Papain Gel: A New Chemo-Mechanical Caries Removal Agent

Sandra Kalil Bussadori DDS*/Laura Camacho Castro DDS**/Ana Claudia Galvão DDS***

The chemo-mechanical caries removal method has been a solution for treatment of patients seeking alternatives to conventional methods. Among different kinds of chemo-mechanical caries removal systems, Papacarie® – a papain gel – was found to be easy to manipulate, simple and cheap, as well as effective in removing infected tissues.

J Clin Pediatr Dent 30(20): 115–120, 2005

INTRODUCTION

Caries continues to affect a significant portion of the world population and treatment of the decay is associated with pain by many patients.

Conventional caries removal and cavity preparation entail the use of burs. Disadvantages of this system include (i) the perception by patients that drilling is unpleasant, (ii) local anesthesia is frequently required, (iii) drilling can cause deleterious thermal effects, (iv) drilling can also cause pressure effects on the pulp, and (v) the use of a handpiece may result in removal of softened, but uninfected dentin, resulting in an excessive loss of sound tooth tissue. As a result, there is a growing demand for procedures or materials that facilitate caries management.

The chemo-mechanical method for caries removal was developed to overcome these shortcomings. It is not only more comfortable for the patient but also able to better preserve the healthy tissue.

According to Banerjee *et al*., the chemo-mechanical method is an effective alternative for caries removal because it brings together (i) atraumatic characteristics and (ii) bactericide and bacteriostatic action. The method was created so as that an active ingredient would soften the pre degraded collagen of the lesion without pain or undesirable effects to adjacent healthy tissues.[1]

In 1975, Habib *et al* introduced a method using 5% sodium hypochlorite to remove carious tissues.[2] Since then, many studies have attempted to improve this early technique. The sole use of 5% sodium hypochlorite was known to be toxic and aggressive to adjacent healthy tissues. Therefore, a new solution was developed adding sodium hydroxide, sodium chloride and glycine to the 5% sodium hypochlorite. This modified formula was known as GK-101 and it was comprised by N- monochloroglycine.[3] It was more effective than the hypochlorite alone but was very slow in carious tissue removal. Also, at the time of the introduction of GK-101, the use of adhesive dental materials was not common, and dentists still prepared teeth according to Black's cavity design. Therefore, the use of a method that only removed carious dentin could not significantly reduce the need of drilling to create mechanical retention.

Caridex™ was later developed from a formula made of N-monochloroglycine and amino butyric acid.[4] Caridex™ disrupted the carious dentin collagen making it easier to remove. Despite its effectiveness, Caridex™ had certain clinical limitations, among them, (i) it was expensive, (ii) it required a large reservoir with pump, (iii) it required large quantities of solution, (iv) it presented several problems during heating, and (v) it had a short shelf life.[5]

Recently, Carisolv™ was introduced to the European market as a successor to the Caridex™ system. Carisolv™ reached the market promising to be more effective and easy to manipulate. Carisolv™ key difference to other products already in the market was the use of three amino acids – lysine, leucine, and glutamic acid – instead of the amino butyric acid. These amino acids counteracted the sodium hypochlorite aggressive behavior at the oral healthy tissues.[6] Despite its effectiveness, Carisolv™ was not a blockbuster mainly

* Sandra Kalil Bussadori, Pediatric Dentistry Professor at FUNDECTO/USP, Universidade de São Paulo (USP)

** Laura Camacho Castro, Assistant Clinical Professor Pediatric Dentistry Department, Tufts University School of Dental Medicine

*** Ana Claudia Galvão, Universidade de São Paulo (USP)

Send all correspondence to: Sandra Kalil Bussadori, Universidade de São Paulo (USP), Av. Prof. Lineu Prestes, 2227 – Cidade Universitária, São Paulo – SP – Brazil – 05508-900

Phone: 55-11-3819-6110
Fax: 55-11-3814-1877

Email: skb@osite.com.br

because it required (i) extensive training and registration of professionals and (ii) customized instruments which increased the cost of the solution. As a result, few people had access to the Carisolv™ solution.

In 2003, a research project in Brazil led to the development of a new formula to universalize the use of chemo-mechanical method for caries removal and promote its use in public health. The new formula was commercially known as Papacarie®.

Papacarie® is basically comprised of papain, chloramines, toluidine blue, salts, thickening vehicle, which together are responsible for the Papacarie's bactericide, bacteriostatic and antiinflammatory characteristics.

PAPAIN

Papain is a proteolytic enzyme. It has bactericide, bacteriostatic and antiinflammatory characteristics.[7,8,9] Similarly to the human pepsin, papain acts as a debridant anti inflammatory agent which does not damage the healthy tissue and accelerates the cicatricial process. Papain comes from the latex of the leaves and fruits of the green adult papaya.[10,11] Carica papaya, for instance, is cultivated in tropical regions such as Brazil, India, South Africa, and Hawaii, and is largely used in the food, beverage, and drug industries.

Papain accelerates the cicatricial process. According to Mandelbaum, papain is indicated in all phases of the cicatricial process; dry or exudative wounds, colonized or infected, with or without areas of necrosis. Papain promotes (i) chemical debridement, (ii) granulation and epithelialization, which hastens the phases of cicatrization, and (iii) stimulation of the tensile strength of the scars.[8]

Studies reported by Starley *et al* showed that Carica papaya was used at the pediatric unit of the Royal Victoria Hospital (Banjul). It demonstrated to be the major component of burn dressings. Cheap and widely available, the pulp of the papaya fruit was mashed and daily applied to full thickness and infected burns. It appeared to be effective in removing necrotic tissue, preventing burn wound infection, and providing a granulating wound suitable for the application of a split thickness skin graft.[12]

When the treatment with papain is initiated, it (i) increases the local reparative secretion, (ii) softens the

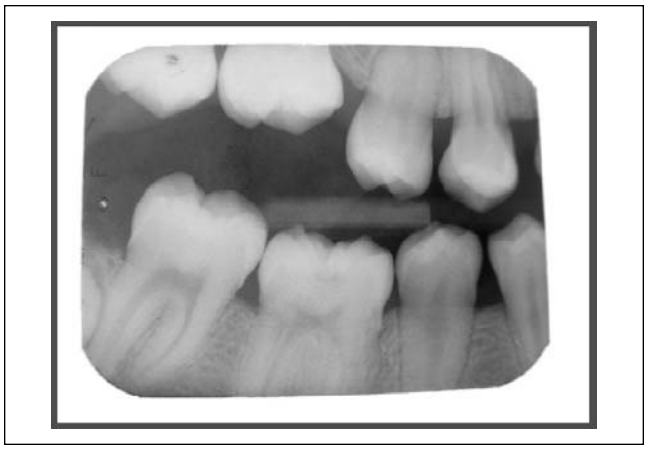

Figure 1. Initial Radiography

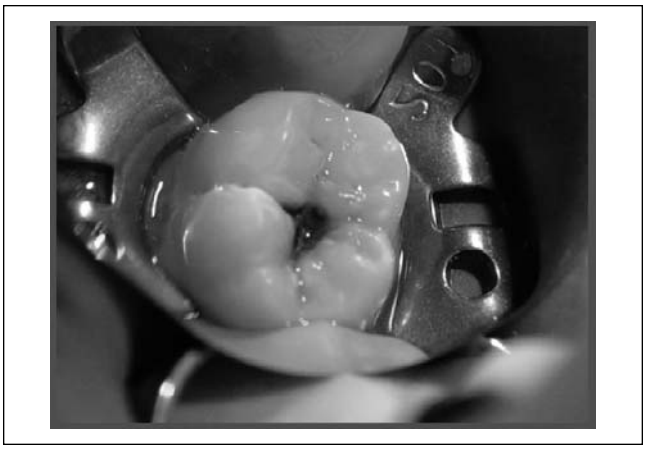

Figure 3. Rinsing with air/water spray

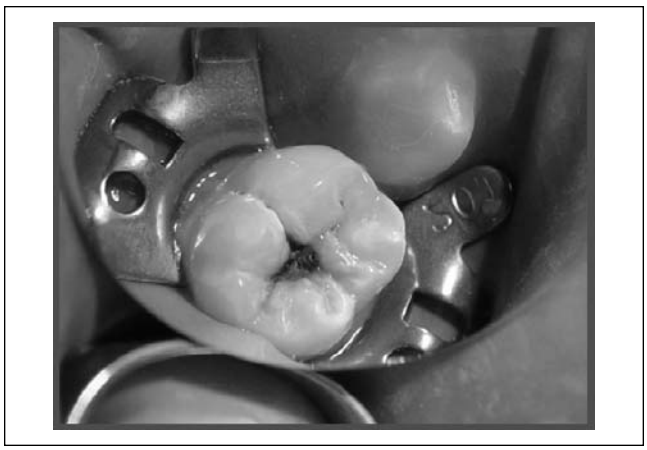

Figure 2. Prophylaxis of the tooth

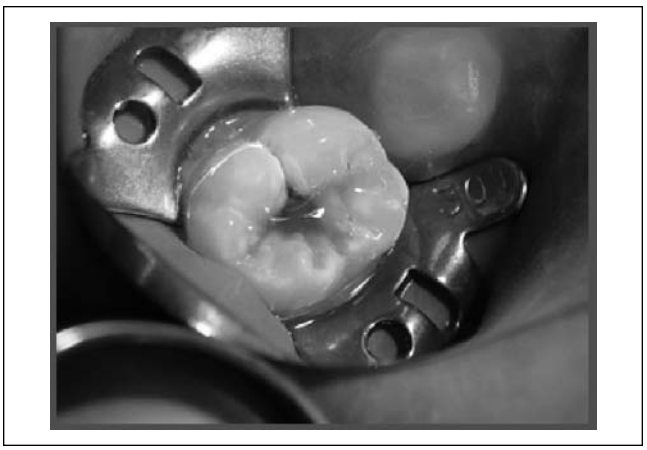

Figure 4. Application of Papacarie

necrotic tissue, (iii) slacks the border of the lesion, and (iv) promotes a small increase in the hyperemic halo diameter. A period after the beginning of the process, the necrotic tissue breaks loose and the hyperemic halo diameter slowly starts to decrease. Therefore, the cicatricial process is accelerated, which reduces the time required for the recovery of the patient's lesion. The topical use of papain softens scabs of lesions and can cause borders to break loose.[13]

Flindt demonstrated that papain acts only in infected tissues because infected tissues lack a plasmatic anti protease called a1-anti-trypisin. The a1-anti-trypisin is only present in sound tissues and it inhibits protein digestion. The absence of the a1-anti-trypisin in infected tissues allows papain to break the partially degraded collagen molecules.[14,15]

Papain facilitates the cleaning of both necrotic tissues and secretions. As a result, it decreases the time required for tissue recovery and does not damage the sound tissues around the lesion.[16]

Dawkins showed that Carica papaya has bactericide and bacteriostatic properties. He investigated antibacterial activity of ripe and unripe Carica papaya on selected microorganisms. They concluded that Carica papaya contain anti-bacterial activity that inhibits growth of gram-positive and gram-negative organisms. Observed activity was independent of fruit maturity.[17]

Studies conducted by Emeruwa also showed significant antibacterial activity of Carica papaya fruit against both gram-positive and gram-negative bacteria (*S. aureus, E. coli, B. cereus, P. aeruginosa and S. flexneri*).[18]

CHLORAMINES

Chloramines are formed during a reaction between chlorine and ammonia. Chloramines are amines which contain at least one chlorine atom, which is directly bonded to nitrogen atoms.

Chloramines have bactericide and disinfectant properties. The disinfectant chloramines T, a well known active chlorine compound, have been demonstrated to inactivate Gram-positive and Gram-negative bacteria *in vitro*, and are also bactericidal *in vivo* when applied to contaminated wounds.[19]

The antiseptic efficacy of chloramines T was recently documented in an *in vitro* study. Fuursted *et al* compared the lag of regrowth and the bactericidal activity

Figure 5. Removal of the softened carious dentin

Figure 7. Restoration

Figure 6. Vitrous aspect of the cavity

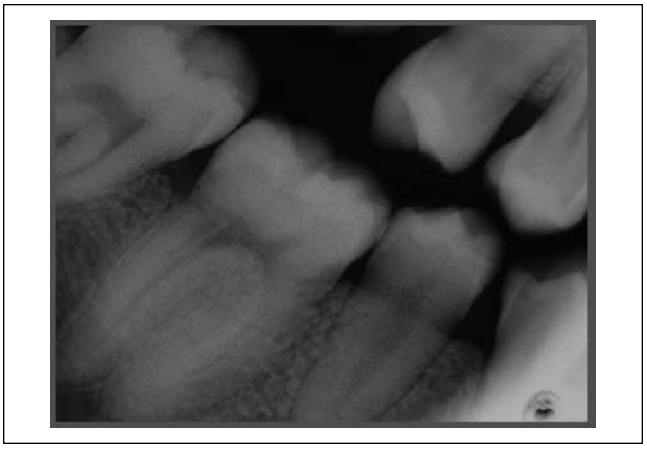

Figure 8. Final Radiography

of five antiseptics (chloramines T, chlorhexidine, povidone-iodine, phenoxyethanol and mandelic-lactic acid) against nine bacterial pathogens. Results showed that the chloramines T and mandelic-lactic acid induced a significantly longer lag as compared with the other agents. Therefore, information on bactericidal activity, as well as the lag of regrowth, could be a useful screening method for efficacy of antiseptics.[20]

Pitten *et al* did an *in vivo* study that showed the antimicrobial efficacy of different mouth rinse solutions. Results allowed them to classify four categories of mouthrinse solutions according to their antimicrobial properties: (i) products without any active antimicrobial effect (sterile water, sage tea, fluormint-lysoform), (ii) products with a weak and temporary effect (hydrogen peroxide, meridol, Listerine, lavasept), (iii) products with a strong immediate effect, but no prolonged activity (betaisodone solution, acriflavine) and finally, (iv) products that exert a sustained effect after application (chloramines T, gurfix, dobendan).[21]

Chloramines are broadly used to chemically soften the carious dentin. According to Maragakis *et al* the partially degraded collagen in carious dentin was chlorinated by chemo-mechanical caries removal solutions. This chlorination affects the secondary and/or quaternary structure of the collagen, by disrupting hydrogen bonding and thus facilitating the carious tissue removal.[22]

Tonami's study reported that (i) the application of chloramines resulted in the opening of dentinal tubules in the outer layer of carious dentin and (ii) occluded dentinal tubules were seen after sodium hypochlorite application. The presence of chloramines and amino acids had some effect on the carious dentin outer layer. However, chloramines activity was supposed to be influenced by the pH of the solution, types of amino acids and proportion of amino acids and sodium hypochlorite.[23]

PAPACARIE®

Before the clinical use of Papacarie®, we conducted several *in vitro* and *in vivo* studies, and considerations regarding materials and procedures must be noted.

Silva *et al* conducted a research in which they concluded that Papacarie® is safe, not citotoxic *in vitro* fibroblast culture, and it is biocompatible to the oral tissues.[24]

Pereira et al used samples of infected dentin cultivated in BHI broth in Petri dish to assess the Papacarie'antimicrobial activity. The samples were analyzed using Kruskall test and Anova complemented by Turkey. The results showed the largest papacarie'activity in *streptococcus* and *lactobacillus.* Authors concluded that papacarie® was antimicrobial.[25]

Reda *et al*. distributed 200 questionnaires to professionals and graduate students to verify their opinion regarding Papacarie's effectiveness, action time, consistency, oxygen liberation, and patient symptom. Using the Siegel test to analyze the relationship among the above mentioned variables, the researchers found out that the gel showed (i) fast action, (ii) ideal consistency, (iii) effectiveness, (iv) no sensitivity, and (v) almost no bubbling during the oxygen liberation.[26]

Mechanism of action

Anti-trypisin inhibits protein digestion but infected tissues do not usually show anti-trypisin. Since papain can digest only dead cells, it acts breaking the partially degraded collagen molecules, contributing to the degradation and elimination of the fibrin "mantle" formed by the carious process.

Right after the degradation, oxygen is freed, bubbles appear on the surface, and a blearing of the gel is thus noted. These signs demonstrate that the removal process can be started. For removal, we recommend the use of the opposite side of an excavator, like a pendulum movement and without cutting. The instrument should scrap the carious tissue without promoting any kind of stimulus or pressure.

The main characteristic of the complete removal of the infected dentinal tissue is the vitreous aspect of the cavity which appears after using Papacarie®.

Material Presentation

Papacarie® is a gel syringes that have 3 ml of solution.

Instructions for Use

The use of Papacarie® for carious tissue removal must be done in accordance with the following methodology:

- Radiograph of the target tooth;
- Prophylaxis of the region using rubber cup and slurry of pumice;
- Rinsing with air/water spray or cotton pellet with water;
- Isolation of target tooth
- Application of Papacarie®, allowing the chemistry to work for 30 to 40 seconds
- Removal of the softened carious dentin using the opposite side of the excavator and promoting a pendulum movement. The softened tissue must be scraped, but not cut
- Application of gel, if necessary. There is no need for rinsing the cavity between applications.
- The vitrous aspect of the cavity appears when the cavity feels free from caries
- Rinsing 0.12%, 1% or 2% chlorhexidine or water spray
- Drying with moisture-free and oil-free air
- Restoration with a suitable filling material according to manufacturer's instructions

Final Considerations

The chemo-mechanical removal method has been a solution for the treatment of patients seeking alternatives to conventional methods. The key advantages offered by the chemo-mechanical method are (i) its proven effectiveness, (ii) the method's safety, (iii) the elimination of local anesthesia and bur, (iv) the lower anxiety built in patients, and (v) the conservation of the sound tissue. Among different kinds of chemo-mechanical caries removal systems, Papacarie® has been found to be easy to manipulate, simple and cheap, as well as effective in removing infected tissues. Moreover, its use can be afforded by unprivileged people which otherwise would have no other option.

REFERENCES

1. Banerjee A., WatsonT., Kidd E. Dentine caries excavation: a review of current clinical techniques. Br Dent J 2000; 188:476–482.
2. Habib CM, Kronman J, Goldman M. A chemical evaluation of collagen and hydroxyproline alter treatment with GK-101(N-chloroglycine). Pharmacol Ther Dent, v.2, 209–215, 1975.
3. Goldman M, Kronman JH. A preliminary report on a chemomechanical means of removing caries. J Am Dent Assoc 1976; 93(6): 1149–53.
4. Schutzbank SG, Galaini J, Kronman JH, Goldman M, Clarke REA: A Comparative in vitro study of the effect of GK-101 and GK101E in caries removal. J Dent Res 1978; 57:861–864.
5. Beeley JA, Yip HK, Stevenson AG. Chemomechanical caries removal: a review of the techniques and latest developments. Br Dent J 2000;188:427–430.
6. Ericson D, Zimmerman M, Raber H, Gotrick B, Bornstein R, Thorell J. Clinical evaluation of efficacy and safety of a new method for chemo-mechanicalremovalof caries. Caries Res 1999; 33:171–177.
7. Candido LC. Nova abordagem no tratamento de feridas. São Paulo: Senac-SP 2001. Available: http://www. Feridologo.com.br/curpapaina.htm [2003Dez].
8. Mandelbaum SH, Santis EP, Mandelbaum MHS. Cicatrization: current concepts and auxiliary resources – PartII. An Bras Dermatol 2003; 78(5):525–542.
9. Osato JA, Santiago LA, Remo GM, Cuadra MS, Mori A. Antimicrobial and antioxidant activities of unripe papaya. Life Sci 1999; 53(17):1383–1389.
10. Kimmel JR, Smith EL. Crystalline papain: preparation, specificity and activation. J Biol Chem 1954; 207:514–573.
11. Kimmel Jr, Smith EL. The properties of papain. Adv Enzymol Rel Subj Biochem 1957; 19:267–334.
12. Starley IF, Mohammed P, Schneider G, Bickler SW. The treatment of paediatric burns using topical papaya. Burns 1999; 25(7): 636–639.
13. Guzman AV, Guzman MGS. The enzymatic debridement of suppurations, necrotic lesions and burns with papain. J Int Coll Surg 1953; 20(6):695–702.
14. Flindt M. Health and safety aspects of working with enzymes. Process Biochem 1979; 13(8):3–7.
15. Flindt M. Allergy to amylase and papain. Lancet 1979; 1: 430-432.
16. Velasco MVR. Desenvolvimento e padronização do gel contendo papaína para uso tópico. [Dissertação de Mestrado]. São Paulo: faculdade de Ciências Farmacêuticas da USP; 1993.
17. Dawkins G, HewittH, Wint Y, Obiefuna PC, WintB. Antibacterial effects of Carica Papaya fruit on common wound organisms. West Indian Med J 2003; 52(4):290–292.
18. Emeruwa AC. Antibacterial substance from Carica Papaya fruit extract. J Nat Prod 1982; 45(2):123–127.
19. Nagl m, Nguyen VA, Gottardi W, Ulmer H, Hopfl R. Tolerability and efficacy of N-chlorotaurine in comparison with chloramines T for the treatment of chronic leg ulcers with a purulent coating: a randomized phase II study. Br j Dermatol 2003;149(3):590–597.
20. Fuursted K, Hjort A, Knudsen L. Evaluation of bactericidal activity and lag of regrowth (postantibiotic effect) of five antiseptics on nine bacterial pathogens. J Antimicrob Chemoter 1997; 40(2):221–226.
21. Pitten A, Kramer A. Antimicrobial efficacy of antiseptic mouthrinse solutions. Eur J Pharmacol 1999; 55(2):95–100.
22. Chemomechanical caries removal: a comprehensive review of the literature. Int Dent J 2001; 51(4): 291–299.
23. Tonami K, Araki K, Mataki S, Kurosaki N. Effects of chloramines and sodium hypochlorite on carious dentin. J Med Dent Sci 2003;50(2):139–146.
24. Silva LR, Tonolli G, Santos EM, Bussadori SK. Avaliação da biocompatibilidade in vitro de um novo biomaterial para remoção química e mecânica da cárie. In: 20ª Reunião Anual SBPqO 2003.
25. Pereira AS, Silva LR, Piccinini DPF, Santos EM, Bussadori SK. Comparação in vitro do potencial antimicrobiano de dois materiais para remoção químico-mecânica da cárie.
26. Redá SH, Motta LFG, BussadoriSK. Avaliação do gel a base de papaína para remoção química e mecânica da lesão cárie - Papacárie®.