

Perspective

Research on Sustained Release Systems for Calcium Hydroxide: 3 Key Points to Improve for Avoiding Fast Conclusions

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Introduction

Calcium Hydroxide (CH) is a biomaterial widely used for apexification. Inducing an apical closure requires the presence of CH for obtaining calcium ions (Ca^{++}) and hydroxide ions (OH^-) to promote the activity of cells producing a mineral matrix at the apical zone, and to induce an alkaline environment favoring the formation of mineral tissue [1]. For apexification, the CH is usually mixed with Polyethylene Glycol (PEG) or Propylene Glycol (PPG) to make a simple paste to be placed in the immature root canal. Those polymeric vehicles promote a slow release of CH, indeed a PEG- or PPG-based paste behaves as a Sustained Release System (SRS) [2]. However, the paste will vanish in the fluids at the apical zone because the PEG and PPG are highly Water-Soluble Polymers (WSP), thus its replacement is required several times. To solve that inconvenience, studies have proposed the use of complex vehicles such as gels or micro particles formulated with WSP to release the ions for a time longer than that one performed by a paste. The CH-SRS have a great potential for clinical use. But studies on the topic have showed faults of the formulation of the systems as well as of the evaluation of the ion sustained release, as result they reported unreliable evidence of the advantage of the CH-SRS over the CH pastes. This perspective discusses 3 key points to improve the exploration of CH-SRS.

The vehicle: more than a viscous matter

It is accepted that the ideal vehicle for CH must be a viscous matrix promoting a slow release of Ca^{++} and OH^- [2]. But choosing a vehicle only because of the viscosity property might be a mistake. For instance, the chitosan has been explored as a vehicle gel on the basis of its ability to be highly viscous when it is dissolved in 2% acetic acid [3]. But it has been ignored the acetic acid causes the protonation of the chitosan, and the repulsive electrostatic forces between the cationic polymer and Ca^{++} might compromise the entrapment and release of the CH in the gel. Formulating a CH-SRS must involve more than the issue of viscosity, other characteristics of the carrier must be well considered, such as the electrical charge, the molecular weight, the degradability, and the hydrophobicity. Those properties impact on the interaction between the CH and the carrier, consequently they affect on the release of the ions. A CH-SRS must

be designed under the understanding of physical-chemical bases to get its best performance, i.e. the longest possible sustained release of Ca^{++} and OH^- .

The control paste: a contender of equal weight

The CH-SRS are usually compared to a control paste made of pure CH and PEG or PPG. It is expected that the CH-SRS will keep an ion release for a time longer than that one produced by the paste, because the SRS protects the CH against the apical fluids at the same time that undergoes a slow degradation promoting a sustained release. The superiority of the CH-SRS will be easy to prove if the system competes against a paste made of PEG or PPG that releases the total loading of CH in a time as short as 1 week [4]. The CH-SRS will be even more superior if it loads a mass of CH higher to the mass charged in the control paste, evidently under that condition the ion release originated from the control might finish sooner. To avoid that possible bias, the control paste must have a CH loading similar to that of the CH-SRS, in that way, the behavior of the ion sustained release will be determined by the physical-chemical properties of the matrix entrapping the CH, but not for the amount of CH.

The sustained release: how long should last a sustained release of CH?

From a clinical point of view, there is no a specific time for keeping the Ca^{++} and OH^- in the apical zone to induce the apical closure; the time will be determined by the clinical conditions of the treatment. But regarding the purpose of reducing the number of inter-appointments replacements of the CH, it is expected that a CH-SRS must maintain the release of ions for the longest possible time. It raises the question: how long should be the ideal time for evaluating the sustained release of the CH in a SRS? Some authors have suggested that 30 days is a time enough to investigate the sustained release of CH [3, 4], however 1 month is somewhat limited. For example, a CH-SRS might show a biphasic release ratio at a longer time and that behavior would be unnoticed if the evaluation stops at 1 month. The author's opinion is that the ion release must be evaluated until observe the total release of the CH from the control paste as well as from the CH-SRS. Otherwise, the comparison between the control and the experimental carrier might be misinterpreted. Studies have claimed the efficiency of a gel loaded with CH because a release of ions was observed until the end of the experiment, but they ignored that the control released its ions for the same time [3, 5]. Moreover, studies reported that micro particles and a control paste released about 95% and about 70% of its content of Ca^{++} at the end of the experiment, respectively [6]. In that case, one might expect that if the study will continue, the control paste will show a sustained release longer than the sustained release originated from the micro particles. Thus, only the depletion of the CH in the carrier will show the real capability of the SRS facing a control paste.

Conclusion

The CH-SRS are very attractive as an alternative to the use of a CH paste for apexification. But to date, it is unclear if they show advantages over the pastes. Concerns about the design and evaluation of the CH-SRS must be solved to obtain reliably conclusions about the performance of those carriers.

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