SKIN GRAFTS AND FLAPS (COMPROMISED)

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Rationale

Hyperbaric oxygen (HBO2) therapy is neither necessary nor recommended for the support of normal, uncompromised skin grafts or flaps. However, in tissue compromised by irradiation or in other cases where there is decreased perfusion or hypoxia, HBO2 has been shown to be extremely useful in flap salvage. Hyperbaric oxygen can help maximize the viability of the compromised tissue thereby reducing the need for regrafting or repeat flap procedures. A number of studies have shown the efficacy of HBO2 on enhancement of flap and graft survival in a variety of experimental and clinical situations.

Animal Studies

Champion and colleagues (1), using a pedicle flap model in rabbits, were able to obtain 100% survival of HBO2 treated flaps (2 atm abs for 2 hours twice a day for 5 days) whereas all control flaps had significant areas of necrosis to greater than 40%. Similarly, work by McFarlane and Wermuth (2) concluded that HBO2 was of definite value in preventing necrosis in a pedicle flap in the rat and also has limited the extent of necrosis in a free composite graft. The authors noted that their particular experimental design was a severe test of treatment and attests to the value of HBO2 in preventing necrosis (2).

Shulman and Krohn (3), in a study of healing tissues of full thickness and partial thickness wounds in rats, found that HBO2 shortened the healing time significantly. Further, the combination of repeated skin grafting and HBO2 reduced the healing time of partial thickness wounds to one-half of that of non-treated controls. No attempt at wound sterilization was made in performing these surgeries. Superficial contamination did occur in all animals, but infection was entirely absent in the groups treated with HBO2.

Niinikoski (4) found a 51% improvement in the length of the viable portion of tubed random skin flaps in rats treated with HBO2 (2.5 atm abs for 2 hours twice daily for 2 days) compared to air-breathing controls (PO.001). The author suggested that enhanced diffusion of oxygen into the area of disturbed circulation was the mechanism for improvement of tissue viability. Gruber et al. (5) showed that in skin flaps in rats, HBO2 at 3 atm abs raised mean tissue oxygen tensions to 600 mmHg, whereas 100% oxygen at sea level did not raise mean flap oxygen tension.

Arturson and Khanna (6), in an experimental study on standard dorsal random skin flaps in rats designed to give a predictable and a constant degree of necrosis, revealed that HBO2 therapy had a significant improvement in flap survival over untreated controls ($P<0.05$). Other flap-enhancing agents were studied, and in some cases enhanced flap survival. However, the best results were found in rats treated with HBO2.

Jurell and Kaijser (7), using a cranially based pedicle flap in a rat, showed that rats treated with HBO2 had significantly greater flap survival compared with controls (P<O.OOl). The surviving area of the HBO2 group was approximately twice that of the control group. Even when the start of HBO2 treatment was delayed for 24 hours after surgery, there was still a significantly greater survival area of HBO2 treated flaps when compared with controls ($P<0.01$). However, the increase in surviving area was greater if the HBO2 therapy was begun immediately after surgery. This emphasizes the importance of initiating HBO2 therapy as soon as a flap problem is suspected.

Greenwood and Gilchrist (8) demonstrated the effectiveness of HBO_2 in reducing the extent of ischemic necrosis of skin flaps created in previously irradiated rats. Mean flap necrosis was significantly greater (P<O.05) in the control (air) group vs. the HBO2 group.

Kivisaari and Niinikoski (9) in a study on rats showed that HBO2 at 2 arm abs had no effect on the healing rate of non-compromised open wounds in which the circulation was left intact.

However, when the wound edges were devascularized, HBO_2 significantly enhanced wound closure rates over control groups.

Tan et al. (10) studied the effect of HBO_2 and air under pressure on skin survival in acute neurovascular island flaps in rats. Skin flaps treated with hyperbaric 8% oxygen (equivalent to room ah- at standard HBO_2 treatment pressure) exhibited no improvement in skin survival. Skin flaps treated with hyperbaric 100% oxygen exhibited significant increases in survival.

A controlled, randomized study on the effects of HBO_2 and irradiation on experimental random skin flaps has been performed by Nemiroff et al. (11,12). One hundred eighty-five rats were randomly assigned to one of 15 conditions, including all possible sequencing effects of HBO_2, irradiation, and flap creation, as well as controls which included flap creation only, irradiation only, and HBO_2 groups. Results showed that all groups receiving HBO_2 therapy within 4 h after flap elevation had significantly greater flap survival time (P<O.05), with as much as a 22% increase in surviving flap.

Further work by Nemiroff and Lungu (13) elucidated some of the mechanisms whereby HBO_2 enhanced random flap survival. Skin flaps from animals treated with HBO_2 vs. controls were analyzed in a controlled standardized method. The number and size of blood vessels in the microvasculature was documented. The absolute number of blood vessels in the microvasculature was significantly greater for all of the HBO_2 groups when compared with that in controls (P<0.01). The mean surface area of vessels of the flap- HBO_2 groups was also significantly greater than in controls in all but one group (P<O.01). The authors concluded that HBO_2 significantly enhanced flap survival by increasing and/or maintaining the number and possibly the size of vessels within the microvasculature. To be most efficacious, the authors stated that HBO_2 therapy must be administered as soon after surgery as possible. Other investigators have shown that HBO_2 can enhance healing and flap survival by promoting angiogenesis (14-17).

Manson and associates (14), in studies using histochemical staining with ATPase to visualize small blood vessels, demonstrated that capillaries grew distally almost 3 times further in pedicle flaps of pigs that were treated with HBO_2, compared with age-matched controls.

Rubin et al. (18) studied the hyperoxic effects of composite skin grafts in rabbit ears. Experimental animals received 100% oxygen at 2 atm abs twice daily for 21 treatments. Grafts hi HBO2-treated animals demonstrated significantly greater survival than grafts in control animals.

Nemiroff and colleagues in controlled animal studies using random and axial flap models have clearly shown that HBO_2 therapy can significantly enhance flap survival (11-13,19). NemirofFs (19) study investigated the effects of pentoxifylline and HBO_2 on skin flaps in rats under four conditions. Pentoxifylline is a rheologic agent, which enhances capillary circulation by increasing the flexibility of red blood cells. Sixty animals were randomly divided into one of four groups; 1) a control group, 2) pentoxifylline, 3) HBO_2-treated group, and 4) a pentoxifylline plus HBO2-treated group. Rats that were treated with HBO_2 received a total of 14, 2-hour treatments at 2.5 atm abs in divided doses. Results indicated that the surviving length of flaps in the pentoxifylline or HBO2 treated groups were significantly greater than those in the control group. However, animals treated with both pentoxifylline and HBO_2 therapy had significantly greater flap survival than animals in any of the other three groups (P<0.001). This reflected a 30-39% improvement over pentoxifylline alone or HBO_2 alone treated animals, and an 86% improvement over control animals.

Zamboni et al. (20) examined the effect of HBO_2 administered during and immediately following prolonged total ischemia in axial pattern skin flaps in rats. The animals were divided into a control and three experimental groups: control group, 8 hr flap ischemia, no HBO_2; group 1, HBO_2 therapy during the ischemia; group 2, HBO_2 therapy following the ischemia; group 3 HBO_2 therapy during ischemia but with the flap contained in a metal-coated Mylar bag to prevent oxygen diffusion. Mean flap necrosis for controls was 28% while HBO_2 therapy during ischemia or during reperfusion significantly reduced this necrosis to 9 and 12%, respectively (P<0.01). The percentage of necrosis for group 3, with any local effect of HBO_2 on the flap being blocked by the diffusion barrier was 5%. This was also significantly better than the controls (P<0.0005) but no different from the other two HBO_2 groups. Thus, HBO_2 treatment significantly increased the percentage of axial pattern skin flap survival when administered

during or immediately after total flap ischemia. This beneficial effect was opposite to the author's original hypothesis that HBO_2 would exacerbate reperfusion injury. In a follow-up study, the same skin flap model was used to show that HBO_2 therapy increased microvascular blood flow during reperfusion compared to untreated ischemic controls (21). Kaelin et al. (22) have shown that HBO_2 treatment during reperfusion significantly improved the survival of free skin flaps following microvascular reattachment and ischemia tunes of up to 24 h. The skin flap studies have been corroborated by skeletal muscle experiments which are more important from a clinical point since muscle is more sensitive to ischemia and reperfusion injury. An observation of a skeletal muscle microcirculatory flap model of ischemia-reperfusion injury has given some insight into potential mechanisms for this beneficial response (23). HBO_2 administered during and up to 1 hr following 4 hr global ischemia significantly reduced neutrophil endothelial adherence in venules and also blocked the progressive arteriolar vasoconstriction associated with reperfusion injury. The fact that neutrophil endothelial adherence is dependent on GDI 8 function in this model provides indirect evidence that HBO_2 is affecting the neutrophil CD 18 adhesion molecule.

A beneficial effect of HBO_2 in situations of secondary flap ischemia has been demonstrated in experimental studies. Stevens, et al, using a rat axial skin flap model, induced a primary ischemia of 6 hours followed by 2 hours of reperfusion and then a secondary ischemia tune of 6, 10, and 14 hours (24). The secondary ischemic time at which 50% of the flaps survived (D50) in both, air and 100% oxygen groups, was 6 hours. The secondary ischemic time to D50 in the HBO_2 treated group was significantly increased to 10 hours. In a separate experiment, Wong, et al., used an axial skeletal muscle flap model in rats. Percent necrosis following 2 hour primary ischemia was significantly reduced from 40% to 24% by HBO_2 treatment (25). Adding a secondary 2 hour ischemia time significantly increased necrosis in controls to 85% which was significantly reduced in the HBO_2 treated group to 58%. These studies have important implications in free tissue transfer complicated by postoperative thrombosis.

Erdmann, et al. (26,27), has also evaluated the effect of HBO_2 as treatment from skin allograft rejection. Using a mouse skin allograft rejection model these authors demonstrated that treatment with HBO_2 alone (26) or in combination with cyclosporine (27) lengthened the time to allograft rejection. This effect was more profound in animals receiving more frequent HBO_2 treatment compared to animals receiving lower doses of HBO_2. Renner et al. (28) investigated the efficacy of HBO_2 therapy in improving survival of reattached auricular composite grafts. A prospective, randomized, double-blind study using 20 New Zealand albino rabbits randomized to a treatment or control group. Their study represented a continued investigation following a pilot study, which suggested some enhancement of composite graft survival with the use of HBO_2 therapy in the rabbit ear. Both experiments have demonstrated a slight survival benefit using HBO_2 therapy in auricular composite grafts in the rabbit model.

Lozano et al. (29) evaluated the effect of HBO_2 and medicinal leeching on axial skin flaps subjected to total venous occlusion. Hyperbaric oxygen protocol consisted of 90-minute treatments, twice daily, with 100% 02 at 2.5 atmospheres absolute for 4 days. The leeching protocol consisted of placing medicinal leeches on the congested flaps for 15 minutes, once daily, for 4 days. Laser Doppler measurements of flap perfusion and the percentage of flap necrosis were evaluated. The flaps in the sham group demonstrated 99 percent survival, whereas the flaps in the venous occlusion-only group demonstrated 100 percent necrosis. The flaps in the occlusion with HBO_2, the occlusion with leeching, and the occlusion with HBO_2 and leeching groups demonstrated 1, 25, and 67 percent survival, respectively. This study demonstrated that HBO_2 alone was not an effective treatment for skin flaps compromised by total venous occlusion. The combination of leeching and HBO_2 treatment of total venous occlusion resulted in a significant increase in flap survival above that found with leeching alone. Yucel and Bayramicli (30) investigated the effects of HBO_2 and heparin on the survival of the rat inferior epigastric venous flap. They concluded that the rat inferior epigastric venous flap may be an ischemic flap with capillary circulation through a single venous pedicle, but it needs HBO_2 treatment to survive, especially during the acute period. Heparin treatment, reducing the flap size, and presence of a vascular wound bed also improve survival rates.

Gampper et al. (31) studied the beneficial effect of HBO_2 on island flaps subjected to secondary venous ischemia in the rat superficial epigastric flap model. They concluded, HBO_2 treatment significantly increased the survival of flaps subjected to a secondary ischemia, even if administered before primary ischemia. The effect of administering HBO_2 prior to secondary venous ischemia was marginal, which may be due to the effect of HBO_2 not lasting longer than 5 hours.

Ulkur et al. (32) evaluated the effect of HBO_2 on pedicle flaps with arterial, venous, and combined arteriovenous insufficiency. Their findings indicated that HBO_2 treatment increased the percentage of survival length and mean laser Doppler flows of axial pattern skin flaps with all types of vascular insufficiency. This effect, however, was greatest in the arterial insufficiency flaps.

Clinical Studies

Perrins and colleagues (33-36) demonstrated the value of adjunctive HBO_2 therapy in skin grafts. This was first shown in some case studies (33) and later in controlled clinical trials (34). In the latter study, 48 patients were studied. Half were treated with HBO_2 and half served as controls. Complete survival of grafts occurred in 64% of the treated group as opposed to only 17% of the controls ($P<0.01$). Results of this study suggested that whole-body exposure of HBO2 significantly enhanced flap healing. Similar positive results in the clinical situation have been described by Moines-Chass and Hashmonai (37). In general, these cases represented failures of other available methods, after which HBO_2 therapy was under-taken. Greenwood and Gilchrist (38) examined the effect of HBO_2 therapy and wound healing in postirradiated compromised wounds in laryngectomy patients. The authors conclude that healing was significantly improved by HBO_2 therapy.

Other favorable case reports were noted by Barr et al. (39,40). Bowersox et al. (41) reviewed 105 patients with ischemic skin flaps or grafts where 90% of the graft patients had risk factors that were considered to be poor prognostic indicators of graft or flap survival. They found that 89% of threatened flaps and 91% of threatened skin grafts were salvaged by HBO_2 therapy. Thus, there was an average of approximately 10% failure rate. This observation compares favorably with other studies where failure rates with some complications can reach 67% in compromised tissues (42). HBO_2 also has been shown to improve the survival of ischemic skin flaps of the face, and to be an adjunct in periorbital reconstruction (43). In another clinical study, the salvage of free flaps with secondary ischemia times was significantly enhanced by HBO_2 treatment (44). Necrosis of a free tissue transfer is a significant loss because the defect, which the free flap was used to close, is re-created along with the donor site morbidity. Free flaps compromised by prolonged primary or secondary ischemia in this study responded dramatically to HBO_2 treatment with 100% viability, in most cases, if the time to the initiation of treatment was less than 24 h.

It can be noted that a variety of types of grafts and flaps have been investigated in animal and human studies. Zamboni provides a critical review of HBO_2 and applications to different types of flaps in recent book chapter (45). Results of the preponderance of work in the literature clearly show the efficacy of HBO_2 with respect to enhancement of skin graft and flap survival. Of importance is that different types of flaps have been analyzed in these studies including free skin grafts, pedicle flaps, random flaps, irradiated wounds and flaps, composite grafts, as well as axial pattern flaps. Although each flap problem is unique, a key factor to flap necrosis is tissue hypoxia. The results indicate that viability of flaps can be enhanced by HBO_2: by a reduction of the hypoxic insult. Other mechanisms of action whereby HBO_2 enhances flap survival include the enhancement of fibroblasts and collagen synthesis, creation of neovascularity (19,46), the possibility of closing off arterio-venous shunts (47,48) and the favorable effects on the micro-circulation (23).

Clinical Management

The treatments are given at a pressure of 2.0-2.5 atm abs and range from 90 to 120 min (depending on type of HBO_2 facility available, patient status, etc). Initial treatment should be twice daily. Once the graft or flap appears more viable and stable, once-a-day treatments may

suffice. To be maximally effective, HBO_2 therapy should be started as soon as signs of flap compromise appear. Flap viability can be assessed by clinical judgment as well as by a variety of noninvasive and invasive techniques including transcutaneous oximetry and laser doppler studies.

Utilization Review

Utilization review is required after 20 treatments when preparing a recipient site (such as a radiated tissue bed) for a flap or graft, and following 20 treatments after a flap or graft has been placed into its recipient site.

Cost Impact

Failed flaps are extremely expensive. Adjunctive HBO_2 can reduce these costs by salvaging free skin grafts, pedicle flaps, random flaps, irradiated wounds and flaps, composite grafts, as well as axial pattern flaps.

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