DOI: 10.4081/aiua.2025.13342

ORIGINAL PAPER

The effect of hyperbaric oxygen therapy on hypospadias reconstruction: A preliminary randomized controlled trial study of VEGF levels and HOPE score analysis

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Summary

Introduction: *Hypospadias is a congenital abnormality of the urethral meatus in males. Hypospadias can be corrected by two-stage urethroplasty. Hyperbaric oxygen therapy (HBOT) can accelerate wound healing after surgery by increasing oxygenation, angiogenesis, and collagen synthesis. This study aimed to measure the effectivity of HBOT based on serum vascular endothelial growth factor (VEGF) level and Hypospadias Objective Penile Evaluation (HOPE) score in hypospadias reconstruction patients.*

Methods: *This was a randomized controlled trial study. Hypospadias reconstruction was performed using the Sidik-Chaula and Manset Flap techniques. Each HBOT session ranged from 30-60 minutes, administered at 1-3 atm. Twenty subjects were divided into two groups: the HBOT and control groups. VEGF serum levels were measured 1 hour after the operation and 1 hour after every HBOT session. The HOPE score was assessed at the bedside by the attending physician, consisting of six items: the position of the meatus, the shape of the meatus, the shape of the glans, the shape of the penile skin, and the shape of the penile axis, including penile torsion and penile curvature. The data were analyzed with SPSS version 28, using the Shapiro-Wilk and independent t-test methods.*

Results: *There was a trend of increasing VEGF levels as the number of HBOT sessions increased, with significant increase found in patients who underwent three ($p = 0.038$), four ($p = 0.002$), and five ($p = 0.008$) HBOT sessions. We found a significant increase in the total HOPE score ($p = 0.028$) and penile torsion score ($p = 0.006$) in the HBOT group.*

Conclusions: *HBOT can accelerate wound healing after urethroplasty. Three or more HBOT sessions are recommended after the repair of hypospadias.*

KEY WORDS: *Hypospadias; Urethroplasty; Hyperbaric oxygen therapy; Vascular endothelial growth factor.*

Submitted 4 November 2024; Accepted 3 January 2025

INTRODUCTION

Hypospadias is a congenital abnormality of the male external genital tract, with the characteristic anatomic position of the urethral meatus at the ventral or anterior part of the penile body, often accompanied by urethral spongiosum, widened dorsal prepuce, ventral foreskin, penile chordee, and deviation of the ventral penile body (1). The main treatment remains surgical correction with various techniques, one of which is the two-stage urethroplasty technique, also known as the Sidik-Chaula technique. In the first stage, the chordee is released and a neourethra is created using the distal intraglandular tunnel removed from the preputial vascularized flap. The full-length urethra is then reconstructed in a second stage, using a locally transposed cutaneous flap with minimal manipulation (2).

Hyperbaric oxygen therapy (HBOT) is a therapeutic modality to improve tissue hypoxic conditions by providing high-pressure oxygen so that tissue oxygen tension increases. It thereby improves oxygen delivery to hypoxic tissue because dissolved oxygen can pass through tissue fluids even if the tissue is damaged and has poor blood circulation. Increased oxygen availability in tissue promotes angiogenesis, collagen synthesis, increased reactive oxygen species for bacterial clearance, inhibition

of inflammation, and inhibition of leukocyte adhesion to endothelium. This correlates with increased wound healing, damaged tissue regeneration, and fibroblast scar tissue remodeling (3).

Various reports state that wound healing accelerated with hyperbaric oxygen, including hypospadias reconstructive surgery scars, by increasing the *vascular endothelial growth factor* (VEGF) stimulation of angiogenesis through proliferation. *Neheman et al.* (4) evaluated the use of HBOT to increase the success rate of staged tubularized autograft (STAG) repair in repeatedly failed correction cases. They showed that hyperbaric adjuvant therapy in a pediatric population improved the result of previously failed hypospadias surgery and led to better graft uptake. *Chang et al.* (5) also used HBOT as an adjuvant therapy for hypospadias patients undergoing two-stage correction using buccal mucosal grafts to repair glans penis dehiscence and urethroplasty for urethral strictures after hypospadias correction. They obtained successful outcomes in these cases with HBOT administration.

The optimum scoring system for cosmetic outcomes following hypospadias surgery should be an objective, repeatable, and validated tool measuring each relevant and surgically correctable component of the hypospadias (6). The *Hypospadias Objective Penile Evaluation* (HOPE) score has good validity and reliability, which supports its use as an objective indicator of cosmetic appearance following hypospadias surgery (6-9). The increase in hypospadias cases and the use of HBOT, which plays a role in the wound healing process, has led researchers to examine the effect of HBOT on the success of hypospadias surgery. This study aimed to measure the effectivity of HBOT based on the serum VEGF level and HOPE score in patients after hypospadias reconstruction.

Methods

This was a randomized controlled trial study conducted between December 2021 and December 2022, and conducted per CONSORT guideline 2010 (10).

The data collection and processing were performed at *R.D. Kandou Hospital* and *Siloam Manado Hospital*. The study population inclusion criteria were patients with all types of hypospadias who would undergo surgery and were willing to be participants in the research. We excluded patients with tympanic perforation, endocranial implants, or hearing problems; patients with epilepsy or other types of seizures; patients in chemotherapy; patients with alcoholism or users of psychoactive drugs; heart pacemaker users; patients with claustrophobia or other psychiatric problems; patients with uncontrolled hypertension, heart failure, respiratory failure, pneumothorax, or asthma; and non-cooperative patients.

Urethroplasty procedure

The control and HBOT groups both underwent surgery for hypospadias. Distal, middle, and proximal hypospadias were all repaired using a modified two-stage urethroplasty: the Sidik-Chaula technique. An additional approximation of the bilateral subgranular flap, called the Manset flap, which is especially useful in cases of middle hypospadias, was also used (11).

HBOT Group

Patients in the HBOT group received standard wound dressings, as did the control group. Additionally, they underwent one session of 100% oxygen therapy within 24 hours postoperatively, for 5 consecutive days. Each HBOT session lasted 30-60 minutes and was administered at 2.4 ATM.

Control group

The control group received only standard wound dressings, changed every 2 days with moist sterile gauze, and a 5-day course of oral broad-spectrum antibiotics.

Outcome

The primary outcomes include differences in VEGF levels and HOPE scores before and after *hyperbaric oxygen therapy* (HBOT). Secondary outcomes were the assessment of baseline characteristics of hypospadia repair patients and the number of HBOT sessions required to significantly impact VEGF levels and HOPE scores.

VEGF examination

In the control group, VEGF serum levels were measured once, 1 hour after the operation. In the HBOT group, VEGF serum levels were measured 1 hour after each of the 5 HBOT sessions (HBOT 1, 2, 3, 4, and 5), with a blood sample taken after every session.

The VEGF serum levels were measured in guanidium thiocyanate L6 buffer. The samples were centrifuged for 60 minutes until coagulated, then kept in a -80 °C container until analysis.

All samples were examined using the human VEGF ELISA kit protocol of the SimpleStep ELISA kit from AssayGenie Human VEGF-A with catalog no. HUES01397. The results are expressed in ng/ml.

HOPE score

The HOPE score was assessed at the bedside by the attending physician, consisting of six items: the position of the meatus, the shape of the meatus, the shape of the glans, the shape of the penile skin, and the shape of the penile axis including penile torsion and (if erection was observed) penile curvature. The possible HOPE scores range from 1 to 10 (12). A standardized photograph was taken pre-operatively (under general anesthesia) and six months post operative. Two researchers individually assessed the HOPE score of the patients based on the photograph taken, without knowing the patient's identity. The final HOPE score was taken from mean HOPE score from both assessors.

Randomization

The participants were randomly and equally divided into HBOT and control group using a computer sequence generator. Patients in the HBOT group were allocated to a multichamber hyperbaric unit; therefore, patient blinding was not possible. However, the patients' identities were blinded to the author responsible for allocation, as well as to the assessor who evaluated the HOPE score preoperatively and the assessor who assessed the HOPE score postoperatively.

Statistical analysis

Univariate evaluation was carried out according to the

type of variable: numeric or categorical. The descriptive tabulation of numeric variables is shown as mean, range, and standard deviation. The distribution normality was assessed by the Shapiro-Wilk test. The difference between the two groups in VEGF levels was tested with the independent t-test and Mann-Whitney test. Results are shown for fixed effects in the form of estimates of 95% *confidence interval* (CI) and p-value. The statistical analysis was carried out with SPSS version 28 (*Armonk, NY, USA: IBM Corp.*) and R Software version 3.5.1, assisted by the use of Microsoft Excel spreadsheets.

Results

Kandou Hospital had 20 cases of hypospadias repair within 1 year. Ten were treated with HBOT as an adjuvant treatment, and the other half had conventional post-operation procedures. The patient characteristics are shown in Table 1.

Table 1.
Baseline characteristics of the study population.

Parameter	Control (n = 10)	HBOT (n = 10)	Total (n = 20)
Age (years) (mean ± SD)	7.7 ± 3.0	17.4 ± 7.1	12.6 ± 7.3
Age (years) (range)	8 (3-11)	20 (12-32)	29 (3-32)
Type of hypospadias			
Subcoronal [n (%)]	4 (40.0)	3 (30.0)	7 (35)
Glandular [n (%)]	2 (20.0)	2 (20.0)	4 (20)
Distal penile [n (%)]	1 (10.0)	1 (10.0)	2 (10)
Midshaft penile [n (%)]	1 (10.0)	1 (10.0)	2 (10)
Proximal penile [n (%)]	1 (10.0)	1 (10.0)	2 (10)
Penoscrotal [n (%)]	1 (10.0)	1 (10.0)	2 (10)
Scrotal [n (%)]	0 (0.0)	1 (10.0)	1 (5)

HBOT: Hyperbaric oxygen therapy; SD: standard deviation.

The mean age of the participants was 12.6 years (SD 7.3), ranging from 2 to 32 years old. The most common type of hypospadias found was subcoronal (35%), and the least frequent was scrotal (5%).

The comparison of VGEF serum levels between the control and HBOT groups 1 hour after hypospadias reconstruction is shown in Table 2.

The mean serum VEGF level of the control group was 394.49 ± 107.88 ng/mL. Significant increases in serum VEGF levels were observed in the patients given three (mean difference [MD]=122.0, p = 0.038, 95% CI 7.74-236.26), four (MD 223.6, p = 0.002, 95% CI 94.92-352.27), and five (MD 292.71, p = 0.008, 95% CI 90.13-495.30) HBOT sessions. Overall, the patients in the control group had a lower mean VEGF level compared to the HBOT group, regardless of the number of sessions. Although not significant, a slight increase also occurred in serum VEGF levels after the first (MD 1.73) and second (MD 54.00) HBOT sessions.

Importantly, the concentration of serum VEGF constantly increased after each session of HBOT, despite the wide range of 95% CI.

Ten participants came for follow-up and assessment of the HOPE score. The difference in HOPE scores between both groups is shown in Table 3. A significant difference in favor of the HBOT group was found in penile torsion (p = 0.006) and total HOPE score (p = 0.014). Further, the HBOT group had a higher mean score for all six item variables.

Table 3.
Hypospadias Objective Penile Evaluation (HOPE) scores of hypospadias repair patients.

Variable	n	Control (mean ± SD)	HBOT (mean ± SD)	P-value
Position of meatus	5	4.4 ± 2.6	5.0 ± 4.6	0.500
Shape of meatus	5	5.8 ± 3.4	7.0 ± 3.7	0.304
Shape of glans	5	6.4 ± 3.9	7.6 ± 2.5	0.290
Shape of penile skin	5	5.8 ± 3.4	8.8 ± 2.6	0.058
Penile torsion	5	4.0 ± 3.0	9.4 ± 1.3	0.006
Erection curvature	5	6.4 ± 2.5	7.0 ± 3.7	0.386
Total score	5	32.6 ± 8.6	44.8 ± 8.7	0.028

HBOT: Hyperbaric oxygen therapy; SD: standard deviation; Significant if p < 0.05.

Table 2.
Serum vascular endothelial growth factor (VEGF) of hypospadias repair patients.

Group	n	Mean ± SD (ng/mL)	p-value	Mean diff	95% CI Lower	95% CI Upper
Before surgery	10	396.27 ± 84.62				
After surgery	10	387.74 ± 76.20				
Control	10	394.49 ± 107.88	0.972	1.73	-99.45	102.91
HBOT 1	10	448.49 ± 88.68				
Control	10	394.49 ± 107.88	0.237	54.00	38.78	146.78
HBOT 2	10	448.49 ± 88.68				
Control	10	394.49 ± 107.88	0.038	122.00	7.74	236.26
HBOT 3	10	516.49 ± 133.94				
Control	10	394.49 ± 107.88	0.002	223.60	94.92	352.27
HBOT 4	7	618.09 ± 141.63				
Control	10	394.49 ± 107.88	0.008	292.71	90.13	495.30
HBOT 5	4	687.20 ± 252.75				

HBOT: Hyperbaric oxygen therapy; SD: standard deviation; ng: nanogram; mL: milliliter; CI: confidence interval.

Discussion

A total of 20 patients who met the inclusion criteria and were willing to participate in the study were divided equally into the control and HBOT groups. However, only five patients in the control group and five patients in the HBOT treatment group attended follow-up to assess the HOPE score.

The minimum age of the subjects participating in our study was 3 years and the maximum age was 32 years, with an average age of 12.6 years. If detected early, hypospadias can be corrected surgically at 6 to 18 months of age, depending on the severity (13). No standard age exists for hypospadias repair surgery although if it is performed too early, the penis may be too

small and cause technical difficulties. Some studies suggest that patients should take testosterone supplements until the penis size is sufficient to operate. However, this method is not supported by strong evidence (14).

Performing surgery at an early age is more beneficial in terms of psychology because patients tend not to remember their previous condition, so their body image is more positive. In addition, surgery at an older age is associated with more complications due to increased urethral secretions and nocturnal erections (15).

Several similar studies have recorded younger ages at surgery than the present study, such as *Kocherov et al.* (29.4 months), *Nabil et al.* (17 months), and *Shenoy et al.* (50.4 months) (16-18).

Our study presented a significant difference of age between the HBOT group (17.4 years) and the control group (7.7 years), which complicates result interpretation. Older participants may exhibit different biological responses, while younger ones face surgical challenges. These differences, due to randomization in a small sample size, represent a key limitation of the study.

The type of hypospadias in this study was most often subcoronal (35%), followed by penile (30%) and glandular (20%), and the least common was posterior (15%). This is in accordance with the theory that states that almost 50% of cases are anterior, 20% are penile, and the rest are posterior. Overall, the subcoronal position is the most common for hypospadias (19, 20).

Conditions of oxygen deprivation in tissues often occur after hypospadias reconstruction surgery due to the large number of incisions and flaps on a relatively small area. The placement of skin flaps in hypospadias repair surgery usually requires flap rotation, thus damaging the vascularization of epithelium and inducing vascular spasm in it. Vasospasm is thought to be the main trigger of flap ischemia. Tissue hypoxic conditions complicate the healing process, reduce the success rate of surgery, and increase postoperative complications (21).

HBOT is a therapeutic modality to improve tissue hypoxic conditions by increasing oxygen supply to damaged tissues. Naturally, the process of angiogenesis occurs due to stimulation of the release of growth factors, cytokinases, and lipid mediators produced during injury. One of the proangiogenesis mediators is VEGF. HBOT helps accelerate the process of angiogenesis characterized by an increase in VEGF, which causes an acceleration of the wound healing process (3, 4).

Our study found that VEGF levels in patients who underwent HBOT were higher than in the control group (394.49 ± 107.88 pg/mL). Notably, the gradual increase in VEGF levels was directly proportional to the number of HBOT sessions given to patients. The VEGF level was 392.76 ± 107.50 pg/mL after the first HBOT session, 448.49 ± 88.68 pg/dL after the second HBOT session, 516.49 ± 133.94 pg/mL after the third HBOT session, 618.09 ± 141.63 pg/dL after the fourth session, and 687.20 ± 687.20 pg/dL after the fifth session.

A significant increase in VEGF ($p < 0.05$) was found after the third ($p = 0.038$), fourth ($p = 0.002$), and fifth ($p = 0.008$) HBOT sessions.

The results of this study support previous research by *Oley et al.*, who conducted a study on crush injury patients, who were divided into HBOT and placebo treatment groups. VEGF levels in the HBOT group were 1,505.9 ng/mL and higher that in patients undergoing debridement only.

Similarly, VEGF mRNA expression was 1.2-fold higher in the group receiving HBOT therapy (22). A study by *Chang et al.* on patients who underwent repair of recurrent hypospadias found that the group treated with 2% nitroglycerin and HBOT had a higher success rate (88.8%) compared to the group only given 2% nitroglycerin (69.6%). Fewer complications were found in the HBOT group than in the control group (5).

Hypospadias reconstructive surgery aims to improve functional and cosmetic outcomes for patient satisfaction. The HOPE scoring system objectively evaluates hypospadias surgery outcomes, including complications, cosmetic appearance, and function (12). However, the system has limitations, such as the lack of perioperative assessment of hypospadias severity (23).

This study found that the HBOT group had a significantly better outcome in terms of penile torsion and total HOPE score compared to the control group.

The p-value for both of these findings was less than 0.05, indicating that the differences were statistically significant. This suggests that HBOT may have a positive effect on the clinical appearance of the wound after hypospadias reconstructive surgery. Patients who received HBOT had better cosmetic appearance for meatal torsion variable and the total HOPE score.

Complication rates are high for hypospadias reconstructive surgery, with nearly 40% of surgeries being repeat operations performed to improve cosmetic results. Risk factors include scar tissue, ischemic tissue, negligence in surgical technique, improper sutures, improper suture tension, hematoma, and infection (24). Wound healing has four phases, with chronic tissue hypoxia disrupting the balance of collagen secretion and causing hypertrophy of scar tissue, resulting in wound deformities (25).

Another study found that the neovascularization of tissue through the process of HBOT, characterized by an increase in VEGF, resulted in faster wound healing, avoiding the formation of scar tissue and keloids (26-29).

The study demonstrates that HBOT accelerated wound healing after urethroplasty by increasing serum VEGF levels. However, the study has some limitations, including the relatively high rate of loss to follow-up (50%) for the HOPE score evaluation (due to the COVID-19 pandemic situation).

The study also did not include measurement of the VEGF level before each HBOT session, so we do not know exactly how much the VEGF level increased after each HBOT session. Future work with larger studies is required to determine the exact mechanism of action, with a 2-month post-operation follow-up to measure the clinical and functional outcomes.

Conclusions

This study demonstrated that HBOT accelerated wound healing after urethroplasty by increasing the serum VEGF level. Three or more HBOT sessions are recommended after hypospadias repair.

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Declarations

Ethical approval: *This protocol was approved by the Institutional Review Board at our institution (no. 149/EC/KEPK-KANDOU/IX/2021). All procedures involving human participants were performed in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all child's parents or guardians participants included in the study.*

Availability of data and material: *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.*

Funding: *This research received no specific grant from any funding agency in the public, commercial, or not for- profit sectors.*

Authors' contributions: *All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.*

Acknowledgments: *We acknowledge Fred van der Toorn et al. for the development of the HOPE SCORE.*

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