Journal of Pediatric Urology (2020) **16**, 163.e1–163.e7

Hyperbaric oxygen therapy for pediatric "hypospadias cripple"—evaluating the advantages regarding graft take

Amos Neheman [a,d,1], Yishai H. Rappaport [a,d,*,1], Guy Verhovsky [a], Nicol Bush [b], Warren Snodgrass [b], Erez Lang [c,d], Amnon Zisman [a,d], Shai Efrati [c,d]

[a]Departments of Urology, Shamir (Assaf-Harofeh) Medical Center, Zerifin, Israel

[b]Parc Urology, Frisco, TX, USA

[c]Sagol Center for Hyperbaric Medicine and Research, Shamir (Assaf-Harofeh) Medical Center, Zerifin, Israel

[d]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

* Corresponding author. Department of Urology Shamir Medical Center (Assaf-Harofeh), Zeriffin, 7030000 Israel. Tel.: +972 8 9779409; fax: +972 8 9779402.
yhrapp@gmail.com (Y.H. Rappaport)

Keywords
Hypospadias; Hyperbaric oxygen

Received 8 June 2019
Accepted 7 January 2020
Available online 14 January 2020

Summary

Introduction
Hypospadias cripple patients pose a major surgical challenge with high complication rates attributed mainly to graft contraction. Hyperbaric oxygen therapy (HBOT) is an established treatment for compromised grafts and used extensively as a salvage therapy for compromised grafts and ischemic non-healing wounds.

Objective
We evaluated the graft-take rates in hypospadias cripple cases undergoing a staged tubularized autograft repair (STAG) and compared between patients treated with or without preemptive HBOT.

Materials and methods
All patients underwent a STAG. Patients receiving preemptive HBOT were compared with patients receiving the standard surgical procedure without HBOT. The HBOT protocol included a daily session, 5 days per week for four weeks before the surgery and 10 additional daily sessions immediately after first-stage surgery. Each HBOT session included 90 min exposure to 100% O_2 at 2 atmospheres absolute with 5 min air breaks every 20 min. The primary endpoint was graft take. Sequential tubularization without tension at second stage was defined as success.

Results
Seven boys received HBOT and 14 boys comprised the control group. All patients in the HBOT group had good graft take with no graft contraction. In the control group, 57% had good graft take and could proceed to the second-stage surgery and 43% had graft contraction (Table). Except for one patient who had claustrophobia while entering the chamber, no significant side-effects developed during the HBOT.

Discussion
The basic pathophysiology of compromised flaps includes both ischemia and reperfusion injury, which can be attenuated by HBOT. The beneficial effects of HBOT relates to several mechanisms, including hyperoxygenation, fibroblast proliferation, collagen deposition, angiogenesis, and vasculogenesis. Graft contraction is a well-known complication in hypospadias cripple population with reported failure rate of 39–63%. The HBOT procedure was found to be very effective and the entire HBOT group had a good graft take. Accordingly, all patients in the HBOT group proceeded to a successful second-stage tubularization. In addition, HBOT was found to be safe and generally well tolerated by this pediatric population. Study limitations were a relative small, non-homogenous sample size and lack of prospective randomization. Success was defined as sufficient graft elasticity sufficing for tubularization of the neourethra, and exact graft measurements are lacking in this study.

Conclusions
Preemptive HBOT can be used safely in the hypospadias cripple pediatric population and can potentially reduce the expected high surgical failure secondary to graft contraction.

Summary Table Surgical data and outcome.

Surgical parameters	Hyperbaric oxygen therapy (n = 7)	Control (n = 14)
Type of graft		
Prepuce (%)	–	5 (36)
Cheek (%)	3 (43)	4 (28)
Lower lip (%)	2 (28)	2 (14)
Groin skin flap (%)	2 (28)	3 (21)
Good graft take (%)	7 (100)	8 (57)
Corporoplasty		
Dorsal plication	2	2
Deep horizontal ventral corporal incisions	–	5

[1] The first and second authors have equal contribution.

https://doi.org/10.1016/j.jpurol.2020.01.002

Objective

"Hypospadias cripple" as defined by Horton in 1970, refers to multiple failed hypospadias repair attempts including an admixture of fistulae, strictures, and scarred tissue resulting in debilitating penile deformities with limited options for reconstruction.

Prior failed surgeries result in tissue ischemia because of hypovascularization, reduced perfusion pressure, and a scarred penile tissue at previous suture line. This injury results in inadequate local tissue for performing urethroplasty, needed for correcting residual chordee and performing penile skin coverage. Additional surgical correction attempts are challenging with high failure rates of 14–56% [27].

A modification of the two-stage repair with oral mucosa first described by Bracka in 1995 [4,29] has high reported success rates for redo cases ranging from 40 to 82% [2,30]. Accordingly, such an approach is often recommended as the first-line treatment for hypospadias cripples [7,13,23]. However, others demonstrated that in 39% of the cases, there is a need for additional surgery when a two-stage repair is performed. In most cases, the failure is due to complications in the first grafting stage (failure of graft take) [2]. Therefore, a significant reduction in failure rates or in the possible need for additional surgery might be achieved with improved first-stage graft/flap take.

An established treatment approach for compromised grafts and ischemic nonhealing wounds includes the use of hyperbaric oxygen therapy (HBOT) [1,3,14].

Hyperbaric oxygen therapy is also used as a preemptive treatment for postradiation tissues where tissue ischemia is considered a limiting factor [9]. However, the use of HBOT as a preemptive/adjuvant treatment for hypospadias cripple children who are candidates for a redo-surgery until recently has not been thoroughly investigated [31].

This study focuses on the graft-take rate, a crucial stage in the success of hypospadias cripple repair. The graft take and the postsurgical complication rates after the first stage of hypospadias repair were compared between patients who received preemptive HBOT and those who underwent the first-stage graft hypospadias surgery without HBOT. In a study published recently, using a HBOT protocol similar to ours protocol, graft take and measurements were improved after HBOT treatment when compared with a non-HBOT control group [5].

We hypothesized that treatment with HBOT will improve graft take; therefore, we compared between hypospadias cripple patients with and without HBOT.

Materials and methods

This is a prospective study of prepubertal, Tanner stage 1 hypospadias cripple patients treated at the Urology Department of the Shamir Medical Center between the years 2015 and 2017. The study was approved by the center's institutional review board.

Patients who remained with debilitating penile malformations and insufficient local tissue for performing urethroplasty after prior hypospadias repair were scheduled for a two-stage graft repair. All patients were offered adjuvant HBOT in addition to the surgical intervention. The study compared the surgical outcome of the HBOT-treated group with the group that only had the surgical intervention. This group comprised patients who either refused HBOT or for various reasons were not able to complete HBOT protocol (Fig. 1). The children's guardians signed informed consent to both the surgical procedure and HBOT when indicated.

Surgical procedure

A two-stage tubularized autograft surgical approach was planned for all patients [19,29]. In the first stage, fibrosis and scar tissue were discarded, a penile straightening procedure was performed, and a neourethral plate was formed by grafting the ventral part of the penis with surgeon preference, in the following order, prepuce (when available), lower lip, cheek or skin graft from the groin region. A second stage was carried out six months later and included closure of the urethra.

Hyperbaric oxygen therapy

All patients were evaluated by hyperbaric medicine specialists and by an ENT before HBOT. Exclusion criteria for HBOT include claustrophobia, uncontrolled asthma, pneumothorax, convulsion, or epilepsy not controlled by appropriate medication. None of the patients in the study group was excluded for such reasons. Hyperbaric oxygen therapy was carried out in a multiplace chamber at Shamir's Sagol Center for Hyperbaric Oxygen Medicine and Research. All patients were evaluated before treatment by a hyperbaric medicine specialist. The HBOT protocol included a daily session, 5 days per week for four weeks (20 sessions) before the surgery and 10 additional daily sessions immediately after first-stage surgery (Fig. 2). Each HBOT session included 90 min exposure to 100% O_2 at 2 atmospheres absolute (ATA) with 5 min air breaks every 20 min. If graft take was successful and the second surgical intervention was preformed, 10 additional HBOT sessions were administered after the operation. Ear tube insertion is performed under short general anesthesia. Patients younger than 6 years are usually unable to perform self-equilibration and require ear tube insertion. All patients treated by HBOT underwent insertion of pressure-equalizing (PE) ear tubes before the treatment.

Study endpoints

The primary endpoint was graft take, evaluated under general anesthesia at the beginning of the second-stage surgical procedure. Sufficient elasticity was defined if the neourethra could be tubularized on a 6F stent [29]. Sequential tubularization without tension to the graft was defined as a success. The need for an additional graft due to graft shrinkage, severe scarring, or fibrosis that compromises tubularization and required additional grafting was considered a failure.

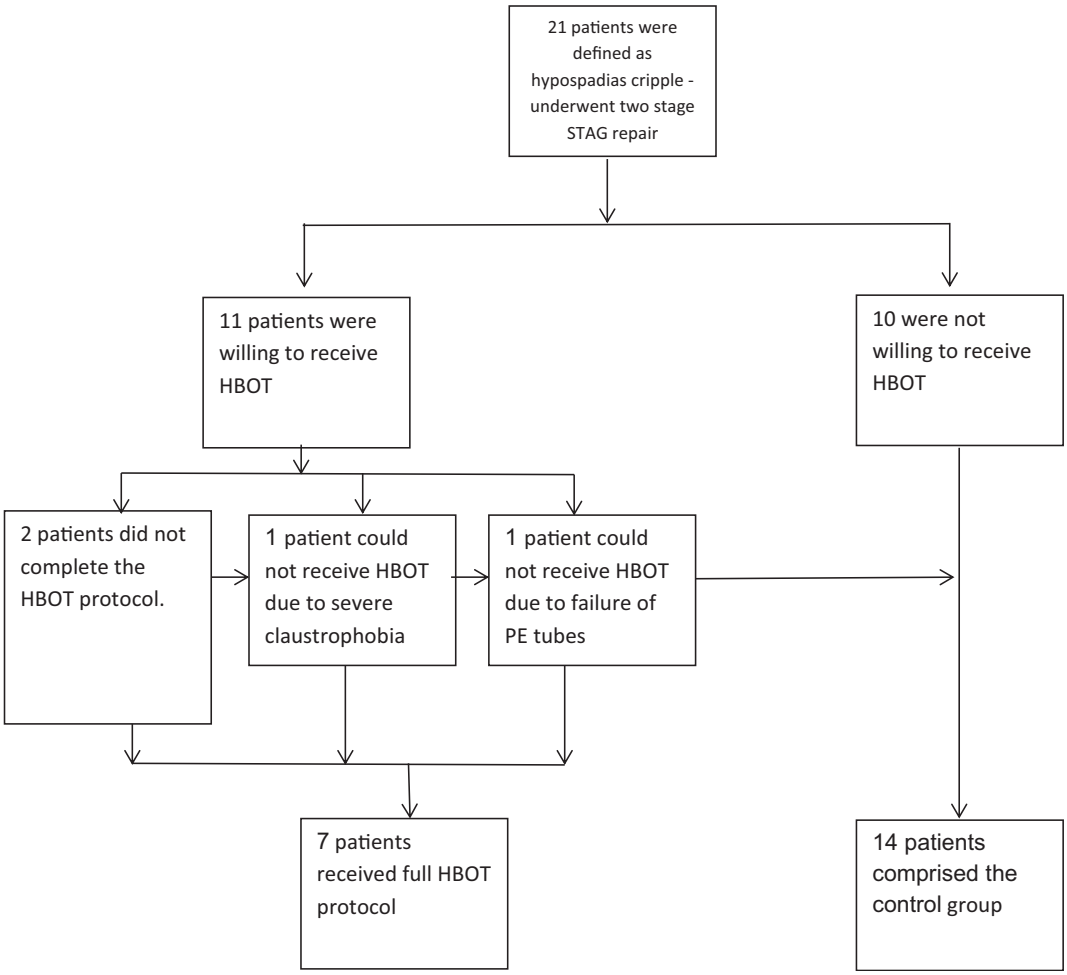

Fig. 1 Consortium diagram. PE, pressure equalization; STAG, staged tubularized graft; HBOT, hyperbaric oxygen therapy.

Statistical analysis

Data are presented as mean ± standard deviations. Continuous variables were compared using the Wilcoxon (Mann–Whitney) test, and dichotomous variables were compared using Fisher's exact test. Data were analyzed using SPSS software (statistical package for the social sciences, version 25, Chicago, IL, USA). A p-value of <0.05 was considered significant.

Results

The study included 21 hypospadias cripple boys who underwent staged tubularized autograft (STAG) two-stage surgical repair intervention. All patients were offered to undergo HBOT. Eleven agreed and signed informed consent. Two patients did not complete the HBOT protocol because of parental concerns, one patient suffered from severe claustrophobia, and one could not perform HBOT because of failure of PE tubes. Eventually, seven boys were allocated to the HBOT group and 14 boys comprised the control group (Fig. 1).

As detailed in Table 1, there were no statistically significant differences between the groups with respect to age (2.7 ± 1.4 years vs. 4 ± 2.2 years), weight (14.3 ± 2.8 Kg vs. 13.7 ± 3.2 kg), original location of the meatus, number of prior procedures for correction of chordee (5/7 (72%) and 9/14 (64%)), or type of graft harvested.

However, patients in the HBOT group were at higher surgical risk because they had a more complex surgical history than the control. The HBOT group had 4.2 prior operations per patient (range 3–5) vs. 3.1 (range 2–5) for the control group. Furthermore, the HBOT group was characterized by overall more complications per case, and in most cases, the indication for revision was multiple complications (5.3 ± 2.1 in the HBOT group vs. 1.7 ± 0.9 in the control group, $p < 0.0001$). For example, patients had both residual chordee and dehiscence in the same case. The HBOT group had overall 37 complications (8 graft contractions, 5 residual chordee, 6 urethral fistula, 9 meatal stenosis, and 9 dehiscence). In comparison, the non-HBOT group had 24 complications (4 graft contraction, 2 residual chordee, 6 urethral fistula, 6 meatal stenosis, and 6 dehiscence).

In the HBOT group, in five of the procedures, the graft origin was oral mucosa (three from the cheek and two from the lower lip), and in two patients, the graft's origin was from the groin. In the non-HBOT group, the origins of the graft were as follows: six oral mucosa (four from the cheek and two from the lower lip), five from the inner prepuce, and three from the groin (Table 2).

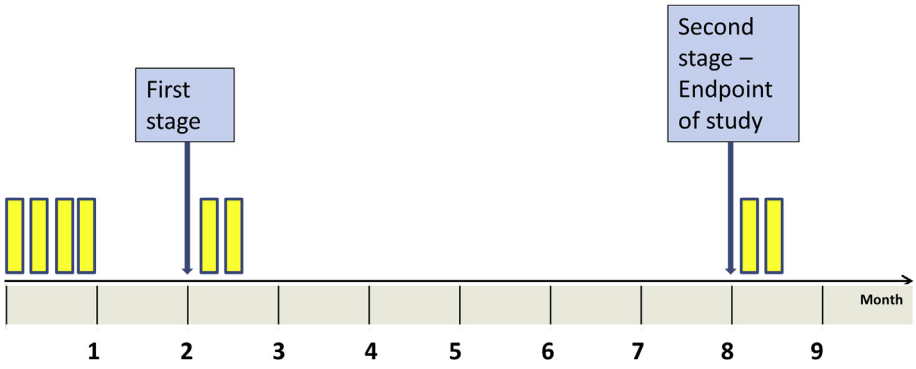

Fig. 2 Study protocol. Each yellow bar represents a weekly session of five HBOT. The interval between the preemptive 20 HBOT treatments and the first stage is one month. Each HBOT session included 90 min exposure to 100% O_2 at 2 ATA with 5 min air breaks every 20 min. Hyperbaric oxygen therapy was administered immediately after the first stage and after the second stage as well. The interval between the first and second stages is six months. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1 Baseline patient characteristics, previous surgical history, and complications.

Clinical parameters	Hyperbaric oxygen therapy (n = 7)	Control (n = 14)	*P* value
Age (years)	2.7 ± 1.4	4 ± 2.2	0.17
Weight (kg)	14.3 ± 2.8	3.2 ± 13.7	0.68
Overall number of previous operations	24	30	
Number of previous operations per patient (mean ± SD)	4.2 ± 2.5	3.1 ± 2.7	0.38
Original meatus location			
Midshaft	1	2	N.S
Penoscrotal	6	12	N.S
Number of corporoplasty (%)	5 (72)	9 (64)	N.S

SD, standard deviation; N.S, non-significant.

Success/failure rates

All patients in the HBOT group had good graft takes with no or minimal graft contraction, all having sufficient elasticity for undergoing the scheduled second-stage repair.

In the control group, only 57% of the patients could proceed to second-stage surgery because of graft failure defined as graft inelasticity and contraction. Accordingly, 43% of the patients in the control group needed a redo or additional surgical procedures for graft implantation.

Table 2 Surgical data and outcome.

Surgical parameters	Hyperbaric oxygen therapy (n = 7)	Control (n = 14)
Type of graft		
Prepuce (%)	–	5 (36)
Cheek (%)	3 (43)	4 (28)
Lower lip (%)	2 (28)	2 (14)
Groin skin flap (%)	2 (28)	3 (21)
Good graft take (%)	7 (100)	8 (57)
Corporoplasty		
Dorsal plication	2	2
Deep horizontal ventral corporal incisions	–	5

Safety of HBOT

Except for the one patient who had claustrophobia while entering the chamber, no significant side effect developed during the HBOT.

One failed ear tube insertion and was excluded from the HBOT protocol, and two patients after signing the informed consent eventually did not proceed with the prescribed HBOT protocol because of familial issues. These cases were allocated to the control group (Fig. 1).

Discussion

The present study demonstrates that adjuvant HBOT in a pediatric population can improve the surgical repair results of hypospadias cripple patients. The primary endpoint of the study was graft take after the first stage for a staged tubularized autograft staged tubularized autograft (STAG)

repair. Hyperbaric oxygen therapy was used as a preemptive measure, before and after the graft implantation.

Graft contraction is a well-known complication in hypospadias cripple population with reported failure rate of 39–63% [10,20,21]. In the present study, as expected in such a high-risk population, 43% of the control group (standard STAG without HBOT) had graft failure. The HBOT procedure was found to be very effective and the entire HBOT group had a good graft take. Accordingly, all patients in the HBOT group proceeded to a successful second-stage tubularization.

Graft contraction can be potentially more prevalent in cases that grafts are applied over corporotomies, although, to our knowledge, such data are lacking. In the control group, ventral corporotomies were performed in five patients, opposed to none in the HBOT group. This was not statistically significant ($p = 0.12$).

Hyperbaric oxygen therapy is currently used as a salvage therapy for compromised grafts and ischemic non-healing wounds [3,14,17]. The basic pathophysiology of compromised flaps includes both ischemia and reperfusion injury, which can be attenuated by HBOT [14]. The beneficial effects of HBOT relates to several mechanisms, including hyperoxygenation, fibroblast proliferation, collagen deposition, angiogenesis, and vasculogenesis [14]. Most of the benefits of HBOT are explained by the simple physical relationships determining gas concentration, volume, and pressure, hence improving tissue oxygenation by increasing the dissolved oxygen in the plasma [6]. By altering conditions of local ischemia, HBOT facilitates most wound healing processes [6]. In addition, hyperoxia induced by HBOT effectively improves endothelial progenitor cell mobilization and stimulates hypoxia-inducible factor. By repeated daily HBOT sessions, new blood vessels are generated (angiogenesis), and the basic pathophysiology responsible for graft failure (tissue ischemia) can be reversed.

In this study, HBOT was used before graft implantation as a preemptive treatment. The rationale is that in hypospadias cripple patients who had multiple failures of previous surgical procedures, the tissue is already impaired and needs to be repaired before the implantation. By administrating 20 hyperbaric sessions, as was performed in the present study protocol before the surgery, HBOT can induce endothelial progenitor cell mobilization and angiogenesis [14]. The administration of additional hyperbaric sessions after grafting further improves tissue oxygenation, facilitating a healthier environment for graft take. An exact protocol for HBOT treatment of complicated hypospadias cases has not been established. We used an established protocol for the treatment of non-healing ischemic wounds based on our experience treating those wounds: 20 sessions are the sum that is usually needed to induce angiogenesis and granulation tissue. Moreover, the 2 ATA protocols using air breaks of 5 min every 20 min reduce the risk from oxygen toxicity to an actual neglectable percentages. The 10 daily sessions used after the surgery is based on our current use of HBOT for ischemic flaps [15,16].

The use of HBOT in children was investigated thoroughly in the past two decades. Hyperbaric oxygen therapy was assessed in randomized controlled trials in 158 children with autism disorder [24–26] and in 190 children with cerebral palsy [8,18,22]. Hyperbaric oxygen therapy was found to be safe and well tolerated with mild middle ear barotrauma as the only significant side-effect. Asthma can rarely be exacerbated under treatment, and thus, patients with asthma should be excluded. In large retrospective studies of over 400 children, the side-effects rate is 5–6%, which is mostly middle ear barotrauma [11,12]. In our practice, children are evaluated and briefed by a qualified hyperbaric physician. In cases of incompetence to equalize pressure, insertion of tympanic tubes can be considered. Ear tube insertion was performed under general anesthesia. Exclusion criteria for tube insertion include ear canal malformations, infection, and fluid discharge. Before tube insertion, a hearing examination is performed to exclude hearing disabilities. None of the patients in both study and control groups were excluded for such reasons.

Seizures secondary to HBOT is considered rare (0.03%) and occurs only in pressures higher than 2.4 ATA and was never reported in sessions of 2 ATA. Thus, our HBOT protocol was based on 2 ATA of 100% oxygen with 5 min air breaks every 20 min. No significant side-effect developed during the current HBOT protocol except for one patient who had claustrophobia.

In this study, all patients underwent multiple surgeries before receiving HBOT. Taking into consideration the good outcome results and the good safety profile of HBOT, it should be used earlier for hypospadias patients, even after the first surgical failure. Although we are advocators of the staged repair, some centers prefer the use of a 1-stage repair. Hyperbaric oxygen therapy can potentially present similar benefits for that procedure as well. However, further studies are needed. Hyperbaric oxygen therapy should also be considered as salvage therapy after surgery, if the surgeon speculates that the surgical technique was suboptimal, for example, when there is an inability to provide sufficient tissue for second layer urethroplasty coverage and in cases where the skin appears dusky/ischemic at end of the procedure.

The present study has several limitations. The first and most important relates to the relative small sample size. However, even with this small sample size, because the control's failure rate was very high (43%), and because none of the HBOT group had graft failure, the results are significant. Reducing the number of surgeries is desirable. As previously reported, each surgical failure increases the odds for oncoming surgery complications by 1.5 fold [28]. This benefit is even further emphasized because of the fact that the HBOT group had in average more previous procedures, increasing risk for additional complication.

Another limitation relates to the fact that the parents were offered to have their child receive HBOT, after a thorough explanation of protocol limitations including lack of vast previous experience and need for PE treatment thus requiring additional anesthesia. This creates a selection bias derived from parent's selection of treatment. Therefore, the study is not prospectively randomized in nature. High treatment cost of HBOT is a potential deterrent for such therapy; however, in our study, the treatment was through a clinical study, eliminating bias due to financial concerns. Presumably, parents of more challenging patients agreed to HBOT treatment. Owing to that selection bias, the HBOT group was at higher surgical risk with higher

prevalence of previous surgical failures. Nevertheless, the higher risk group had better surgical results, which strengthens the benefits of HBOT. Another limitation is the lack of exact graft measurements before and after HBOT treatment. We thus performed a clinical evaluation of success where sufficient elasticity was defined if the neourethra could be tubularized on a 6F stent.

Another limitation is the lack of homogeneity between groups. This is characteristic of tertiary centers, such as ours, where patients underwent previous procedures by different surgeons in various techniques in multiple centers.

Conclusion

Preemptive HBOT can be used safely in the hypospadias cripple pediatric population and reduce the expected high surgical failure risk. Hyperbaric oxygen therapy can improve the success rate of graft take and reduce the need for regrafting before tubularization. Further studies in larger study populations are needed to define the optimal candidate for HBOT in hypospadias cripple patients.

Author statements

Ethical approval

The study was approved by medical centers' institiutional review board (ethical review board for experiments with humans).

Funding

The study was not sponsored or funded by any outside source.

Competing interests

There are no conflicts of interest to disclose by all authors.

References

[1] Ateş F, Malkoc E, Aktas Z, Okcelik S, Dursun F, Memis A, et al. S312: the role of hyperbaric oxygen therapy in adult hypospadias surgery with buccal mucosal tube urethroplasty. Eur Urol Suppl 2014;13(7):e1617.
[2] Guido Barbagli, Michele De Angelis, Enzo Palminteri, Massimo Lazzeri. Failed hypospadias repair presenting in adults. Eur Urol 2006;49(5):887—95.
[3] Baynosa RC, Zamboni WA. The effect of hyperbaric oxygen on compromised grafts and flaps. Undersea Hyper Med: j Undersea Hyper Med Society, Inc. 2012;39(4):857—65.
[4] Bracka A. A versatile two-stage hypospadias repair. Br J Plast Surg 1995;48(6):345—52.
[5] Nicol Bush, Warren Snodgrass. Hyperbaric oxygen therapy improves oral graft take in hypospadias staged tubularized autograft reoperations. J Urol 2019. https://doi.org/10.1097/JU.0000000000000145.
[6] Camporesi EM, Bosco G. Mechanisms of action of hyperbaric oxygen therapy. Undersea Hyperb Med 2014;41(3):247—52.
[7] Castagnetti M, El-Ghoneimi A. Surgical management of primary severe hypospadias in children: systematic 20-year review. J Urol 2010;184(4):1469—74.
[8] Collet JP, Vanasse M, Marois P, Amar M, Goldberg J, Lambert J, et al. Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. HBO-CP Research Group. Lancet 2001;357(9256):582—6.
[9] Feldmeier JJ. Hyperbaric oxygen therapy and delayed radiation injuries (soft tissue and bony necrosis): 2012 update. Undersea Hyperb Med 2012;39(6):1121—39.
[10] Fichtner J, Filipas D, Fisch M, Hohenfellner R, Thuroff JW. Long-term followup of buccal mucosa onlay graft for hypospadias repair: analysis of complications. J Urol 2004;172(5 Pt 1):1970—2. discussion 2.
[11] Frawley G, Bennett M, Thistlethwaite K, Banham N. Australian paediatric hyperbaric oxygen therapy 1998-2011. Anaesth Intensive Care 2013;41(1):74—81.
[12] Frawley GP, Fock A. Pediatric hyperbaric oxygen therapy in victoria, 1998-2010. Pediatr Crit Care Med : a J Society Crit Care Med world Fed Pediatr Intensive Crit Care Societies 2012;13(4):e240—4.
[13] Gill NA, Hameed A. Management of hypospadias cripples with two-staged Bracka's technique. J Plast Reconstr Aesthet Surg : JPRAS 2011;64(1):91—6.
[14] Gould LJ, May T. The science of hyperbaric oxygen for flaps and grafts. Surg Technol Int 2016;28:65—72.
[15] Hadanny A, Meir O, Bechor Y, Fishlev G, Bergan J, Efrati S. The safety of hyperbaric oxygen treatment—retrospective analysis in 2,334 patients. Undersea Hyperb Med 2016;43(2):113—22.
[16] Hadanny A, Meir O, Bechor Y, Fishlev G, Bergan J, Efrati S. Seizures during hyperbaric oxygen therapy: retrospective analysis of 62,614 treatment sessions. Undersea Hyperb Med 2016;43(1):21—8.
[17] Kang N, Hai Y, Liang F, Gao CJ, Liu XH. Preconditioned hyperbaric oxygenation protects skin flap grafts in rats against ischemia/reperfusion injury. Mol Med Rep 2014;9(6):2124—30.
[18] Lacey DJ, Stolfi A, Pilati LE. Effects of hyperbaric oxygen on motor function in children with cerebral palsy. Ann Neurol 2012;72(5):695—703.
[19] Lam PN, Greenfield SP, Williot P. 2-stage repair in infancy for severe hypospadias with chordee: long-term results after puberty. J Urol 2005;174(4 Pt 2):1567—72. discussion 72.
[20] Long CJ, Chu DI, Tenney RW, Morris AR, Weiss DA, Shukla AR, et al. Intermediate-Term followup of proximal hypospadias repair reveals high complication rate. J Urol 2017;197(3 Pt 2):852—8.
[21] Metro MJ, Wu HY, Snyder 3rd HM, Zderic SA, Canning DA. Buccal mucosal grafts: lessons learned from an 8-year experience. J Urol 2001;166(4):1459—61.
[22] Muller-Bolla M, Collet JP, Ducruet T, Robinson A. Side effects of hyperbaric oxygen therapy in children with cerebral palsy. Undersea Hyperb Med : j Undersea Hyperb Med Society, Inc. 2006;33(4):237—44.
[23] Pfistermuller KL, Manoharan S, Desai D, Cuckow PM. Two-stage hypospadias repair with a free graft for severe primary and revision hypospadias: a single surgeon's experience with long-term follow-up. J Pediatr Urol 2017;13(1). 35.e1-.e7.
[24] Rossignol DA, Rossignol LW, James SJ, Melnyk S, Mumper E. The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: an open-label pilot study. BMC Pediatr 2007;7:36.
[25] Rossignol DA, Rossignol LW, Smith S, Schneider C, Logerquist S, Usman A, et al. Hyperbaric treatment for children with autism: a multicenter, randomized, double-blind, controlled trial. BMC Pediatr 2009;9:21.
[26] Sampanthavivat M, Singkhwa W, Chaiyakul T, Karoonyawanich S, Ajpru H. Hyperbaric oxygen in the

treatment of childhood autism: a randomised controlled trial. Diving Hyperbar Med 2012;42(3):128—33.
[27] Shukla AK, Singh AP, Sharma P, Shukla J. Two stages repair of proximal hypospadias: review of 700 cases. J Indian Assoc Pediatr Surg 2017;22(3):158—62.
[28] Snodgrass W, Bush NC. Re-operative urethroplasty after failed hypospadias repair: how prior surgery impacts risk for additional complications. J Pediatr Urol 2017;13(3):289. e1-. e6.
[29] Warren Snodgrass, Nicol Bush. Staged tubularized autograft repair for primary proximal hypospadias with 30-degree or greater ventral curvature. J Urol 2017;198(3):680—6.
[30] van der Werff John FA, van der Meulen Jacques C. Treatment modalities for hypospadias cripples. Plast Reconstr Surg 2000; 105(2):600—8.
[31] White CM, Hanna MK. Salvaging the dehisced glans penis. J Pediatr Urol 2018;14(5):422—e1—422—e5. https: //doi.org/10.1016/j.jpurol.2018.04.028.