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Combination of calcium hydroxide and ellagic acid with polyethylene glycol solvent on pH and calcium ion release

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Abstract

Background: Calcium hydroxide is one of the pulp capping materials that can increase the mineralization process and inhibit the growth of bacteria. This material works by dissociating into calcium ions and hydroxyl ions and causes the pH to increase locally. Calcium ions are related to the remineralization process. The hydroxyl ion is associated with antibacterial properties. Calcium hydroxide with an alkaline pH can cause inflammation and tissue necrosis that occurs when applied in the initial period. Ellagic acid is added as an anti-inflammatory and polyethylene glycol used as a solvent which can maintain the form of Ca (OH)2 paste for a long time.

Purpose: This research aimed to determine the pH changes and the release of calcium ions calcium hydroxide and ellagic acid combination using polyethylene glycol as a solvent

Methods: A total of 72 samples of 4 groups consisting of the control and treatment groups which were soaked in water for 1, 3 and 7 days. The pH was examined with a pH meter and calcium ions release were examined with ICP-OES test.

Result The treatment group showed an increase in pH and release of calcium ions with the highest result at a ratio of 97:3.

Conclusion: The combination of calcium hydroxide and ellagic acid mixed with polyethylene glycol solvent can increase the release of calcium ions and pH.

Keywords: Calcium Hydroxide; Dentistry; Ellagic Acid; Polyethylene Glycol; Ph; Calcium Ion Release

1. Introduction

Calcium hydroxide is one of the pulp capping ingredients that can enhance the mineralization process and inhibit bacterial growth [1]. Calcium hydroxide has become the gold standard in direct pulp capping treatment. The alkaline nature of calcium hydroxide is beneficial in the form of antibacterial and remineralization. This material works by dissociating into calcium ions and hydroxyl ions and causes the pH to increase locally. Calcium ions are related to the remineralization process to form hard tissue by activating ATP and stimulating the expression of the fibronectin gene. The hydroxyl ion is related to the antibacterial properties of calcium hydroxide [2].

Calcium hydroxide is generally used as a pulp capping material but it has disadvantage that causing inflammation and tissue necrosis when applied in the initial period. This inflammation is caused by hydroxyl ions in calcium hydroxide

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which are part of the Reactive Oxygen Species (ROS) [2]. Based on previous research, macrophage infiltration occurs more when using calcium hydroxide compared to Mineral Trioxide Aggregate (MTA) [3]. In this research, ellagic acid is added in order to reduce the lack of calcium hydroxide. Ellagic acid can be found in fruits such as pomegranate, strawberry, raspberry, blackberry, cranberry, and goji berry [4]. Ellagic acid has anti-inflammatory properties, namely inhibiting the production of IL-6 and PGE-2 and leads to inflammation and tissue necrosis reduction [5].

The solvent used together with the calcium hydroxide powder will affect the rate of dissociation and release of calcium and hydroxyl ions. The solvent used can be aqueous, viscous, and oily. Aqueous solvents such as aquadest is a liquid and dissolve easily, whereas viscous solvents such as polyethylene glycol can slow down the process of releasing calcium and hydroxyl ions [6].

The polyethylene glycol solvent was chosen on this research because it does not damage the tissue and can maintain the Ca(OH)2 paste for a longer time.[7] At a weight of 200-600 PEG has a thick liquid texture and PEG 400 is a suitable solvent for calcium hydroxide paste because it provides better ion release compared to aqueous solvents.[8] A recent study shows polyethylene glycol as a viscous vehicle is capable of giving prolonged release of hydroxyl ion, therefore creating a high alkaline environment which is not suitable for bacteria.[8] The alkaline pH value is beneficial in the remineralization process, namely increasing alkaline phosphatase which can help the process of hard tissue formation and the expression of Bone Morphogenic Protein 2 (BMP-2) as a stimulus for pulp repair.[9] The aim of this study is to analyse pH value and calcium ion release of a calcium hydroxide and ellagic acid combination using a polyethylene glycol solvent

2. Materials and methods

2.1. Equipment's

Equipment's used in this study are

pH meter and ICP-OES

2.1.1. Preparation of sample

Four groups of samples including control group (K) and treatment group (P1, P2, P3) are made:

- Group K: Ca (OH)2-ellagic acid (formed by mixing 0,198 gr of CaOH with 0,002 gr ellagic acid with 0,2 ml aquadest as a solvent)
- Group P1: Ca (OH)2-ellagic acid (formed by mixing 0,99 gr of CaOH with 0,01 gr ellagic acid with 1 gr PEG 400 as a solvent)
- Group P2 Ca (OH)2-ellagic acid (formed by mixing 0,97 gr of CaOH with 0,03 gr ellagic acid with 1 gr PEG 400 as a solvent)
- Group P3: Ca (OH)2-ellagic acid (formed by mixing 0,95 gr of CaOH with 0,05 gr ellagic acid with 1 gr PEG 400 as a solvent)

A mixture of calcium hydroxide and ellagic acid powder was put into the sample mold with a height of 2 mm and a diameter of 10 mm using a plastic filling instrument and the setting was waited for 1 hour and 30 minutes. The required number of samples is 72 and divided into 12 groups with 6 samples in each group. Four groups (K, P1, P2, P3) were soaked in distilled water for 1 day, the next four groups were immersed in distilled water for 3 days, and the last four groups soaked in distilled water for 7 days. The pH and calcium ion release of the water was measured at regular intervals over 1,3-, and 7-days using pH meter and ICP-OES.

3. Results

Based on Table 1, it can be seen that at 1 day of incubation, the group that had the highest average pH was the P3 treatment group while the lowest average pH was in the control group.

Table 1 The mean value of pH on the combination of calcium hydroxide and ellagic acid

Treatment groups	Incubation period		
	Day 1	Day 3	Day 7
K	12.252 ± 0.031	12.470 ± 0.102	12.273 ± 0.042
P1	12.692 ± 0.085	12.483 ± 0.034	12.711 ± 0.131
P2	12.718 ± 0.029	12.512 ± 0.093	12.715 ± 0.039
P3	12.787 ± 0.024	12.762 ± 0.047	12.843 ± 0.037

The normality test shows that the overall pH data in this study is normally distributed ($p > 0.05$). The homogeneity test showed that the data of pH measurements is not homogeneous at 1 day, 3 days, and 7 days (0.000; 0.003; and 0.000) so that it is continued with Games-Howell. The Welch ANOVA test was carried out to determine the difference in the pH value of each treatment at each soaking time because the data are not homogeneous.

Table 2 Welch ANOVA test results in all treatment groups

	Sum of Squares	df	Mean Square	F	p
Between Groups	2.053	3	0.684	56.460	0.000
Within Groups	0.824	68	0.012		
Total	2.877	71			

Based on Table 2 it is known that there is a significant difference in the four treatments as indicated by a significant difference value of 0.000 ($p < 0.05$). Follow-up test using Games-Howell obtained the following results.

Table 3 Games-Howell Test

Incubation period	K1	K3	K7	P1-1	P1-3	P1-7	P2-1	P2-3	P2-7	P3-1	P3-3	P3-7
K1	-	SD	NS	-	-	-	-	-	-	-	-	-
K3	SD	-	SD	-	-	-	-	-	-	-	-	-
K7	NS	SD	-	-	-	-	-	-	-	-	-	-
P1-1	-	-	-	-	SD	NS	-	-	-	-	-	-
P1-3	-	-	-	SD	-	SD	-	-	-	-	-	-
P1-7	-	-	-	NS	SD	-	-	-	-	-	-	-
P2-1	-	-	-	-	-	-	-	SD	NS	-	-	-
P2-3	-	-	-	-	-	-	SD	-	SD	-	-	-
P2-7	-	-	-	-	-	-	SD	SD	-	-	-	-
P3-1	-	-	-	-	-	-	-	-	-	-	NS	SD
P3-3	-	-	-	-	-	-	-	-	-	NS	-	SD
P3-7	-	-	-	-	-	-	-	-	-	SD	SD	-

SD = Significant Difference; NS = Not Significant

Based on the Table 3. Games-Howell results, it was found that the pH value in group P3, namely 0.95 g of calcium hydroxide powder mixed with 0.05 g of ellagic acid powder and 1 gram of polyethylene glycol, had the highest and most significant pH value compared to the other groups.

4. Discussion

Based on the results of the average pH data, it can be seen that during the 1day incubation period, the group that had the highest average pH was the P3 treatment group with a value of 12.787 while the lowest average pH was in the control group with a value of 12.252 and was still in an alkaline condition. The same thing also happened to the length of incubation of 3 days and 7 days. The lowest pH was in the control group with a ratio of 99:1 because the solvent used was aqueous, namely distilled water. Overall, the pH value is in the range of 12 which indicates that the treatment group has an alkaline pH value.

Polyethylene glycol solvent was added in this study in the hope of maintaining a high pH. Polyethylene glycol is a viscous solvent with a high molecular weight that can maintain the Ca(OH)2 paste form for a long time and does not damage tissues.7 The pH test results of the treatment group with PEG 400 increased from day 1 to day 7. This is due to the large number of ethylene oxide groups that allow PEG to form complexes with metal cations including calcium ions. The binding of calcium ions will encourage the dissociation of calcium hydroxide so that more hydroxyl ions are released. [10] PEG 400 solvent is better in producing a maximum pH of 13 compared to saline solvents and is able to slow down the release of calcium and hydroxyl ions compared to aqueous and oily solvents. [11] Necrosis caused by calcium hydroxide can be minimized by PEG 400. Based on previous research, there was a decrease in the number of multinucleated giant cells, leukocytes, and neutrophils from the 7th to the 30th day using PEG 400 solvent.[12]

Previous studies said that alkaline pH can increase alkaline phosphatase which can help the process of hard tissue formation and also the expression of Bone Morphgenic Protein 2 (BMP-2) which is a stimulus for pulp repair. Calcium ions are related to the mineralization process which is able to form a dentinal bridge by activating pyrophosphatase and activating Transforming Growth Factor Beta One (TGF-B1) in the biomineralization process.9 Calcium ion levels in the combination of calcium hydroxide and ellagic acid with polyethylene glycol solvent can be observed through the ICP-OES (Inductively Coupled Plasma-Optical Spectroscopy) test. The ICP=OES test in the control group and each treatment group showed an increase in calcium ion release on day 1 to day 7 with the highest value of 1107.4 ppm in group P3 on day 7. This occurs due to ethylene oxide group on PEG encourages the formation of complexes with metal cations including calcium ions. The binding of calcium ions will promote the dissociation of calcium hydroxide [10]. The test results showed an increase in the release of calcium ions and pH of each treatment group on day 1 to day 7 which proved that polyethylene glycol was a candidate for calcium hydroxide solvent because it can work for a longer period of time and can reduce necrosis.

5. Conclusion

Based on the results of the study it can be concluded that the combination of calcium hydroxide and ellagic acid in a ratio of 99:1, 97:3, 95:5 mixed with polyethylene glycol solvent can increase the release of calcium ions and pH

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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