The Effect of Odontoblast Formation on Reversible Pulpitis After Application of Calcium Hydroxide and Mineral Trioxide Aggregate: Literature Review

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Abstract. Reversible pulpitis is a mild to moderate inflammatory condition of the pulp caused by a stimulus, and when the stimulus is removed, the pulp returns to normal. Reversible pulpitis can be caused by several factors, such as dental caries, thermal stimulation, chemical stimulation, and mechanical trauma during cavity preparation. Pulp capping is used to treat reversible pulpitis, which aims to protect the dental pulp by applying medicaments directly to the pulp, which functions to maintain pulp vitality and stimulate the formation of dentinal bridges. Pulp capping treatment is divided into 2 types, namely direct pulp capping performed on exposed pulp that has perforated due to iatrogenic factors, and indirect pulp capping performed on pulp that is not exposed and still has a thin layer of dentin. Calcium Hydroxide and Mineral Trioxideaggregate (MTA) are two commonly used medications that are directly applied to the pulp tissue. The main goal of pulp cap treatment is the formation of reparative dentin, which is formed from odontoblast cells and other pulp cells that indicate a reparative response of the pulp tissue. Odontoblast-like cells are produced from undifferential mesenchyme cells after death. The purpose of this paper is to determine the differences in the formation of odontoblasts in reversible pulpitis cases using Calcium Hydroxide and Mineral Trioxideaggregate (MTA) medicaments. This paper concludes that the two pulp capping medicaments can stimulate the formation of odontoblast cells with Mineral Trioxide Aggregate (MTA) has the best rate of formation speed, followed by Calcium Hydroxide.

Keywords: Reversible pulpitis · Odontoblast · Calcium Hydroxide · Mineral Trioxideaggregate (MTA)

1 Introduction

Dentin is one of the structures involved in tooth formation, which consists of 70% inorganic material, 20% organic matter, and 10% water. Dentinal tubules, which extend from the pulp to the dentinoenamel junction and contain many odontoblast cells, are found within the dentin. This hard tissue protects the dental pulp from the dangers of microorganisms that can cause the pulp to die [1].

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The injured pulp will hold a defensive reaction that includes an inflammatory response, collagen synthesis, and reparative dentin formation. However, if the injury is left untreated for an extended period of time, the pulp will die. The most common cause of pulp death is caries. Caries is the most common type of dental disease, accounting for 45.68% of all cases, and is included in the 10 major diseases affecting the community [2].

Reversible pulpitis is inflammation that occurs in the pulp but is not severe. Reversible pulpitis can be caused by a variety of factors, for example, the presence of caries on the teeth, thermal stimulus, chemical stimulus, and mechanical trauma during cavity preparation. Reversible pulpitis is typically characterized by intermittent pain caused by a stimulus that subsides when the stimulus is removed [3].

Pulp capping is the treatment for reversible pulpitis. There are 2 types of pulp cap treatments, namely direct pulp cap and indirect pulp cap. Direct pulp capping is a method of closing the pulp by applying dressing material over the exposed pulp. Meanwhile, indirect pulp capping is a procedure of leaving a thin layer of dentine on the pulp that has not been exposed before applying a dressing [4].

Pulp vitality can be maintained by the formation of reparative dentine. The initial response to the formation of reparative dentin is the formation of *odontoblast-like cells. Odontoblast-like cells* are cells that can form dentine in response to caries, trauma, or restorative procedures. The dentine formed by *odontoblast-like cells* is generally disorganized when compared to primary dentin and secondary dentin [1]. *Odontoblast-like cells* begin to form on day 14 [5]. Materials that can be used as triggers to stimulate the formation of *odontoblast-like cells* are calcium hydroxide and mineral trioxideaggregate (MTA) [6].

Although calcium hydroxide can be used to stimulate the formation of odontoblast-like cells, several studies indicate that tertiary dentine formed by calcium hydroxide has porous properties. As for MTA material, although it forms tertiary dentine which is thicker than calcium hydroxide material, it has drawbacks, including a long setting time and the possibility of discoloration in the tooth tissue [5].

2 Literature Review

Pulpitis is an inflammation of the tooth pulp. It occurs in the pulp tissue which is usually a continuation of the caries process; if not treated, it can result in pulp death, also known as pulp necrosis. Clinically, pulpitis is classified as either reversible or irreversible pulpitis. The most important factor to consider in diagnosing pulpitis is whether or not the pulp tissue can still be maintained [7].

Reversible pulpitis is a condition in which pulp inflammation occurs at a mild to moderate level, and is not severe. If the cause is removed, the pulp returns to normal. However, if reversible pulpitis is left untreated, it can progress to irreversible pulpitis, which can lead to the death of pulp necrosis. Reversible pulpitis can be caused by a chemical stimulus, such as sweet foodstuffs and carious bacteria, dehydration of the cavity with excessive alcohol or chloroform, stimulation of the cervix of a tooth whose dentin is exposed, or thermal shock, for example from an overly long bur causing heat. Symptoms of reversible pulpitis can be both symptomatic and asymptomatic. Symptomatic symptoms such as aching pain when drinking sweet, sour, hot, or cold beverages do not arise

spontaneously and do not persist if the cause is removed. Asymptomatic symptoms, on the other hand, can be caused by newly formed caries and can be returned to normal if the caries are removed and the teeth are properly restored [9].

Pulp capping is the treatment for reversible pulpitis. There are 2 types of pulp cap treatment, namely direct pulp cap and indirect pulp cap. Direct pulp capping is a procedure in which medicament is placed over exposed pulp due to iatrogenic factors by providing dressing material over it. Meanwhile, indirect pulp capping is a treatment procedure that leaves a thin layer of dentin on the pulp that has not been exposed before applying a dressing [4].

Odontoblast-like cells are cells that can form dentine in response to caries, trauma, or restorative procedures. Dentin formed by *odontoblast-like cells* is also known as reparative dentin, and it is typically disorganized when compared to primary and secondary dentine [1]. These *odontoblast-like cells* can be found in the vicinity of the injury. The growth factor is the most important thing in the formation of *odontoblast-like cells* because it has a role to stimulate fibroblast cells to become odontoblast-like cells which will then mineralize and become reparative dentin mineral trioxide aggregate (MTA) [6].

Calcium hydroxide is a material that is the gold standard in the treatment of pulp caps, but it is not without flaws. The weakness of calcium hydroxide is that the reparative dentin structure of Calcium Hydroxide is porous due to bacterial micro-leakage, so it can stimulate pulpal inflammation and reduce the area of formation of odontoblast-like cells. In the long term, microfiltration occurs due to mechanical resistance, and the results are not durable [12–14]. Calcium hydroxide is manipulated by dividing the base and catalyst, stirred with a stainless spatula on a glass plate that has been given a paper pad until a homogeneous dough is obtained. Some common trade names for calcium hydroxide in paste form are Pulpdent, Calxyl, Dycal, and Calcium Hydroxide Plus Points. One of the hard-setting calcium hydroxide materials that are frequently used as a pulp capping material is Dycal issued by Dentsply. Dycal is a calcium hydroxide material that works on the basis of a two-paste system consisting of a base paste and a catalyst paste; it is used by mixing the base paste and catalyst paste in the same amount ratio [29].

The mechanism of calcium hydroxide in the treatment of pulp caps is that with a high pH of 12.4, this material will produce superficial necrosis when applied directly to the pulp tissue. This material has antibacterial properties and will stimulate mineralization (the formation of hard tissue such as dentin which will separate the pulp from the necrotic capping material). Chemically, calcium hydroxide has strong basic properties and its main action is caused by the dissociation between Ca2+ ions and OH− ions, which results in the induction of hard tissue deposition and antibacterial properties. According to Rehman et al., the calcium hydroxide material dissociates into calcium and also hydroxyl ions. The hydroxyl ion is involved in the highly alkaline and bactericidal properties of calcium hydroxide, as well as the mineralization process [30].

Mineral Trioxide Aggregate (MTA) has a high pH of 12.5 [33]. By creating extremely high pH conditions, MTA is not only bacteriostatic but also bactericidal. MTA does not irritate tissue but can stimulate tissue regeneration (Enny, 2019). Furthermore, MTA also has several advantages over Calcium Hydroxide, namely, it is an antimicrobial material, biocompatible with tissues, has low cytotoxicity, has better mineralization ability, and induces more dentin bridges. In addition, the dentin that is formed is denser and it does not form tunnels, resulting in much less inflammation in the pulp tissue, good radiopacity, low solubility, and excellent post-setting expansion capacity, to minimize leakage which can be a breeding ground for bacteria and has mechanical strength to protect the pulp from physical and mechanical stress. Although MTA is a nearly ideal pulp capping material, it has several drawbacks, namely the possibility of releasing harmful substances into the body, difficult application, long setting time, discoloration of the tooth structure, and high cost. Some of the trade names for MTA materials are ProRoot MTA®; and MTA Angelus® [31]. The MTA materials are manipulated by mixing powder to liquid with a ratio of 3:1 on a glass plate using a stainless spatula until a homogeneous mixture is obtained, after which it is applied to the teeth being treated [32].

3 Research Methods

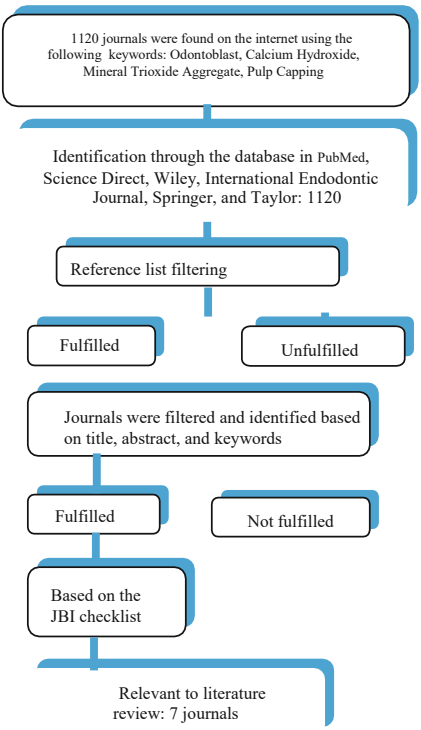
3.1 Inclusion Criteria

a. Articles published within the last 10 years (2012–2022).
b. Articles are written in English and can be accessed in full text.
c. Journal that discusses the formation of odontoblasts using $Ca(OH)^2$ and mineral trioxide aggregate (MTA) in pulp capping treatment.
d. Journal that discusses the formation of reparative dentin using $Ca(OH)^2$ and mineral trioxide aggregate (MTA) in pulp capping treatment.

3.2 Exclusion Criteria

a. Articles are in the form of abstract or not accessible.

3.3 Flow Chart Map



3.4 Validity Test

The remaining 7 articles were selected based on a checklist developed by the Joanna Briggs Institute (JBI) for cross-sectional studies.

3.5 Result of the Literature Review

Five articles from the relevant journals were written in English, and published between 2012 and 2022. There were 2 articles published in 2014, and 1 article published in 2012, 2022, 2013, 2017, and 2021. The articles were obtained through searches on PubMed and Wiley databases.

No.	Author and Article Source	Result of the Literature Review
1.	Swarup et al., (2014). The Journal of Clinical Pediatric Dentistry	The histological examination showed that in the group using MTA material, dentin bridge formation began on the 15th day and continued on the 30th day. However, no dentin bridges were formed in the calcium hydroxide material group in the 15th and 30th day periods [23]

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No.	Author and Article Source	Result of the Literature Review
2.	Elwardany et al., (2022). Al-Azhar Assiut Dental Journal	The histological examination showed that in the MTA material group, complete dentine bridge formation occurred after the end of the follow-up period, namely on the 42nd day. The use of MTA as a treatment for pulp caps had a fairly positive histological reaction on dentine and pulp when compared to calcium hydroxide materials [25]
3.	Marijana et al., (2013). Acta Veterinaria (Beograd)	The histological examination revealed that after 4 weeks of direct pulp capping treatment with MTA material, the healing process took place without complications and complete formation occurred [26]
4.	Jalan et al., (2017). Journal of Conservative Dentistry	The histological examination confirmed that there was a thicker and more continuous formation of dentine bridges after pulp capping using calcium hydroxide, and the appearance of dentin-like tissue was observed 4 weeks after treatment [27]
5.	Octiara et al., (2021). Advances in Health Sciences Research	This research found there were no odontoblast cells in any of the material samples in the 2nd week of the study, but new odontoblast cells were formed in the 4th and 6th weeks of the study [28]
6.	Shayegan et al., (2012). Pediatric Dentistry	The histological examination showed that on the 28th day using calcium hydroxide a complete calcified bridge was formed with normal pulp tissue and intact odontoblast-like cells under the exposed pulp site [34]
7.	Moazzami et al., (2014). Iranian Endodontic Journal	The histological examination demonstrated that the use of MTA material for direct pulp capping resulted in the formation of dentine bridges on the 14th day. On the 60th day, there were well-organized odontoblast-like cells, predentin and reparative dentine [35]

4 Discussion

If there is an injury to the pulp tissue, an inflammatory process occurs. Inflammation aims to protect the pulp tissue from potentially harmful irritants. During inflammation, fibroblasts migrate to the area affected by the irritant to proliferate and produce a large amount of collagen matrix, which is useful in repairing damaged tissue. When the inflammatory process occurs, growth factors have a significant influence on the tissue repair response. Irritants will stimulate odontoblast activity to increase the expression of transforming growth factor-beta 1 *(TGF– β1). TGF-β1* is an important regulator in the proliferation and differentiation process of pulp mesenchymal cells. This *TGF-β1* will activate the cell cycle, causing the cells to proliferate, mitotically divide, and differentiate into *odontoblast-like cells* [16].

During pulp life, the primary function of *odontoblast-like cells* is to produce and deposit dentin. In this case, the secretion of intertubular and peritubular dentine is required, which will form the dentinal tubules as the main strength of the dentin. Another function is to maintain the balance of ions and proteins in the dentinal tubules. In addition, *odontoblast-like cells* also act as a balancing hydrokinetic force that can regulate the level of sensitivity of the teeth. In terms of repair by injury, *odontoblast-like cells* will act as signal catchers when there is an injury to the tooth, causing reactionary dentine formation as a repair mechanism for injury [17].

Calcium hydroxide is a material obtained from the reaction of calcium carbonate [CO3Ca = CaO + CO2CaO + H2O = Ca(OH)2] with a pH of around 12,4. This substance is used in the treatment of direct and indirect pulp caps [18]. $Ca(OH)^2$ releases calcium ions, which stimulates the synthesis of fibronectin and tenascin glycoproteins in the dental pulp, triggering the differentiation of dental pulp cells into mineral-forming cells, which are the main cells in the formation of *odontoblast-like cells* [17]. Ca(OH)2 will also stimulate the release of adrenomedullin and TGF-β from the human dentin matrix, both of which are pluripotent growth factors [19].

MTA medicaments have a high capacity in stimulating cell differentiation to form a hard tissue matrix. This MTA medicament can induce osteogenic cells and stimulate the production of *BMP-2* and *TGF- β1* from fibroblasts, resulting in the formation of *odontoblast-like* cells. The advantages of MTA are that it is biocompatible, has hydrophilic properties for moisture control, has a high alkaline pH as an antibacterial, and can stimulate the formation of dentine bridges [20, 21].

Histological examination performed by Swarup (2014) in his research showed that the formation of dentine bridges occurred on the 15th day and continued on the 30th day in the samples from the MTA material group. However, no dentine bridge formation was seen in the calcium hydroxide material group samples on the 1st, 15th, or 30th day. All groups performed well in hard tissue formation, inflammatory response, etc. The response of Calcium Hydroxide material in the formation of dentine bridges was lower in the 30th day period when compared to MTA materials in the 30th day and 60th day period. All groups showed an increase in inflammatory cell infiltration during the 15th day. The MTA group had the least infiltration, while the calcium hydroxide showed the most inflammation. It can be seen that the infiltration of inflammatory cells decreased as the number of days increased in all group samples [23]. Parolia et al (2010) stated that on day 15, there was a visible formation of dentine bridges in pulps treated with direct pulp capping using MTA [24]. Based on research by Dwiandhono, treatment of direct pulp caps using MTA material in humans could form dentine bridges on the 15th day, whereas in the group of calcium hydroxide materials dentin bridges were not found [16]. Meanwhile, according to Gurcan AT, Calcium Hydroxide can form dentin bridges which then induce the formation of reparative dentine [22], Dentin bridges were not formed in the Calcium Hydroxide application test over 15 days in the majority of samples [23].

Elwardany (2022) argued that the results of the histological examination in the 7th-day MTA material group showed the formation of granulation tissue with several macrophages, and fibroblasts, as well as the formation of newly proliferating blood vessels, and the presence of mild inflammatory cell infiltrates. This is because MTA is less

toxic, causing less pulp inflammation, and has the ability to stimulate the differentiation of odontoblastic cells that secrete reparative dentin. On day 7, the Ca(OH)2 group showed liquefaction necrosis with multiple areas of clotted blood, and a high inflammatory cell infiltrate. The results of the histological examination of the MTA group on day 14 showed hard tissue calcification covering the exposure site, mild inflammatory cell infiltrates, very high mitotic fibroblasts, and migration to form odontoblast-like cells. The results of histological examination of the Ca(OH)2 group on the 14th day revealed the formation of granulation tissue under the covering material, without signs of hard tissue formation. On day 42, the MTA histological examination showed the formation of a partial to complete dentin bridge covering the exposure site, and a mild inflammatory reaction. While, the histological results of the Ca(OH)2 group on day 42 showed the formation of partial and thin fibrous tissue at the exposure site whereas, in some granulation tissue specimens covering the exposure site, inflammatory cells infiltrated. When compared to Ca(OH)2, the use of MTA as a pulp capping treatment has a fairly positive histological reaction on dentin pulp organs [25].

Marijana's research (2013) found that direct pulp capping with ProRoot MTA® on histological examination resulted in a healing process without any complications, complete dentin bridge formation was formed in 4 teeth, incomplete dentin bridge formation in the form of dentine which only partially covered the space occurred in samples of 6 teeth. Experimental studies showed the presence of inflammatory cells in the coronal and radicular areas of the pulp for all materials used. In the MTA material group, only a few samples showed the presence of lymphocytes, macrophages, and plasma cells. Dentine bridge formation occurred in all samples in the ProRoot MTA® material group [26].

Research conducted by Jalan in 2017 showed that on histological examination, complete dentin bridge formation was observed in 16 samples of Biodentine material and 4 samples of Dycal material, and the average thickness of dentin bridges in the Biodentine group was 0.58 mm, and Dycal which is 0.17 mm. In this study, it was shown that the dentine bridges formed more and more continuously after the treatment of pulp cavities using calcium hydroxide, which was observed 4 weeks after treatment. Yoshiba et al. discovered that after pulp capping treatment with calcium hydroxide, dentin-like tissue was observed 4 weeks later. As a result, the 45-day period is justified for studying dentinal bridge formation histologically. Both materials induced the formation of dentin bridges in the pulp tissue in this study. Laurent et al. reported that direct pulp capping treatment with MTA and Ca(OH)2 materials on human teeth induced *odontoblast-like cell* differentiation. The presence of dentin and odontoblastic molecular markers revealed by immunohistochemistry confirms this [27].

Research conducted by Octiara in 2021 revealed that no *odontoblast-like cells* were formed in the second week of the study, but new odontoblast cells were formed in the 4th and 6^{th} weeks. In the 6-week study, odontoblast cells were more abundant. The calcium hydroxide sample group demonstrated that 70% had completely formed dentin bridges and 30% had covered more than half of the exposed area. After 4 weeks and 6 weeks, it was discovered that the calcium hydroxide material produced better results in terms of inflammation level, intensity, and type [28].

A study conducted by Shayegan in 2012 showed that histological examination with calcium hydroxide on day 28 formed a complete calcified bridge with normal pulp tissue and intact *odontoblast-like cells* below the exposed pulp site. MTA material demonstrated that all samples formed complete calcified bridges. On day 90, the calcium hydroxide material group showed complete calcified bridges with normal pulp tissue. In all samples, the MTA group had fully calcified bridges, intact *odontoblast-like cells*, and normal pulp tissue free of inflammation. According to a study on MTA, it has superior biocompatibility and ideal properties when used as a pulp sealant. However, it is important to consider the disadvantages, such as slow MTA setup time, the difficulty of use, and relatively high cost. In fact, calcium hydroxide is generally considered to be an excellent material for pulp capping, as it maintains pulp vitality [34].

Moazzami's 2014 research revealed that on the 14th day of direct pulp cap treatment with MTA material, dentine bridge formation, and odontoblastic differentiation occurred. MTA demonstrated the ability to form dentin bridges within 2 weeks in this study, as it has in previous studies. On the 60th day, there are well-organized odontoblast-like cells, predentin as well as reparative dentine. Dentin bridges form beneath the pulp cap, pulp horn, and floor of the pulp chamber wall treatment area. A well-organized formation of tubular dentin bridges occurs beneath the pulp cap, accompanied by layers of dentine and odontoblasts, whereas reparative dentin has atubular structures filled with lacunae in the pulp horns and at the pulp bed. This atubular dentine was mostly detected in the MTA group. In another study, MTA was chosen as the material of choice for direct pulp cap treatment because of its biocompatibility, sealing ability, and dentin-bridging quality. Therefore, MTA was chosen as the gold standard for pulp-capping materials in this study [35].

5 Conclusion

This research found that the pulp cap material can form odontoblast cells which are good for pulp tissue. The best rate of formation of odontoblast cells is by Mineral Trioxideaggregate (MTA) material followed by Calcium Hydroxide material.

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