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# Endodontic therapy future in biomimetics dentistry

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## Abstract

Biomimetics refers to human-made processes, substances, systems, or devices that imitate nature. The art and science of designing and building biomimetic apparatus are called biomimetics. This method can be widely used in dentistry to restore the structure and function of normal tooth structure. Traditional approaches to treating damaged and decayed teeth require more aggressive preparation to place a "strong," stiff restoration. The emphasis was made on the strength of the restoration as well as its function and mechanical properties, despite several disadvantages like tooth fracture, making future treatment more difficult and invasive.

Regenerative endodontic procedures have been described for over a decade as a paradigm shift in the treatment of immature necrotic permanent teeth, owing to their ability to allow root maturation with subsequent enhancement of the tooth's fracture resistance in addition to the potential for regeneration of vital intracanal tissues. Concomitantly, minimally invasive endodontics is another rising concept with the main concern of preservation of tooth structure. Stemming from their potential to preserve the original tooth structure, both regenerative and minimally invasive endodontics could be considered as two revolutionary sciences with one common goal. Achieving this goal would entail not only employing the appropriate strategies to recreate the ideal regenerative niche but modifying existing concepts and protocols currently being implemented in regenerative endodontics to address two important challenges affecting the outcome of these procedures; conservation of tooth structure and achieving effective disinfection. Therefore, the search for new biomimetic cell-friendly disinfecting agents and strategies is crucial if such a novel integratory concept is to be foreseen in the future. This could be attainable by advocating a new merged concept of "minimally invasive regenerative endodontic procedures (MIREPs)," through modifying the clinical protocol of REPs by incorporating a minimally invasive access cavity design/preparation and biomimetic disinfection protocol, which could enhance clinical treatment outcomes and in the future .

Biomimetic materials for hard and soft tissues have advanced in the fields of tissue engineering and regenerative medicine in dentistry , between 2010–2020 Over 500 articles were obtained under clinical trials, randomized clinical trials, metanalysis, and systematic reviews developed in the past 10 years in three major areas of dentistry: restorative, orofacial surgery, and periodontics. Clinical studies and systematic reviews along with hand-searched preclinical studies as potential therapies have been included. They support the proof-of-concept that novel treatments are in the pipeline towards ground-breaking clinical therapies for orofacial bone regeneration, tooth regeneration, repair of the oral mucosa, periodontal tissue engineering, and dental implants. Biomimicry enhances the clinical outcomes and calls for an interdisciplinary approach integrating medicine, bioengineering, biotechnology, and computational sciences to advance the current research to clinics. We conclude that dentistry has come a long way apropos of regenerative medicine; still, there are vast avenues to endeavor , seeking inspiration from other facets in biomedical research.

## Introduction

In the 1950s, Otto Schmitt a biomedical engineer introduced the term "biomimetic" **[1]** .The true concept of "biomimicry or biomimetics" is to develop manmade design while taking inspiration from nature **[2].** Biomimicry is a Greek word (bios, meaning life, and mimesis, meaning to imitate), envisioned as a completely or partly induced biological phenomenon **[3].** In the medical, dental, biotechnological, and pharmaceutical fields, the failure of conventional materials is due to the lack of the ability of these materials to follow a cellular pathway to fit in with biological systems **[4].** Biomimetic dentistry is the art and science of restoring or repairing damaged teeth with various approaches that mimic natural dentition in terms of aesthetics and function These approaches involve minimal invasive-dental management by the use of bioinspired materials to achieve remineralization**[5] .**Endodontic therapy is a common dental technique used to repair teeth whose pulp tissues have become permanently irritated or decaying as a result of caries or dental trauma. This treatment, which comprises mechanical and chemical root canal preparation, may affect numerous mechanical and physical aspects of the tooth structure **[6]** . Root filled teeth may fail due to either biological or structural reasons. Causes of failure include persistent or recurrent endodontic disease, unrestorable caries, restorative failure, irretrievable cusp or crown fracture, vertical root fracture or periodontal disease. Whilst endodontic research is replete with clinical studies on the success rate of root canal treatment, it is acknowledged that structural failure is the most common reason for the extraction of root filled teeth **[7].** In Biomimetic approach, the concept of less or no dentistry is the best dentistry has been adopted. It is conservative and only focuses on restoring the teeth and simulating the natural dentition as much as possible. The biomimetic restorative protocols aim to achieve these results by stress-reducing protocols and bond-maximizing protocols. Cavities and other lesions are carefully repaired using advanced materials and adhesives so the tooth retains its inherent natural properties **[8]**. Contemporary endodontic regeneration involves a revascularization process in which the root-canal system is disinfected using the intracanal medicaments and a blood clot is formed by stimulating the tissues of the root apex. The presence of blood clots mimics a natural scaffold inside the root canal that facilitates the proliferation and differentiation of the pulp-dentin stem cells **[9,10] .**The ultimate outcome of regenerative endodontics is enhanced patient management which could be done by various strategies that translate the biological aspects of the regeneration of pulp into the clinical aspects. These clinical protocols varied from relating the natural ability of the pulp to heal to regenerating the affected pulp-dentin complex or achieving revascularization of the empty-root canal **[9].**

# 1. Review

## 1.1. Direct pulp capping (DPC) :

is considered to be one efficient, conservative treatment option , during this procedure, after caries excavation, a dental biomaterial is placed directly over the exposed dental pulp. This helps to promote the mineralized tissue formation that is ubiquitously used to protect the vitality of the dental pulp **[11].** Studies revealed that a tooth is more likely to survive if the exposure to the pulp is mechanical compared to dental caries **[12,13].** Pulpal inflammation results from dental caries causing bacterial invasion which penetrates the pulp. Nevertheless, it is possible that the pulpal tissue remains inflamed even after the dental operative procedure has been completed. Consequently, it is more likely to have chronic .[low-grade inflammation, and due to this reason, the pulp is less able to react, and healing would be delayed **[14,15] .** Generally, reduced pulp inflammation occurs after the elimination of infectious bacteria and the ability of the pulp immune system to neutralize intratubular diffusing substances such as intratubular immunoglobulins (IgG1, IgA1, IgA2, IgM, etc.). These two mechanisms contribute to the decreased synthesis of pro-inflammatory cytokines **[16].** Eventually, following a significant reduction in inflammation, the pulp tissue starts the healing process. The freshly formed odontoblast-like cells replace the nearby odontoblasts that used to be a part of the mineralized tissue barrier.[or reparative dentin bridge at the exposed site] **[14]** . However, the most challenging part of the DPC procedure is the accurate identification and removal of the severely inflamed tissue that has been damaged by prolonged contact with oral bacteria **[17].**

## 1.2. Mechanism of action of DPC:

The mechanisms of most DPC biomaterials cause superficial necrosis after placement directly over the exposed pulp tissue. The DPC biomaterial possesses antimicrobial properties and induces mineralization **[15].** With the release of hydroxyl ions by DPC biomaterials, which raised the pH of the underlying tissue, causing a thin necrotic layer between the vital pulp tissue and the DPC agent **[18,19].** Due to the existence of this necrotic zone, the vital pulp cells that lie beneath it are protected from the alkaline pH of the material . Additionally, it enables the underlying pulp cells to perform the repair and regeneration processes **[20].** It has been suggested that the presence of such a high alkaline pH is responsible for the formation of reparative dentin by the DPC agent . Furthermore, mineralization has been proven to be inhibited by pH levels above 8.0 **[21].** The high pH might also have an anti-inflammatory effect through the denaturation of proinflammatory cytokines and activation of the regulatory IL-10 **[22,23].** Further research is required to determine the precise effects of high pH on reparative dentin formation because it is technically challenging to measure the pH at or near the interfaces between DPC materials and pulp tissue. Following pulp exposure and DPC, early changes include hemorrhage and moderate inflammation, resolved during the first week **[24].** In turn, this might also provide a conducive environment for the formation of reparative dentin if the bacterial irritation and inflammatory reaction are successfully mitigated.

Hence, such effects are indirect, the elimination of bacterial organisms does not directly contribute to the production of reparative dentin . Therefore, it is unclear if the DPC materials' anti-microbial action is a molecular factor in the formation of reparative dentin **[21].** The release of calcium ions from the DPC biomaterials stimulates the precipitation of calcium carbonate in the wound area and thereby contributes to the initiation of mineralization. The pulp cells then begin to differentiate; these cells have odontoblast-like behavioral traits and start to produce a collagen-rich matrix that resembles predentin **[24].** Although one of the main substances released by DPC materials is calcium ions **[25 , 26].** However, little is known about how calcium ions play a role in the formation of reparative dentin throughout the repair process. On the other hand, new data suggests that calcium ions serve essential roles in sustaining and regulating regular biological activities, as well as in the development of mineralized matrixes and the propagation of intracellular signaling pathways **[21].** Furthermore, calcium ions released by pulp-capping materials may have a role in the formation of reparative dentin, according to recent studies **[20,26].**

## 1.3. Materials used for DPC:

Through the years, many dental materials have been introduced with the goal of prompting the safest tissue response and optimizing patient outcomes **[27].** New biomaterials for preserving pulp vitality through conservative and restorative dental procedures have evolved as knowledge of the dentin-pulp complex healing mechanism has grown **[28, 29].** Because there are so many different biomaterials that may be used for DPC, it can be challenging to determine which pulp capping material would work best in each clinical scenario **[27].**The ideal DPC material would have the following characteristics: simple handling during an operative procedure; adhesion to dental substrate; antibacterial properties; excellent sealing ability; insolubility in tissue fluids; biocompatibility and bioactivity; promotion of mineralized tissue barrier formation; radiopacity and does not cause tooth discoloration **[30].**

### 1.3.1. Calcium hydroxide

In previous decades, calcium hydroxide (CH) has been the material of choice and gold standard for DPC **[31,31,33,34].** One of the desirable properties of CH is that it has a high pH, which is responsible for the stimulation of fibroblasts **[35].** It raises the pH of acidic solutions, inhibits microorganism’s growth, and encourages the healing and defense mechanisms of pulp tissue **[36,37].** In addition to having high solubility and poor adherence to hard tissues, it does not offer the best attainable seal. CH shows a tunnel defect like phenomenon in the dentin bridge, although there is evidence to show that the expression of these defects improves with improved dentin-bridge thickness **[38,39,40].** According to studies that followed patients for up to 10 years, CH, as a DPC material, has shown successful clinical outcomes **[41,42,43].** The development of superficial necrosis is the first consequence after CH placement on the exposed pulp **[44].** The pulp is stimulated to protect and heal itself to produce a reparative dentin bridge through the processes of cellular differentiation, extracellular matrix secretion, and eventual mineralization when firm necrosis is present. This causes a very minor irritation **[44].** It has been found that 89% of dentin bridges formed below CH revealed tunnel defects. This is despite the fact that the formation of a dentin bridge has been thought to be the key to the clinical effectiveness of DPC **[40].** Not only are these tunnel defects in the heterogeneous dentin barrier provide inadequate

durable barrier, but they are also not capable of forming a long-term effective seal against pathogenic bacteria. Another drawback of CH is dissolution **[45,46].**

CH has been shown to stimulate hard tissue repair, but the exact processes behind this effect are unknown **[47].** It has been hypothesized that the surface of the necrotic layer acts as a barrier between the vital tissue and the wound, allowing the pulp to heal on its own **[44].** It has been speculated that the induction of hard tissue healing can be attributed to the production of a microenvironment that is supersaturated with calcium ions and is located adjacent to the pulp. However, this theory was challenged by the fact that the calcium ions integrated into the mineralized hard tissue barrier emerged from the underlying tissues instead of deriving from the pulp-capping materials itself **[48,49].** In addition to this, it has been suggested that the tissue may have a favorable outcome to the high pH condition that is produced because of the release of hydroxyl ions **[50].** Studies with long-term clinical follow-up of DPC with CH found success rates ranging from 37% to 81.8%, despite the fact that a number of studies have shown that CH is helpful in promoting pulp healing **[42,43,51,52].**

### 1.3.2. Mineral trioxide aggregate

As an alternative to CH, mineral trioxide aggregate (MTA) has gained widespread acceptance because of its potential to promote wound healing of the dentin-pulp complex **[48,53].** MTA is mainly derived from Portland cement and the main components are tricalcium silicate, dicalcium silicate, and tricalcium aluminate, in addition to bismuth oxide for radiopacity **[54].** The major benefits include excellent biocompatibility when applied to the pulp wound, superior sealing ability, which allows excellent cell/material adhesion, low solubility, inhibition of bacterial invasion, and induction for dentin bridge formation **[55].** MTA possesses favorable physiochemical properties that induce reparative dentin formation by the recruitment and activation of hard tissue forming cells, contributing to matrix formation and mineralization **[56].** In addition, MTA has the potential to reduce the levels of pulp inflammation, hyperemia, and necrosis and has the ability to solubilize bioactive proteins that are involved in the process of tooth repair **[57,58,59].** Moreover, the inflammation induced by MTA is only short-term, which is less severe than CH **[60].** On the other hand, MTA presents some disadvantages, such as long setting time, difficult handling characteristics, discoloration, and high cost **[53].** After placing MTA material over the exposed pulp, MTA activates the progenitor cells (fibroblast) migration from the central pulp to the exposure area. This helps to promote their proliferation and differentiation into odontoblast-like cells without inducing apoptosis in the pulp cells **[56].** MTA induces a time-dependent environment that is pro-inflammatory and promotes wound regeneration through upregulation of cytokines **[61].** Cytokine upregulation is responsible for the induction of biomineralization by the production of collagen fibrils or apatite-like clusters at the dentin-MTA interface. MTA releases calcium ions which exert antibacterial effects and promote mineralization beneath the pulp exposure area and has the potential to maintain the vitality of the pulp **[62].** MTA prevents bacterial leakage when used with a sealed restoration and might help to protect the pulp tissue, promote healing, and maintain pulp vitality **[63,64].** The main calcium ion released by the MTA reacts with phosphates in tissue fluid to form hydroxyapatite, which makes the material biocompatible and able to provide an appropriate seal **[65].** This hydroxyapatite layer formation is

a crucial factor for the chemical seal between the wall of the dentin and the MTA, although it cannot be considered as a true bonding process **[66].** Despite this, there is a possibility of bacterial leakage when there is an inadequate seal, which could result in the DPC treatment failure **[67].** Recent studies have demonstrated that MTA has a higher clinical success rate and results in less pulpal inflammatory response and more predictable mineralized tissue barrier formation than CH in DPC **[68,69].** A study conducted on 49 teeth with carious pulp exposure of 37 patients capped with MTA showed a 97.96% overall success rate after 9 years **[63].**

### 1.3.3. Biodentine

Biodentine is an innovative cement made of tricalcium silicate that also exhibits remarkable bioactive characteristics **[70].** It was reported that the effectivness of biodentine in DPC over mechanically exposed pulps was comparable to that of MTA **[67].** Pure tricalcium silicate, calcium carbonate, and zirconium oxide are predominantly found in biodentine as its compositions **[53].** Contrary to MTA, biodentine does not include inorganic compounds such as calcium aluminate, calcium sulfate, or bismuth oxide **[71].** Bismuth oxide, which is included in MTA, is known to slow the setting process, adversely affect the biocompatibility, and cause discoloration. Nevertheless, biodentine does not contain bismuth oxide, which is a crucial factor in the characteristics of this material **[72,73,74].** Biodentine has been shown to have superior mechanical properties, improved color stability, an easier application process, and a faster initial setting time compared to MTA **[75,76,77,78].** Its main drawbacks are its limited radiopacity and the difficulty of attaining the desired or optimized consistency **[79,80] .** It has been found that the amounts of calcium that are released by biodentine are substantially higher than those released by CH cement and MTA **[81,82,83,84].** An increase in the amount of calcium released is indicative of an increase in the amount of hydroxyl ions released as well. The antibacterial properties of biodentine are attributed to its high pH, which is achieved by the action of hydroxyl ions on the surrounding tissue **[85,86].** A thin layer of coagulative necrosis forms between the vital pulp tissue and the pulp capping material because of the increase in pH **[87].** The necrotic zone serves as a barrier between the alkaline pH of the substance and the pulp cells that lie underneath it. Furthermore, a reparative dentinal bridge will form adjacent to the necrotic zone , It has additionally been observed that biodentine releases silicon ions into the surrounding dentine. It has been hypothesized that the silicon ions produced by biodentine assist in the production of dentin bridges and accelerate mineralization **[71].** After DPC with biodentine, studies demonstrated that the creation of a complete dentinal bridge, a less inflammatory pulp response, and layers of well-arranged odontoblasts and odontoblast-like cells **[88].** The clinical success rate of biodentine as a DPC material compared with MTA was evaluated in several investigations. In a study that was carried out over the course of six months, 24 teeth that had carious pulp exposure and had been capped with either MTA or biodentine demonstrated overall success rates of 91.7% and 83.3%, respectively **[89].** MTA and biodentine exhibited overall success rates of 93.5% and 93.1%, respectively, after six months of treatment on 68 teeth with carious pulp exposure in 54 patients in a separate trial. After a period of twelve months, the MTA and biodentine treatments had a success rate of 100% and 96%, respectively. Follow up with patients for three years after treatment, the overall success rate for MTA and biodentine was found to be 96% and 91.7%, correspondingly **[80].** It was revealed that when utilized as DPC materials in permanent mature teeth with carious

exposure, biodentine and MTA have favorable and comparable success rates. Therefore, the long-term success of DPC may crucially depend on the amount of healthy tooth structure that remains and the durability of the coronal restoration **[90].** According to the findings of these studies, biodentine may have a high level of efficacy in the DPC of exposed pulp. Nevertheless, more evidence is needed from clinical trials of longer follow-ups. In addition, the efficacy of the treatment and the prognosis are dependent on the age, type, exposure area, and intensity of pulp exposure. It is important to take into consideration the fact that MTA has been subjected to more extensive evaluation as a DPC material than biodentine. Moreover, as compared to studies of MTA, the current studies on biodentine had a smaller number of participants in their tested sample **[71].**

## 1.4. Mineralized tissue formation ability :

In contrast to the formation of reparative or reactionary dentin, the formation of mineralized tissue following the loss of the odontoblast is a more complicated process **[91].** Without odontoblasts, dentin formation would not be possible **[92].** The formation of mineralized tissue is mainly characterized by heterogeneity, amorphousness, and tubular architecture **[93].** However, it is debatable as to whether it can be referred to as a dentin bridge. If dentin were to be formed further, a different kind of cell would have to replace the initial odontoblast that had been destroyed already. It is remained unknown where these initial cells derived from or how they differentiated **[94].** After the DPC on the human teeth with either CH or MTA, recent studies have found no histological evidence for the formation of replaced odontoblasts or new odontoblast-like cells **[95,96]** . Because of this, secondary odontoblasts or cells that behave similarly to odontoblasts which cannot be identified histologically **[97].** It is also currently unknown if the hard tissue development is replicated in the dentin or just a hypoplastic intrapulpal mineralization as a reaction to inflammation **[98].**

## 1.5. Revascularization or Revitalization :

Teeth with apical periodontitis and Immature root apex having periapical infection underwent the revascularization process in 1971 **[116].** However, due to limitations in materials, instrumentation, and techniques, this attempt failed. However, with the constant innovations and developments of techniques, materials, and instruments now, several case reports have used and incorporated this technique into everyday use with success. The process of revascularization technique is different from both apexification and apexogenesis **[117,118] .** Apexification is defined as ‘an apical barrier to avert the route of toxins and bacteria into periapical tissues from root canal” [**101,119].** In most pulp-diseases scenario and apical periodontitis, calcium hydroxide Is used. Due to its improving success rate, easy availability for the clinician and affordability for patients, it is considered one of the most important medicaments that have shown promising results **[120,121].** Traditional apexification procedures were the only option for clinicians to treat pulpal necrosis of immature teeth before 2004 whichh presents a unique challenge to the dentist. Calcium-hydroxide dressing was considered the prImary material to be used in these traditional apexification-treatment procedures. Apexification has proven to be highly foreseeable **[101].** However, the disadvantage

of this procedure is that over a period of months, It requires multiple appointments In addition to the higher incidence of cervical fracture **[112].** ProRoot Mineral Trioxide Aggregate (MTA) is used In the artificial-apical- barrier technique to facilitate root-canal-obturation procedures **[119].**

When the pulp is inflamed with an incompletely developed tooth, apexogenesis is carried out **[122].** Apexogenesis is a technique that discourses the inadequacies involved with capping the inflamed dental pulp. The objective of apexogenesis is the conservation of vital pulp tissue so that continuous development of roots with apical closure may occur. Calcium-hydroxide paste is placed as a wound dressing after removing most or all of the coronal pulp **[123].**

In recent years the treatment of necrotic-immature teeth has been changed due to the various pros and cons of apexification and artificial-barrier procedures. Revascularization is the terminology that is used to describe the treatment of immature-necrotic teeth which involves the proliferation of the tissues in the pulp space of the involved tooth **[115].**

Pulp revascularization has become a new method for the treatment of periapical diseases in young permanent teeth in recent years. Through root canal flushing and disinfection, avoiding mechanical preparation, guiding apical stem cells into the root canal and promoting the continuous development of tooth roots, it has achieved good clinical curative effects **[97,98].**

Initially, lstimulated apical tissue bleeding to treat young permanent tooth periapical disease according to the mechanism of trauma healing caused by blood clots **[99].** They used the blood cells of necrotic teeth to regenerate tissue in the root canal but only formed approximately 2 mm of granulation tissue in the root tip. With the improvement of root canal disinfection and crown sealing technology, in 2001 placed antibiotics in the root canal for disinfection when treating a young permanent tooth patient with chronic periapical disease, stimulated apical bleeding and filled the root canal. Finally, the crown was tightly sealed with mineral trioxide aggregate (MTA). After 30 mo of follow-up, the root of the affected tooth continued to develop, the root canal wall thickened, the root tip closed, and an electrical activity test continued to show positive results . An increasing number of clinicians have used this method and obtained similar results **[100].**

The biological mechanism of pulp revascularization Is still unknown. The main process is thorough and effective root canal disinfection. Root canal disinfection and chemical irrigation are used to remove infectious materials in the root canal. Commonly used rinsing fluids include 1.5%-3% sodium hypochlorite solution and 17% EDTA solution **[96].** After chemical preparation, the root canal is sealed with a triple antibacterial paste, which is generally composed of ciprofloxacin, metronidazole and minocycline **[102,103].**

During the treatment process, it is best to protect the residual dental pulp tissue, dental pulp stem cells and apical papillary stem cells. Studies have shown that stem cells that isolated from various problems of the oral cavity have emerged as important sources for bone and dental regulation, given stem cells plasticity, they can differentiate into specific cell lineages with a capacity of almost unlimited self-renewal and release of trophic/immunomodular factors **[104-106].** These stem cells have different differentiation potentials induced by signalling molecules and the bioactive material MTA, which can form dental pulp and dentin and periodontal ligaments **[107,108].** Subsequently, a regenerative scaffold based on blood clots is formed, and growth

factors are provided. Some scholars have added platelet-rich plasma or platelet-rich fibrin .The effect is good, but this approach involves blood product extraction and technical sensitivity **[109].**

### 1.5.1. Advantages of the Revascularization

1. Technically simple approach.

2. There is no need of using expensive biotechnology due to currently available instruments and medicament techniques.

3. There are almost negligible chances of immune rejection as this approach relies on the patient's own blood.

4. Bacterial microleakage can be eliminated through the induction of stem cells into the root canal space, followed by the intra-canal barrier, inducing a blood clot.

5. The concerns of restoration retention need to be overcome.

6. When this approach is applied to immature teeth, it reinforces their root walls.

7. As the avulsed immature tooth has necrotic-pulp tissue along with an open apex, and short and intact roots; therefore, the newly formed tissue will easily reach the coronal-pulp horn because proliferation in a short distance is required. Therefore, the strategy behind the development of new tissue is to maintain the balance between the pulp-space infection and the proliferation of new tissue.

8. Additional growth of open-apex root takes place due to minimum instrumentation that will preserve viable pulp tissue.

9. The potential to regenerate more stem cells and the rapid capacity to heal the tissue in young patients needs to be recognized **[124,125,126].**

### 1.5.2. Disadvantages of the Revascularization Approach

1.The origin of where the tissue has been regenerated from is yet to be known.

2. According to researchers, effective composition and concentration of cells are mandatory for tissue engineering. However, these cells are entombed in fibrin clots; therefore, researchers do not rely on blood-clot formation for tissue engineering function.

3. Treatment outcomes will be variable by the variations in the composition and concentration of the cells **[124,125,126] .**

### 1.5.3. Prerequisites for Revascularization Approach

Revascularization studies have established the following prerequisites:

1.There should be open apices and necrotic pulp secondary to trauma.

2.In addition, open apex should be less than 1.5 mm.

3. The following agents can be incorporated to remove microorganisms from the canal.

○ Antibiotic paste

○ Calcium hydroxide

○Formocresol

4.The coronal seal should be effective.

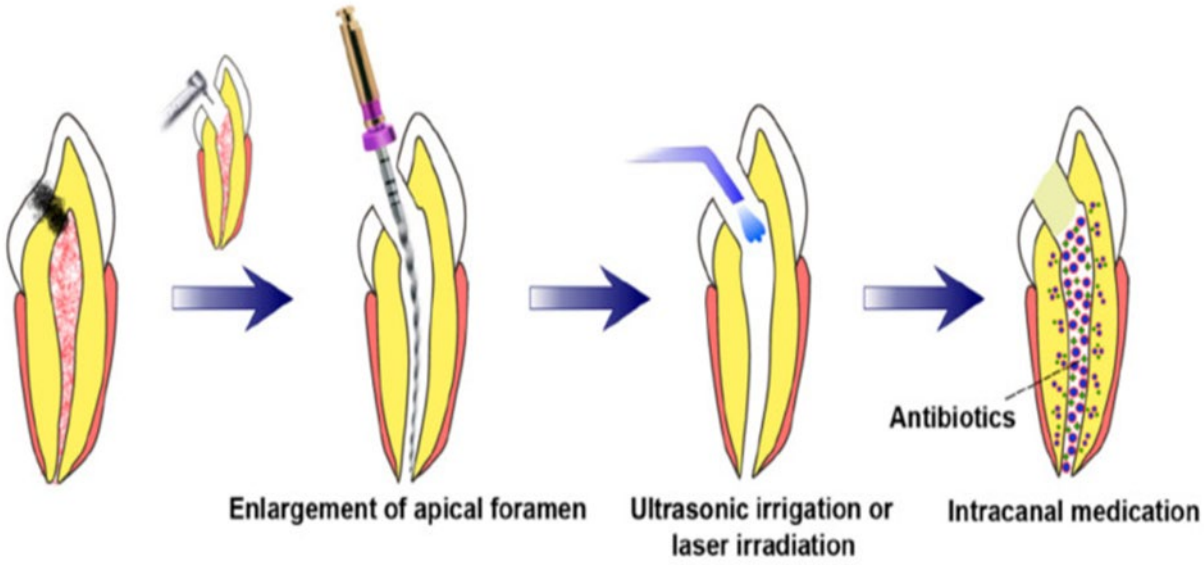
5. There should be a matrix or the growth of new tissues.

6. When trying to induce bleeding, anaesthesia should be used without a vasoconstrictor

7.Canals should not be instrumented.

8. Sodium hypochlorite should be used as the irrigant .

9.There should be blood-clot formation **[114,128,129,130].**




Requisite preconditions for pulp regeneration (root canal disinfection and enlargement of the apical foramen) **[131].**

A common complication of revascularization is tooth discoloration. Previous studies have suggested that tooth discoloration is related to the triple antibiotic paste. Minocycline is considered to form a chelate with calcium ions in dentinal tubules, which changes the refractive index of teeth and causes tooth discoloration **[110].** Cefaclor is an antibiotic alternative to minocycline **[111 ,112]** proposed replacing minocycline with cefaclor and reported successful regenerative treatment using

this technique. It has also been suggested that the possible mechanism of tooth discoloration may be related to the interaction between MTA and blood and the blockade of dentinal tubules **[113].**

At present, there is no consistent standard for evaluating the efficacy of pulp revascularization. The curative effect has been mainly based on clinical manifestation, pulp vitality examination and radiographic examination. According to the American Association of Endodontists guidelines, the primary goals are healing apical periodontitis and eliminating clinical symptoms. Increased thickening of the canal walls and/or continued root development as well as a positive response to cold and hot pulp sensitivity tests are desirable but not essential to determine success.

## 1.6. Ever X Flow :

reinforcement of dental composite is another improvement that was introduced to increase dental composite restorations toughness and fracture resistance **[140,141,142].** it was found that fiber reinforced composite preserved its fracture resistance after repair significantly better when compared to other bulk-fill composites without fibers **[143].** Furthermore, fiber reinforced composite specimens remain attached even after failure **[144].** Various methods have been proposed to maintain the structural integrity of residual enamel and dentin and enhance the lifespan of large composite restorations **[145].** Among them one option is using discontinuous or short flowable fiber-reinforced composites (SFRCs) to replace dentin and conventional PFC composite to replace enamel, known as a biomimetic restorative approach **[146, 147].** High fracture toughness restorative materials are in high demand because they are less likely to fractureand be at risk for crack propagation. Many authors have stated that flowable SFRC (everX Flow, GC, Japan) has substantially improved mechanical features, especially in the context of fracture toughness compared to PFC composites **[148,149].** According to the literature, the reinforcing capability of SFRC increased with increasing the volume of the material. Some researchers have even extended the application of SFRC beyond dentin restoration, encompassing the reconstruction of missing interproximal walls **[150].** EverX Flow was introduced in 2019 as the flowable version of packable SFRC (everX Posterior) manufactured by the same company (GC, Japan). It is made up of an inorganic silanated particle filler (45 wt%), a resin matrix (30 wt%), and randomly oriented glass microfibers (25 wt%). The diameter of the used glass microfibers is 6 μm and the length between 200 and 300 μm **[151].** By comparison, everX Posterior has fiber of 17 μm in diameter and length in the range of 0.3–1.5 mm **[152].** Hence, it is unsurprising that everX Flow exhibits superior surface properties when compared to everX Posterior **[153].** (In another studies by Lassila et al., and Uctasli et al., flowable SFRC showed surface gloss values and color stability which was comparable to other tested conventional PFC and fluoride-releasing composites **[154].**

## 1.7. Physical properties :

### 1.7.1. Modulus of elasticity

The modulus of elasticity (Young's modulus) is a measure of the rigidity of the material and is defined by the initial slope of the stress-strain curve. A high modulus of elasticity means that the material is rigid and stiff. A material with a low modulus of elasticity is more flexible and is better able to buffer the masticatory pressure **[140].**

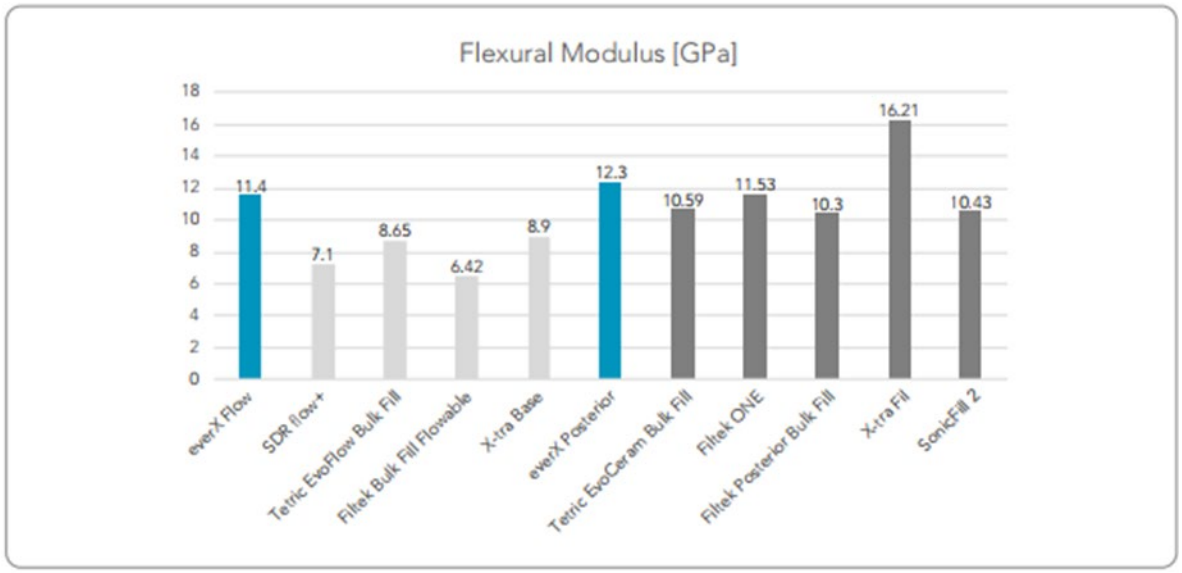



**Figure 1 :** Modulus of elasticity of everX Flow compared to other bulk flowable & paste composites .

### 1.7.2. Flexural strength

Flexural strength is defined as a material's ability to resist deformation under load. In clinical situations, dental restorations need to withstand repeated masticatory forces. A high flexural strength is desired to maintain the shape when these forces impact the restorations**[141].**

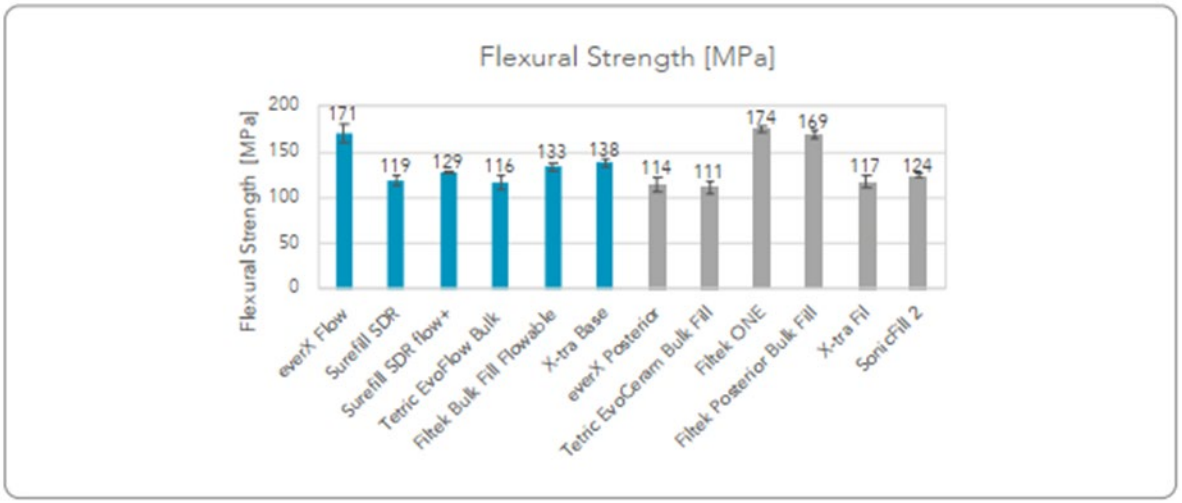



**Figure 2 :** Flexural strength of ever X Flow compared to other flowable and paste bulk composites .

### 1.7.3. Fracture toughness

As a result of fibre incorporation, everX Flow reduces the risk of filling, cusp and root fracture by preventing the crack propagation from the surface of the material into deeper areas of the restored tooth structure. The very high fracture toughness of this material provides a durable foundation for composite restorations. As a result, everX Flow resists continuous mastication forces exceptionally well and prevents fractures of the filling and surrounding tooth structure**[142].**

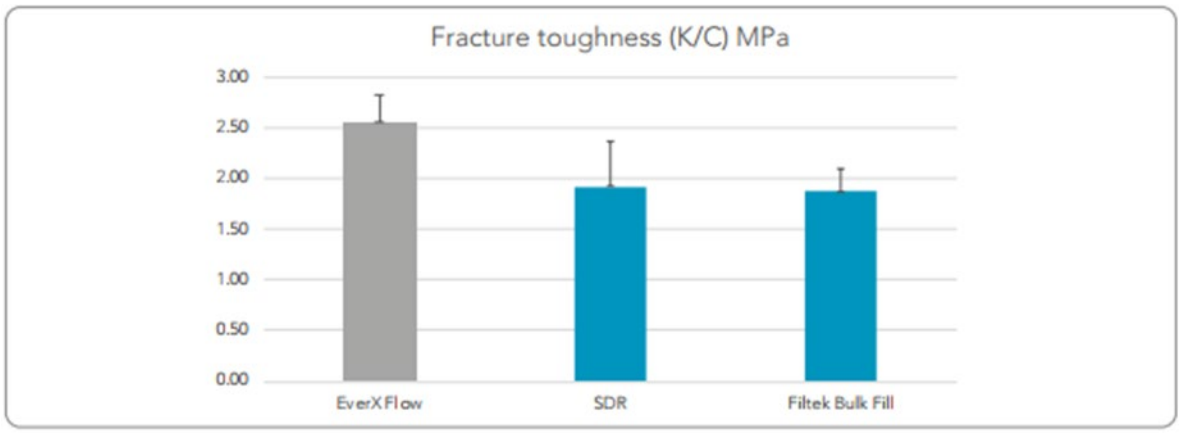



**Figure 3 :** Fracture toughness of ever X Flow and other paste & flowable bulk-fill composites .

## 1.7.4. Radiopacity

For restorative materials, a high radiopacity is required in order to distinguish the material from the remaining tooth structure. As such, the follow-up of the restoration and the detection of potential secondary caries will be made possible. The radiopacity of specimens is compared with that of an aluminium sample of the same thickness **[143].**

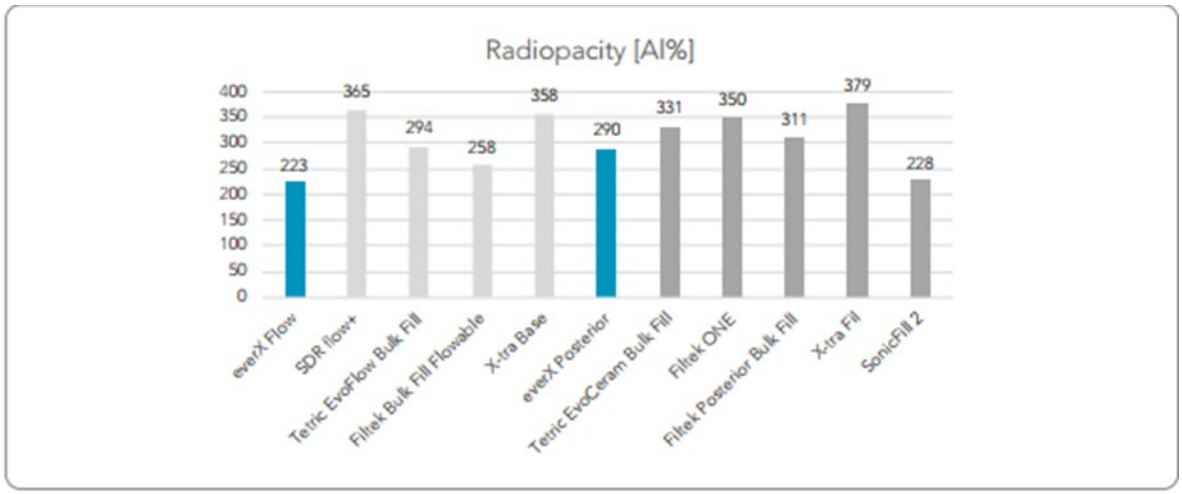



**Figure 4 :** Radiopacity of ever X Flow compared to other flowable & paste bulk composites .

## 1.7.5. Shrinkage

Shrinkage is inherent to all dental composites. Due to the confinement inside the cavity, shrinkage may manifest itself as shrinkage stress. Shrinkage stress is a complex phenomenon and it is not linearly related to volumetric shrinkage. Rather, it is dependent on many factors, such as material's properties (elastic modulus, water sorption and shrinkage kinetics) as well as clinical circumstances (cavity size and configuration) and thus may differ per indication. In fact, there is no proven correlation between the volumetric shrinkage of dental composite restorations and their clinical outcome**[144].**

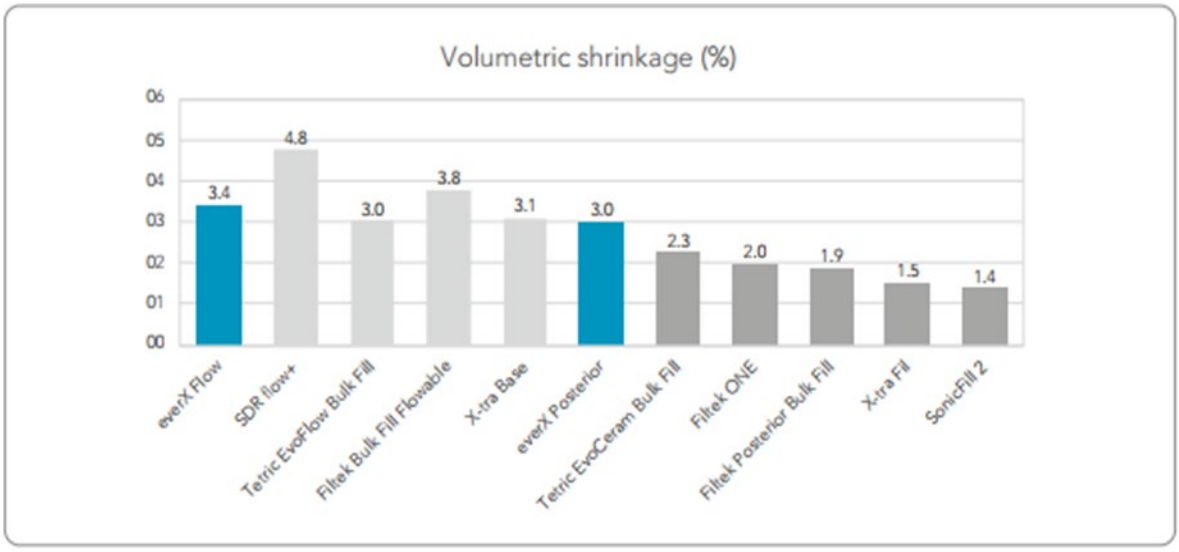



**Figure 5 :** Volumetric shrinkage of ever X Flow compared to other bulk flowable & paste composites .

## 1.8. Interventions restorative treatment

A single trained operator performed all the restorations. All patients received local anesthesia (Artinibsa 4% 1:100.000, Inibsa Dental, Spain). Multiple teeth isolation was done using a rubber dam (Sanctuary® powder free latex dental dam, Malaysia). Preparation of all cavities was applied using # 245 and # 1, 2 round carbide burs with an air/water-cooled high speed handpiece with the aid of a sharp excavator in accordance with the cavity preparation principles for adhesive composite restorations and the recent clinical recommendations for caries excavation.For the restorative procedures, first, the lost proximal wall was replaced using an appropriate pre-contoured sectional matrix complemented by the corresponding separating ring (TOR VM, Russia) and an appropriately dimensioned wooden wedge (Fig. 1). The prepared cavity was cleansed by applying a thorough water rinse then application of the bonding protocol. All teeth in both groups received the same adhesive protocol. A selective enamel etching approach was made by applying 37% phosphoric acid gel (Scotchbond, 3M ESPE, USA) for a duration of 15 s. Subsequently, the tooth underwent a 15 s rinsing procedure with water and was gently dried using brief air blasts and cotton pellet blotting. A one-step self-etch bonding agent application (G-ænial Bond, GC) involved a thorough and careful process where a disposable microbrush was used to gently spread the bonding agent over the surfaces of the prepared cavity. Following this application, it was left for a period of 10 s before being exposed to the highest air pressure for 5 s. Subsequently, the light-curing procedure was performed utilizing an LED light-curing unit with an intensity surpassing 700 mW/cm2 (LED.F, Woodpecker, China) for a total time span of 10 s. In the intervention group, flowable SFRC (everX Flow) was injected as dentin replacement including the proximal wall (Fig. 1) leaving about 1–2 mm of space for an occlusal surface layer of the conventional PFC. SFRC was subjected to light curing for 20 s. A capping or surface layer of the conventional micro-hybrid PFC (G-ænial Posterior, GC) was applied and underwent light curing for a period of 20 s as

well.While for the control group, the cavities were completely filled with conventional PFC, using an oblique 2 mm incremental layering technique, and each increment subjected to light curing separately for 20 s.After checking centric and eccentric occlusion by an articulating paper, restoration finishing was done, using fine grit bud-shaped diamond stones (Microdont, Brazil) then polishing by rubber points and bristle brushes with ultrafine Microdont diamond paste (Microdont) **[150 , 151 , 152 , 153 , 154].**

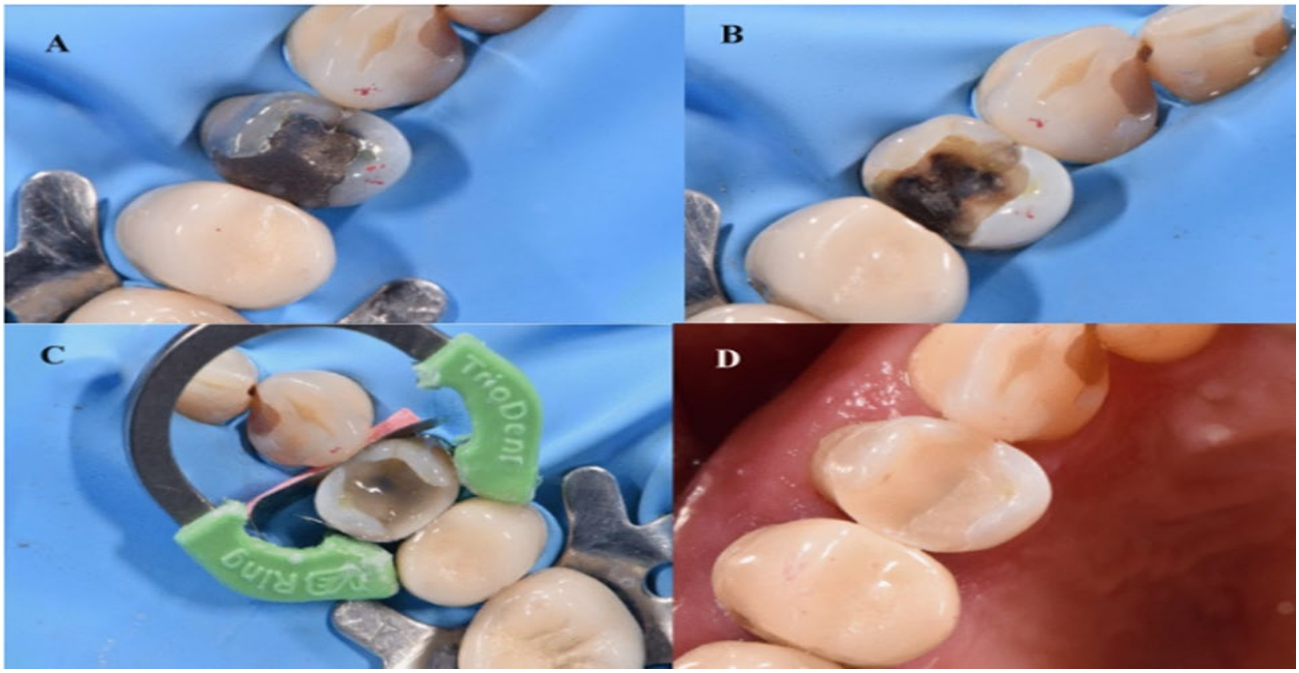



**Figure 6 : (A)** Preoperative view **(B)** after removal of the old restoration **(C)** interproximal walls were built by flowable SFRC **(D)** post-operative view.

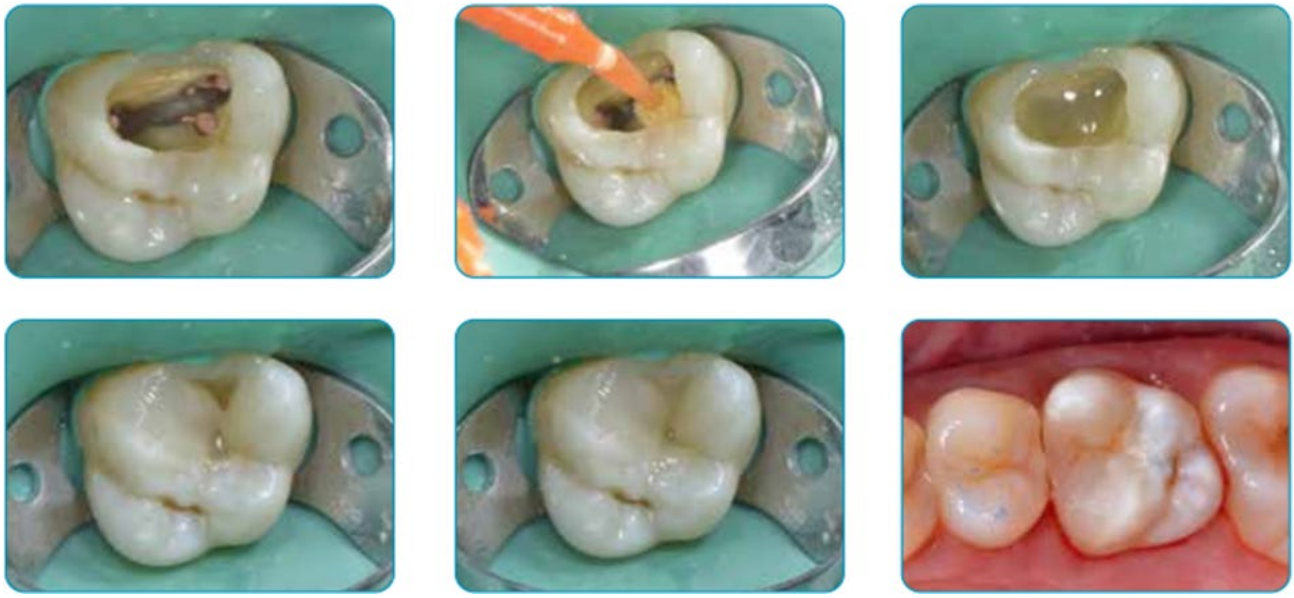


**Figure 7 :** The cavity is completely filled with everX Flow (Bulk shade), only leaving sufficient space for the enamel layer. The ever X Flow core is then covered by a final layer of G-ænial Universal Injectable. Despite the use of the more translucent Bulk shade, the outcome is aesthetically pleasing.

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