The Role of HBOT on Pulp Capping Treatment in Enhancing TGF-β Levels: Scoping Review

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Abstract

Deep caries could harm the vitality of the pulp, so it is necessary to protect the pulp with pulp capping procedure. Pulp capping material will release growth factors, one of it is TGF-β which plays a role in pulp tissue repair. Hyperbaric Oxygen Therapy (HBOT) is a treatment that can be used as an adjunct therapy in wound healing. TGF-β levels can be increased by HBOT procedure. This study aimed to determine the role of HBOT on the success of pulp capping treatment in terms of increasing levels of growth factor TGF-β.

A scoping review was conducted refers to PRISMA Extension for Scoping Reviews (PRISMA-ScR) Protocols through 4 databases included PubMed, Science Direct, Wiley Online Library and Google Scholar. Inclusion and exclusion criteria according to the Population, Concept, and Context (PCC) framework.

A total 6 articles showed an enhancing in TGF-β levels after HBOT with difference of HBOT treatment, other treatment, and measurement of TGF-β expression.

Administration of HBOT will increase levels of TGF-β growth factor in the process of tissue repair. Thus, has the potential to increase the success of pulp capping treatment in terms of increasing levels of TGF-β growth factor.

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Introduction

The vital pulp can become exposed by deep caries or iatrogenic trauma during cavity preparation close to the pulp-dentin complex.[1] Treatment that can be done to maintain pulp vitality is pulp capping.[2] Pulp capping is a procedure in which a medicament is placed directly over the exposed dental pulp.[3] Pulp capping treatment plays a role in the regeneration of the pulp-dentin complex to maintain pulp vitality and promote the formation of a dentinal bridge.[4] Pulp capping material releases growth factors in the dentin matrix that contribute directly to modulating the cascade cellular events on pulp tissue repair.[5]

Dentin acts as a barrier to the dental pulp from direct contact with potentially damaging external stimuli. Tertiary dentin is the tissue formed as a response to various stimuli that can increase the thickness of the dentin barrier.[1] Tertiary dentin is a dentinal deposit secreted by odontoblasts in response to tooth injury.[6] Tertiary dentinogenesis is divided into reactionary dentinogenesis and reparative dentinogenesis. This depends on the severity of the initial response and the condition of the newly deposited dentin matrix.[7]

Pulp tissue repair is a molecular and cellular process in which various growth factors play a role in the process.[8] The TGF-β superfamily is a group of growth factors that play an important role in regulating growth regulation, differentiation, and cell function as well as the process of tissue repair after tooth injury.[7] In the process of reactionary dentin formation, growth factors play a role in cell proliferation, maintaining homeostasis as a mediator of odontoblast differentiation, dentin mineralization, and repair of tooth tissue after injury.[9] The process of reparative dentin formation consists of three

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stages, those are: (1) recruitment of progenitor cells, (2) signaling of odontoblast-like cell differentiation, and (3) regulation of matrix secretion by cells.[10] The progenitor cells formed will induce molecular signals for the initiation of odontoblast-like cell proliferation, migration, and differentiation.[11] After odontoblast differentiation, growth factor secretion occurs as a signal for reparative dentin formation by odontoblast-like cells.[9]

The process of successful healing of pulp tissue is influenced by the oxygen content in the blood vessels. This is related to the pulp which has high vascularity and is effective in supplying nutrients for tooth regeneration.[12] One of the therapies that can be used to stimulate the process of accelerating tissue healing is to use hyperbaric oxygen therapy.[13,14] Hyperbaric Oxygen Therapy (HBOT) is therapeutic administration of 100% oxygen at pressure higher than 1 absolute atmosphere (ATA) with a maximum desired pressure of 3 ATA for 60 to 120 minutes.[14,15]

The mechanism that occurs in HBOT therapy in general is an increase in ambient pressure and oxygen pressure (PaO_2).[16] An increase in PaO_2 will increase dissolved oxygen in the plasma which will diffuse into the extravascular and intracellular spaces, then be used by cells for metabolism.[17,18] This situation will triggers increased fibroblast activity, angiogenesis for neovascularization, collagen synthesis, and increased leukocyte phagocytic effect.[18] Oxygen molecules produce Reactive Oxygen Species (ROS) such as free radicals, superoxide ions, and hydrogen peroxide (H_2O_2) which release "respiratory brust" rapidly to destroy pathogens.[19] ROS, Nitric Oxide (NO), and Reactive Nitrogen Species (RNS) play a role in signaling molecules for transduction cascades of various growth factors, cytokines, and hormones.[20] Thus, this scoping review study aimed to determine the effect of hyperbaric oxygen therapy on the success of pulp capping treatment in terms of increasing levels of growth factor TGF-β.

Materials and methods

This research was conducted using a scoping review method by searching for articles based on the PCC (Population-Concept-Context) framework. Population: Hyperbaric Oxygen Therapy (HBOT), Concept: TGF-β in the process of tissue repair, and Context: Original research articles. The process of searching and selecting articles was based on the PRISMA Extension for Scoping Reviews (PRISMA-ScR) Protocols. The article search strategy was carried out on the PubMed, Science Direct, Wiley Online Library, and Google Scholar databases. The search was carried out on the database using keywords combined with Boolean Operators as follows ((hyperbaric oxygen therapy) OR (hyperoxia) OR (HBOT)) AND ((wound healing) OR (tissue repair)) AND (increase) AND ((transforming growth factors-β) OR (TGF-β)). The PRISMA-ScR flow chart can be seen in Figure 1. After that, full-text articles were selected according to the inclusion and exclusion criteria (Table 1) and then analyzed.

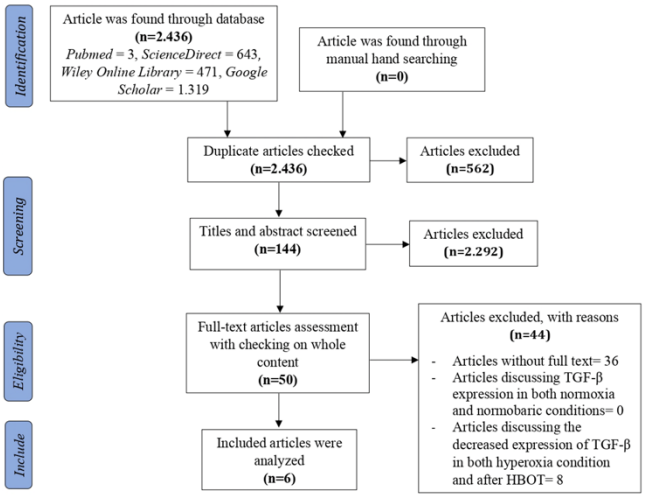

Figure 1. PRISMA-ScR Flow diagram.

Result

After searching and selecting articles, 6 articles were obtained that matched the inclusion criteria. The articles analyzed showed a significant increase in TGF-β levels after HBOT treatment with differences in HBOT treatment, other treatments, and measurement of TGF-β expression. (Table 2.)

Discussion

Increased levels of TGF-β after HBOT treatment were reported in six articles. In a study conducted by Arya et al. reported that administration of HBOT to 24 guinea pigs C. Cobaya which had been fitted with a rubber

separator to induce OTM (orthodontic tooth movement), showed an increase in TGF-β expression on the tension side compared to the pressure side.[21] OTM (orthodontic tooth movement) is a results from remodelling of the periodontal ligament and alveolar bone. The process of bone remodelling is regulated by osteoblasts and osteoclasts. Osteoclasts in pressure areas will resorb so that the tooth movement and this phenomenon will be balance by osteoblast in the tension area. TGF-β1 stimulates osteoblastogenesis and new bone formation along with inhibiting osteoclastogenesis in the process of bone resorption.[22]

Article by Praveen et al. compared the results of administering HBOT to the periodontal tissue of maxillary molar on days 15 and 28 with a sample of 17 adult male Wistar rats. The results showed that on day 15, TGF-β1 mRNA levels increased significantly compared to day 28. It was found that the tissue remodelling process was faster in rats treated with HBOT than in the control group. Injured periodontal tissue will usually experience hypoxia due to the presence of cells with high oxygen demand and impaired blood supply.[23] This is similar with study from Dilek and Apdhogan, which described that periodontal infection will cause hypoxia which can cause vascular changes.[24] Hyperoxia due to the use of HBOT causes an increase in TGF-β levels which will increase the concentration of oxygen in the plasma so it help the healing process by preventing further inflammation and tissue damage.[17,25]

Article written by Kun et al. in 6 Sprague Dawley rats that had been injected with rat c6 glioma cells, showed an increase in TGF-β levels in the group with glioma tumor tissue treated with HBOT.[26] Similar with the study from Lucy et al, that during glioma development or following therapeutic treatment, areas of necrotic glioblastoma develop into hypoxic areas that promote tumor development, potential for infiltration and migration, and recurrence.[27] According to Younis, hypoxic is an early stage in injury resulting in vascular disruption, and increased cellular metabolism, as well as oxygen consumption.[19] The use of HBOT in this condition will increase PaO_2 levels much higher above normal healthy tissue.[28] This is similar with study by Mohamed et al, showed that an increase in PaO_2 correlated with an increase in TGF-β1 levels which play a role in tissue repair.[29]

Article by Jacek et al. in 83 patients treated with hyperbaric treatment showed that the effect of HBOT on blood levels of cytokines and arginine derivatives in conditions of inflammation and endothelial injury. Prolonged inflammation induces oxygen deficiency in the involved tissues due to capillary destruction, edema, and bacteria under hypoxic conditions.[30] Endothelial cells respond to these conditions through a signaling cascade that is dependent on oxygen levels. This is similar with study by Reila et al, which described hypoxic conditions are influenced by oxygen levels and the presence of cytokines, one of which is TGF-β.[31] HBOT significantly increases the concentration of oxygen in blood plasma that diffuses into damaged tissues to eliminate anaerobic bacteria and increase neutrophil-mediated inflammatory responses.[30]

Article written by Fang et al in 168 Sprague Dawley rats described received HBOT treatment with TBI (Traumatic Brain Injury), showed a significant increase in TGF-β1 levels at 72 hours and 7 days. Increased levels of TGF-β1 will induce inflammation and apoptosis so that it can increase the microimmunity environment for neurons to survive.[32] Rachel et al explained that TGF-β1 activation plays a role in inflammatory and apoptotic processes that affect blood vessel circulation and the formation of blood-brain barrier in brain injury.[33] The use of 100% O_2 HBOT with >1 ATA in TBI patients increases the plasma O_2 concentration which has an effect on increased delivery of O_2 to diffuse into brain tissue.[34]

Article written by Na et al. in 102 patients with delayed encephalopathy after carbon monoxide poisoning (DEACMP), showed that glucocorticoid treatment in combination with HBOT could increase TGF-β1 levels resulting in significant tissue repair.[35] Lina et al. concluded that the use of HBOT in patients with delayed encephalopathy plays a role in repair of brain injury and neural regeneration by circulating stem cell mobilization.[36] The use of HBOT will increase the production of Reactive Oxygen Species (ROS)[37] by activating and stimulating the expression and secretion of TGF-β1.[38] TGF-1 plays a role in the development and homeostasis of central nervous system immunity.[39]

Oxygen plays an important role in energy production and cell metabolism. In this case,

oxygen is required for intracellular processes such as biosynthesis, transport, and cell survival. Oxygen also plays a role in the respiratory burst process (release of reactive oxygen species). ROS are very important in the growth factor signaling process, leukocyte recruitment, cell motility, angiogenesis, and extracellular matrix formation involved in wound healing.[40] It should be noted that several conditions are contraindications to the use of HBOT, such as heart disease, high fever, upper respiratory tract infection, and emphysema with CO_2 retention.[41] In dentistry, the use of HBOT as an adjunct therapy after pulp capping has the potential to increase TGF-β levels. This plays a role in accelerating the regeneration process of the pulp-dentin complex to maintain pulp vitality.

The limitation of this study is that there are no articles explaining the use of HBOT after pulp capping treatment. Further experimental research is needed to determine the effect of HBOT treatment in dentistry, especially endodontics.

Conclusion

Based on the analysis of all articles, administration of HBOT will increase levels of TGF-β growth factor in the process of tissue repair. Thus, has the potential to increase the success of pulp capping treatment in terms of increasing levels of TGF-β growth factor.

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Declaration of Interest

The authors report no conflict of interest.

Inclusion Criteria	Exclusion Criteria
1. Full-text articles in Indonesian and English 2. Articles published between 2016-2022 3. Articles discussing increased TGF-β expression after HBOT 4. Articles discussing increased TGF-β expression in hyperoxia condition	1. Articles without full text 2. Articles discussing TGF-β expression in both normoxia and normobaric conditions 3. Articles discussing the decreased expression of TGF-β in both hyperoxia condition and after HBOT.

Table 1. Inclusion Criteria and Exclusion Criteria.

Author (Year)	Title	Study Design	Sample	Method		Measurement of TGF-β Expression	Results	Conclusion
				HBOT Treatment	Other Treatment			
Arya et al.[21] (2021)	The effect of hyperbaric oxygen 2.4 absolute atmospheres on transforming growth factor-β and matrix metalloproteinase-8 expression during orthodontic tooth movement in vivo	Analytic Observational	n= 24 guinea pigs C. Cobaya male weighing 300-400 gr Sample= maxillary teeth and bones	Control Group= N/A Test Group 1= N/A Test Group 2= • Level O_2= 100% • Pressure = 2.4 ATA • Duration= 3 x 30 minutes • Total sessions= 7 days	Control Group= N/A Test Group 1= Paired with a rubber separator to induce OTM (orthodontic tooth movement) before HBOT Test Group 2= Rubber separator was installed to induce OTM (orthodontic tooth movement) before HBOT	Using staining of paraffin block preparations with immunohistochemistry on the side that is subjected to tension and compression during OTM (orthodontic tooth movement)	In Test Group 2, TGF-β expression increased on the tension side an average of 1.79 ± 0.37 ($p < 0.05$) compared to 0.79 ± 0.16 ($p < 0.05$) on the pressure side.	In vivo, the use of ROBOT can increase TGF-β expression on the tension site compared to the pressure site during OTM.
Praveen et al.[23] (2017)	Increased oxygen exposure alters collagen expression and tissue architecture during ligature-	Animal Research	n = 17 adult male Wistar rats aged 18 weeks Sample = periodontal tissue	Control Group = N/A Test Group= • Level O_2= 100%	N/A	Measurement of TGF- β1 expression was carried out by real-time PCR (polymerase chain reaction) using samples that had been	TGF-β1 mRNA levels increased significantly at day 15 ($p = 0.66$) but decreased on day 28 ($p = 0.21$) in the hyperoxia-	After 15 days, TGF-β1 expression was increased after hyperoxia treatment

	induced periodontitis		in the maxillary molar segment	• Pressure = 2.5 ATM • Duration= 2 x 2 hours • Total sessions= 14 and 28 days		frozen in 1 mL of TRIzol and stored at -80°C.	treated group compared to the control group	
Kun et al.[26] (2019)	Hyperbaric oxygen suppresses stemness-associated properties and Nanog and oncostatin M expression, but upregulates β-catenin in orthotopic glioma models	Animal Research	n= 6 Sprague Dawley rats aged 12 weeks weighing 250-280 gr Samples were taken using the flow cytometry method	Control Group= N/A Test Group= • Level O_2= 100% • Pressure = 3 ATM • Duration= 1 hour • Total sessions= 6 days	N/A	TGF-β concentrations were analyzed using the Rat TGF-β ELISA kit according to the manufacturer's instructions	TGF-β levels increased in the glioma tumor tissue group that received HBOT treatment (p= 0.013)	TGF-β levels increased in the group receiving HBOT treatment
Jacek et al.[30] (2021)	Effect of hyperbaric oxygen on blood cytokines and arginine derivatives; no evidence for induction of inflammation or	Retrospective	n= 83 Patients in the Hyperbaric Health Department Sample= Blood serum (n=45) patients with idiopathic	Control Group= N/A Test Group= • Level O_2= 100%	Control Group= N/A Test Group= • ISSNHL patients= systemic steroid therapy	TGF-β levels were measured using an enzyme-linked immunoasorbent assay (ELISA) kit before HBOT and after the 15th session.	Comparison of TGF-β levels in ISSNHL and NSTI patients after HBOT treatment (p=0.004) Comparison of TGF-β levels in	In injured endothelial cells, HBOT treatment increased TGF- levels
	endothelial injury		sudden sensory neural hearing loss (ISSNHL), (n=18) necrotizing soft tissue infection (NSTI), dan (n=6) aseptic bone necrosis (ABN)	• Pressure = 0.25 MPa • Duration= 60 minutes • Total sessions= 28 weeks (the number of sessions per patient differs dependin g on the indication for his treatment)	concurrently with HBOT • NSTI patients= local surgical treatment and concurrent broad-spectrum antibiotic therapy with HBOT • Patient ABN= N/A		NSTI and ABN patients were higher after HBOT treatment (p=0.0003) Comparison of TGF-β levels in ISSNHL and ABN patients were higher after HBOT treatment (p=0.03)	
Fang et al.[32] (2021)	Effect of hyperbaric oxygen therapy on polarization phenotype of rat microglia after traumatic brain injury	Animal Research	n= 168 Sprague Dawley rats 8 weeks old weighing 250-500 g Sample= Frozen brain tissue	Control Group= N/A Test Group 1= • Level O_2= 95% • Pressure = 2 ATA • Duration= 60 minutes	Control Group= Sham-operated Test Group 1= Sham-operated Test Group 2= Percussion injuries were performed using a percussion hammer until edema and	TGF-β1 levels were analyzed using the TGF-β1 ELISA kit according to the manufacturer's instructions	TGF-β1 levels were significantly higher in the Traumatic Brain Injury + HBOT group at 72 hours and 7 days (p<0.05)	HBOT upregulates TGF-β1 in a proinflammatory to anti-inflammatory state after TBI and enhances the microimmunity environment to allow neuronal survival.

				• Total sessions= 1 hour, 6 hours, 12 hours, 24 hours, 72 hours, 7 days and 14 days Test Group 2= N/A Test Group 3= • Level O_2= 95% • Pressure = 2 ATA • Duration= 60 minutes • Total sessions= 1 hour, 6 hours, 12 hours, 24 hours, 72 hours, 7 days and 14 days	bleeding were marked by discoloration and protrusion of the durameter before HBOT was performed. Test Group 3 = Percussion injury was performed using a percussion hammer until edema and bleeding were marked by discoloration and protrusion of the durameter before HBOT was performed			
Na et al.[35] (2018)	Efficacy of combined glucocorticoid and hyperbaric oxygen therapy against delayed encephalopathy after carbon monoxide poisoning, and its effect on expression of immune-associated cytokines	Retrospective	n= 102 Patients with delayed encephalopathy after carbon monoxide poisoning (DEACMP) Sample= Fasting venous blood serum (5 mL) stored in a refrigerator (-20°C)	Control Group= • Level O_2= N/A • Pressure = 0.2-0.25 MPa • Duration= 20 minutes • Total sessions= 10 days Test Group= • Level O_2= N/A • Pressure = 0.2-0.25 MPa • Duration= 20 minutes • Total sessions= 10 days	Control Group= N/A Test Group= Hydrocortisone therapy with 300 mg hydrocortisone added to 250 mL of 5% glucose and dripped every 3-4 hours, tapering off gradually and discontinuing after 2 weeks	Measurement of TGF-β1 levels was carried out using the enzyme linked immunoasorbent assay (ELISA) kit	TGF-β1 levels in the test group were significantly higher than the control group (p>0.05)	Glucocorticoids combined with HBOT showed increased levels of TGF-β1 resulting in significant tissue repair in DEACMP patients.

Table 2. Results of Article Analysis.

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