more than usual atmospheric pressure. It is used to treat cases of disease with underlying hypoxia. HBOT causes biochemical and various physiological changes at the cellular level[3]. Multiple studies show that HBOT overcomes ischemia, greatly influencing the processes of angiogenesis and neovascularization. In general, several clinical reports state that HBOT is beneficial in the process of successful replantation surgery.

Case Presentation

A 32-year-old woman suffered from a post-replantation wound on the proximal phalanx of the left manus after being cut by a knife while cooking in the kitchen. The patient took analgesic medication and kept the finger warm. 2 days after replantation, the tissue experienced cyanosis, and part of the skin at the fingertips experienced necrosis in **Picture I**.

Picture I: Phalanx distal digiti II manus sinistra of the patient (pre HBO)



There was no history of previous illness, and vital signs (blood pressure, heart rate, respiratory rate, body temperature) were normal. No infection and the haematology examination results were normal, as shown in **Table I**. Because the results of the hematology examination before HBOT were normal, the hematology examination after the 18th HBOT did not need to be carried out again.

Table I: Vital Signs and Hematology Report

Parameter	Results		Limits
Vital Signs			
Blood Pressure	110/70	mmHg	110-120/70-80
Heart Rate	72	bpm	60 - 80
Respiratory Rate	16	bpm	12 - 18
Body Temperature	36.4	^{o}C	36.1 - 37.2
Hematolgy			
White Blood Cells (WBC)	7.2 x	10^{8}9 /L	4.0 - 10.0
Lymphocytes % (LYM%)	21.5	%	20.0 - 40.0
Mid-cells % (MID%)	6.9	%	1.0 - 15.0
Neutrophils % (NEUT%)	63.6	%	50.0 - 70.0
Lymphocytes (LYM)	1.4 x	10*9 /L	0.6 - 4.1
Mid-cells (MID)	0.5 x	10*9 /L	0.1 - 1.8
Neutrophils (NEUT)	5.3 x	10*9 /L	2.0 - 7.8
Red Blood Cells (RBC)	4.16 x	10*12/L	3.50 - 5.50
Hemoglobin (HGB)	11.8 x	g/dL	11.0 - 16.0
Hematocrit (HCT)	34.6	%	36.0 - 48.0
Mean Corpuscular Volume (MCV)	83.4	fL	80.0 - 99.0
Mean Corpuscular Hemoglobin (MCH)	28.3	pg	26.0 - 32.0
Mean Corpuscular Hemoglobin Concentration (MCHC)	34.1	g/dL	32.0 - 36.0
Platelet Count (PLT)	370 x	10*9 /L	100.0 - 300.0
Mean Platelet Volume (MPV)	10.2	fL	7.4 - 10.4
Platelet Distribution Width (PDW)	15.0	%	10.0 - 17.0
Procalcitonin (PCT)	0.37	%	0.10 - 0.28
Platelet-large Cell Ratio (P-LCR)	28.3	%	13.0 - 43.0

Case History

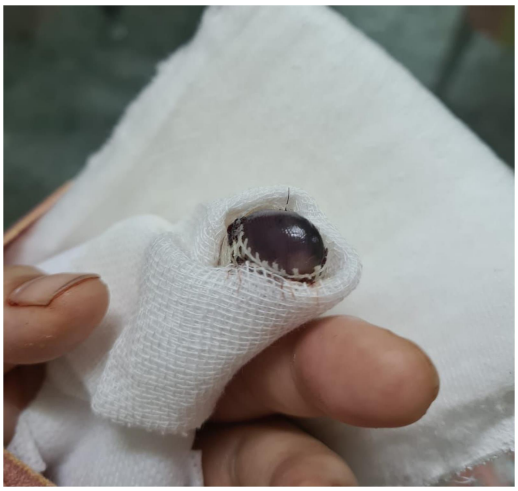
The timeline of the development of the patient's finger condition can be seen in **Table II**.

Table II: HBOT Treatment TimeLine

Day to	Date	Time	HBOT	Condition of the Digiti
0	27-1-2023	0	0 time	tissue experienced the fingertips cyanosis, and part of the skin experienced necrosis
1	29-1-2023	07.00 - 09.00 WIB	1 time	
2	30-1-2023	07.00 - 09.00 WIB	2 times	expansion of necrosis and cyanosis
	31-1-2023	07.00 - 09.00 WIB	3 times	
		17.00 – 19.00 WIB	4 times	
	01-2-2023	07.00 - 09.00 WIB	5 times	
		17.00 – 19.00 WIB	6 times	
5	02-02-2023	07.00 - 09.00 WIB	7 times	the cyanosis had decreased, and the necrosis had not spread,
		17.00 – 19.00 WIB	8 times	
	03-02-2023	07.00 - 09.00 WIB	9 times	
		17.00 – 19.00 WIB	10 times	
	04-02-2023	07.00 - 09.00 WIB	11 times	
		17.00 – 19.00 WIB	12 times	
	05-02-2023	07.00 - 09.00 WIB	13 times	
8		17.00 – 19.00 WIB	14 times	the cyanotic and necrotic tissue had begun to shrink and again showed very significant progress
	06-02-2023	07.00 - 09.00 WIB	15 times	
		17.00 – 19.00 WIB	16 times	
	07-02-2023	07.00 - 09.00 WIB	17 times	
10		17.00 – 19.00 WIB	18 times	structure on the patient's fingers had returned to normal without cyanosis and necrosis of external skin tissue

After that, the patient was directed to undergo HBOT therapy. During one HBOT session, the patient inhales 100% O_2 3 times 30 minutes, 2 times 5-minute intervals and breathes normal air at a room pressure of 2.4 atmosphere absolute (ATA) daily to save post-replantation tissue. We used doses according to standard operational procedures for clinical diseases set by the Naval Health Institute Surabaya Indonesia based on previous research referring to the US Navy Table 9 doses for decompression sickness and carbon monoxide poisoning. At 2.4 ATA breathing 100% pure oxygen, there was an increase in the ideal dissolved oxygen content approaching 5.6 vol%[4]. Arterial oxygen measurement using oximetry on the distal phalanx of digiti was not performed because it will apply pressure that risks damaging finger tissue. After the patient received HBOT twice, the patient's finger had not improved, and there was expansion of necrosis and cyanosis, which can be seen in **Picture II**.

Picture II: There is widespread cyanosis and necrosis in the patient's fingers after undergoing HBOT therapy twice

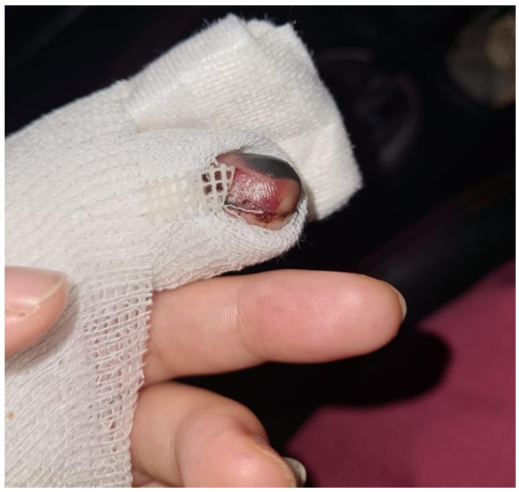


When he saw that the patient's finger condition was getting worse, the doctor stated that doing HBOT once a day for 2 days was not effective. Then, the patient was advised to take HBO therapy twice a day with a gap of 8 hours between each therapy period. On the fifth day after receiving HBOT 8 times, the patient's fingers improved, the cyanosis decreased, and the necrosis did not spread, as seen in **Picture III**.

Picture III: Condition of the patient's finger on day 5 after undergoing HBOT 8 times (2 times HBOT once a day, followed by 6 times HBOT twice a day)

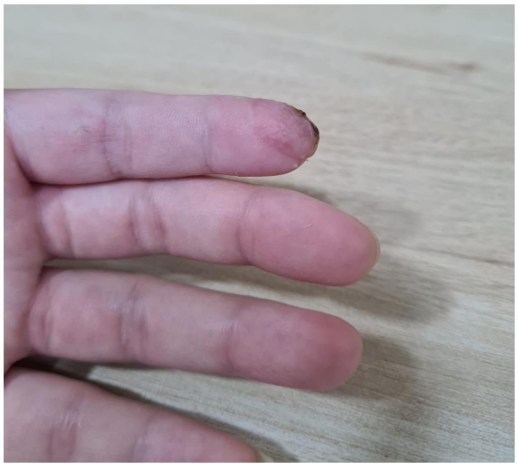
Because there was significant improvement in the patient's finger, the doctor advised the patient to continue HBOT using the twice-daily method and then re-evaluate on day 8 (14th HBOT). After the 14th HBOT, the cyanotic and necrotic tissue on the patient's fingers began to shrink and showed significant progress, as seen in **Picture IV**.

Picture IV: Condition of the patient's finger on the 8th day after undergoing HBOT 14 times



HBOT was continued every 2 days up to 18 times; the results were very satisfactory, and the patient's finger structure had returned to normal without cyanosis and necrosis of external skin tissue which can be seen in **Picture V**.

Picture V: Condition of the patient's finger on day 10, after undergoing HBOT 18 times



DISCUSSION

Several studies state that HBOT is an effective treatment method for healing wounds, especially wounds that are difficult to heal with breathing using oxygen levels approaching 100% at 2-3 ATA. HBOT at higher pressures increases oxygen levels in the blood (hyperoxemia) and tissues (hyperoxia). The increased pressure and bioavailability of oxygen are associated with many applications, especially in hypoxic areas[5]. The concept of hyperbaric oxygen dose is derived from the definition of HBO as a drug. HBO dose includes O2 level, pressure depth, duration, interval and frequency. HBOT causes the environment to become conducive to injured tissue, accelerating healing. HBOT stimulates the processes of antimicrobial, immunomodulatory, angiogenesis, collagen matrix formation, and epithelialization. HBOT encourages the processes of angiogenesis, collagen matrix formation, and epithelialization. Angiogenesis involves the role of several cells, including blood cells, endothelial cells, other blood vessel wall cells, and inflammation-related cells. Angiogenesis is influenced by various growth factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). Acute hypoxia causes the production of reactive oxygen species (ROS), an essential stimulator of angiogenesis, by inducing the synthesis of VEGF through the activation of macrophages, fibroblasts, endothelial cells, and keratinocytes. Still, prolonged hypoxia will inhibit VEGF synthesis [5,6].

Several studies say that hyperoxia will stimulate VEGF receptors. Apart from VEGF, PDGF also affects angiogenesis, promoting wound healing. PDGF is functional, activating fibroblasts to produce collagen as the main component of the new extracellular matrix (ECM). Fibroblasts then differentiate into myofibroblasts, arranged in one row on the latest cellular matrix. This myofibroblast formation is a tense and strong cell construction. This structure is a wound bed where endothelial cells migrate to form new blood vessels. Fibroblasts will produce several growth factors, one of which is tumor growth factor-β (TGF β), which stimulates keratinocytes to migrate to the wound area. Keratinocytes will proliferate to form an epithelial layer to cover the wound [7].

Fibroblast proliferation, transformation and collagen synthesis involving PDGF-BB by activating the phosphatidylinositol 3'-kinase(PI3K)-Akt is a signaling pathway. PDGF-BB induces

phosphorylation of threonine 308 and serine 473 via PI3K, which AKT activates, ultimately promoting collagen proliferation and expression. Some of these effects are also mediated by the hypoxia-inducible factor (HIF)-1a signaling pathway [7,8] In addition, PDGF-BB promotes cellular matrix collagen remodeling mediated by integrin α1β1 with increased activity of extracellular signal-regulated kinase (ERK)/activator protein-1 (AP-1). Integrins and growth factors have been shown to mediate signaling by influencing cellular behaviors such as migration, proliferation, and survival. Integrin regulation is critical for wound healing[9].

Collagen is a protein found in 30% of skin, tendons, cartilage and organs. PDGF-BB, which can increase collagen matrix remodeling, is very important for reducing inflammation in the wound-healing process. Something that seems contradictory is that angiogenesis is also stimulated and regulated by various cytokines, most of which are produced by macrophages and platelets. Tumor necrosis factor-α (TNF-α) produced by macrophage-induced leucine-rich-alpha-2-glycoprotein 1 (LRG1) stimulates angiogenesis, but TNF-a can also inhibit collagen formation [10]. Hyperoxia due to HBOT can reduce TNF-a at the end of the inflammatory phase, resulting in collagen formation [11].

The use of HBOT as adjuvant therapy after the replantation process is starting to be developed. HBOT can have the effect of slowing down the process of metabolic acidosis in amputated limbs and then helping the tissue retain oxygen delivered in hyperbaric/high-pressure conditions. This therapy can provide hyperoxygenation conditions for tissue that has undergone replantation so that oxygen reaches the edges of the graft and wound to maintain viability and help the angiogenesis process. HBOT also reduces edema due to general vasoconstriction.

In the case of patients with replantation of phalanx distal digiti II manus sinistra on the first day until the second day, there were no significant changes found in the digit II of the left manus in patients who were given HBOT once a day, then starting from the third day HBOT was given twice a day with a distance of 8 hours between each -each therapy and significant changes were found in the patient's Digiti II Manus Sinistra on the 5th day, 8th day and 10th day.

CONCLUSION

Giving HBOT twice a day with a gap of 8 hours between each therapy in Manus Sinistra Digiti II Replantation Patients is more effective than providing HBOT once a day.

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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Harnanik T: Conceptualized and compiled the case design, analyzed and interpreted data
Pradnyapramesti MKE: Helped organize the article's writing and analyze the data critically
Jayarta NS: Revised the original draft and polished the manuscript.

REFERENCES

1. Alshehri FM, Ahmed SA, Ullah S, Ghazal H, Nawaz S, Alzahrani AS. The Patterns of Acquired Upper and Lower Extremity Amputation at a Tertiary Centre in Saudi Arabia. Cureus. 2022; doi:10.7759/cureus.24026.
2. Altam A, Obadiel Y, Alazaiza RS, Alshujaa MA, Alhajami F, Ahmed F et al. Microsurgical Digits Replantation in Resource-Limited Setting: A Retrospective Study. Open Access Emerg Med. 2024; 16: 1–13. doi: 10.2147/OAEM.S443219.
3. Sen S. Therapeutic effects of hyperbaric oxygen: Integrated review. Med Gas Res. 2021; 11: 30-33 Preprint at https://doi.org/10.4103/2045-9912.310057.
4. Jain KK. Physical, Physiological, and Biochemical Aspects of Hyperbaric Oxygenation. in Textbook of Hyperbaric Medicine. 11–22 (Springer International Publishing, 2017). doi: 10.1007/978-3-319-47140-2_2.
5. Ortega MA, Fraile-Martinez O, García-Montero C, Callejón-Peláez E, Sáez MA, Álvarez-Mon MA et al. A general overview on the hyperbaric oxygen therapy: Applications, mechanisms and translational opportunities. Medicina (Lithuania). 2021; 57. Preprint at https://doi.org/10.3390/medicina57090864.
6. Mao, Y, Liu, X, Song Y, Zhai C, Zhang, L. VEGF-A/VEGFR-2 and FGF-2/FGFR-1 but not PDGF-BB/PDGFR-β play important roles in promoting immature and inflammatory intraplaque angiogenesis. PLoS One. 2018; 13, doi: 10.1371/journal.pone.0201395.
7. Wang K, Wen D, Xu X, Zhao R, Jiang F, Yuan S et al. Extracellular matrix stiffness - The central cue for skin fibrosis. Frontiers in Molecular Biosciences. 2023; 10. Preprint at https://doi.org/10.3389/fmolb.2023.1132353.
8. Chen Y, Jiang L, Lyu K, Lu J, Long L, Wang X et al. A Promising Candidate in Tendon Healing Events—PDGF-BB. Biomolecules. 2022; 12. Preprint at https://doi.org/10.3390/biom12101518.
9. Zhang Z, Yao L, Yang J, Wang Z, Du G. PI3K/Akt and HIF-1 signaling pathway in hypoxia-ischemia (Review). Molecular Medicine Reports. 2018; 18: 3547–3554. Preprint at https://doi.org/10.3892/mmr.2018.9375.
10. Wang Y, Xu J, Zhang X, Wang C, Huang Y, Dai K et al. TNF-α-induced LRG1 promotes angiogenesis and mesenchymal stem cell migration in the subchondral bone during osteoarthritis. Cell Death Dis. 2017; 8: e2715–e2715. doi: 10.1038/cddis.2017.129.
11. de Wolde SD. The Effect of Hyperbaric Oxygen Therapy on Markers of Oxidative Stress and the Immune Response in Healthy Volunteers. Front Physiol. 2022; 13. doi: 10.3389/fphys.2022.826163.