

ORIGINAL ARTICLES

Hyperbaric Oxygen Therapy in Non Healing Wounds in a Referral Hospital of Bangladesh

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Summary:

Introduction: The therapeutic use of oxygen under pressure is known as hyperbaric oxygen therapy (HBOT) and has been used to assist wound healing for almost 40 years. The purpose of the present study was to see the outcome of hyperbaric oxygen therapy following its use in non healing wounds.

Methods: This prospective observational study was conducted in the Department of Plastic Surgery, Dhaka Medical College Hospital, Dhaka, from March 2016 to February 2017 for a period of 12 (twelve) months. The study was carried out on patients with non healing wounds. Patients were initially assessed with detailed history, clinical examination and investigations, and then treated with hyperbaric oxygen therapy for 90 minutes per session in 6 days a week for 25 cycles. Wound was assessed clinically, and with transcutaneous oximetry and laboratory investigations.

Results: Eighty patients were included, where 52 (65.0%) patients had diabetic ulcer, followed by post traumatic wound (14) and venous ulcer (7). Fifty nine (73.75%) patients had initial wound size of < 50 cm² with mean size 14.78 ± 12.5 cm². Wound size reduction rate after 15 cycles

of HBOT was 42.78%, and after 25 cycles of HBOT it was 61.21%. Among the 80 patients, 60 (75.0%) had moderate amount of discharge before HBOT; 19 (31.67%) & 25 (41.67%) reduced to small & no discharge after 25 cycles of HBOT respectively. 39 (48.75%) patients had serosanguineous discharge before HBOT, followed by 36 (45.0%) and 5 (6.25%) patients with purulent and serous discharge. Among the 39 patients with serosanguineous discharge, 15 (38.46%) & 20 (51.28%) patients had serous & no discharge after 25 cycles of HBOT respectively. Before starting HBOT, mean transcutaneous oximetry was 58.26 ± 3.84 mmHg, and it was 62.1 ± 6.27 mmHg and 66.92 ± 7.52 mmHg after 15 and 25 cycles of HBOT respectively.

Conclusion: So it can be stated that the hyperbaric oxygen therapy is a good option in treating different non healing wounds.

Key words : Hyperbaric oxygen therapy, Non healing wounds.

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Introduction:

Oxygen is one of the most versatile and powerful agents available to the modern medical practitioner. The

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therapeutic use of oxygen under pressure is known as hyperbaric oxygen therapy (HBOT) and has been used to assist wound healing for almost 40 years. It is a procedure of providing 100% oxygen at higher-than-atmospheric pressure to an individual in a closed chamber. This is a treatment procedure in which the patient is placed in a chamber and breathes oxygen at higher pressure. The entire chamber is pressurized with near 100% oxygen, and the patient breathes the ambient chamber oxygen directly or it can be pressurized with air and patient breaths 100% oxygen via masks or hoods. It has positive effects on hyper-oxygenation of tissue, vasoconstriction, down regulation of inflammatory cytokines, up-regulation of growth factors, antibacterial effects, and potentiation of antibiotics.¹

Most oxygen carried in the blood is bound to haemoglobin, which is about 97% saturated at standard pressure. Some oxygen, however, is carried in solution, and this portion is increased under hyperbaric conditions. Tissues at rest extract 5-6 ml of oxygen per decilitre of blood, assuming normal perfusion.

Administering 100% oxygen at normobaric pressure increases the amount of oxygen dissolved in the blood to 1.5 ml/dl; at 3 atmospheres, the dissolved oxygen content is approximately 6 ml/dl, which is more than enough to meet resting cellular requirements without any contribution from haemoglobin. Because the oxygen is in solution, it can reach areas where red blood cells may not be able to pass and can also provide tissue oxygenation in the setting of impaired haemoglobin concentration or function.²

Hyperoxia in normal tissues causes vasoconstriction, but this is compensated by increased plasma oxygen content and microvascular blood flow. This vasoconstrictive effect reduces post-traumatic tissue oedema, which contributes to the treatment of crush injuries, compartment syndromes, and burns.

Hyperbaric oxygen therapy increases the generation of oxygen free radicals, which oxidize proteins and membrane lipids, damage DNA, and inhibit bacterial metabolic functions. It is particularly effective against anaerobes and facilitates the oxygen-dependent peroxidase system by which leukocytes kill bacteria. The unique ability of HBOT to induce neovascularization accounts for its persistence in the clinical armamentarium of chronic wound treatments.³

Normal wound healing proceeds through stages of hemostasis, removal of infectious agents, resolution of the inflammatory response, reestablishment of a connective tissue matrix, angiogenesis, and resurfacing. Chronic or non healing wounds are those which do not proceed completely through this process because of any number of local and systemic factors. For this reason, non healing wounds are often categorized as diabetic wounds, venous stasis ulcers, pressure ulcers etc.⁴

Wounds that fail to heal are typically hypoxic.⁵ Multiple components of the wound healing process are affected by oxygen concentration or gradients, which explains why hyperbaric oxygen therapy is an effective therapy to treat chronic or non healing wounds. Angiogenesis occurs in response to high oxygen concentration.⁶ This is a multifactorial effect of HBOT. First, fibroblast proliferation and collagen synthesis are oxygen

dependent,⁷ and collagen is the foundational matrix for angiogenesis. In addition, HBOT stimulates growth factors involving angiogenesis and other mediators of the wound healing process.⁸ Hyperbaric oxygen also has been shown to have direct and indirect antimicrobial activity.

The patient can be administered systemic oxygen via two basic chambers: Multiplace and Monoplace. Both types can be used for routine wound care, treatment of most injuries, and treatment of patients who are ventilated or in critical care.

A multiplace chamber treats multiple patients at the same time, generally with a nurse or another inside observer who monitors the patients and assists with equipment manipulation or emergencies. Patients in a multiplace chamber breathe 100% oxygen via a mask or close-fitting plastic hood.⁹

A monoplace chamber compresses one person at a time, usually in a reclining position. The gas used to pressurize the vessel is usually 100% oxygen. Some chambers have masks available to provide an alternate breathing gas, such as air. Nurses tend to the patient from outside of the chamber and all the equipments remain outside the chamber. Only certain intravenous lines and ventilation ducts penetrate through the hull.⁹

The hyperbaric oxygen therapy centre of Department of Plastic Surgery of Dhaka Medical College Hospital has two Monoplace Hyperbaric System chambers.

The reasons for this study was to see the outcome of hyperbaric oxygen therapy following its use in non healing wounds, with special interest to assess the changes in wound size, to observe any change in wound discharge, to determine whether there is any change in oxygen tensions following HBOT by percutaneous measurement, and to observe the changes in antibiogram.

Materials and methods:

It was a prospective observational study, performed on the patients of Department of Plastic Surgery at Dhaka Medical College Hospital, Dhaka, Bangladesh, over a period of one year from March 2016 to February 2017. Total 80 patients with non healing wounds were

included in the study between 18 and 65 years, presented with different non healing wounds, including diabetic foot ulcers, venous ulcers, ischaemic ulcers. We excluded patients with chronic obstructive pulmonary disorder, recent myocardial infarction, seizure disorder, claustrophobia, pregnancy, and patients that refused to give consent to take part in the study.

Different types of variables were evaluated like age, sex, aetiology, dimension of the wound, discharge from the wound, Transcutaneous oximetry (TCOM), total and differential counts of white blood cells, and wound swab findings.

After admission at the hospital, informed written consent was obtained. Then history of illness was taken

and clinical examination done for initial assessment of the wound. Transcutaneous oximetry, and relevant laboratory investigations were also done. Patient was then treated with hyperbaric oxygen therapy for 90 minutes per session in 6 days a week for 25 cycles. Wound was assessed again clinically after 15 cycles and after 25 cycles, and with transcutaneous oximetry and laboratory investigations.

Ethical approval was taken prior to this study.

Equipments used:

- Two Monoplace Hyperbaric System chambers for hyperbaric oxygen therapy (Sigma 34, Perry Baromedical Corporation, USA).
- One instrument for transcutaneous oximetry (PeriFlux 6000, Perimed AB, Sweden).



Fig.-1: Hyperbaric oxygen chambers used in the study



Fig.-2: Transcutaneous oximetry done in the study

Results:

All data were compiled in a master table first. Computer based statistical analysis were carried out with appropriate techniques and systems. All data were recorded systematically in a pre-designed data collection sheet. Quantitative data were expressed as mean and standard deviation, and qualitative data were expressed as frequency distribution and percentage. Statistical analysis was performed by using windows based computer software devised with SPSS for Windows version 22, with the assistance from a statistician.

Among the patients, maximum 20 (25.0%) patients were in age group 36-45 years followed by 17 (21.25%) and 15 (18.75%) patients were in age group 18-25 years and 56-65 years respectively.

Table –I

Distribution of study subjects by age (N=80)

Age group (years)	Frequency	Percentage
18 – 25	17	21.25
26 – 35	14	17.5
36 – 45	20	25.0
46 – 55	14	17.5
56 – 65	15	18.75
Total	80	100.0

Among the 80 patients, 63 (78.75%) patients were male and 17 (21.25%) were female. Majority of the

patients (52/80) had diabetic ulcer, while seven (8.75%) patients had venous ulcer. Radionecrotic ulcer and thalassaemia were found in 4 (5%) and 3 (3.75%) patients respectively. A considerable number of patients (14, 17.5%) had post traumatic wound.

Table-II

Distribution of study subjects by aetiology (N=80)

Aetiology	Frequency	Percentage
Diabetic ulcer	52	65.0
Venous ulcer	7	8.75
Radionecrotic ulcer	4	5.0
Thalassaemia	3	3.75
Post traumatic	14	17.5
Total	80	100.0

Among the total 80 patients, 59 (73.75%) had initial wound size of $< 50 \text{ cm}^2$ with mean size $14.78 \pm 12.5 \text{ cm}^2$. After 15 cycles of HBOT, the mean size reduced to $8.46 \pm 11.64 \text{ cm}^2$ with reduction rate of 42.78%; and after 25 cycles of HBOT, the mean size reduced to $5.73 \pm 9.03 \text{ cm}^2$ with reduction rate of 61.21%. 17 (21.25%) patients had initial wound size of 50-100 cm^2 with mean size $64.71 \pm 15.23 \text{ cm}^2$. After 15 cycles of HBOT, the mean size reduced to $55.82 \pm 11.85 \text{ cm}^2$ with reduction rate of 13.73%; and after 25 cycles of HBOT, the mean size reduced to $45.68 \pm 10.59 \text{ cm}^2$ with reduction rate of 29.41%.

**Fig.-3:** Result of use of hyperbaric oxygen therapy

Table-III*Distribution of study subjects by dimension of wounds and reduction of wound size (N=80)*

Initial size of wound	Wound before HBOT		After 15 cycles HBOT		p-value
	Frequency	Mean wound size (cm ²) ± SD	Mean wound size (cm ²) ± SD	Reduction	
< 50 cm ²	59 (73.75)	14.78 ± 12.5	8.46 ± 11.64	42.78%	< 0.001
51-100 cm ²	17 (21.25)	64.71 ± 15.23	55.82 ± 11.85	13.73%	0.001
> 100 cm ²	4 (5.0)	191.50 ± 1.0	164.50 ± 23.0	14.1%	0.012

Initial size of wound	Wound before HBOT		After 25 cycles HBOT		p-value
	Frequency	Mean wound size (cm ²) ± SD	Mean wound size (cm ²) ± SD	Reduction	
< 50 cm ²	59 (73.75)	14.78 ± 12.5	5.73 ± 9.03	61.21%	< 0.001
51-100 cm ²	17 (21.25)	64.71 ± 15.23	45.68 ± 10.59	29.41%	< 0.001
> 100 cm ²	4 (5.0)	191.50 ± 1.0	141.75 ± 16.5	25.98%	0.011

Among the 80 patients, 60 (75.0%) had moderate amount of discharge, and 20 (25.0%) patients had profuse discharge. Among the 20 patients with profuse discharge, 17 (85.0%) reduced to moderate amount of discharge after 15 cycles of HBOT, and 12 (60.0%) & 8 (40.0%) patients reduced to moderate & small

amount of discharge after 25 cycles of HBOT respectively. Among the 60 patients with moderate discharge, 40 (66.67%) reduced to small amount of discharge after 15 cycles of HBOT, and 19 (31.67%) & 25 (41.67%) patients reduced to small & no discharge after 25 cycles of HBOT respectively.

**Fig.-4:** Result of use of hyperbaric oxygen therapy

Table-IV*Distribution of study subjects by change in amount of discharge after HBOT (N=80)*

Amount	Profuse discharge before HBOT (n _{pr} =20)			
	After 15 cycles HBOT		After 25 cycles HBOT	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Profuse	3	15.0	0	0.0
Moderate	17	85.0	12	60.0
Small	0	0.0	8	40.0
Nil	0	0.0	0	0.0
Total	20	100.0	20	100.0

Amount	Moderate discharge before HBOT (n _{mo} =60)			
	After 15 cycles HBOT		After 25 cycles HBOT	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Profuse	0	0.0	0	0.0
Moderate	20	33.33	16	26.67
Small	40	66.67	19	31.67
Nil	0	0.0	25	41.67
Total	60	100.0	60	100.0

Among the total 80 patients, 39 (48.75%) patients had serosanguineous discharge, followed by 36 (45.0%) and 5 (6.25%) patients with purulent and serous discharge respectively. Among the 36 patients with purulent discharge, 24 (66.67%) & 4 (11.11%) had serosanguineous & serous discharge after 15 cycles of HBOT respectively, and 21 (58.33%), 7 (19.44%) & 4 (11.11%) patients had serosanguineous, serous &

no discharge after 25 cycles of HBOT respectively. Among the 39 patients with serosanguineous discharge, 32 (82.05%) had serous discharge after 15 cycles of HBOT, and 15 (38.46%) & 20 (51.28%) patients had serous & no discharge after 25 cycles of HBOT respectively. Among the 5 patients with serous discharge, 2 (40.0%) patients had no discharge after 25 cycles of HBOT.



Before HBOT

After 15 cycles of HBOT

After 25 cycles of HBOT

Fig.-5: Result of use of hyperbaric oxygen therapy

Table-V*Distribution of study subjects by change in type of discharge after HBOT (N=80)*

Amount	Purulent discharge before HBOT (n _{pu} =36)			
	After 15 cycles HBOT		After 25 cycles HBOT	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Purulent	8	22.22	4	11.11
Serosanguineous	24	66.67	21	58.33
Serous	4	11.11	7	19.44
Nil	0	0.0	4	11.11
Total	36	100.0	36	100.0

Amount	Serosanguineous discharge before HBOT (n _{ss} =39)			
	After 15 cycles HBOT		After 25 cycles HBOT	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Purulent	0	0.0	0	0.0
Serosanguineous	7	17.95	4	10.26
Serous	32	82.05	15	38.46
Nil	0	0.0	20	51.28
Total	39	100.0	39	100.0

Amount	Serous discharge before HBOT (n _{se} =5)			
	After 15 cycles HBOT		After 25 cycles HBOT	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Purulent	0	0.0	0	0.0
Serosanguineous	0	0.0	0	0.0
Serous	5	100.0	3	60.0
Nil	0	0.0	2	40.0
Total	5	100.0	5	100.0

Before starting HBOT, mean transcutaneous oximetry (TCOM) was 58.26 ± 3.84 mmHg, and it was 62.1 ± 6.27 mmHg and 66.92 ± 7.52 mmHg after 15 and 25 cycles of HBOT respectively.

Table-VI*Distribution of study subjects by transcutaneous oximetry (TCOM) (N=80)*

	Mean TCOM (mmHg) \pm SD	p-value
Before HBOT	58.26 ± 3.84	< 0.001
After 15 cycles HBOT	62.10 ± 6.27	
Before HBOT	58.26 ± 3.84	< 0.001
After 25 cycles HBOT	66.92 ± 7.52	

Before starting HBOT, mean WBC count was 10681.25 ± 3066.07 /cmm, and it was 9946.25 ± 2589.46 /cmm and 9322.5 ± 2313.09 /cmm after 15 and 25 cycles of HBOT respectively. Among the 80 patients, all 80

(100.0%) had presence of infection by different micro-organisms before starting HBOT, but it was reduced to 56 (70.0%) patients after 15 cycles of HBOT and 38 (47.5%) patients after 25 cycles of HBOT.

Table-VII*Distribution of study subjects by presence of infection according to antibiogram (N=80)*

Infection	Before HBOT		After 15 cycles HBOT		After 25 cycles HBOT	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
Present	80	100.0	56	70.0	38	47.5
Absent	0	0.0	24	30.0	42	52.5
Total	80	100.0	80	100.0	80	100.0

Discussion:

In the study, the distribution of subjects by aetiology of wounds was recorded. Among all patients, 52 (65.0%) patients had diabetic ulcer, followed by 14 (17.5%) and 7 (8.75%) patients had post traumatic wound and venous ulcer respectively.

The distribution of study subjects by dimension of wounds was recorded. Among the total 80 patients, 59 (73.75%) had initial wound size of < 50 cm² with mean size 14.78 ± 12.5 cm². After 15 cycles of HBOT, the mean size reduced to 8.46 ± 11.64 cm² with reduction rate of 42.78%; and after 25 cycles of HBOT, the mean size reduced to 5.73 ± 9.03 cm with reduction rate of 61.21%. 17 (21.25%) patients had initial wound size of 50-100 cm² with mean size 64.71 ± 15.23 cm². After 15 cycles of HBOT, the mean size reduced to 55.82 ± 11.85 cm² with reduction rate of 13.73%; and after 25 cycles of HBOT, the mean size reduced to 45.68 ± 10.59 cm with reduction rate of 29.41%. Hammarlund et al showed that the mean decrease of the wound areas at weeks 4 and 6 in the oxygen group were 22% (SD ± 13), and 35.7% (SD ± 17) respectively, and in the air group, 3.7% (SD ± 11), and 2.7% (SD ± 11) respectively.¹⁰ So the present study reports similar results. Londahl et al also showed that complete healing of the index ulcer was achieved in 52% of the patients in the HBOT group and 29% in the placebo group at 1 year follow up.¹¹

The distribution of study subjects by amount of discharge before and after administration of HBOT was recorded. Here profuse discharge was mentioned where wound tissues were bathed in fluid, drainage freely expressed, may or may not be evenly distributed in wound and drainage involves > 75% of dressing; moderate discharge mentioned where wound tissues were saturated, drainage may or may not be evenly distributed in wound and drainage involves > 25% to < 75%

dressing; and small amount of discharge mentioned where wound tissues were wet, moisture evenly distributed in wound and drainage involves < 25% dressing.¹² Among the 80 patients, 60 (75.0%) had moderate amount of discharge before HBOT, and 20 (25.0%) patients had profuse discharge. Among the 20 patients with profuse discharge, 17 (85.0%) reduced to moderate amount of discharge after 15 cycles of HBOT, and 12 (60.0%) & 8 (40.0%) patients reduced to moderate & small amount of discharge after 25 cycles of HBOT respectively. Among the 60 patients with moderate discharge, 40 (66.67%) reduced to small amount of discharge after 15 cycles of HBOT, and 19 (31.67%) & 25 (41.67%) patients reduced to small & no discharge after 25 cycles of HBOT respectively.

The distribution of study subjects by type of discharge before and after administration of HBOT was recorded. Purulent discharge was mentioned to describe thin or thick opaque discharge, tan to yellow in colour; serosanguineous was thin watery discharge, red to pink in colour; and serous was thin watery clear discharge.¹² Among the total 80 patients, 39 (48.75%) patients had serosanguineous discharge before HBOT, followed by 36 (45.0%) and 5 (6.25%) patients with purulent and serous discharge respectively. Among the 36 patients with purulent discharge, 24 (66.67%) & 4 (11.11%) had serosanguineous & serous discharge after 15 cycles of HBOT respectively, and 21 (58.33%), 7 (19.44%) & 4 (11.11%) patients had serosanguineous, serous & no discharge after 25 cycles of HBOT respectively. Among the 39 patients with serosanguineous discharge, 32 (82.05%) had serous discharge after 15 cycles of HBOT, and 15 (38.46%) & 20 (51.28%) patients had serous & no discharge after 25 cycles of HBOT respectively. Among the 5 patients with serous discharge, 2 (40.0%) patients had no discharge after 25 cycles of HBOT.

The distribution of study subjects by transcutaneous oximetry (TCOM) was recorded. Transcutaneous oximetry provides a simple, reliable noninvasive diagnostic technique for the objective assessment of wound perfusion and oxygenation.¹³ It can be used for serial assessment of tissue perfusion in the vicinity of the foot ulcer. Transcutaneous oximetry may be used in the assessment of healing potential and patient selection for HBOT.¹⁴ Before starting HBOT, mean TCOM was 58.26 ± 3.84 mmHg, and it was 62.1 ± 6.27 mmHg and 66.92 ± 7.52 mmHg after 15 and 25 cycles of HBOT respectively. The difference between the results was statistically significant ($p < 0.001$). So in the present study it showed TCOM increase of 8.66 mmHg after 25 cycles of HBOT, which is similar to Faglia et al who showed that the transcutaneous oxygen tension measured on the dorsum of the foot significantly increased in subjects treated with hyperbaric oxygen therapy: 14.0 ± 11.8 mmHg in treated group and 5.0 ± 5.4 mmHg in non-treated group.¹⁵

The distribution of patients by presence of infection according to antibiogram is recorded. Among the 80 patients, all 80 (100.0%) had presence of infection by different micro-organisms before starting HBOT, but it was reduced to 56 (70.0%) patients after 15 cycles of HBOT and 38 (47.5%) patients after 25 cycles of HBOT. Doctor et al showed the control of infection and wound healing was achieved with the help of hyperbaric oxygen therapy. The control of infection spread was quicker. Positive cultures decreased from initial 19 to 3 in study group as against from 16 to 12 in the control group.¹⁶

Limitation of the study

The study was conducted in a single centre in Dhaka city which may not be representative for the whole population. The sample size was small in the present study, which compromises the generalizability of the study. If the study could have been done for a longer period of time, more significant data and results could have been yielded.

Conclusion:

The standard of care for treating non healing wounds includes the use of debridement, antibacterials, dressings, administration of antibiotics to control infection, adequate nutrition, maintenance of optimal

blood glucose levels, and pressure relief in the areas that are most subject to weight bearing. But when these measures are not enough to combat the difficult situation, administration of hyperbaric oxygen therapy is a very reliable option.

The present study revealed many important aspects of administration of hyperbaric oxygen therapy in non healing wounds. Wound size was reduced significantly after administration of HBOT. Amount of discharge from the wound was reduced. Wound perfusion and oxygenation was increased, which was evident in transcutaneous oximetry; and the presence of infection by different micro-organisms was reduced. So hyperbaric oxygen therapy has proven to be effective for different types of non healing wounds where other traditional treatment modalities are being ineffective.

Recommendation:

A large scale multi-centred study is recommended for more in-depth analysis of the role of hyperbaric oxygen therapy in non healing complex wound management in Bangladesh.

References:

1. Ahmed T, Kalam MA, Khondoker MS, Awwal R, Imam H. Hyperbaric Oxygen Therapy: Role in Medical Practice. *Bangladesh Journal of Plastic Surgery* 2014; 5(2): 50-61.
2. Feldmeier J. Hyperbaric Oxygen 2003: Indications and Results-The Hyperbaric Oxygen Therapy Committee Report. Kensington, Maryland: Undersea and Hyperbaric Medical Society, Inc.; 2003.
3. Fife CE, Hopf H. Discussion. Hyperbaric oxygen: its mechanisms and efficacy. *Plast Reconstr Surg* 2011; 127(Suppl 1): 142S-143S.
4. Latham E. Hyperbaric Oxygen Therapy. (July 2016). <http://emedicine.staging.medscape.com/article/1464149>
5. Hunt TK, Twomey P, Zederfeldt B, et al. Respiratory gas tensions and pH in healing wounds. *Am J Surg* 1967; 114(2): 302-307.
6. Knighton DR, Silver IA, Hunt TK. Regulation of wound-healing angiogenesis - effect of oxygen gradients and inspired oxygen concentration. *Surgery* 1981; 90(2): 262-270.
7. Hunt TK, Pai MP. The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. *Surg Gynecol Obstet* 1972; 135(4): 561-567.
8. Sheikh AY, Gibson JJ, Rollins MD, et al. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. *Arch Surg* 2000; 135(11): 1293-1297.
9. Kindwall E, Whelan H. *Hyperbaric Medicine Practice*. 2nd ed. Flagstaff, AZ: Best Publishing Company; 2004.
10. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: A randomized double-blind study. *Plast Reconstr Surg* 1994; 93: 829-833.

11. Londahl M, Katzman P, Nilsson A, et al. A prospective study: Hyperbaric oxygen therapy in diabetics with chronic foot ulcers. *J Wound Care* 2006; 15: 457-469.
12. Bates-Jensen BM, Vredevoe DL, Brecht M-L. Validity and reliability of the pressure sore status tool. *Decubitus* 1992; 5(6): 20-28.
13. Matos LA, Nun˜ez AA. Enhancement of healing in selected problem wounds. In: Kindwall E, editor. *Hyperbaric medicine practice*, 1994. Flagstaff, AZ: Best Publishing Co., 1994: 589-612.
14. Niinikoski J. Hyperbaric oxygen therapy of diabetic foot ulcers, transcutaneous oxymetry in clinical decision-making. *Wound Repair Regen* 2003; 11: 458-461.
15. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. *Diabetes Care* 1996; 19(12): 1338-1343.
16. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. *J Postgrad Med* 1992; 38(3): 112-114.
17. O'Reilly D, Linden R, Fedorko L, et al. A prospective, double-blind, randomized, controlled clinical trial comparing standard wound care with adjunctive hyperbaric oxygen therapy (HBOT) to standard wound care only for the treatment of chronic, non-healing ulcers of the lower limb in patients with diabetes mellitus: A study protocol. *Trials* 2011; 12: 69.