OxyBand™ Dressing Accelerates Wound Healing in Two Randomized Controlled Trials

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ABSTRACT:

The efficacy of the OxyBand™, a novel wound dressing pre-filled with oxygen, is evaluated in two clinical studies of epithelialization of burn wounds on healthy volunteers. The OxyBand™ wound dressing is compared to a standard polyurethane dressing, Tegaderm™ and to an identical placebo dressing after superficial Erbium laser burns where patients served as their own controls. The OxyBand™ v. Tegaderm™ study was conducted on 30 paired control/test wounds 5mm in diameter (total area 19.6 mm^2) with 50 microns ablation/25 microns coagulation. The OxyBand™ (95% oxygen) v. placebo (21% oxygen, simulating air) study was conducted on 19 paired control/test wounds 25.4 mm square shape (total area 645 mm^2) with 100 microns ablation/25 microns coagulation. Results showed the area of wound epithelialized by day 3 were 12.8 mm^2 for Oxyband™ and 4.9 mm^2 for Tegaderm™ treated wounds, and by day 7 were 17.8 mm^2 and 14.1 mm^2 for Oxyband™ and Tegaderm™, respectively. Wounds treated with OxyBand™ healed 28.4% faster compared to the wounds treated with a placebo dressing (mean time to 100% epithelialization was 6.2 days $\pm$ 0.9 for OxyBand™ treated wounds and 8.8 days $\pm$ 0.7 for placebo treated wounds). In addition, perceived pain, redness, and level of exudate formation was less in wounds treated with the Oxyband™ wound dressing compared to placebo dressing. The results of the present studies suggest that OxyBand™ dressings deliver oxygen at levels that

significantly increase healing and reduce pain, and thus may be well suited for the treatment of superficial burns, abrasions, and uncomplicated wounds or aesthetic procedures.

INTRODUCTION:

The effects of oxygen on healing wounds show that oxygen is essential for tissue repair including angiogenesis, collagen synthesis, epithelialization, wound contraction, and prevention of infections (Whitney, 1989; Hopf et al, 2005; Gordillo & Sen, 2003; Rahat et al., 2006). Research in animals and humans demonstrates the basic physiology of wound healing is oxygen dependent, and several aspects of the healing process are accelerated with oxygen. For example, collagen synthesis is enhanced under hyperoxic conditions (Prockop, 1963; Niinikoski, 1969; Hunt & Pai, 1972). Angiogenesis, on the other hand, appears to be stimulated by both a hypoxic tissue gradient, with new capillaries extending in the direction of lower oxygen concentration, and at hyperoxic conditions (Hopf et al, 2005).

The supply of oxygen to healing tissue derives from three sources: oxygen chemically bound to hemoglobin in whole blood; oxygen dissolved in plasma; and oxygen which diffuses into wound fluid or tissue from the exterior. For surface wounds, all sources of oxygen are important.

Prior studies of wounds covered with plastic films found that the higher the oxygen permeability of the film, the greater the healing rate (Winter, 1977; Silver, 1972). Furthermore, the films prevent scab formation, allowing for epidermal cell migration across the wound surface. The use of wound dressings that prevent scab formation and have increased oxygen permeability are understood to increase the rate of wound healing.

Low oxygen levels in wounds delays healing, results in higher rates of infection, impaired fibroblast proliferation and collagen deposition, reduces tensile strength, and reduces mobility of various cells (Gordillo & Sen, 2003; Rahat et al., 2006; Tandara & Mustoe, 2004). Oxygen levels in tissue drops initially upon wounding due to disrupting the vascular supply and increasing oxygen consumption (Tandara & Mustoe,

2004; Chang et al., 1983); this drop is a key factor that limits the rate of healing (Khanna &Wallace, 2002.). Stress also delays healing through multiple mechanisms in superficial and surgical wounds including peripheral vasoconstriction which limits wound perfusion and thus systemic delivery of oxygenation (Broadbent et al., 2003; West, 1990).

A recent study using an ischemic rabbit ear model demonstrates the efficacy of sustained 100% topical oxygen using an oxygen generator at 3cc hr^{-1} on epithelialization in wound healing (Said et al., 2005). This model simulates the conditions that result in chronic ischemic wounds. Histologic analysis of the full thickness 7mm punch wounds evaluated on day 5 and day 8, post procedure shows significantly greater healing in response to oxygen treatment and most significantly, epithelial wound coverage almost doubles in treated ear wounds when compared with controls (Said et al., 2005).

Even moderate increases in oxygen levels at normal atmospheric pressure have shown increases in the closure rate of open wounds, with an improvement in healing rate demonstrated with continuous exposure up to 45% (Utkina, 1964). It has also been demonstrated that 93% of the oxygen incorporated into the hydroxyl groups of newly synthesized hydroxyproline, a key element in epidermal wound healing is derived from the atmosphere (Prockop, 1963). Since the control of the local wound environment is dependent on local perfusion and the diffusion of oxygen from the atmosphere, treatment that encourages an increase in oxygen (O_2) tension in the wound fluid will tend to increase the rate of healing (Winter, 1970; Silver, 1980). Despite the research in this field, topical oxygen treatments are not standard of practice.

While hyperbaric oxygen is a standard of practice and reimbursed for treating chronic non-healing wounds, clinical studies applying various topical oxygen modalities for wound care have been criticized historically for being collective case studies and anecdotal in nature rather than controlled clinical trials that can clearly delineate and quantify outcomes (Feldmeier, 2005). The clinical studies reported here were designed to address these issues by randomized controlled clinical trials against both a standard of care dressing as well as a placebo to demonstrate the outcomes for a specific and unique topical oxygen modality applied to simple standardized wounds at atmospheric pressure.

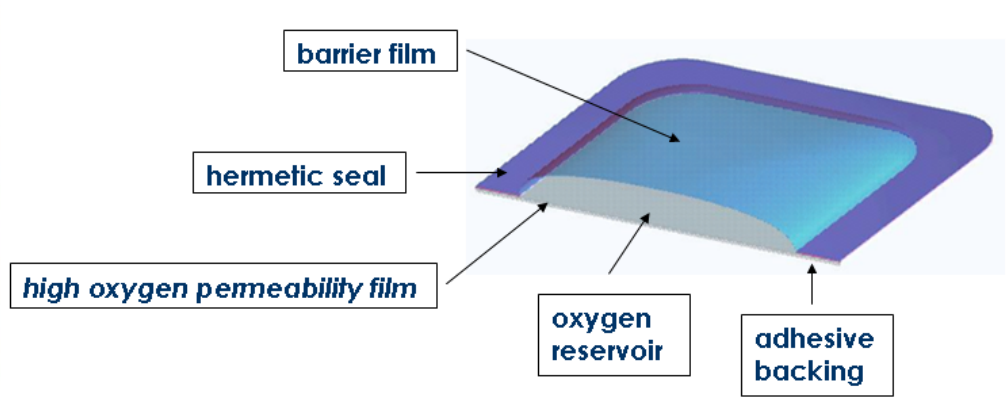
A number of methods exist for delivering topical oxygen, most of which requires either oxygen tanks, battery or AC-powered generators, chemical generation, or oxygenated solutions/foams. The key feature of the OxyBand™ is that it supplies oxygen from the oxygen reservoir continuously to a wound as needed for multiple days within a simple occlusive wound dressing. The OxyBand™ is a bi-layer wound dressing pre-filled with oxygen designed to maximize the oxygen saturation in the wound fluid. Driven by the diffusion gradient, the OxyBand™ raises and maintains the dissolved oxygen (PO_2) levels in the wound fluid, replenishing the wound with oxygen as it is consumed.

Herein we report findings from two clinical studies conducted using OxyBand™. The efficacy of the OxyBand™ wound dressing (containing 95% oxygen) on standardized laser burns was compared to a standard polyurethane wound dressing (Tegaderm™). In a double blind experiment, the efficacy of OxyBand™ to accelerate wound healing as measured by re-epithelialization of standardized laser burn wounds was compared to an identical placebo dressing containing 21% oxygen.

METHODS:

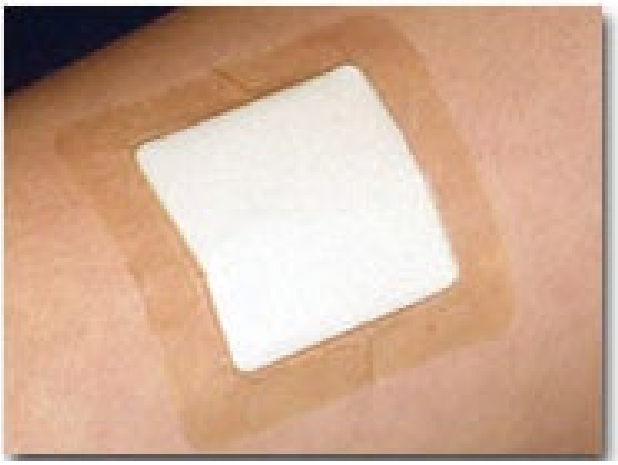
Dressings

OxyBand™ Wound Dressing. The OxyBand™ (OxyBand Technologies, Inc) is a FDA 510(k) cleared wound dressing for continuous delivery of oxygen into the wound for 5 days. The bi-layer wound dressing comes pre-filled with high levels (95±5%) of oxygen between the layers. An open cell foam spacer maintains the shape of the reservoir.



Tegaderm™ Wound Dressing. Tegaderm (3M, St. Paul, MN) is a thin film polyurethane dressing.

Placebo Wound Dressing. OxyBand™ Wound Dressings which were fabricated to contain 21% oxygen in the reservoir to simulate the levels in air served as the placebo wound dressing.



Clinical Studies

Oxyband™ v. Tegaderm™ 7 day Study. Five healthy male and female volunteers received six standardized laser wounds in identical patterns on the medial aspect of each upper arm (12 wounds per subject). Identical burns measuring 5 mm (total area 19.6 mm^2) in diameter were produced using an Erbium 2940 wavelength laser (**fill in Manf, city, state**) set at an ablation depth of 50 microns and a thermal coagulation depth at 25 microns. Thirty wounds were treated with OxyBand™ and thirty wounds

served as the control and were treated with the Tegaderm™ dressing. The burns on one arm of each subject were treated with OxyBand™ while the burns on the opposite arm of each subject were treated with Tegaderm™. Subjects were unaware of which dressing was used on which set of wounds and dressings were randomly assigned to either arm for each subject. Wounds were evaluated by board certified plastic surgeons blinded to which was the control and which was the treatment wound. The dressings were removed on day 3 and wounds were evaluated for lesion size, subjective pain (evaluated utilizing a 10-point scale ranging from not painful to very painful). Fresh test and control dressings were applied and a second evaluation of the wounds was performed on day 7.

Oxyband v. Placebo Study. Twenty-eight healthy male and female volunteers received standardized laser wounds in a similar pattern on the inner aspect of each upper arm. The burns measured 625 mm^2 (1" by 1") and were produced using an Erbium laser (2940 nm wavelength) set to an ablation depth of 100 microns and a thermal coagulation depth of 25 microns. Wounds were dressed by random assignment with the treatment dressing, OxyBand™ (95% oxygen $\pm$ 5% oxygen) or the control, placebo dressing (air filled, 21% oxygen). Each subject served as his or her own control. In order to double blind the experiment, dressings were randomly assigned red or blue color-codes and the set of coded dressings were placed in individual plastic bags and marked for each subject number.

Wounds were evaluated by two board-certified plastic surgeons experienced in wound care, assisted by two trained nurse practitioners. Wounds were evaluated 3 days after the laser procedure (day 1 being the day of the laser wound procedure) except for subjects who had difficulty with keeping their dressings adhered. Under these circumstances subjects were evaluated sooner. Whenever one dressing was replaced, both dressings were replaced. Observers again evaluated subject wounds on day 6. A few subjects were evaluated between day 3 and day 6 because the observer determined on day 3 (visual examination) that that their wounds were likely to be 100% epithelialized sooner than day 6. Subjects were asked to return more often subsequent for evaluations of wounds until 100% epithelialization was observed.

During follow up visits, the dressings were removed, and wounds assessed for pain, redness and exudate on a scale of 1-5 comparing the red and blue sides. The percentage epithelialization (0% to 100%) was estimated by the physicians, and wounds were marked and photographed. New dressings were applied on both sides and the process was repeated until wounds were 100% epithelialized.

A final evaluation for assessment of scar appearance was performed at 30 days. Upon enrollment, subjects were given instructions for participating in the study that included “not to remove or detach the dressings” and “to contact the clinical trial staff if the dressings detached from over the wounds at any time.” Subjects who did not comply with instructions or schedules were discontinued from the study.

RESULTS:

The first study demonstrated the efficacy of OxyBand™ wound dressings in a standardized wound compared to Tegaderm™ wound dressing over 7 days. In all cases, the un-epithelialized lesion size (mm) of the wounds treated with OxyBand™ was reduced significantly compared to the lesion size of the wounds treated with Tegaderm™ as measured with calipers. Results in Table 1 show the area of wound epithelialized by day 3 were 12.80 mm^2 for OxyBand™ and 4.98 mm^2 for Tegaderm™ treated wounds, and by day 7 the un-epithelialized regions remaining were 1.79 mm^2 for OxyBand™ and 5.51mm^2 for Tegaderm™. On day three, 2.6 times more wound area had epithelialized by the OxyBand™ treatments, and by day seven the standard of care Tegaderm™ treated wounds had 3.2 times more un-epithelialized area than the OxyBand™ treated wounds. Further analysis showed a mean reduction in wound diameter of the OxyBand™ treated wounds by 1.37 mm $\pm$ 0.68 at $p < .001$ compared to the Tegaderm™ treated wounds on day three. OxyBand™ treated wounds demonstrated a significantly greater reduction in mean diameter by 3.49 mm $\pm$ 0.27 at $p < .001$ on day seven compared to the Tegaderm™ treated wounds (Photos IA & IB).

Photograph 1. Wounds Measured With Calipers On Day 3

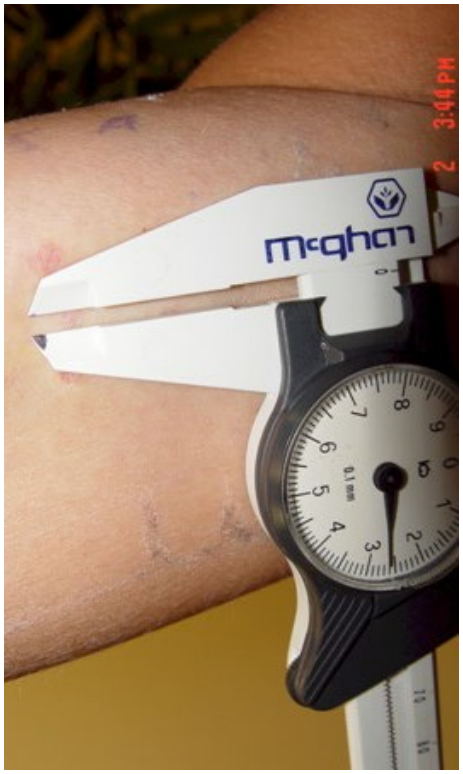


Photo IA: OxyBand™ Treated

Photo IB: Tegaderm™ Treated

Table 1: The Reduction In The Size Of Wounds Treated With OxyBand™ vs. Traditional Polyurethane (Tegaderm™) Dressings After Three and Seven Days

	Day 1		Day 3		Day 7	
Treatment	OxyBand™	Tegaderm™	OxyBand™	Tegaderm™	OxyBand™	Tegaderm™
N number of wounds	30	30	30	30	30	30
Mean Wound Diameter (mm)	5.00	5.00	2.95	4.32	1.51	2.65
Wound Area Remaining Un-epithelialized	19.63	19.63	6.83	14.65	1.79	5.51

Wound Area Epithelialized			12.80	4.98	17.84	14.12
% Diameter Reduction			41%	14%	70%	47%
% Wound Area Reduction			65%	25%	91%	72%
% of Wound Area Remaining Un-epithelialized			35%	75%	9%	28%

In addition to measuring changes in the size of the wounds, pain was assessed by asking subjects to describe their level of pain on a graphic scale from 1 to 10. All subjects reported less pain from the OxyBand™ treated wounds without prior knowledge of which wounds were test vs control dressings. Additionally there was less pain reported upon removal of the OxyBand™ dressing compared to the Tegaderm™ dressing. It was observed that there was less ecchymosis and crusting on the wounds treated with OxyBand™ vs. the Tegaderm™ and that there was more edema observed on the Tegaderm™ treated wounds vs. the OxyBand™ treated wounds. No infections or other complications were identified in either group.

A second clinical study was conducted to test the efficacy of Oxyband™ dressings in re-epithelialization of standardized laser burn wounds compared to an identical placebo dressing. Table 2 presents the mean scores for epithelialization (1% - 100%), exudate (1 – 5 point scale), redness (1 – 5 point scale) and pain (1 – 5 point scale) for all nineteen subjects who completed the study, including follow up evaluations on days 3, 5, 6, 7, 8, 9, and 10. Nine of subjects did not complete the study due to lack of compliance. Although the protocol for the study did not specify as many days of wound evaluation, schedules and interest permitted more follow up visits. Analysis of the data shows a significant difference between the wounds treated with OxyBand™ dressing and the wounds treated on the same subject with the placebo dressing.

The primary endpoint for the second study was 100% epithelialization. By day five, 5 out of 19 OxyBand™ treated wounds reached 100% epithelialization (Table 3 and Photos 2A & 2B). By day 6 this number increased to 10 and by day 7, 19 out of 19 OxyBand™ treated wounds were 100% epithelialized. No placebo treated wounds reached 100% epithelialization until day 8 and all placebo treated wounds reached 100% epithelialization on day 10. All OxyBand™ treated wounds were fully epithelialized between day 5 and day 7 compared to placebo treated wounds that were fully epithelialized between day 8 and day 10 (including the day of the laser procedure) (Table 3). The mean time to 100% epithelialization for wounds was 6.2 Days $\pm$ 0.9 for OxyBand™ treated wounds and 8.8 days $\pm$ 0.7 for placebo treated wounds. The difference between the means was 2.6 days faster on the OxyBand™ side. A difference was significant at $p < .001$. OxyBand™ treated wounds healed 28.4% faster as measured by % epithelialization compared to placebo treated wounds on the same subject.

There was a dramatic difference in amount of exudate between the OxyBand™ and the placebo treated wounds on days 3 (Photos 3A & 3B, R and B on arms = Red and Blue coded dressings) through 7. Table 2 also shows a significant difference in the mean scores for exudate. On day 3, the mean exudate was essentially twice as much for the placebo treated wounds when measured on the 5-point scale compared to the OxyBand™ treated wounds. Beyond this time, there was no significant exudate in either wound, the mean difference between the groups was .77 score (on a 1 to 5 scale for exudate) or significantly more exudate for the placebo treated wounds compared to the OxyBand™ treated wounds.

Redness on the placebo wounds was greater, especially in the initial days of evaluation (Table 2). The placebo treated wounds were significantly redder, mean score 1.09 out of a 5 point scale for the placebo treated wounds compared to .29 for the OxyBand™ treated wounds over follow up evaluations. The difference between the means for the mean redness scores was significant; placebo treated wounds had a mean redness score that was .80 greater than the OxyBand™ treated wounds on a 5-point scale.

Mean pain scores also indicate significantly greater pain in placebo wounds compared to OxyBand™ treated wounds. The mean pain score for placebo was nearly 3 times greater than OxyBand™ wounds on day 3 (Table 2). Mean pain scores continued to be significantly greater for the placebo treated wounds compared to the OxyBand™ treated wounds on days 5 and 6.

Table 2: Mean Epithelialization, Exudate, Redness And Pain For OxyBand™ vs. Placebo

	Day3		Day 5		Day 6		Day 7		Day 8		Day 9		Day 10	
Treatment	OxyBand	Placebo	OxyBand	Placebo	OxyBand	Placebo	OxyBand	Placebo	OxyBand	Placebo	OxyBand	Placebo	OxyBand	Placebo
(N) Number of Wounds	19	19	19	19	19	19	19	19	19	19	19	19	19	19
Mean Epithelializtion	13%	0%	31%	14%	92%	63%	100%	67%	100%	87%	100%	94%	100%	100%
Mean Exudate Score	1.21	2.42	0.50	1.50	0.32	1.21	0.00	0.05	0.00	0.00	0.00	0.00	0.00	0.00
Mean Redness Score	1.89	3.05	1.67	2.83	0.84	2.37	0.23	0.95	0.11	0.53	0.00	0.43	0.00	0.75
Mean Pain Score	0.84	2.32	0.50	1.33	0.32	0.83	0.00	0.07	0.00	0.05	0.00	0.00	0.00	0.00

Table 3: Cumulative Subjects Fully Epithelialized

Cumulative Subjects Fully Epithelialized

Oxy/P	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
OxyBand	0	0	5	10	19	19	19	19
Placebo	0	0	0	0	0	7	16	19

Photograph 2. Epithelialization of Wound, Day 5, (R and B = Red and Blue Coded Dressings)

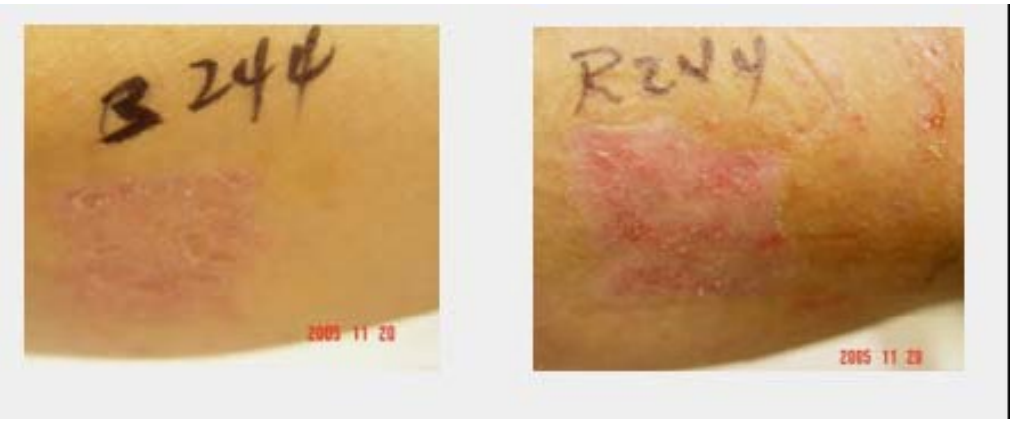


Photo 2A: OxyBand™ Treated Photo 2B: Placebo Treated

Photograph 3. Wound exudate on Day 3, (R and B = Red and Blue Coded Dressings)

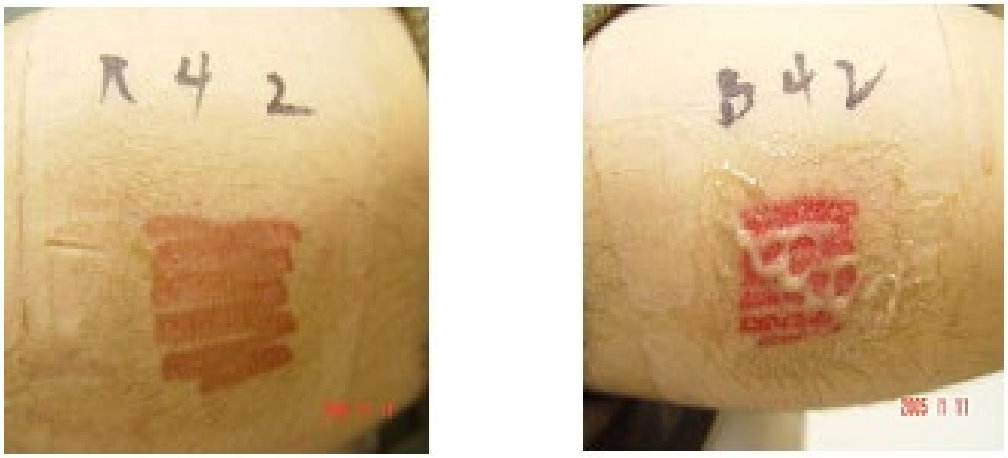


Photo 3A: Oxyband™ treated Photo 3B:placebo treated

It should be noted that there were no patients who had more pain, redness or exudates on the OxyBand treated wound compared to the placebo .

Scars were evaluated 30 days after the laser procedure. As would be expected in a wound of this type, there was minimal visible scarring. However there were differences observed in the appearance of scars 30 days after the procedure for OxyBand™ treated wounds compared to placebo treated wounds. Scored on scale from 0 to 5 (0 being no scar), the OxyBand™ mean scar score (0 – 5) 1.2, 30 days post procedure compared to the placebo mean scar score (0 – 5) 2.3, 30 days post procedure. A significant difference of 1.1 was found between the mean scar scores. The scar from the OxyBand™ treated wound had 48% better visual scar appearance at 30 days post laser procedure than scar from the placebo treated wound. A few of the subjects in the present study returned after 90 days (not required) for scar evaluation. Although there were not enough subjects to show statistical significance, a more dramatic difference was seen in the scar appearance between the OxyBand™ and placebo treated wounds in these few cases 90 days post laser surgery.

DISCUSSION:

Previous studies have demonstrated the importance of oxygen in accelerating wound healing and decreasing infection in both acute and chronic wounds. Standard wound dressings often block or reduce oxygen access to the wounds, creating a further oxygen deficiency for wounds. When wounds are hypoxic, they are impaired in their resistance to infection (Hopf et al., 1997), in fibroblast activity (Jonsson et al., 1986; Silver, 1973), collagen deposition (Hunt & Pai, 1972), angiogenesis (Gibson et al., 1997) and epithelialization (Niinikoski et al., 1983) The tradeoffs associated with oxygen treatment with hyperbaric chambers such as cost, time consuming treatment schedules, toxicity, CNS complications is well documented and makes this therapy impractical for treating most acute wounds. Other topical modalities have various limitations such as having to be tethered or battery powered oxygen source, uncontrolled oxygen delivery, inability to achieve or sustain high oxygen levels.

OxyBand™ technology is based on the principal of oxygen diffusion from a higher oxygen tension to a lower oxygen tension in the wound. OxyBand™ dressings containing oxygen gas were applied to the wound bed with the permeable membrane

placed in contact with the wound interface, sealing circumferentially to be occlusive to outside bacteria and loss of oxygen. Although oxygen tension in the healing wounds for these studies was not measured, previous benchtop testing of the dressing indicates that oxygen transfer from the reservoir to the target site is diffusion controlled, the oxygen levels across the film increase rapidly, level out and is sustained over multiple days, dropping less than 5% per day. Testing was conducted over 6 days on a customized test bed that incorporated an MI- 730 MicroElectrode oxygen sensor (Microelectrodes,Inc.Bedford, NH). This suggests that OxyBand™ can deliver oxygen continuously to a wound bed for multiple days. It therefore follows that such a dressing could provide beneficial effects of oxygen to a standardized burn wound as it holds the oxygen over the wound. The bottom layer is a high transfer rate polyurethane film, allowing oxygen to diffuse into the wound until the wound fluid is saturated with oxygen. The dressing acts like an oxygen reservoir allowing the wound to utilize as much oxygen as needed rather than being limited to atmospheric levels.

The ease of use applying a simple OxyBand™ dressing to administer high concentrations of oxygen over multiple days was noted in both trials.

CONCLUSION:

In two studies, we have shown that the use of OxyBand™ wound dressings for up to 7 days in superficial burn wounds results in a statistically significant enhancement in the speed of wound re-epithelialization, and a correlative decrease in pain. The first study used the standard polyurethane dressing, Tegaderm™ as the control. The second study was a double blind randomized, controlled trial comparing the OxyBand™ dressing to a placebo dressing on standardized wounds, which also demonstrated an impressive difference in the speed of wound re-epithelialization of wounds as well as a correlative decrease in pain, exudate, redness and scar appearance 30 days later.

Taken together, these randomized controlled clinical trials on simple standardized wounds suggest that the improved outcomes demonstrated for the

OxyBand™ treated wounds compared to treatments using a standard of care polyurethane or placebo control dressings are related to the specific oxygen delivery modality of the OxyBand™ dressings. Thus, OxyBand™ is a simple to use wound dressing that provides potential benefits for various types of acute and superficial wounds, including post aesthetic procedures. Further studies should be considered to expand the application of this useful oxygen delivery technology in wound care including larger and deeper wounds, as well as surgical and chronic wounds.

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