Case-controlled Study

Effects of hyperbaric oxygen therapy on the healing of thermal burns and its relationship with ICAM-1: A case-control study

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ABSTRACT

Background: The damaging effects of thermal burns need to be managed holistically in order to create a suitable environment for wound healing. The purpose of our study was to investigate the effects of hyperbaric oxygen therapy (HBOT) on the healing of thermal burns and its relationship with intercellular adhesion molecule 1 (ICAM-1).

Methods: Twenty patients with thermal burns were randomly divided into two groups: the group to receive HBOT and the control group. Levels of the *ICAM*-1 mRNA gene and ICAM-1 serum along with the degree of wound epithelialization were examined before and after treatment. Laboratory and physical findings between the groups were compared.

Results: In the HBOT group compared with the control group, thermal wound complications were significantly reduced ($p = .006$), while length of stay in hospital was substantially reduced ($p = .001$). ICAM-1 serum levels strongly correlated with *ICAM*-1 mRNA gene expression ($R^2 = 0.909$, $p < .001$). The expression of the *ICAM*-1 mRNA gene (12.32 ± 1.31 vs. 10.79 ± 1.38) and ICAM-1 serum level (231.46 ± 37.20 vs. 158.23 ± 68.30) in patients with at least a 50% burn area exceeded those of patients with a smaller burn area. HBOT significantly decreased ($p < .05$) the expression of the *ICAM*-1 mRNA gene and ICAM-1 serum level ($p = .004$). The number of HBOT sessions strongly correlated with ICAM-1 serum level ($p = .043$) but poorly correlated with *ICAM*-1 mRNA gene expression ($p = .22$). The expression of the gene, however, strongly correlated with ICAM-1 serum level ($r = -0.988$, $p < .001$).

Conclusion: HBOT can reduce thermal wound complications, length of stay in hospitals due to thermal burns, *ICAM*-1 mRNA gene expression, and ICAM-1 serum level.

1. Introduction

Thermal burns are serious injuries with detrimental effects that require prompt treatment. More than two-thirds of deaths due to thermal burns occur in underdeveloped and developing countries in Africa and the Asia-Pacific region [1]. Thermal burns can also cause high morbidity, prolonged hospitalization, disability, and limitations in performing daily activities, not to mention generate high costs [2].

The inflammatory process that occurs due to burns increases the production of pro-inflammatory cytokines [3], which in turn stimulate the production of intercellular adhesion molecule 1 (ICAM-1) via nitrogen oxide cells [4]. The receptor of ICAM-1, a human protein coded by the *ICAM*-1 mRNA gene, attaches to endothelial cells such that leukocytes can firmly attach to the endothelial surface. When that binding occurs, leukocytes spread and slowly migrate through the endothelium [5,6].

The chief goals of thermal burn management are to reduce the occurrence of edema, maintain the viability of tissue in the static zone, protect microvascular circulation, and bolster the immune system [7]. As thermal burns heal, the regeneration of wound cannot occur without the required balance between patient, injury and treatment factors. Without that balance, prolonged healing processes can cause extensive scarring [8]. To mitigate such outcomes, hyperbaric oxygen therapy (HBOT) works by increasing the pressure of oxygen such that it can directly diffuse into various tissues. The inhalation of 100% oxygen at pressures greater than sea level at 2.0–2.5 atm absolute (ATA) for 90–120 min, twice daily, is recommended by the Undersea & Hyperbaric Medical Society [9]. The effects of increased oxygen supply include angiogenesis, the inhibition of aerobic bacterial growth, increased fibroblast proliferation, increased leukocyte activity, reduced tissue edema, and vascular contraction, the last of which reduces stromal fluid transudation and the occurrence of edema [10,11].

Against that background, our study's aim was to investigate and describe the effects of HBOT on the healing of thermal wounds and its relationship with ICAM-1.

2. Materials and methods

Our randomized prospective study involved 20 patients 18–60 years old who presented thermal burn injuries with burn areas of 20%–60% at two hospitals in Manado, Indonesia (i.e., Siloam Hospital Manado and Kandou Hospital Manado). All patients received appropriate wound care according to the respective hospital's standard procedures. For the study, the patients were randomly divided into two groups—ones who received HBOT (i.e., HBOT group) and ones who did not (i.e., control group)—and patients in the HBOT group were subdivided according to total body surface area (TBSA) of their burns: ones with ±40% TBSA and ones with 50–60% TBSA. Patients with thermal burn injuries who presented with additional conditions such as other forms of trauma, smoke inhalation, pregnancy, or underlying diseases (e.g., diabetes, stroke, or chronic kidney disease) were excluded from the sample. Our study was approved by the ethics commission of Kandou Hospital Manado license no. 198/EC-KEPK/VI/2017 and has been registered with the Research Registry no. 6223. This study has been reported in line with the Strengthening the reporting of cohort studies in surgery (STROCSS) Guidelines [12,13].

2.1. HBOT procedure

Patients exhibiting burns of ±40% TBSA received three, 120-min HBOT sessions per week for 2 weeks, whereas ones with burns of 50–60% TBSA received six similar HBOT sessions per week. Before and after each session, the patients were examined regarding their expression of the *ICAM*-1 mRNA gene, serum ICAM-1 level, and degree of wound epithelialization.

2.2. Sample examination

ICAM-1 mRNA gene expression was measured with real-time polymerase chain reaction (PCR) assay and analyzed using Bio-Rad CFX96 Manager 3.1 (USA). The *ICAM-1* used was a specifically targeted to the oligonucleotide primary gene, while 18SRib served as the internal control. The nucleotide sequences of the primer for *ICAM-1* were F: 5′-GGCTGGAGCTGTTTGAGAAC-3′ and R: 5′-ACTGTGGGGTT-CAACCTCTG-3′. Meanwhile, the nucleotide sequences for 18SRib as the housekeeping gene were F: 5′-GTAACCCGTTGAACCCCATT-3′ and R: 5′-CCATCCAATCGGTAGTAGCG-3′ (Macrogen, Inc., South Korea). mRNA was isolated using the RNeasy Mini Kit (74,106; QIAGEN, USA), according to the manufacturer's instructions [14–17]. The mRNA was reverse-transcribed using SuperScript III (18,080–051; Invitrogen, USA) with random hexamer primers. Quantitative PCR was performed in triplicate using the Quantitect SYBR Green PCR kit (204,143; QIAGEN). Amounts of PCR product were quantified using the real-time PCR system (CFX96 Touch Real-Time PCR Detection System, Bio-Rad, USA). The threshold cycle number was measured, and the relative expression of ICAM-1 was adjusted for the threshold cycle for the detection of 18SRib. Results were recorded as the Mean ± SD of the triplicate experiments from the specimens. Last, serum ICAM-1 level was measured according to protocol of the SimpleStep ELISA kit (Abcam, cat. no. ab174445 – ICAM-1, UK) [18].

2.3. Statistical analysis

Data were processed and analyzed using SPSS version 20 (IBM, Armonk, NY, USA). The effects of HBOT on the expression of the *ICAM*-1 mRNA gene, serum ICAM-1 level, and degree of wound epithelialization were measured with the independent *t*-test and Wilcoxon test, and a *p* value of less than 0.05 was considered to be significant.

3. Results

The ability of HBOT to reduce thermal wound complications is detailed in Table 1. The control group was more prone to experience severe complications (60%) than the HBOT group (0%). A *p* value of less than 0.05 indicates that HBOT can reduce complications in patients with thermal wounds.

Table 2 shows that of the 20 patients with thermal injuries, 9 of the 10 patients who received HBOT experienced complete epithelialization, whereas in the control group, only 7 of the 10 patients achieved complete epithelialization (70.0%). Even so, the results were not significant (*p* > .05).

Next, Table 3 shows the difference in length of hospital stay in patients with thermal burns who received HBOT and ones who did not. The results of the independent *t*-test revealed a significant difference (*p* < .05) in the average length of stay between patients in the HBOT group (17.5 d, 4.3%) and ones in the control group (26.3 d, 7.6%).

Fig. 1 illustrates the robust correlation ($R^2 = 0.909$, *p* < .001) between *ICAM*-1 mRNA expression and serum ICAM-1 level. In short, the greater the expression of *ICAM*-1 mRNA, the higher the serum ICAM-1 level.

Table 4 shows that the expression of the *ICAM*-1 mRNA gene in patients with burns with at least 50% TBSA was greater than that in

Table 1
Correlations between HBOT and degree of complication in the healing of thermal wounds.

Group	Degree of complication				*p*
	None *n* (%)	Mild *n* (%)	Severe *n* (%)	Total *n* (%)	
HBOT	4 (40)	6 (60)	0 (0)	10 (100)	.006
Control	0 (0)	4 (40)	6 (60)	10 (100)	
Total	4 (20)	10 (50)	6 (30)	20 (100)	

Table 2
Correlations between HBOT and degree of epithelization in the healing of thermal wounds.

Group	Degree of epithelization			p
	Complete n (%)	Incomplete n (%)	Total n (%)	
HBOT	9 (90)	1 (10)	10 (100)	.291
Control	7 (70)	3 (30)	10 (100)	
Total	16 (80)	4 (20)	20 (100)	

Table 3
Correlations between HBOT and length of hospital stay in patients with thermal wounds.

Group	Length of stay (in days)			p
	Mean ($\pm SD$)	Min.	Max.	
HBOT ($n = 10$)	17.5 (4.3%)	12	26	.001
Control ($n = 10$)	26.3 (7.6%)	14	35	
Total		12	35	

patients whose burns had TBSAs less than 50% (11.61 ± 1.63 vs. 9.85 ± 1.27). That trend also emerged in the HBOT group, in which *ICAM*-1 mRNA level was greater in patients with at least a 50% burn area than the others (12.32 ± 1.31 vs. 10.79 ± 1.38, $p < .05$). The same additionally applied to serum ICAM-1 level between those subgroups (231.46 ± 37.20 vs. 158.23 ± 68.30, $p = .09$).

Table 5 indicates that HBOT significantly decreased ($p < .05$) the expression of the *ICAM*-1 mRNA gene by 2.50 (i.e., from 11.55 ± 1.50 to 9.05 ± 0.85). Similarly, serum ICAM-1 level also dropped by 101.87 (i.e., from 194.84 ± 64.64 to 92.97 ± 54.76).

Last, Table 6 shows that patients who received six HBOT sessions exhibited significant decreases in serum ICAM-1 level ($p < .05$) than ones who received only three HBOT sessions (152.53 ± 71.48 vs. 51.22 ± 61.78). However, *ICAM*-1 mRNA gene expression (3.18 ± 1.77 vs.

1.82 ± 1.99) was not statistically significant ($p > .05$).

4. Discussion

Complications from burn injuries can become major health concerns when they cause limitations and even disability for patients in

Table 4
Correlation between burn area and *ICAM*-1 mRNA gene expression and ICAM-1 serum level.

Variable	Burn area (%)	Statistical value			p
		Total ($n = 20$)	p	HBOT ($n = 10$)	
ICAM-1 mRNA	<50	($n = 13$) 9.85 ± 1.27	.015	($n = 5$) 10.79 ± 1.38	.05
	>50	($n = 7$) 11.61 ± 1.63		($n = 5$) 12.32 ± 1.31	
ICAM-1 serum	<50	–	–	($n = 5$) 158.23 ± 68.30	.09
	>50	–		($n = 5$) 231.46 ± 37.20	

Table 5
Effects of HBOT on *ICAM*-1 mRNA gene expression and ICAM-1 serum level.

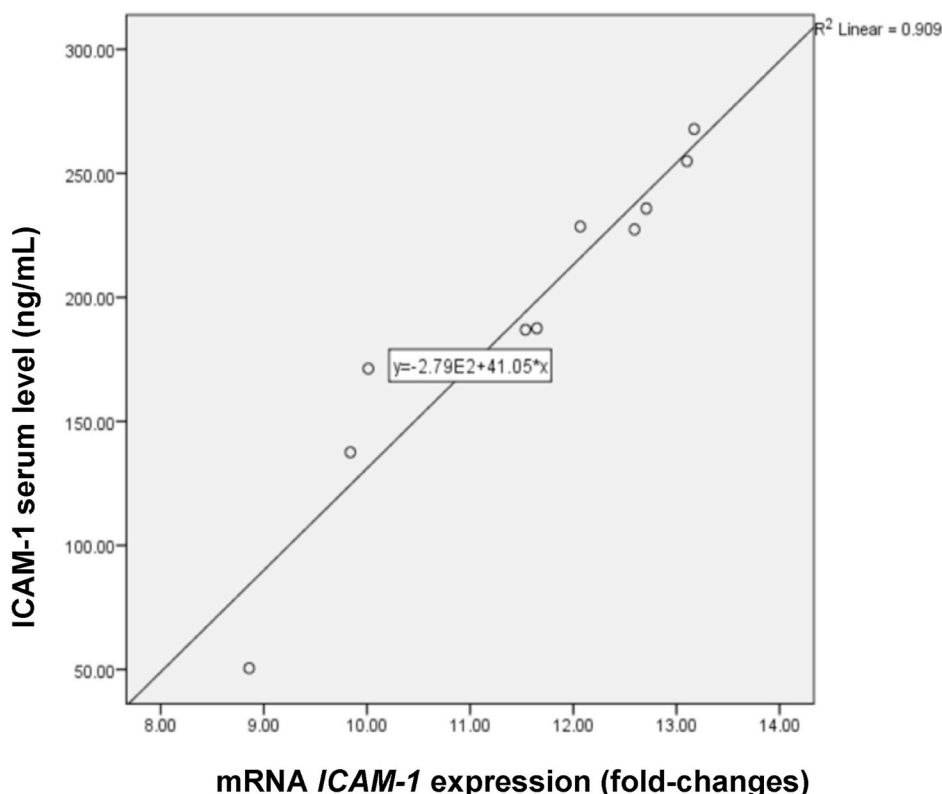| Variable	Group	Statistical value			p
		Before	After	Change	
ICAM-1 mRNA expression	HBOT ($n = 10$)	11.55 ± 1.50	9.05 ± 0.85	2.5 ± 1.91	.003
	Control ($n = 10$)	9.38 ± 0.78			
Serum ICAM-1 levels	HBOT ($n = 10$)	194.84 ± 64.64	92.97 ± 54.76	101.87 ± 82.57	.004
	Control ($n = 10$)				

Fig. 1. Correlation between ICAM-1 mRNA gene expression and serum ICAM-1 levels.

Table 6

Number of HBOT sessions on *ICAM*-1 mRNA gene expression and serum ICAM-1 level.

Variable	Number of HBOT sessions	Statistical value			p
		Before	After	Changes	
ICAM-1 mRNA	3 (n = 5)	10.79 ± 1.38	8.96 ± 1.07	1.82 ± 1.99	.222
	6 (n = 5)	12.32 ± 1.31	9.13 ± 0.67	3.18 ± 1.77	
Serum ICAM-1	3 (n = 5)	158.23 ± 68.30	107.01 ± 56.45	51.22 ± 61.78	.043
	6 (n = 5)	231.46 ± 37.20	78.93 ± 55.39	152.53 ± 71.48	

performing daily activities. On top of that, burn scars typically cause chronic sensory disturbances, pain, and itching [19]. Tissue damage caused by thermal burns occurs due to the failure of the surrounding tissues to provide oxygen and nutrients for the survival of cells adjacent to the injury. Obstructed circulation in the tissue underneath the injury results in the wound becoming less moisturized, chiefly by hindering fluid from passing through capillaries, which causes thrombus and obstruction due to leukocytes that generally delay the natural wound-healing process [20].

HBOT works by administering oxygen at a pressure exceeding 1 ATA, which allows intracellular oxygen diffusion. Adequate oxygen perfusion in tissues increases enzymatic metabolism in cells and accelerates wound healing [20]. Studies conducted with humans and animals on using HBOT to manage thermal burns have shown consistent, significant results in preventing skin ischemia, reducing edema, modulating the stasis zone, preventing further tissue damage, maintaining cellular metabolism, and promoting healing [21,22]. Those findings are in line with the results of our study, which revealed a significant correlation in the degree of complication between the HBOT group and control group (p = .006).

Epithelialization is an important event in the wound-healing process because it marks the initial stage of healing [23,24]. HBOT affects epithelialization by minimizing damage caused by thermal burns, thereby allowing new tissue to form on the wound's surface. Moreover, by accelerating cell division and the migration of epithelial cells, it can expedite healing [24]. In support, Susilo et al. found a significant correlation in epithelialization in rabbits between their HBOT group and control group (p = .024) [25]. As shown in Table 2, our study did not reveal a significant correlation between HBOT and degree of epithelization (p = .291), because most patients eventually underwent the epithelialization process. However, because a lesser degree of complication indicates faster epithelialization, it could be concluded that HBOT factors into accelerating the process.

Hart et al. reported a shorter length of hospital stay for patients with thermal burns who received HBOT than patients in their control group [26]. That finding was supported by other studies years later showing that the use of HBOT had significantly reduced the number of complications in the incidence of sepsis in patients with thermal burns due to prolonged hospital stays [27–30]. In our study, the length of hospital stay for patients who received HBOT (17.5 ± 4.3 d) was significantly less (p < .05) than that of patients in the control group (26.3 ± 7.6 d).

The *ICAM*-1 mRNA gene appears in low concentrations in the membrane of leukocytes and endothelial cells. With the stimulation of cytokines, the concentration of *ICAM*-1 mRNA increases and stimulates the formation of *ICAM-1* [31], a transmembrane protein that plays an important role in maintaining intercellular interactions and facilitating leukocyte migration [32]. *ICAM*-1 has sites that bind to macrophage adhesion ligand-1, leukocyte function-associated antigen (LF-1), and fibrinogen [33]. Those three proteins reside in endothelial cells and facilitate the firm adhesion between leukocytes and endothelium [33, 34]. That process relates to results in Fig. 1, which shows that as the expression of *ICAM*-1 mRNA increased in patients in our study, ICAM-1

serum level also increased, and the correlation was significant (R^2 = 0.909, p < .001).

Regarding the expression of the *ICAM*-1 mRNA gene and ICAM-1 serum level in patients who received HBOT, *ICAM*-1 mRNA expression in ones whose burns had TBSAs of at least 50% exceeded the expression in ones with burns with smaller TBSAs (11.61 ± 1.61 vs. 9.85 ± 1.27). The trend was the same for *ICAM-1* gene mRNA level, which was higher in patients whose burns had at least 50% TBSA than in ones with smaller TBSAs (12.32 ± 1.31 vs. 10.79 ± 1.38, p = .056), and for serum ICAM-1 level (231.46 ± 37.20 vs. 158.23 ± 68.30, p = .095). The data indicate that even if the results did not include any significant correlation, *ICAM*-1 mRNA gene expression was greater in patients in the HBOT group whose burns had TBSAs of at least 50%. A study by Zhu et al. confirmed that the enhanced expression of *ICAM-1* relates to the severity of the wound [35].

When local microcirculation is impaired for up to 24 h after burn injury, the process of edema soon follows. That process involves increased capillary permeability, decreased oncotic pressure, increased interstitial oncotic pressure, the widening of the interstitial space, and lymphatic damage. Changes at the microvascular level include the adhesion of neutrophils to the venule walls and the occurrence of platelet thromboembolism [36].

Treating burns focuses on reducing dermal ischemia, reducing edema, and preventing infection. During the initial hemodynamic period, the edema-reducing effect plays an important role in preventing the progression of thermal burns [37]. In our study, the HBOT group experienced a 2.50-decrease in the expression of the *ICAM*-1 mRNA gene before HBOT, from 11.55 ± 150 to 9.05 ± 0.85. Likewise, ICAM-1 serum level decreased by 101.87 from 194.84 ± 64.64 to 92.97 ± 54.76. Those results align with the findings of Yogaratman et al. who demonstrated that HBOT downregulates ICAM-1 [38]. In other work, Zamboni et al. also demonstrated HBOT's role as a potential inhibitor of neutrophil's adherence to endothelial cell walls, thereby breaking the cascade and prompting microvascular damage. Such microvascular damage generally occurs secondary to burns [39]. Beyond that, Wasiak et al. have reported HBOT's mechanism of inhibiting ICAM-1's activation and allowing microvascular flow to the burn area [40]. That effect lasts quite a long time and shows the benefits of HBOT on microcirculation [41–43].

As for the final variable, patients who received 6 HBOT sessions had significantly lower ICAM-1 serum levels (p < .05) than those who received only three sessions (152.53 ± 71.48 vs. 51.22 ± 61.78), although the expression of mRNA of the *ICAM*-1 mRNA gene (3.18 ± 1.77 vs. 1.82 ± 1.99) was not statistically significant (p > .05). In general, the longer that patients are exposed to HBOT, the shorter their inflammation period becomes, which consequently lowers their ICAM-1 levels. Cianci et al. have advised administering 6 to 10 HBOT sessions for patients with TBSA burns with TBSAs exceeding 40% [29,30]. That recommendation is consistent with Yogaratman et al.'s findings that HBOT inhibits ICAM-1. In short, more HBOT sessions lower the ICAM-1 serum level and increasingly accelerate wound healing [38].

5. Conclusion

Our study revealed several benefits of HBOT, including its ability to reduce thermal wound complications, the length of hospital stays due to thermal burns, and both *ICAM*-1 mRNA gene expression and ICAM-1 serum level. Those effects of HBOT have proven supportive in holistically managing thermal burns. A limitation of our study, however, was that the speed of epithelization between the HBOT group and control group was not compared, such that no significant correlation could be captured. Other applications of HBOT in managing thermal burns should be further examined in future studies.

Provenance and peer review

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Ethical approval

All procedure for human experiment has been approved by Ethics Commission of Kandou Hospital Manado, Number: 198/EC-KEPK/VI/2017.

Consent

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent on admission to use their prospective data base and files for research work.

Author contribution

MHO, MCO, DMA, JAK, AAI, MH, FJ, and MF wrote the manuscript and participated in the study design. MHO, MCO, DMA, and JAK drafted the manuscript. AAI, MH, FJ, and IJP checked the manuscript and made corrections. IJP performed bioinformatics analyses and revised the manuscript. MHO, and MCO provided the overall guidance and support. All authors read and approved the final manuscript.

Registration of research studies

This study has been registered with the Research Registry 6223 https://www.researchregistry.com/browse-the-registry#home/registrationdetails/5fa5324a8cf4a00018ab9176/

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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