Hyperbaric Oxygen Therapy Reduces Inflammation in Nickel Hypersensitivity

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Abstract

Nickel material is long-established used in dentistry due to its several advantages. Nickel's use in the alloy is mainly because of the reasonable price compared to precious alloy, has sufficient hardness, and good physical and mechanical properties. However, the use of Nickel has a risk of causing an allergic reaction, that is, type IV hypersensitivity. Nickel allergy prevention can be done by genetic therapy but at an expensive cost. This study used an alternative hyperbaric oxygen therapy (HBOT) 2,4 ATA, which has anti-inflammatory effects, inhibits inflammatory cytokines, and affects epithelial thickness.

This study was carried out to determine the influence of HBOT on changes in the number of macrophages cells, neutrophils cells, and epithelial thickness in inflammation caused by hypersensitivity reaction of BALB/C mice induced by Nickel.

Fifteen BALB/C mice were randomly divided into three groups: a negative control group without therapy, a positive control group using corticosteroid therapy, and an HBOT group. All groups were given an intraperitoneal injection of NiCl2+IFA on the first sensitization and NiCl2+CFA on the second sensitization intradermally. The positive control group was given the corticosteroid dexamethasone at a dose of 0.02 mg/mouse/day on days 11-13; the HBOT group was given HBOT 2.4 ATA for 3x30 minutes with 5-minute intervals for three days on days 11-13. The ears of BALB/C mice were taken 48 hours after the second injection and examined with Haematoxylin Eosin staining. The data were analyzed by using One Way ANOVA and Tukey-HSD test.

There were a significant decrease in the epithelial thickness and both macrophages and neutrophil cells by using HBOT. It was shown that HBOT effectively reduced inflammation in the ears of mice with nickel hypersensitivity.

Experimental article (J Int Dent Med Res 2022; 15(2): 587-593)

Keywords: Nickel hypersensitivity, inflammation, macrophages, neutrophils, hyperbaric oxygen therapy.

Received date: 05 December 2021 **Accept date:** 03 January 2022

Introduction

Nickel is one of the metal materials often used as a mixture in alloys. Nickel as a base metal in alloys, among others, nickel-titanium alloys in orthodontic wire (archwire) and endodontic instruments, NiCr (nickel-chromium) alloys are widely used as orthodontic wires, metal-based denture frames, crowns, and bridges.[1,2] Nickel is widely used because Nickel has several advantages; among others, it is easy to apply, resistant to high temperatures, and has good attractiveness and physical properties. Nickel can increase the strength and hardness of an alloy and whiten the alloy's color.[3,4]

Stainless steel immersed in various brands of mouthwash and artificial saliva solutions with various toothpaste brands. However, the use of dental materials that have a base material or a mixture of Nickel can cause hypersensitivity due to the presence of corrosion and high levels of oxidation. Allergic reactions occur when individuals with allergic predisposing factors who have been sensitized are re-exposed to the same allergen and then caused allergic inflammation. In a study conducted by Minaga et al., 2016[5] the results were obtained in releasing nickel ions in orthodontic wires.

Based on research conducted by Wawrzynski (2017)[6,] the prevalence of nickel

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allergy reaches 15.5% of the North American population. According to Schmalz and Bindslev (2009)[7], one in 400 patients in prosthodontics has an allergy to base metals used in dentistry, or it can be called, 15% of patients from the general population have an allergy to Nickel, 8% to cobalt, and 8% to chromium.

Hypersensitivity is when the body's immune system responds excessively to an antigen. Hypersensitivity is related to inappropriate immunological reactions in the body's efforts to heal the injury, which can cause more extensive tissue damage and is a process of the course of the disease.[8] Hypersensitivity is divided into four types based on cells. The immune system that plays a role in the mechanism is a type I, II, III, and IV.[9]

Hypersensitivity caused by Nickel is a type IV hypersensitivity reaction or delayed-type hypersensitivity.[10] This hypersensitivity reaction can provide an inflammatory response that is not easily distinguished from an inflammatory reaction due to a non-allergic process.[2] In type IV hypersensitivity, CD4+ Th1 cells activate macrophages that act as cell effectors and induce inflammation.[9] When inflammation occurs, the number of macrophages will increase rapidly due to an increase in monocytes in the blood and macrophage division in the tissue.[11] Tissue damage in DTH (delayed-type hypersensitivity) is caused by macrophage products that are activated by lytic enzymes, reactive oxygen intermediates, nitric oxide, and pro-inflammatory cytokines.[12]

In type IV hypersensitivity, CD4+ Th1 cells release the cytokine IFN-α which will activate macrophages so that they secrete TNF, IL-1, and chemokines that will produce inflammation.[9] Neutrophils will secrete pro-inflammatory cytokines and anti-inflammatory cytokines and secrete proteases to degrade the remaining extracellular matrix. At the time of inflammation, the number of macrophages will increase rapidly due to increased monocytes in the blood and the division of macrophages in the tissue.[13] Tissue damage in DTH (delayed-type hypersensitivity) is caused by macrophage products activated by lytic enzymes, reactive oxygen intermediates, and nitric oxide. And pro-inflammatory cytokines.[8]

In humans, the clinical manifestations of allergic reactions to Nickel are burning, inflammation, pain, and dryness of the mucosa to non-specific stomatitis and cheilitis. A study conducted by Watanabe et al. (2011)[14] showed a picture of infiltration of inflammatory cells in the connective tissue and ear tissue of mice that were given Ni injection. Clinically there was an increase in thickness and swelling of the ear of the mouse. [10] In a study conducted by Ashrin et al. in 2014[15], namely by administering siRNA injections of TSLP (Thymic Stromal Lymphopoietin) and atelocollagen in Nickel model mice ears three days before the elitism phase or the second injection of nickel induction could provide a significant reduction effect on mice ear thickness compared to the nickel model mice that were not given any therapy.

The therapy commonly used for type IV hypersensitivity is symptom suppression by reducing inflammation using corticosteroids.[9] However, large amounts of corticosteroids for a long time have side effects.[16] Some examples of side effects associated with corticosteroids are bone disorders, adrenal suppression, hyperglycemia, cardiovascular disease, dyslipidemia, hypertension, and immunosuppression. One alternative treatment for inflammation is the administration of HBOT, which can also be used in patients with chronic inflammation where NSAIDs are contraindicated or where NSAIDs are ineffective.[17,18]

Giving HBOT is a therapeutic method using 100% pure oxygen with air pressure greater than normal atmospheric pressure, namely, 2-3 ATA (Absolute Atmosphere). It is commonly used as therapy in decompression sickness patients and can regulate osteoblast differentiation.[19] Administration of HBOT can increase the amount of dissolved oxygen in the body plasma. A condition is reached where oxygen demand can be met from dissolved oxygen without using oxygen bound to hemoglobin. Administration of HBOT can also help prevent infection, reduce inflammation and accelerate wound healing. [20] Administration of HBOT with a pressure of 2,4 ATA can increase Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS); ROS function as signaling molecules in transduction for various growth factors, ATP synthesis, and hormones that stimulate angiogenesis as well as osteoblastic and osteoclastic activity.[19,21]

In the Brahmanta study (2019),[19] administration of HBOT 2,4 ATA for 3x30 minutes with 5-minute intervals performed 7 to 10

days during tooth movement can increase the volume of trabecular bone and the amount of trabecular bone, indicated by the amount of osteoblast activity. It showed a beneficial effect in the 2-4 day trial compared with the 1-day trial in inhibiting active inflammation (reduced levels of pro-inflammatory cytokines IL-1β and TNF-α, inhibited oxidative stress, and increased production of anti-inflammatory cytokines). inflammation (IL-10) in mouse brain induced by MCAO (middle cerebral artery occlusion).[22]

Macrophages isolated from mice exposed to HBOT produced fewer pro-inflammatory cytokines than cells from unexposed controls, reducing inflammation.[23] Administration of HBOT has also been shown to have an anti-inflammatory effect obtained by inhibition of IFN-γ, TNF-α, IL- 1, and IL-6, which will cause a decrease in the number of macrophages after the elitism phase, which will trigger a decrease in the inflammatory response.[24]
Researchers hope that the administration of HBOT can reduce inflammation in hypersensitivity caused by the use of Nickel in dentistry. Based on the description above, researchers are interested in knowing the effect of giving HBOT as an alternative therapy that can reduce the inflammatory response in nickel hypersensitivity. This study will observe the administration of HBOT 2,4 ATA for 3x30 minutes with an interval of 5 minutes for three days to observe the inflammatory response (macrophages, neutrophils, epithelial thickness).

Materials and methods

This research was an experimental laboratory type with a post-test-only control group design. The experimental unit used was 16 male Mus Musculus Balb/C aged 2-3 months. The sampling technique used was the simple random sampling technique. Mus Musculus Balb/C was divided into three groups: nickel-induced group as the negative control group, nickel-induced with corticosteroid therapy group as the positive control group, and nickel-induced with HBO therapy treatment. All groups were sensitized using a combination injection of NiCl2 and Incomplete Freud's Adjuvant (IFA) with a composition of 125µl NiCl2 and 125 µl IFA intraperitoneally on the first day. Positive groups were given corticosteroid medication orally on days 11-13, while HBO therapy groups were given HBO therapy 3x30 minutes at 5-minute intervals on days 11-13. Ethical clearance for this research was obtained from the Ethics and Scientific Research Committee of Experimental Animal Use in the Faculty of Dentistry Universitas Hang Tuah.

Before intradermal injection into mice ears, anesthesia was administered 10% ketamine at a 0.1 ml/kg BW intramuscularly. On the 14th day, the intradermal injection was carried out in the ears of mice in all groups with a combination of NiCl2 solution and Complete Freud's Adjuvant (CFA) with a composition of 10µl NiCl2 and 10µl CFA used a 26G needle to obtain a type-4-hypersensitivity response (delayed-type hypersensitivity). [14-15] Then, on the sixteenth day, all groups were sacrificed by first euthanizing using ketamine plus xylazine and cutting the ears to observe the number of macrophages, neutrophils, and epithelial thickness in histopathological inflammation Haemotoxylin and Eosin staining.

Results

Data tabulation on the observation of the number of neutrophils carried out on the third day using the image raster® application can be seen in Figures 1 and 4. The data tabulation and analysis results using the Tukey-HSD test are shown in Table 1. Statistical analysis showed a significant difference between the negative control groups with the positive control group given corticosteroids (K+) and the group given HBOT. A non-significant difference was shown in the K+ group with HBOT.

The data tabulation and analysis results using the Tukey-HSD test are shown in Table 1. Data tabulation on the observation of the number of macrophages which was also carried out on the third day using the image raster® application can be seen in Figures 2 and 4. Statistical analysis showed significant differences between groups K- with K+, K- group with HBOT and K+ with HBOT.

Data tabulation on the observation of epithelial thickness on the third day using the image raster® application can be seen in Figures 3 and 5. The data tabulation and analysis results using the Tukey-HSD test are shown in Table 1. Statistical analysis shows a significant difference between the K-group with K+ and HBOT, while no significant difference was shown in the K+

group with HBOT.

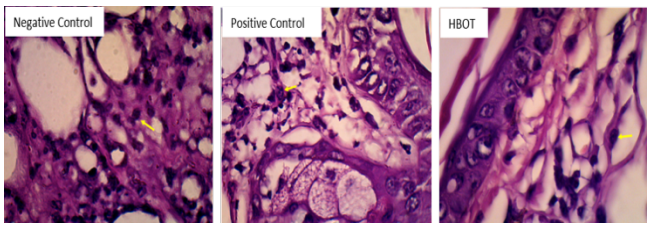

Figure 1. Histological section of neutrophils with nickel-induced and treatment by corticosteroid and HBOT in BALB/c ears.

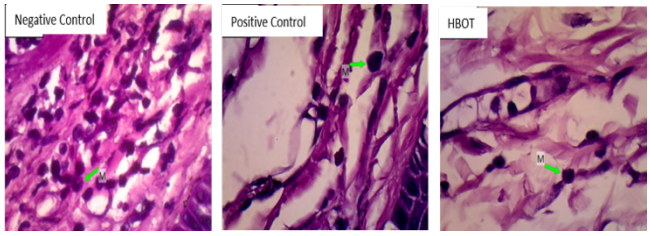

Figure 2. Histological section of macrophages with nickel-induced and treatment by corticosteroid and HBOT in BALB/c ears.

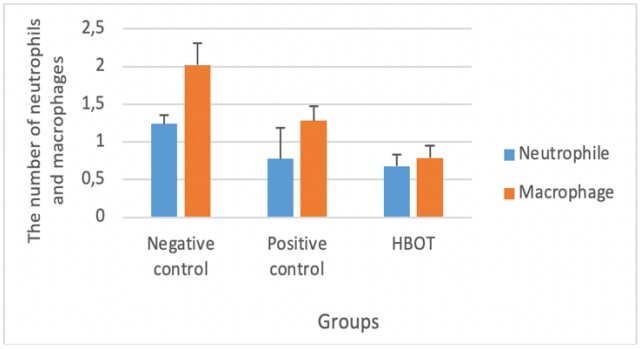

Figure 3. The graph on the observation of neutrophils and macrophages in the negative control group (nickel-induced), positive control group (nickel-induced and corticosteroid treatment), and the HBOT group (nickel-induced and HBOT).

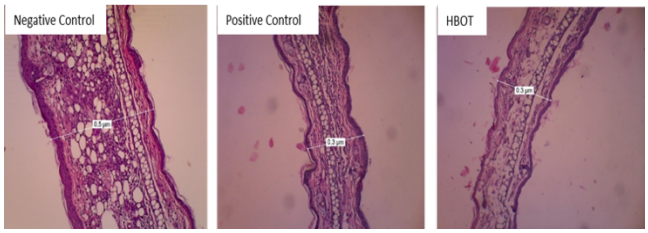

Figure 4. Histological section of the thickness of epithelium with nickel-induced and treatment by corticosteroid and HBOT in BALB/c ears.

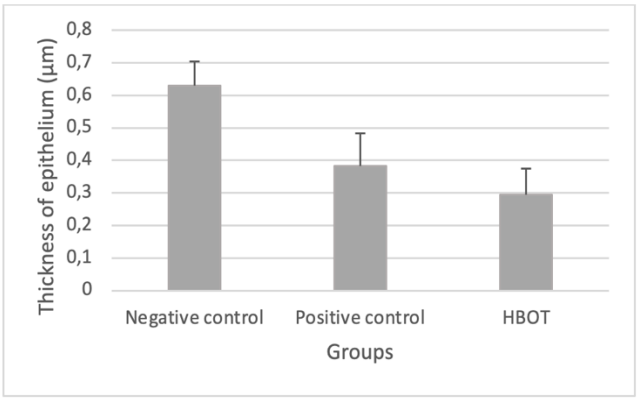

Figure 5. The graph on the observation of the thickness of epithelium in negative control group (nickel-induced), positive control group (nickel-induced and corticosteroid treatment), and the HBOT group (nickel-induced and HBOT).

groups	Neutrophile	Macrophage	The thickness of epithelium (µm)
	X ± SD	X ± SD	X ± SD
Negative control	1.2400 ± 0.11402[a]	2.0200 ± 0.28636[a]	0.6300 ± 0.07314[a]
Positive control	0.7740 ± 0.40912[b]	1.2800 ± 0.19235[b]	0.3820 ± 0.10085[b]
HBOT	0.6800 ± 0.14832[b]	0.7900 ± 0.15969[c]	0.2940 ± 0.08173[b]
One way Anova analysis	0.000*	0.011*	0.000*

Table 1. Analysis of observational data on the thickness of the epithelium, neutrophils, and macrophages in BALB/c ears.
Note : *significant difference. [a,b,c] The difference between groups with a significance level of 5% ($p < 0.05$) in the Tukey-HSD analysis.

Discussion

Hyperbaric therapy is known to have many advantages in curing various diseases. Hyperbaric oxygen therapy for wound healing in BALB/C mice at a pressure of 2.4 ATA for 30 minutes was the most effective time. The use of HBOT 2,4 ATA for 3x30 minutes with an interval of 5 minutes for three days was provided to prevent inflammation in cases of nickel allergy. This study was conducted to determine the number of macrophages, neutrophils, and epithelial thickness seen from histology examination because, according to the research of Andriani et al. (2021)[25], analysis of the differential count of inflammatory cells in the blood of mice with a nickel allergy model did not show significant changes in the allergic nickel group compared to the control group.

In this study, nickel allergy or delayed-type allergy, or Type IV reaction was obtained by employing two inductions. The first phase is the

sensitization phase, and the second phase is the sensitization phase. Previous studies reported that in the ears of mice with a nickel allergy model, swelling, increased epithelial thickness, and infiltration of inflammatory cells such as mononuclear cells, neutrophils, monocytes, and macrophages were found.[15,26,27]

Neutrophils play a role in the sensitization phase of Contact Hypersensitivity.[28] Neutrophils can exert potent antimicrobial and pro-inflammatory reactions and release various cytokines.[29] The release of these cytokines increases tissue inflammation and results in a prolonged healing process and chronic inflammation.[30] This study showed high neutrophil counts in the nickel allergy group and low neutrophil counts and significantly different from systemic corticosteroid therapy and HBOT. The result shows that the administration of both therapies can reduce the number of neutrophils. The decrease in neutrophils is a sign of reduced inflammation in the nickel allergy model.

In the statistical analysis, the number of neutrophils in the nickel allergy group treated with corticosteroids compared with the nickel allergy group treated with HBOT showed no significant difference. Both therapies have the same ability to reduce the number of neutrophils. Topical or systemic glucocorticoids are commonly used in contact dermatitis, an allergic condition caused by exposure to low molecular weight compounds such as metals.[31] Dexamethasone is a glucocorticoid that prevents activation, adhesion, adhesion function, and phagocytosis of neutrophils.[32] The decreasing effect of HBOT is consistent with several studies showing that hyperbaric oxygen therapy (HBOT) has the ability to promote healing in patients with diabetic ulcers and chronic wounds due to the reduction of inflammatory cytokines and a significant reduction in the recruitment of neutrophils to the damaged area.[33]

Research by Nakasone et al. (2018)[27] showed a large number of macrophages on the first day after sensitization of the second nickel allergy model using 2,4-dinitro-1-fluorobenzene (DNFB). In this study, the number of macrophages was highest in the nickel allergy group and decreased in receiving systemic corticosteroid therapy and HBOT. This result suggests that an increase in epithelial macrophages initiates inflammation in this allergy model. Inflammation in nickel allergy in oral mucosa is initiated by macrophage response to Nickel and subsequent infiltration of T cells in mucosal tissue after the presentation by antigen-presenting cells on macrophages.[27]

In addition, this study also showed that the administration of both therapies for three days could reduce the number of macrophages. Macrophages are cells that play a role in homeostasis and inflammation. Macrophages differentiate into an M1 phenotype that plays a role in the inflammatory response by producing pro-inflammatory cytokines, chemokines (TNF-α, IL-1β, IL-12, etc.) and promoting innate immunity. In contrast, the M2 phenotype plays a role in the inflammatory response in tissue repair and remodeling. by releasing anti-inflammatory cytokines, chemokines, and growth factors (IL-10, TGF-β, CCL18).[34,35] In this study, the decrease in the number of macrophages indicates reducing inflammation and accelerating healing.

The number of macrophages differed significantly in the treatment group treated with corticosteroids compared to the nickel allergy group treated with HBOT. The number of macrophages in HBOT was less than in the corticosteroid therapy group. Dexamethasone is known to be a glucocorticoid that has sound anti-inflammatory effects. This anti-inflammatory effect is obtained because glucocorticoids can inhibit the production of pro-inflammatory cytokines produced by monocytes and macrophages, including IL-1β, IL-6, IL-12, TNFα, or GM-CSF, and have a down-regulating effect on the expression of chemokines such as IL. -8, RANTES, and MCP-1.[36] In this study, HBOT therapy was able to reduce the number of macrophages more than dexamethasone. HBO2 has essential effects on the biology of cytokines and other inflammatory mediators. This therapy can downregulate pro-inflammatory cytokines, affect TNF- and upregulate growth factor VEGF (vascular endothelial growth factor), and reduce PGE2 and COX-2 mRNA.[24]

Epithelial thickness indicates the presence or absence of inflammation in the induced area. This study showed an increase in epithelial thickness in the nickel allergy or control groups. Watanabe et al. (2011)[14] reported the presence of inflammation in the ears of rats induced by Nickel, seen from redness in the ears and an increase in the thickness of the ear epithelium. Nakasone et al. (2018)[27] reported an increase in mucosal thickness, indicating

inflammation in mice with a nickel allergy model. Histologically, the epidermal area of the mouse ear induced with Nickel added to IFA and CFA showed edema, and a large number of inflammatory cell infiltrates, including mononuclear cells, monocytes, neutrophils, and macrophages.[14]

Compared with the nickel allergy group, the group with systemic corticosteroid therapy and HBOT showed decreased epithelial thickness. It showed that the administration of therapy reduces the thickness of the epithelium. There was no significant difference between the two groups. These results showed that both therapies have the same effect in reducing inflammation in the nickel allergy group. The results of our study are in line with the study by Khalmuratova et al. (2011)[37] showed that dexamethasone therapy could reduce the epithelial thickness index in the septal mucosa of injured rats compared to normal controls. Kim et al. (2014)[38] reported a decrease in the thickness of the ear epithelium and a reduced effect of inflammation in the ears of mice with atrophic dermatitis. Our study showed that HBO therapy effectively reduced inflammation in the ears of mice with nickel allergy.

Conclusions

In this study, it was generally concluded that HBOT 2.4 ATA 3x30 minutes at intervals of 5 minutes for three days before the second sensitization of Ni could reduce the number of macrophages, neutrophils, and the epithelium thickness in the inflammatory area due to hypersensitivity of nickel material. This effect reduces inflammation in the ears of mice with nickel allergy and has the same ability compared with dexamethasone. The result shows that HBOT is a promising therapy for nickel allergy.

Acknowledgments

This research was supported by the Grants-in-Aid for Scientific Research from the Indonesian Ministry of Research and Technology. The authors would like to thank F. Batul, MSWP. Artha, MRP. Prabowo, FR. Humairoh, D. Atika and AI. Pramana for technical supports.

Declaration of Interest

All authors report no conflict of interest.

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