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Evaluation of pulp response and formation of Dentin Bridge after capping with stem cells and MTA

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ORIGINAL STUDY

Evaluation of Pulp Response and Formation of Dentin Bridge After Capping With Stem Cells and Mineral Trioxide Aggregate: An Animal Study

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Abstract

Purpose: The objective of the current study was to assess the efficacy of direct pulp capping (DPC) with dental pulp stem cells (DPSCs) and mineral trioxide aggregate (MTA) on the formation of dentin bridges. **Materials and methods:** Forty teeth from dogs were included in the current study. Class V cavities were prepared, followed by pulp exposure for the application of the DPC materials. Two groups of teeth consisting of 20 teeth in each following the DPC material used, either MTA or DPSCs ($N = 20$), were used. Afterward, teeth were restored with glass ionomer as a final restoration. Histopathological evaluation was done after two-time intervals of 1 week and 45 days. **Results:** Regarding the capping materials, the results showed an inflammatory cell response for both materials at both time intervals. DPSCs showed mild inflammation at 1 week and 45 days, while MTA showed moderate inflammation at 1 week and mild inflammation after 45 days. There was a statistically significant difference at 1 week between both groups, while after 45 days there was no statistically significant difference between both groups. Regarding the formation of dentin bridge in the DPSCs group, there was no statistical significance at 1 week, while after 45 days, there was a statistically significant difference. Dentin bridge formation was absent in both groups at 1 week, while after 45 days, it was formed in both groups. **Conclusion:** Among both groups DPSCs showed a higher significant difference and were considered one of the best DPC options.

Keywords: Dental pulp stem cells, Dentin bridge formation, Direct pulp capping, Mineral trioxide aggregate

1. Introduction

Pulp vitality is the main goal of conservative and restorative dentistry. Vital pulp therapy is done to achieve this goal either directly or indirectly by using a pulp capping material [1]. Vital pulp therapy aims to evaluate and control pulpal inflammation and preserve pulp vitality by stopping inflammation from progressing to pulp necrosis and avoiding root canal treatment [2].

Direct pulp capping (DPC) main objective is to maintain pulp vitality by preventing bacterial infiltration, stimulating dentin bridge, and pulp healing [2]. DPC is done using a biocompatible material placed over the exposure site that occurred due to caries or traumatic injury to stimulate the mineralized tissue formation and reparative dentin [3].

The pulp capping material is a crucial factor for the accomplishment of successful DPC and should possess certain characteristics to increase the success rate of this procedure, such as biocompatibility, bioactivity to stimulate dentin bridge formation, insolubility in tissue fluids with good sealing ability and no tooth discoloration effect [4].

Many materials have been used for pulp capping. Calcium-silicate materials are a group of materials that are new and have been used extensively as pulp capping materials for their superior characteristics; however they are still under experimentation [5].

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Mineral trioxide aggregate (MTA) is the first generation of CSMs. Its major contents are tri-calcium silicate, di-calcium silicate, and tri-calcium aluminate [6]. MTA has superior properties as a pulpal capping material as it is biocompatible with pulp tissue, bioactive promotes the formation of mineralized tissue, stimulates dentin bridge formation, has excellent sealing ability, antibacterial effect, radio opacity, and is a nonabsorbable material [7]. Despite the presence of many pulp capping materials, there is still no available ideal material without any drawbacks.

There are still many challenges with these materials and their restorative techniques, and therefore, further studies are done in an attempt to find the ideal pulp capping material [8]. Tissue engineering and the development of regenerative techniques to stimulate the formation of mineralized tissue barriers have been the focus of many recent studies, such as using stem cells in DPC.

Stem cell therapy is becoming a very encouraging field for research. Stem cells are unspecialized cells with a high ability for differentiation and self-renewal [9]. Stem cells have been used for DPC recently in many studies, showing promising results in dentin bridge formation [8].

Dental pulp stem cells (DPSCs) have unique qualities, such as high growth capacity and multipotency, so they are considered the main source of cells in tissue regeneration. They also have self-renewal and differentiation properties into odontoblasts-like cells that can produce mineralized tissue and dentin bridge [3]. Understanding the nature of DPSCs and their use in tissue engineering is beneficial for their application in DPC [10].

Therefore, the objective of this study was to evaluate and assess the pulpal response to DPC with MTA and DPSCs and their effect on the formation of dentin bridges.

The null hypothesis of the current study is that there is no difference between the two DPC materials used on pulpal response and dentin bridge formation.

2. Materials and methods

2.1. Ethical approval

The ethical approval from the ethical committee of the Faculty of Dental Medicine for Girls, Al-Azhar University was received (REC-OP-24-02).

2.1.1. Selection of experimental animals

Two healthy mongrel dogs with a weight of the average of 15–20 kg, ages between 9 and 18 months old, with sound permanent dentition, were selected for the current study. Dogs were dewormed, vaccinated, and kept in separate cages during the experiment period.

2.1.2. Samples grouping

Forty teeth were used in the current study. Teeth were divided into two main groups ($n = 20$) according to the used material in DPC M1: stem cells in plasma and M2: MTA, then histological evaluation of these two different materials was done at two different time intervals of 1 week and 45 days.

2.1.3. Operative procedures

All the operative procedures were done under general anesthesia, which was injected into the cephalic vein of each dog. The anesthetic solution was a mixture of xylazine 1 mg/kg in combination with ketamine hydrochloride 5 mg/kg [10]. The anesthetic level was controlled during the procedure by the application of incremental doses of 2.5 % thiopental sodium 25 mg/kg body weight intravenously [11]. The dogs were put in a supine position with their heads were adjusted to avoid any airway passage obstruction.

2.2. Stem cell isolation and preparation

After general anesthesia for each dog, the jaws were opened using a specialized mouth gag for dogs to keep the jaws open during the operative procedures. Access cavities were done in the upper premolars of the left quadrant with round high-speed carbide bur size 2 (Mani Wetzlar, Germany) and sufficient coolant. Extirpation of pulp tissues was done using a sterile barbed broach (size 490, length 021; Mani). Following this step, the extirpated pulp was put in phosphate buffer saline inside a sterile tube and then transferred to the laboratory to obtain the stem cells from the dental pulp. All the procedures were done in a sterile laminar flow cabinet [12].

The pulp tissues collected from each dog were gathered and digested with collagenase enzyme type II (0.3 mg) for 2 h at a temperature of 37 °C. For single-cell suspension, a cell strainer was infiltrated, and then centrifugation was done at 1800 rpm for 8 min to collect suspended cells. The cells were cultured in RPMI-1640 medium with L/glutamine, in addition to10 % fetal bovine serum (LSP) and 1 % penicillin and streptomycin (Biowest Massachusetts, USA). Then they were incubated inside a CO_2 incubator (5 %). The culture medium was checked every 3 days and replaced with a new medium till 80–90 % confluence for three passages. The plating medium was supplied

with 50 μg/ml ascorbic acid, 5 ml/Mol β-glycerophosphate, and 10 mM dexamethasone media used was changed every 3 days. Cells were cultured at a density of 1×10^5 per dish [12].

2.3. Characterization of stem cells

DPSC culture was checked under the inverted microscope (LeicaDM750, Germany) for confirmation of the characteristic form of stem cells, which is the spindle fusiform, and to examine their plastic adherence.

2.4. Immunological characterization of dental pulpal stem cells

To indicate mesenchymal cells presence and exclusion of nonmesenchymal cells, flow cytometry analysis with a flow cytometer (Thermo Fisher Attune, USA) was done to confirm surface antigens to CD105 and stem cell marker CD 29, and it was negative to CD45, excluding hematopoietic and endothelial cells [12].

2.5. Pulp capping materials application

After the isolation of DPCs, they were suspended in blood plasma as a delivery vehicle that was obtained from a blood sample taken from each dog.

All operative procedures were performed under aseptic conditions with sterilized tools and general anesthesia with the same technique mentioned before. The teeth were cleaned, polished, and disinfected with chlorohexidine 0.2 %, and a rubber dam was applied for isolation [13]. Class V cavities were done on the buccal surface of the selected teeth. Cavities were done 2 mm away from the gingival margin with dimensions of 3 mm width and 3 mm depth by a high-speed round bur# 1 (Mani) with copious air–water spray coolant to avoid excessive heating. Each cavity was done using a new bur to avoid any cross-infection and to obtain efficient cutting. Dentin ships or debris were washed away, and a cotton pellet with sterile saline was used to stop any bleeding [11].

In the first group, DPC was done with DPSCs in plasma that were prepared before using a plastic insulin syringe directly at the exposure site. A bioabsorbable collagen barrier (Hypro-sorb) was placed over the exposure site after the DPSCs application.

The second group, DPC with MTA, was done following the manufacturer's instructions. The MTA powder was mixed using distilled water on a clean glass slab with a ratio (3 : 1 P/L) by weight for 1 min to get the adequate putty-like consistency, and the final restoration was done using glass-ionomer Fuji IX (GC, Japan shade A2, 0.5 g).

2.6. Teeth preparation for histological assessment

After the time intervals of 7 and 45 days, the animals were euthanized by injecting 10 % thiopental sodium overdose (EPICO, Egypt). Dogs' jaws were separated and divided into two quadrants, and then fixation was done in formaldehyde (10 %) for 10 days.

Demineralization of jaws was done using formic acid (50 %) and sodium citrate (25 %) for a period of 2 months. After complete calcification, teeth were removed with a specialized scalpel and kept in a demineralizing solution for 2 weeks [13].

After complete demineralization of teeth, specimens were placed in paraffin wax and sectioned into 20 sections of 0.5 mm thickness using a microtome (Microm HM 360, Germany) and then stained with hematoxylin and eosin for histological evaluation.

2.7. Histopathological evaluation of the samples and image analysis

Histopathological evaluation was done by using a light microscope (Leica Quin 500) according to the scoring criteria [14] (Table 1).

2.8. Statistical analysis

Medcalc software, version 22 for Windows (MedCalc Software Ltd, Ostend, Belgium), was used to analyze the data. Both frequency and percentage were used to characterize categorical data. The χ^2

Table 1. Scoring system.

Criteria	Score 1	Score 2	Score 3	Score 4
Inflammatory cell response	No/few inflammatory cells	Mild inflammatory cell infiltration (<10 cells)	Moderate inflammatory cell infiltration (10–25 cells)	Severe inflammatory cell infiltration (>25 cells)
Hard tissue formation	Absence of any hard tissue formation	Deposition of hard tissue laterally on cavity walls or exposure site	Partial hard tissue bridge	Complete formation of hard tissue bridge or closing of site of exposure
Dentin bridge thickness	0 mm	<0.1 mm	0.1–0.25 mm	>0.25 mm

test was used to compare categorical data between groups. The χ^2 test was used to compare groups within each intervention. All tests were two-tailed, and a P value of less than or equal to 0.05 was classified as statistically significant. The study's statistical power was determined at 80 % with a 95 % confidence level.

2.9. Inflammatory cell response

Intergroup comparison between stem cells and MTA has shown a statistically significant difference at 1 week ($P = 0.0004$), while after 45 days, no statistically significant difference ($P = 1.0000$). Intragroup comparison in the stem cells group showed no statistically significant difference between the follow-up periods ($P = 1.0000$), while intragroup comparison in the MTA group showed statistically significant difference between follow-up period ($P = 0.0004$) (Table 2, Fig. 1).

Table 2. Frequency and percentage of inflammatory cell response scores for the intergroup comparison between materials at each follow-up and intragroup comparison for each material between different periods of follow-up.

	Stem cells [n (%)]		MTA [n (%)]		P value
	Score 2	Score 3	Score 2	Score 3	
1 week	10 (100)	0	2 (20)	8 (80)	$P = 0.0004$[a]
45 days	10 (100)	0	10 (100)	0	$P = 1.0000$
P value	$P = 1.0000$		$P = 0.0004$[a]		

MTA, mineral trioxide aggregate.
[a] Denotes statistically significance.

2.10. Hard tissue formation

Intergroup comparison between stem cells and MTA showed no statistically significant difference at 1 week ($P = 0.3736$), while after 45 days, a statistically significant difference was found ($P = 0.0025$). Intragroup comparison in the stem cells group showed a statistically significant difference between the follow-up periods ($P = 0.0002$). Intragroup comparison in the MTA group showed a statistically significant difference between the follow-up periods ($P = 0.0039$) (Table 3, Fig. 2).

2.11. Dentin bridge thickness

Intergroup comparison between stem cells and MTA showed no statistically significant difference either at 1 week or 45 days ($P = 1.0000$ and 0.1311). Intragroup comparison in stem cells group showed a statistically significant difference between periods of follow-up ($P = 0.0001$), and intragroup

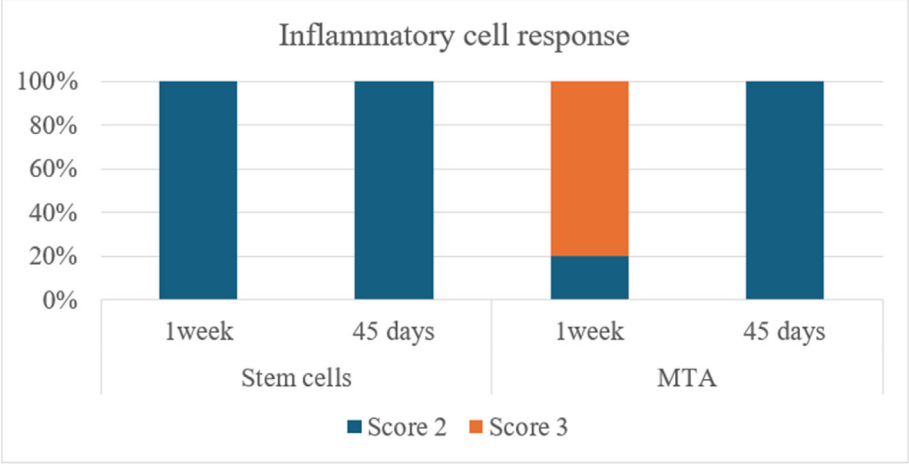

Fig. 1. Bar chart showing inflammatory cell response scores for each material within each follow-up period.

Table 3. Frequency and percentage of hard tissue formation scores of the intergroup comparison between materials at each follow-up and intragroup comparison of each material between different periods of follow-up.

	Stem cells [n (%)]				MTA [n (%)]				P value
	Score 1	Score 2	Score 3	Score 4	Score 1	Score 2	Score 3	Score 4	
1 week	3 (30)	7 (70)	0	0	5 (50)	5 (50)	0	0	$P = 0.3736$
45 days	0	0	3 (30)	7 (70)	0	4 (40)	6 (60)	0	$P = 0.0025$[a]
P value	$P = 0.0002$[a]				$P = 0.0039$*				

MTA, mineral trioxide aggregate.
[a] Denotes statistically significance.

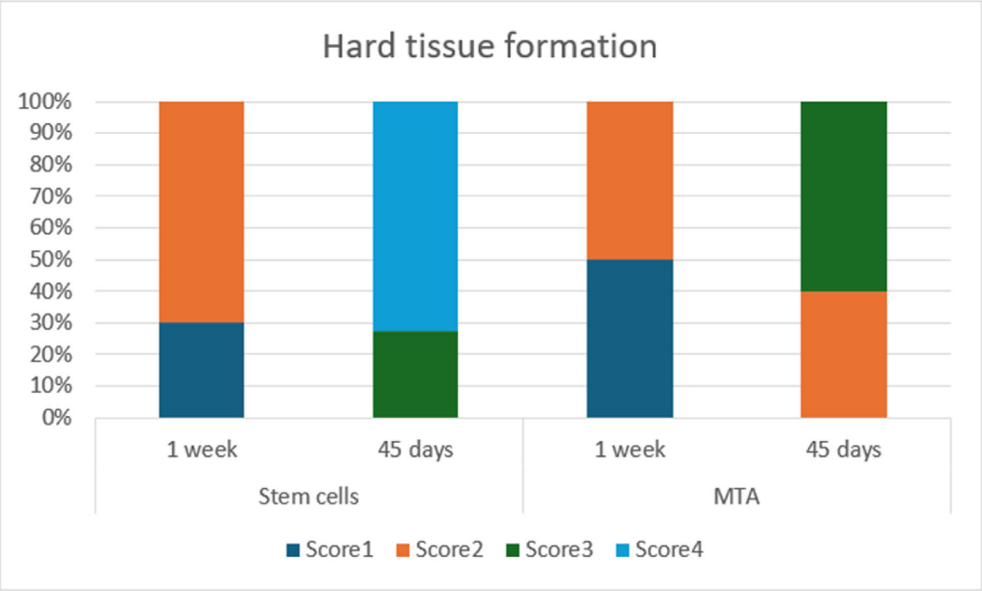

Fig. 2. Bar chart showing hard tissue formation scores for each material within each follow-up period.

Table 4. Frequency and percentage of dentin bridge formation scores of the intergroup comparison between materials at each follow-up and intragroup comparison for each material between different periods of follow-up.

	Stem cells [*n* (%)]		MTA [*n* (%)]		*P* value
	Score 1	Score 4	Score 1	Score 4	
1 week	10 (100)	0	10 (100)	0	$P = 1.0000$
45 days	1 (10)	9 (90)	4 (40)	6 (60)	$P = 0.1311$
P value	$P = 0.0001$[a]		$P = 0.0043$[a]		

MTA, mineral trioxide aggregate.
[a] Denotes statistically significance.

comparison in the MTA group showed a statistically significant difference between periods of follow-up ($P = 0.0043$) (Table 4, Figs. 3–5).

3. Discussion

In regenerative dentistry and stem cell research, animal models are indicated to be used before the clinical application of any procedure or material on humans to confirm the clinically relevant data and safety of patients [15]. Dogs were ideal for this study because their dentin synthesis is similar to humans,

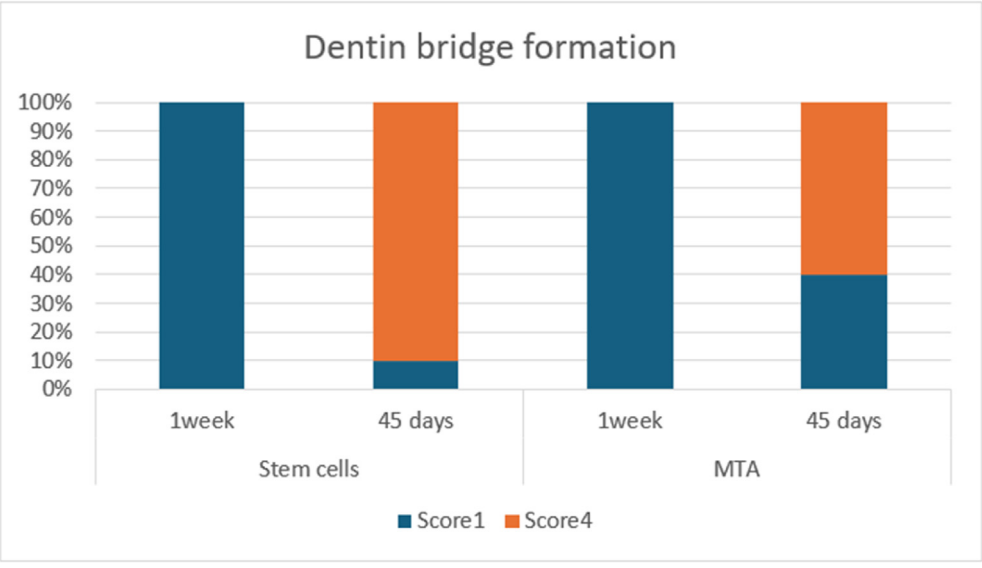

Fig. 3. Bar chart showing dentin bridge formation scores for each material within each follow-up period.

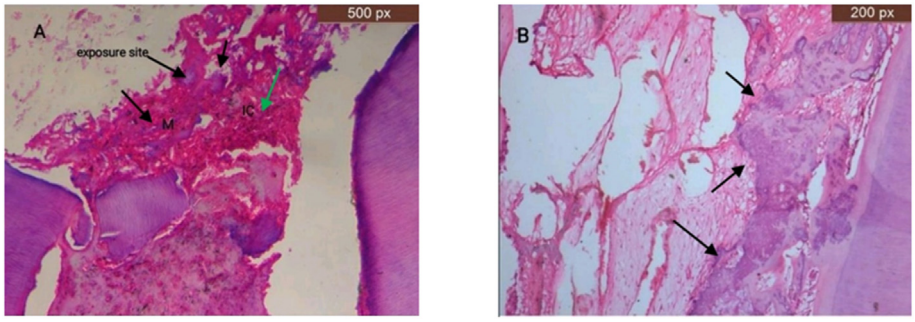

Fig. 4. Photomicrograph of DPC with MTA at 1 week and 45 days. (A) MTA after 1-week. M, mineralized areas of hard tissue (black arrows); IC, inflammatory cells (green arrows). (B) MTA after 45 days shows areas of calcifications and the formation of predentin structures (black arrows). DPC, direct pulp capping; MTA, mineral trioxide aggregate.

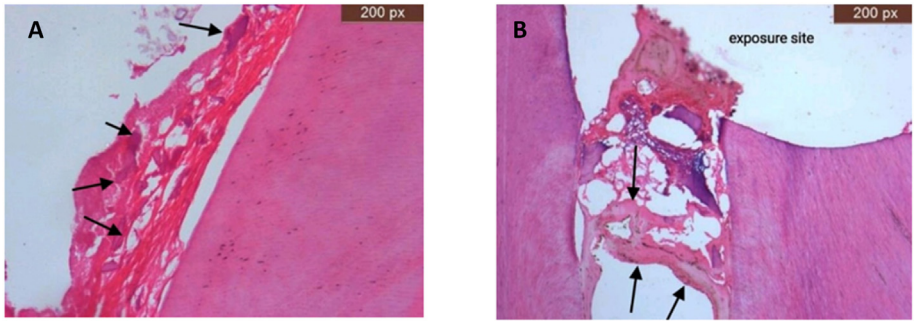

Fig. 5. Photomicrograph of DPC with DPSCs at 1 week and 45 days. (A) Hard tissue formation appearing as globules of calcified areas (black arrows). (B) Formation of dentin bridge seen at the dentin/pulp interface (black arrows). DPC, direct pulp capping; DPSC, dental pulp stem cell.

and there is a resemblance between their pulp and the human pulp, in addition to its proper size, which can be ideal for histopathological evaluation [16]. The dogs also provide an adequate number of teeth for applying and comparing different materials and techniques [17].

Class V cavities were done because this cavity design facilitates the accessibility to the pulp tissue. Cavity preparation was done using a new bur for every tooth to maintain the precision of cutting and avoid any cross-infection [18].

DPSCs were used for this study because of their superior properties of high proliferation, multipotency, and differentiation into different types of cells [19]. They are also easily accessed, isolated, and obtained with minimally invasive methods in comparison to the other types of stem cells [20].

Plasma was used as a delivery vehicle or a scaffold for DPSCs as plasma has growth factors that have a significant effect on tissue regeneration by binding to stem cells' receptors and aiding in the induction of cell proliferation and cell differentiation. Plasma also has platelets, which have platelet-derived growth factors that enhance the proliferation of odontoblasts [19].

The time intervals that were selected for the evaluation of the two pulp capping materials were 1 week and 45 days. The short time interval of 1 week was selected to detect the presence of inflammatory response towards the DPC materials [17], while 45 days, a longer time interval, was chosen to detect the formation of dentin bridge.

On comparing the pulp response regarding the capping material used in the current study, inflammation was found in both groups at both time intervals where either MTA or DPSCs were used. This can be explained by the fact that various stages of pulp inflammation were found after DPC, which included either mild, moderate, or even severe inflammation. The initial stage of the inflammation process is considered a process of recovery for the injured pulp. Although inflammation is a kind of destructive process, it acts as a trigger for accelerating the healing process by the immune response [4]. Trauma, whether iatrogenic or caused by caries, triggers both inflammatory responses and regenerative effects at the tissue molecular and cellular levels. Accordingly, the inflammation and regeneration processes are interconnected [18].

The results of the current study revealed that regarding the inflammatory cell response, a statistically significant difference between the two groups at 1 week was found, but after 45 days, there was no statistically significant difference. In the DPSCs group, there was mild inflammation at both time intervals of 1 week and 45 days. In comparison to the MTA group, that was moderate at 1 week and changed to mild after 45 days. This can be attributed to the fact that DPSCs have anti-inflammatory capacity and immune-modulatory effect. Their immune-modulatory effect comes from the fact that they can modulate different immune-cell types such as T-lymphocytes, B-lymphocytes, and natural killer cells, and this inhibits the proinflammatory process and activates the anti-inflammatory mechanism [18].

In the MTA group, according to the scoring system, inflammation was moderate at 1 week, then it became mild after 45 days. This is due to the fact that inflammation induced by MTA is only for a short time. MTA also can reduce pulpal inflammation, hyperemia, and necrosis [4].

Regarding the hard tissue formation, after 1 week, 70 % of the DPCS group had a score of 2, showing lateral deposition of hard tissue, and in the MTA group, 50 % had a score of 2. After 45 days, 70 % of the DPSCs had a score of 4, showing complete formation of the hard tissue bridge, and 60 % of the MTA group had a score of 3, showing partial formation of hard tissue. After 1 week, there was no statistically significant difference, as both showed no dentin bridge formation, while after 45 days, there was a statistically significant difference between the two groups regarding hard tissue bridge formation. According to the scoring system used, the DPSCs group showed more formation of hard tissue at both time intervals.

As for the dentin bridge thickness, after 1 week, 100 % of both DPSCs and MTA groups had scored 1 as there was no dentin bridge formed at this time interval, while after 45 days, 90 % of the DPSCs group had a score of 4 showing dentin bridge thickness more than 0.25 mm and 60 % of the MTA group also had score 4.

These findings could be explained by the fact that DPSCs have high proliferation and differentiation abilities as they contain mainly cells of mesenchymal origin that are multipotent and characterized by their ability to regenerate and differentiate into different cell types [8]. They have self-renewal properties and the ability to differentiate into odontoblast-like cells that can produce mineralized tissue and dentin bridge [21]. DPSCs also have the ability of symmetric division, so they can produce daughter cells with developmental potential similar to the original cells [18]. The findings were in agreement with previous studies, which demonstrated that the DPC was more effective when DPSCs were used as they have the ability to dentin bridge formation [3,15].

Although the hard tissue formed by the MTA group was less than that formed by the DPSCs group, MTA has the ability of hard tissue formation and this could be explained by the fact that MTA is a biocompatible, bioactive material with high compatibility with dental pulp cells, it minimizes the pulp inflammation and enhances pulp healing [22]. MTA can induce the formation of reparative dentin by activating the hard tissue-forming cells and sharing in the formation of the matrix and its mineralization [4]. It promotes cell differentiation and proliferation of odontoblast-like cells [21].

The findings were in agreement with other studies that evaluated the effect of MTA as a DPC material, and they concluded that MTA had demonstrated significant efficacy in stimulating the deposition of hard tissue, particularly in cases of pulp exposure. MTA can also effectively induce the formation of a dentin bridge. MTA is recognized as a reliable material for promoting hard tissue deposition and facilitating the formation of a dentin bridge, making it a valuable tool in restorative dentistry [4,5,16].

3.1. Conclusions

Under the limitations of this study, DPSCs could be considered as a successful and highly promising option for DPC.

3.2. Recommendations

It is recommended that more research be done, and given the limitations of this study, which are the small number of used dogs and relatively short periods of evaluation. Further clinical trials will be recommended.

Ethical statement

The ethical approval from the ethical committee of the Faculty of Dental Medicine for Girls, Al-Azhar University was received (REC-OP-24-02).

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Biographical information

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Conflicts of interest

There are no conflicts of interest.

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