Hyperbaric Oxygen Therapy Improves Oral Graft Take in Hypospadias Staged Tubularized Autograft Reoperations

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Purpose: Increased complications following failed hypospadias repairs suggest that impaired wound healing is a contributing factor. We used perioperative hyperbaric oxygen therapy to promote wound healing determined by graft take in staged tubularized autograft reoperations using oral graft.

Materials and Methods: Hyperbaric oxygen therapy was recommended for patients with 3 or more failed hypospadias repairs, comprising 20 preoperative and 10 postoperative sessions. All patients underwent reoperative staged tubularized autograft repair using oral mucosa. Graft lengths and widths were measured at grafting and again at the second stage, from which graft area was calculated. The primary outcomes were percent graft contracture and graft failure, defined as contracture 50% or greater. Patients who received hyperbaric oxygen therapy were compared to other patients who underwent reoperative staged tubularized autograft who did not receive therapy.

Results: Among 57 patients 32 received hyperbaric oxygen therapy and 25 did not as they had fewer than 3 prior repairs, or were not able to receive treatment due to insurance issues or lack of local availability. Grafts were healthier in those receiving hyperbaric oxygen therapy, with significantly less percent area contracture (9% vs 26%, $p=0.04$) and graft failure (6% vs 28%, $p=0.03$) compared to those not receiving therapy, although treated patients had significantly more prior failed hypospadias repairs.

Conclusions: Hyperbaric oxygen therapy improved graft take in hypospadias reoperations. This observation also calls attention to wound healing as another variable to consider in hypospadias surgery.

Key Words: hypospadias, reoperation, postoperative complications, autografts, hyperbaric oxygenation

Abbreviations and Acronyms

HBOT = hyperbaric oxygen therapy

STAG = staged tubularized autograft

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The risk of additional complications increases with each reoperative hypospadias urethroplasty, reaching greater than 40% with 3 or more reoperations.[1] We speculated that this trend was related in part to reduced tissue vascularity and that additional therapies were needed to improve wound healing. The only currently available therapy proven to impact wound healing is hyperbaric oxygen, which is thought to decrease hypoxia and edema, release stem cells and stimulate angiogenesis.[2–4] Prior studies have shown efficacy in promoting split-thickness skin graft take.[5,6]

We previously reported that most patients undergoing hypospadias reoperation after 2 or more urethroplasties were treated with STAG repair using oral mucosa grafts to create a neourethral plate.[7] Beginning in December 2014 we incorporated HBOT into the care of these patients and now report

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graft healing in those who received treatment vs those who did not.

MATERIALS

Study inclusion criteria were 2 or more failed hypospadias repairs and STAG reoperation using oral graft, which was preferentially taken from the lower lip unless it had been previously harvested. Measurements to determine graft area were done at initial grafting and again at the beginning of the second stage operation 6 or more months later, before skin incisions (fig. 1). Graft length was the distance from the glans tip to the proximal urethrostomy. Graft width was measured at the corona, mid portion and just above the proximal urethrostomy. These measurements were made with traction on the glans stay stitch and with the graft stretched wide using forceps at each of these points. Graft area (mm^2) was calculated as length times average width. Percent graft contracture was calculated by 100-(area1/area2) $\times$ 100. Contracture 50% or greater was considered graft failure.

Among these patients HBOT was recommended for those with 3 or more failed hypospadias repairs. Our protocol called for 20 preoperative and 10 postoperative dives. These were done at 2 atmospheres pressure with 100% fraction of inspired oxygen and 2 to 3 "air breaks," when the oxygen concentration was temporarily reduced to room air (21%) for 5 minutes before returning to 100%. Each dive lasted 90 minutes.

The primary outcome in this descriptive study was percent graft contracture. Graft failure occurred in a subset of these patients with contracture 50% or greater. These results were compared between patients receiving HBOT vs those not receiving HBOT. Data were entered prospectively at time of service and reviewed with institutional review board approval (IRB No. PARC1003).

Patients undergoing reoperative STAG after fewer than 3 failed repairs, and those with 3 or more prior repairs who were unable to receive HBOT due to lack of local availability or refusal of insurance authorization, comprised the comparison group.

Postoperative care was otherwise the same for all patients, including application of Aquaphor® to the graft and adjacent skin with each diaper change or 4 times daily beginning when the tie-over bandage was removed at 1 week, and application of 0.1% betamethasone ointment 2 times daily beginning 1 month postoperatively and continuing for 3 months.

Continuous variables were normally distributed and results were analyzed by t-test, while categorical variables were compared by chi-square and Fisher's exact test with $p < 0.05$ considered significant (www.graphpad.com).

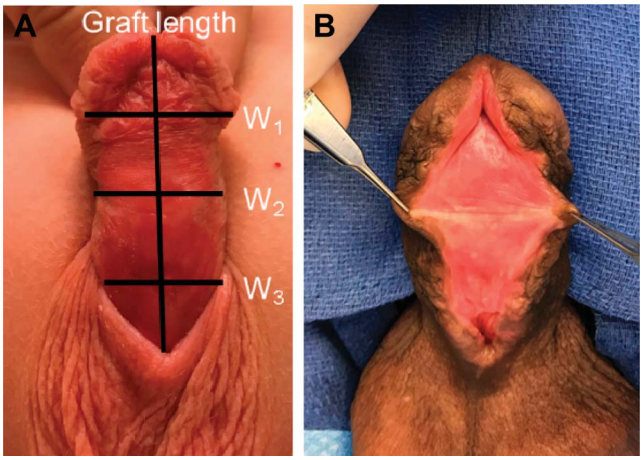

Figure 1. Graft measurements. *A*, graft width W_1 was measured at corona, W_2 at mid portion and W_3 at base just above proximal urethrostomy. Graft length was measured from proximal urethrostomy to distal end of graft. *B*, graft measurements were taken with graft stretched for W_2 measurement.

RESULTS

Of the 57 patients 32 were treated with HBOT and 25 without HBOT. Demographics are shown in the table. There were no differences in these 2 groups regarding age, meatal location or glans width. However, those receiving HBOT had significantly more prior failed repairs (mean 3.5 vs 2.5, respectively, $p=0.001$). In the nonHBOT group 17 (68%) had 2 prior failed surgeries, with failure of 3 to 5 surgeries in 8 patients. The number of failed prior surgeries ranged from 3 to 7 in the HBOT group.

Total graft area was similar in the 2 groups at the first stage ($p=0.59$; HBOT mean 1,107 mm^2 [SD 709], median 952 [IQR 678] vs nonHBOT mean 1,221 mm^2 [SD 882], median 851 [IQR 740]). However, there was significantly less percent graft contracture noted at the second stage in those treated with HBOT, at 9% vs 26% ($p=0.04$; HBOT mean 972 mm^2 [SD 625], median 692 [IQR 879] vs nonHBOT mean 869 mm^2 [SD 717], median 640 [IQR 1,191]). Similarly, there was less graft failure in the HBOT group vs those not treated, at 6% vs 28% ($p=0.03$). In the untreated group graft failure occurred in 6 patients, including 4 after 2 failed prior repairs, 1 after 3 failed operations and 1 after 5 failed repairs. Among those treated with HBOT graft failure occurred in 2 patients, in 1 after 3 prior failed surgeries (the graft contracted in an area noted to have extensive left corporal scarring from initial surgeries performed elsewhere) and in another patient who had 7 prior operations.

No adverse effects were reported from HBOT, except for ear pain during treatment that required myringotomy tube placement in a 7-year-old boy with

Patient characteristics and results of 57 reoperative STAG repairs using oral mucosa grafts

	Without HBOT	With HBOT	p Value
Mean pt age	11	12	0.71
No. postpubertal pts (%)	7 (28)	10 (31)	0.79
No. proximal hypospadias (%)	22 (88)	25 (78)	0.53
Av glans width (mm)	19.2	19.3	0.96
Av No. surgeries	2.5	3.5	0.001
% Overall graft contracture	25.7	8.8	0.044
No. graft failure (%)	7 (28)	2 (6)	0.034

an underlying medical history of extreme prematurity and multiple surgeries for craniosynostosis. Three (9%) patients were less than 3 years old, of whom 2 received myringotomy tubes for HBOT, while the third was treated before each dive with nasal decongestant and oral antihistamine and did not require tubes.

DISCUSSION

Despite having undergone more attempts at repair, patients with hypospadias receiving perioperative HBOT had significantly less graft contracture and graft failure than those who did not receive HBOT. Given the increased risk of complications with increasing numbers of operations, these observations suggest that HBOT improved wound healing and graft take.

There are few reports concerning HBOT and hypospadias repair[8–10] or graft healing. To our knowledge, ours is the first series showing its efficacy in promoting take of full-thickness grafts using objective measurements. Our results are similar to the beneficial effects reported in a study of split-thickness grafts that showed 29% improved graft area and better complete graft take (64% vs 17%) in patients receiving HBOT vs others not treated.[5]

We chose percentage of graft take as the primary outcome to best isolate the effect of HBOT. Surgeons would prefer there be no graft shrinkage and our findings indicate there was significantly less with HBOT than without. The need to patch a graft or to completely regraft was not used as an outcome because other factors besides the percentage of take influence those decisions. For example, some contractures can be compensated by incorporating adjacent shaft skin, when available, into the urethroplasty, or by incising the graft in the midline and inlaying additional graft at the second stage. Likewise, we did not use urethroplasty complications as an end point since they can occur despite 100% graft take, or not occur despite varying extents of graft contracture.

Typically, HBOT has been initiated when grafts appear compromised postoperatively. However, in a study of 105 patients 9 considered to have an unfavorable recipient bed due to diabetes mellitus or peripheral vascular disease were treated preoperatively to stimulate angiogenesis before grafting.[6] We similarly used preoperative treatment with the goal of improving the vascularity of the recipient site.

Our experience began with an adult who presented after 10 failed hypospadias repairs and underwent dorsal inlay graft repair using upper lip. The repair healed with a distal shaft fistula and at surgery to close it the tissues were visibly ischemic. When the fistula recurred early postoperatively we recommended HBOT as the only currently available and approved therapy to improve tissue vascularity. At the next fistula closure the tissues appeared healthier and this repair was successful. The patient remains without fistula or other complications 3.5 years later. We subjectively noted similar visually improved vascularity in the patients included in this study who received HBOT.

Because prior operations decrease wound vascularity, especially toward the distal extent of the penis furthest from the blood supply, we began a protocol to improve vascularity and promote better graft healing in patients anticipated to undergo reoperative STAG repair for unsuccessful hypospadias surgery. We chose 3 or more prior operations as the indication for treatment based on our observation that complications develop in more than 40% following reoperations in these patients.[1] All patients with 3 or more prior repairs were recommended to receive HBOT. Those who did not receive HBOT because of social issues or no insurance coverage comprised a control group. The control group also included those undergoing reoperative STAG with fewer than 3 prior repairs, who were not recommended for treatment because their complication risk was considered lower and because HBOT is a time-consuming inconvenience for families. We could not compare treated patients to our previous patients undergoing STAG repair since we did not routinely measure graft dimensions in them.

Available data suggest that approximately 20 dives are needed to stimulate angiogenesis, which improves the recipient bed, while postoperative dives initiated as soon after surgery as possible increase available tissue oxygen.[11] These treatments were initiated based on chronic nonhealing and the presumed risk to grafts since the tie-over compression bandage used for urethroplasty grafts conceals them. Because of this bandage, visible ischemic changes that have prompted HBOT for partial-thickness grafts in other circumstances cannot be seen.

Recommended HBOT parameters for compromised flaps or grafts include treatment at 2 to 2.5 atmospheres absolute for 90 to 120 minutes.[3] Our protocol was 2 atmospheres absolute for 90 minutes. We cannot determine if treatment at higher pressure and/or longer duration would have resulted in additional benefit for our patients.

The improved graft healing we documented from HBOT in patients with an average of 3.5 prior operations compared to others not treated with an average of 2.5 operations suggests that it may be advantageous to use therapy sooner, especially when STAG with oral grafting is likely, such as in patients with obvious ventral curvature. However, HBOT is not recommended for grafts in primary repairs, given their successful take in more than 90%[12–14] and the complexity of providing HBOT to infants and young children.

Figure 2. Boy in monochamber "spaceship" receiving therapy

The average age of patients receiving HBOT was 12 years, with the youngest being 2 years old. Boys less than 3 years old usually require myringotomy with tube placement before treatment since they are not able to equilibrate the increased pressure across their inner ear, although 1 avoided tube placement using decongestants and antihistamines. In our series a 7-year-old experienced pain during a dive and also required myringotomy tube placement. This was the only adverse event. No patients had the only absolute contraindication to HBOT, which is an untreated pneumothorax.

Most patients were treated in chambers designed for a single person, although some were accompanied by a caregiver in multiperson chambers. Younger boys were easily coaxed into monochamber "spaceships," as shown in figure 2, where they could watch videos through a plexiglass window. This idea was circulated by a mother who enhanced it with "astronaut" cotton pajamas, space themed movies and posttreatment freeze-dried "space" ice cream.

Although HBOT is widely available, therapy is time-consuming and challenging for families, especially for those who do not live near a facility. Treatment is typically done on weekdays, meaning a course of 20 dives lasts for 1 month. Each session lasts approximately 1.5 hours. Caregivers accepted these drawbacks in the hope that treatment would help achieve a successful repair. The fact that HBOT decreased overall graft contracture and graft contracture 50% or greater is important, since such patients may need to undergo partial or complete regrafting when this occurs. Even when urethroplasty can proceed, partial graft contracture increases the complexity of tubularizing the neourethra.

Our study was only designed to test the effect of HBOT on full-thickness oral graft take, and cannot determine the optimal regimen of perioperative treatment to promote wound healing in hypospadias reoperations. Generally 30 sessions comprise usual HBOT for a variety of indications, and we designed our protocol to provide preoperative neovascularity and postoperative increase in local tissue oxygen.

Limitations of our study include potential variability in treatments from the protocol we recommended. Families did not always recall exactly how many dives their child had, and some may have undergone fewer than the 20 preoperative and 10 postoperative dives. Patients were evaluated as treated even if they did not have all the prescribed dives since the minimum number of dives to reliably aid graft healing is not known.

In addition, as previously mentioned our study focused on graft healing and not urethroplasty complications. Therefore, the impact of HBOT, if any, on complications remains to be determined in a larger series with additional followup.

While our finding that grafts healed better with HBOT is important for management after failed surgeries, the cost and complexity of this treatment also emphasize the need for surgeons to get the first repair right. Nevertheless, there will always be a need for reoperations in reconstructive surgery. This experience suggests that consideration of impaired wound healing and therapies to address it should have a role in patient care.

CONCLUSION

Perioperative HBOT improves graft take in patients undergoing hypospadias reoperations.

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EDITORIAL COMMENTS

The authors propose hyperbaric oxygen therapy as a perioperative adjunct to improve oral graft take in reoperative hypospadias repairs, in theory improving the vascularity of the recipient penile tissue. Their assessment was limited to the percentage of graft contracture 6 months after placement, with failure defined as contracture50% or greater. They believed that hypospadias repair outcome and the need for graft augmentation/replacement proved too variable a measure. They found less graft contracture and graft failure for those patients who underwent HBOT.

The authors highlight challenges in the treatment of boys with a history of multiple prior hypospadias repairs. Although they are not the first to describe the use of HBOT in hypospadias repairs (references 8-10 in article), they should be congratulated for thinking "inside the dive box" to improve outcomes for these boys. HBOT is a potential tool to consider in the hypospadias armamentarium. However, one must use caution when interpreting these data. Discussion of graft replacement or augmentation rates as well as the presence of penile curvature or the use of corporotomies at the time of graft placement would have been valuable additions to the assessment of graft take to understand the clinical relevance and confounding factors for the contracture. Finally, since the financial and time commitment for the family, and the potential side effects for younger patients, may prove to be a hindrance to more widespread use, further study identifying specific surgical characteristics and optimized minimal exposure to HBOT could advance this work and make it more universally applicable.

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The authors should be commended for persisting in their quest for better outcomes and for prospectively collecting data. This study demonstrates improved graft take with HBOT after hypospadias cripple reoperations. Enhanced graft take might correlate with decreased urethroplasty complications, fewer reoperations, better flow rates and/or improved cosmesis. However, the study was not designed to measure these end points and, thus, one cannot conclude that HBOT is clinically beneficial. Median postoperative grafted area was 692 mm^2 in HBOT vs 640 mm^2 in the no treatment arm, which translates to a difference between a 40 $\times$ 17.3 mm graft and a 40 $\times$ 16 mm graft.

The more costly, burdensome or invasive the treatment, the stricter the evidence supporting its use should be. Urologists recommend parasacral transcutaneous nerve stimulation, despite suboptimal evidence of effectiveness, because it is inexpensive/harmless. This cannot be said about HBOT, therefore we should subject claims regarding its benefits to greater scrutiny.

Technical aspects may affect graft take. For example, Bush and Snodgrass spatulate the urethra ventrally, split the graft proximally and suture graft alongside the urethra. This method creates 2 graft strips with 2 suture lines on either side. Alternatively, spatulating the urethra dorsally (Bracka)[1] and maintaining an intact graft proximally with fewer suture lines may improve graft take. Regarding future research, one could compare HBOT with less cumbersome alternatives such as nitroglycerin paste or other local therapies to promote graft take.

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REPLY BY AUTHORS

Failed surgery on the penis harms the penis. Consequently, hypospadias reoperations have significantly more complications than primary repairs, and technical modifications that improve outcomes of primary operations have less impact on reoperations (reference 1 in article). Treatments such as testosterone and nitroglycerin ointment have not promoted healing in compromised tissues.[1]

However, HBOT has been shown to improve wound healing in compromised tissues (reference 3 in article). Although it is cumbersome and expensive, HBOT is also safe, painless and readily accepted even by young patients. Insurance typically covers HBOT for compromised skin flaps and grafts.

There are also costs when grafts fail. There is the expense of additional surgery and a further increase in risk for still more complications. In addition, there is the emotional toll of another failed operation on the patient and his family. These issues are not insignificant, and it is our experience that caregivers readily accept the bother of HBOT for the hope, and now the proof, that it helps achieve successful grafting.

This is only a first step toward perioperative therapies to promote wound healing after hypospadias surgery. Fortunately, HBOT works. That success should stimulate our field to support additional research into penile wound healing. As the best methods to surgically correct hypospadias become increasingly clear, means to support their success are the next frontier.

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