A PROSPECTIVE ANALYSIS OF PERIOPERATIVE PAIN FOLLOWING VPT ON PERMANENT TEETH WITH MATURE APICES

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ABSTRACT

Mark Shallal-Ayzin: A Prospective Analysis of Perioperative Pain Following VPT on Permanent Teeth with
Mature Apices
(Under the direction of Asma Khan)

Vital pulp therapy (VPT) remains a treatment option for cariously exposed teeth that reach the

dental pulp. To our knowledge no study has examined whether perioperative pain predicts the outcome

of VPT. The aim of this study is to examine the between perioperative pain and the progression of pulpal

disease into a more inflamed or necrotic state. Direct pulp caps or partial pulpotomies using MTA were

performed on permanent teeth with carious pulpal exposures. Patients were contacted at 24 hours, one

week and three months following treatment and data was collected on pain experienced and analgesic

intake using a standardized questionnaire. At six and 12 months after treatment an in-person clinical

exam was performed on each subject which included standard vitality tests along with exposure of a

periapical radiograph. Success was defined as an asymptomatic, functional tooth that does not present

with any clinical or radiographic pathology and has not had previous root canal treatment. Statistical

analysis was performed using logistic regression. Results from this study support a correlation between

perioperative pain at 3 months and the outcome of VPT.

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REVIEW OF LITERATURE

There are many purposes for the treatment of teeth needing endodontic therapy, but all of these can be summed into three separate goals: 1) Prevention and elimination of disease 2) Manage pain 3) Maintaining tooth survival, and more specifically, 4) Preserve vitality. Traditionally, the primary way to prevent and eliminate disease in teeth with pulpal necrosis is to perform root canal treatment. Root canal treatment has been shown to be 93-96% successful in teeth with vital pulps (1–3). In teeth with necrotic pulps and periapical radiographic lesions, root canal treatment has been shown to be 69-86% successful (1–4). The predictability of root canal treatment is much greater in teeth that contain a vital pulp at the time of the procedure. In general, if done appropriately, root canal treatment is relatively successful and predictable, but one thing root canal treatment does not do is maintain the vitality of the tooth by preserving the pulpal tissue.

As endodontists, the primary tissue of importance in our discipline is the pulp. Rather than looking to extract the pulp tissue, like we do during root canal treatment, it is important to find ways to maintain the vitality of the pulp while limiting or even stopping progression of disease into the pulp. This is important because the pulp has several important functions. The pulp has a large role in the innate and adaptive immune response to noxious stimuli entering the tooth such as certain bacterial microorganisms (5–7). A vital pulp will help increase the outward flow of dentinal fluid as a result of the positive intra-pulpal pressure (6,7). This reduces the diffusion of bacteria and their by-products from progressing toward the pulp chamber. This point is supported by the fact that non-vital teeth have a significantly higher bacterial invasion rate than vital teeth (8). Additional to the physical barrier, dentinal fluid has been shown to contain serum proteins and immunoglobulins (9).

Dentinal tubules, in teeth which contain a vital pulp, also have odontoblastic processes extending up to half the length of the tubule which is another physical barrier for bacteria to evade and also act as the first-line immune surveillance for initial bacterial invasion (10). Odontoblastic processes can express low levels of interleukins, chemokines, chemokine receptors, and toll-like receptors all related to innate immunity from invading organisms. Once the odontoblast is challenged by a microorganism, it upregulates expression of cytokines and chemokines such as TGF-B, VEGF, and MMPs for recruitment of cells such as macrophages, dendritic cells, lymphocytes, natural killer cells, and angiogenic cells (6). A living odontoblast also has the ability to lay down dentin. When the tooth is traumatized due to bacterial invasion and loses inorganic structure, it helps when odontoblasts retain the ability to lay down tertiary dentin to compensate for the loss in tooth structure (6,7,11). This additional dentin that is created can also act as an extra barrier for the microorganisms to traverse so as to limit their progression into the pulp.

If the bacteria get through these initial barriers and enter the bulk of the tissue, the pulp is equipped with the cellular components necessary for the initial recognition and the subsequent processing of antigens, which results in its ability to elicit an adaptive immune response. The normal, uninflamed pulp contains important immune cells such as helper and cytotoxic T cells. Dendritic/antigen presenting cells as well as macrophages are also present in the pulp, located below the odontoblastic layer (5,7). Neuropeptides such as calcitonin gene-related peptide (CGRP), substance P (SP), and neurokinin A (NKA) are detected in the normal pulp (6,12). All of these cells have a role in immuno-regulatory function which acts to stave off bacterial invasion. During pulpal inflammation, levels of CGRP, SP, and neuropeptide Y (NPY) are elevated (13,14). This is important because each of these peptides has an important signaling mechanism to upregulate for the purpose of immune function. Substance P increases T cell chemotaxis, and increases the production of interleukins such as IL-2, IL-8, and IFN-Y. CGRP and SP cause increases in pulpal blood flow, vascular permeability, and vasodilation

(15,16). Bacterial proteins that leak into the interstitial space will cause macrophages, T cells, and B cells to fight the invasion, and increases in interstitial fluid pressure from chemotactic actions escalate outward flow of fluid (6).

The sensory function of the pulp is also a very important aspect for the defense of the tooth. With its vast innervation of nerve fibers, the pulp is able to give an indication or warning when it is under attack from noxious stimuli. It has been postulated the A-delta fibers in the pulp produce the initial rapid sharp pain in response to external stimuli because of their peripheral location, low threshold of excitability and fast conduction. On the other hand, the smaller C fibers cause a slow, dull and aching pain related to pulp tissue damage and the inflammatory process due to their higher threshold of excitability and slow conduction (7,17). In addition, the proprioceptive function of the pulp limits the load imposed on teeth by the masticatory muscles, thus further protecting the tooth from injury (7,18). For these reasons it is crucial to develop and evaluate treatments that preserve the vitality of the pulp which will subsequently maintain all the functions of the pulp that were previously stated.

Vital pulp therapy (VPT) is a generic term meant to encompass the range of procedures that can be performed on a tooth with an exposed pulp in order to sustain long term pulpal vitality. Traditionally, procedures such as direct pulp cap, partial pulpotomy, full pulpotomy, and apexogenesis fall under the category of VPT. VPT is not necessarily a new idea as it is performed all over the world in a fairly large number. Some Scandinavian groups have performed the procedure for the past 40-50 years. Also, we know that according to Kakehashi, Stanley, and Fitzgerald (19) as long as exposed pulps are bacteria free, they will heal and a hard tissue barrier will form, which is the guiding principle of all vital pulp therapy procedures. One of the very first VPT studies done by Cvek in 1978 showed that out of 60 permanent incisors, 58 (96%), had a successful outcome by performing partial pulpotomy on them (20). However, the reason for the high success rate is due to a few key factors: 1) The cause of the pulp exposure was that of complicated crown fracture from trauma and 2) Both mature and immature teeth

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were used in this study and not analyzed separately. Even though VPT is done on traumatized and immature teeth, developing a predictable method of VPT for pulps of cariously exposed, mature, permanent teeth is of higher priority since these cases are more frequently encountered in clinical practice.

The main reason that VPT is not as commonly performed compared to traditional root canal therapy has to do with predictability. The American Association of Endodontics (AAE) definition of "irreversible pulpitis" is: "A clinical diagnosis based on subjective and objective findings indicating that the vital inflamed pulp is incapable of healing" (21). Undisputedly, when a pulp is necrotic or irreversibly inflamed the tooth will need root canal treatment in order to prevent apical periodontitis. However, we lack accurate diagnostic assessments of the difference between reversible and irreversible pulpitis (22,23). As of right now, the only true way to distinguish between reversible and irreversible pulpitis is histologically (24,25). Clinically, our current methods of determining pulpal status is through a series of diagnostic sensibility tests and questions. However, these are very subjective and can be inaccurate at times. Our diagnostic tests, wrongly termed vitality tests, actually measure responses of nerves innervating the pulp-dentin complex and do not determine vitality. Thus, the overall subjectivity in diagnosing a given pulp as reversible or irreversible complicates the practitioner's decision making because diagnosis leads to treatment. So, often times, when a pulp may histologically be seen as reversible pulpitis, it will be clinically diagnosed as irreversible and a root canal will be performed unnecessarily. On the contrary, when a pulp would be histologically identified as irreversible inflammation, it will be diagnosed as reversible pulpitis by the provider and an unsuccessful VPT will be completed. These are the fine lines of clinical decision-making the provider must endure to choose the right procedure for a given pulp, and much of it based on subjectivity.

Even with all of this diagnostic uncertainty, endodontists have done fairly well with VPT due to the current best evidence in the literature available today. Various important factors from prior research

on VPT lay a crucial foundation for what we believe the correct protocol should be and trends for more successful outcomes. One factor extremely important to increase the success of VPT is the material chosen as the capping/sealing agent. The two main materials that have been extensively studied are calcium hydroxide (CH) and mineral trioxide aggregate (MTA). CH is one of the most widely used materials in endodontics since its introduction in 1920 by Hermann. It is a substance beneficial in endodontic therapy due to its strong alkalinity (pH approximately 12.5) from dissociating into calcium and hydroxyl ions in an aqueous solution (26). Other properties of CH, which include antimicrobial activity (27,28), tissue-dissolving ability (28,29), and induction of repair by hard tissue formation (26,30), make the material beneficial for use during VPT. The effect of calcium hydroxide on viable pulp is an important aspect of why this material was commonly used as a capping agent. CH initially develops a superficial layer of necrosis in order to disinfect the pulp. Chemical injury caused by the hydroxyl ions induces this layer to firm necrosis in which the pulp tissue and the bacteria associated with it are broken down, but this superficial layer of necrosis causes the underlying tissue of the pulp irritation which stimulates pulpal cells for differentiation and repair. Vascular and inflammatory cell migration and proliferation occurs to control all the noxious stimuli. This is followed by a repair process with the formation of collagen as a result. Soon after, odontoblast differentiation occurs and a hard tissue barrier is laid down by the resident odontoblast-like cells which takes the form and appearance of dentin (30). However, this hard tissue substance has tunnel-defects and does not create a hermetic seal, making CH less than an ideal substance for pulp capping (31,32) .

CH was commonly used in the past but, since the introduction of MTA in the 1990s, VPT procedures have trended more toward the use of MTA. Original ProRoot MTA (Dentsply Tulsa Dental Specialties) is composed of 75% Portland cement, 20% bismuth oxide, and 5% calcium sulfate dehydrate. The Portland cement is made up of approximately 55% tricalcium silicate, 19% dicalcium silicate, 10% tricalcium aluminate, 7% tetracalcium aluminoferrite, 2.8% magnesium oxide, 3% sulfate,

and 1% free calcium oxide (32,33). More recent MTA products, such as MTA Angelus (Angelus, Londrina, PR, Brazil), are composed of almost entirely the same ingredients except for deletion of tetracalcium aluminoferrite which can easily stain teeth due to its iron material (32). The mechanism of action of MTA is similar to that of CH in that MTA is thought to produce calcium hydroxide as a by-product of its setting. MTA also forms a superficial layer of necrosis due to its high alkalinity in much the same way CH does. However, the main advantages of MTA over CH are believed to be its sealing ability, biocompatibility, bioactivity, and ability to promote mineralized tissue formation (32–34). Additionally, when compared to CH, MTA produces a more uniform and thicker dentinal bridging, with less inflammatory response and minimal necrosis of the existing pulpal tissue (32,35–37). MTA has some disadvantages however, in that it has long setting times, poor handling characteristics, and may cause discoloration of teeth, especially older formulations of the product.

A number of studies have examined the outcomes of VPT performed with CH and/or MTA. One early study on VPT with CH reports a success rate of 96% (20). However, the etiology for the VPT in this study was trauma, which has a far more favorable prognosis than a pulp exposed to microorganisms from carious lesions. Studies evaluating the success of VPT, regardless of capping agent, when the etiology of the pulpal exposure is from caries disease progression report success rates ranging from 37%-87% (38–43) after a five-year recall, while after a ten-year recall the success rates dropped to 13%-59% (38,43,44). Other studies on the outcome of VPT performed with MTA suggest that it is superior to CH (41–43,45) and even has a high success rate after use in full pulpotomy (46,47). In a recent meta-analysis comparing the two materials, MTA showed a 2.26 greater odds ratio for success compared to CH, and additionally showed less inflammatory response of the pulp as well as thicker dentin bridge formation (44). Other similar studies on MTA report that successful outcomes are noted in 87%-91% of teeth (42,45,48) after 1 year and 67%-84% after 3-5 year recalls (41,43). A long-term assessment, showed that after a 9 year recall with a very meticulous protocol that MTA direct pulp capping had a

97% success outcome (49). Presently, there is sufficient evidence to conclude that MTA is a superior material compared to CH when used as a pulp capping agent in VPT.

Much of the variation in the current evidence regarding outcome of VPT can be attributed to the lack of standardization of the study protocol and the different types of studies conducted. As previously mentioned, many of the older studies use CH as the pulp capping agent of choice, whereas more recent ones have chosen MTA. Other researchers have chosen to look at outcome in a retrospective manner (38,39,41,43) versus evaluating success through a prospective study design (40,45,47–49). The main concern with retrospective studies is that they lack the strict standardization of the study protocol to control for variables that may potentially influence the outcome of interest. In contrast, prospective studies have a well-controlled protocol and do not allow for deviation from a set procedure. This makes prospective studies superior in evidence to retrospective studies. Additionally, many of the aforementioned studies have very different intraoperative materials and methods which makes it very difficult to compare outcome from one study to another. For instance, many of the studies do not standardize their protocol for caries removal to eliminate any subjectivity. Some studies indeed use caries dye indicator (38,40,48,49) while most others do not (39,41–47). Some studies use sodium hypochlorite for post-caries removal disinfection and hemostasis (40,42,45,47,49) and others use agents such as hydrogen peroxide, chlorhexidine, or sterile saline (38,40,41,43,46,48). Some studies place permanent restorations within 7-10 days (38,41,43,45,47,49) while others wait months to place a permanent restoration (39,40,42,46,48). Some studies specify what level of training and how many operators there are doing the procedure, such as dental students vs residents vs endodontists (38,39,42,43,45,49), while many others are ambiguous as to what type of provider is performing treatment (40,41,47,48). All of these factors become important when comparing outcome between studies because one cannot rule out the possibility of one or several of these variables having an impact on the outcome.

Another issue with evidence currently available on VPT is that the reported outcome of most of the studies are based on a range of different recall periods. An overall analysis of all VPT data will show that success is dependent upon time of recall in the sense that the longer the follow-up time the less likely the procedure is to be successful. However, congruence between studies from this aspect is insufficient. There are studies that only recall their patients for one year or less (45,46,48), have recall periods between 1-5 years (39–42,49) and some that recall from 5-10 years (38,43). Thus, comparing the reported mean success rates from each article with one another can lead to a false understanding of VPT outcome.

Even with the current lack of well designed, adequately powered studies on VPT, there are some factors that have been shown to play an important role on treatment outcome. This includes the aforementioned evidence that suggest MTA is a superior pulp-capping material than CH and that longer recall times may be needed to adequately determine success. At this point in time, there is little known about perioperative factors that may influence the results of the treatment.

Several studies have attempted to analyze perioperative factors such as age, gender, type of tooth, location of pulp exposure, timeline of permanent restoration placement, ability to control hemostasis, type of restorative material, etiology of pulp exposure, and primary vs. secondary caries. However, there is not one of these factors that the current literature unanimously agrees has a statistically significant impact on the outcome of VPT. One factor that is believed to pose some influence on outcome is timing of permanent restoration placement, with some evidence showing that restoring the tooth immediately or within two days of treatment will optimize success (38,43). Other studies suggest that the patient's age is correlated to outcome of VPT, mostly defining subjects less than 40 years old to have greater success than those over 40 years of age (42,48). It has been hypothesized that an axial/cervical carious pulp exposure will negatively impact success versus an occlusal exposure (42,45). Furthermore, there may be a possible link to carious exposures decreasing outcome of VPT

compared to mechanical exposures (41), females having better outcome compared to males (39), and inability to control bleeding from the pulp as an indicator for decreased success (40). Ultimately, the lack of standardization between studies is a detriment to understanding what factors may be significant to clinical success of VPT.

As previously mentioned, arguably the greatest concern for endodontists should be to maintain the vitality of the pulp if at all possible. That is why it is so crucial to optimize and enhance the success of any VPT procedure, and equally as essential, is to know in what clinical situations to perform VPT vs. RCT. We know that doing RCT on a vital tooth can have success of greater than 95% (1,2), while, depending on the study, VPT can have success around 90% (43,44,50). Begrudgingly, if an endodontist must perform RCT on a tooth after a failed VPT, the success of that RCT will drop 15-20% due to invasion of microorganisms into the root canal system (2–4). That is why understanding which perioperative factors are influential upon the success of VPT is important because it will help maximize the predictability of the treatment's success. The clinician should understand the importance of case selection when deciding VPT vs. RCT as this one decision could be the difference between 15-20% of successful outcomes.

Among the other high priorities for a practicing dentist/endodontist is to manage a patient's pain, and certainly from a patient's perspective this might be the most essential act a provider can give to them. Thus, it is extremely relevant to understand what information tooth pain can relay in regards to the outcome of VPT and in the context of the perioperative factors of a given case. Some studies have shown evidence that preoperative or intraoperative pain may have a correlation to outcome of traditional primary RCT. In a longitudinal, prospective study, which investigated the prevalence of post-obturation pain after root canal treatment and evaluated the influence of factors affecting the pain experience, found that preoperative pain and swelling may lead to more incidence of inter-appointment or post preparation pain (51). Another prospective clinical trial, which evaluated overall incidence of

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flare-ups and how different demographic and treatment factors affected it, found that more people who had preoperative severe pain had a greater chance of having a postoperative flare-up (52). Additionally, a prospective study investigating factors influencing periapical status of teeth following primary root canal treatment found a relationship between preoperative pain and inter-appointment flare up and decreased success rates of non-surgical RCT (4). However, the effect of this relationship declined at around 22 months following treatment. Other studies have similarly correlated preoperative pain as a predictor for postoperative pain (53,54), and it is this persistent pain that may prompt patients to seek further endodontic treatment or tooth extraction sooner rather than later after treatment. Thus, pain can indeed have a negative impact on tooth survival after an endodontic procedure, including VPT. It is in our best interest as providers to try and maximize our understanding of how perioperative pain can influence not only the outcome alone, but also how it influences patients' decisions in managing postoperative chronic tooth pain from a given procedure. Unfortunately, there is little to no data concerning pain and vital pulp therapy.

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (50). Even though experience of pain is subjective, perception of pain can be governed by such interaction such as gender, race, and age among others (55). Since pain is a primary outcome measure in endodontic literature, it is important to utilize the most appropriate way to measure it despite its nature of subjectivity and its multidimensional characteristics. Features of pain data that would be prudent to gather and analyze are intensity of pain, type of pain, how long pain lasts, triggers of pain, and if the pain requires any relief from medications. One of the more common methods for measuring intensity of pain is through the numerical rating scale (NRS). The NRS usually consists of a 10, 20, or 100 point scale, with anchors of no pain and worst pain and is delivered to the patient either verbally or graphically. Since this study design calls for phone call questionnaires for pain data, the verbal NRS is conveyed in

this manner. The type of pain will be categorized as either evoked pain or spontaneous pain. Evoked pain is commonly associated with reversible pulpitis whereas the AAE provides "additional descriptors" such as lingering thermal pain, spontaneous pain, and referred pain in association with irreversible pulpitis. Obtaining a proper and detailed description of a patient's pain may give insight into the actual diagnosis of the pulp at a given time point after VPT. Additionally, it would be especially useful to know if certain pain descriptors were correlated to the ultimate outcome and success of VPT.

To our knowledge, no prospective, observational study using a standardized treatment protocol, including MTA as a pulp capping agent, has been conducted in order to examine perioperative pain as a predictor of success of VPT. Our null hypothesis is that perioperative pain is not associated with the outcome of VPT in asymptomatic, mature, permanent teeth with a carious pulpal exposure.

MANUSCRIPT

Section 1.1 Introduction:

Traditionally, carious pulp exposures have led to management in the form of root canal therapy

(RCT) based on the mantra "diagnosis leads to treatment". Justification for this treatment is founded

upon the American Association of Endodontist's definition of asymptomatic irreversible pulpitis: "A

clinical diagnosis based on subjective and objective findings indicating that the vital inflamed pulp is

incapable of healing" (21). Recently, there have been an increase in the number of publications on

various forms of vital pulp therapy (VPT). These publications provide evidence that VPT is a viable

treatment option for teeth with carious pulp exposures and normal apical tissue. As endodontists, some

of the primary goals in our discipline are to 1) Prevent or eliminate disease 2) Manage pain 3) Maintain

tooth survival, and more specifically, 4) Preserve vitality. Only VPT accomplishes all four of these goals.

Vital pulp therapy is shown to have a success rate that can range from as low as 37% to as high

as 97% (38–40,45,46,48,49). Much of the variability between studies can be attributed to the

differences in study design and lack of standardization. For instance, they differ in design by being

retrospective (38,39,41–43), while others are prospective (40,45,47–49). Earlier studies on VPT have

used calcium hydroxide as the material of choice (38–40), however, newer publications use tricalcium

silicates, such as mineral trioxide aggregate (MTA) (43,45,48,49). Much of the current literature on VPT

varies regarding the period of time for which these teeth were followed up after treatment. For example

some studies had a follow-up time of only 1 year (42,45,48), while others are up to as many as 10 years

(38,39,41,43,49). Ultimately, the lack of standardization between studies is a detriment to

understanding what factors may be significant to the clinical success of VPT.

As previously mentioned, success rates after vital pulp therapy are reported to be as high as 98% (42,48,49). It is clear, from the aforementioned studies, that the one factor associated with these high success rates is the use of MTA as opposed to CH (41,43,44). From these studies, and others, we know that VPT is a treatment option that results in a successful outcome which is in the best interest for the patient. However, it is yet to be determined why VPT works in some cases and not in others. Data from prior studies suggest that perioperative factors may influence the outcome of VPT. For example, factors such as age (38–43), gender (39,41–43), tooth type (38–43), and location of pulp exposure (38,41–43,45,48) may influence the outcome of VPT. To date, no prospective studies have examined whether these perioperative factors are associated with the outcome of vital pulp therapy.

Among the highest priorities of a dental practitioner is the ability to manage a patient's pain, and certainly from a patient's perspective, this might be the most essential act a provider can give to them. Presence of pain is consistently used as one of the factors that define success of dental treatments. Some studies have shown evidence that preoperative or intraoperative pain are associated with pain after completion of primary RCT (4,51–54). Persistent pain may prompt patients to seek further endodontic treatment or tooth extraction. Thus, pain can indeed have a negative impact on tooth survival after an endodontic procedure.

This prospective, observational clinical study evaluates the patients' experience of perioperative pain and its potential association with the outcome of VPT. This was done by gathering pertinent information about pain experience such as presence of pain, type, intensity, triggers of pain, and also analgesic use postoperatively.

Section 1.2 Materials and Methods:

This study was approved by the office of Human Ethics and Research at our Institution. Healthy men and women (aged 15 years or older) seeking dental care were recruited for the study. Any time a

carious pulpal exposure occurred in the clinic, one of three standardized investigators would attend to the case while a standardized and trained provider would perform the treatment itself. When the carious pulpal exposure occurred, the investigator would determine through the inclusion/exclusion criteria if the patient qualified for the study. Inclusion criteria were: 1) Carious pulp exposure 2) Tooth is restorable 3) Mature, permanent tooth with closed apices. Exclusion criteria were: 1) Medically compromised patients classified as American Society of Anesthesiologists Class III through V 2) History of spontaneous pain on tooth of interest 3) History of recent trauma on tooth of interest 4) Non-English speaking patient.

All treatment was done by trained operators. Standardization and training of the protocol was obtained through a series of lectures that were repeated every 4-6 months. Verbal and written consent was obtained prior to any treatment. If the tooth was not already isolated, isolation was secured with either a rubber dam or isolite (Isolite Systems, Santa Barbara, Calif). Caries removal was determined by the use of a caries dye indicator (Sable Seek, Ultradent Products, South Jordan, UT, USA). Next, a partial pulpotomy was performed with a 1mm diameter round diamond bur and a sterilized cotton pellet soaked in 4.25% sodium hypochlorite was placed with firm pressure for 60 seconds over the exposure until hemostasis was achieved. If, after 60 seconds, hemostasis was not achieved then a partial pulpotomy was performed again circumferentially for another 1mm and a different sterilized sodium hypochlorite pellet was placed with firm pressure for an additional 60 seconds. This was performed up to three times in order to obtain hemostasis. If hemostasis was not obtained the tooth was excluded from the study. Once hemostasis was achieved, MTA Angelus (Angelus, Londrina, PR, Brazil) was mixed and placed according to the manufacturer's recommendations in a standardized 3mm layer of thickness over the exposure site with a Dovgan carrier (Quality Aspirators, Duncanville, Texas). Once the MTA was placed, Vitrebond (3M Corporation, St. Paul, MN) was mixed and placed, according to manufacturer's recommendation, over the MTA and light cured. Next, the tooth was restored with amalgam or a resin

based restorative material. A periapical radiograph was then exposed. The patient was reassured of the possibility that postoperative pain might be experienced, and if they felt the pain to be severe enough for an emergency evaluation, they were instructed to call one of the investigators to schedule an in-person examination. No instruction was given, as to type, dosage, or frequency, of any particular analgesic intake after the VPT procedure, but it was specified to take pain medication if the patient deemed necessary.

Data on postoperative pain was gathered through a standardized questionnaire via a phone call at three determined follow-up times: 24 hours, 1 week, and 3 months after the procedure. At six months and one year after the procedure, an in-person clinical examination was done to assess treatment outcome. Success was defined as "an asymptomatic, functional tooth without any clinical or radiographic pathology". If any additional endodontic treatment had been performed on the tooth after the VPT procedure it was considered a failure. All clinical examinations were performed by the three operators who were standardized by independent assessments of in-person clinical endodontic diagnostic testing. These results were assessed and cross referenced for accuracy and precision between operators. The in-person examination included endodontic diagnostic testing such as percussion, palpation, cold (Coltène Whaledent, Cuyahoga Falls, Ohio), electric pulp test (EPT), mobility, and periodontal probing to determine any signs of clinical pathology and a periapical radiograph was exposed.

Data was analyzed by logistic regression to determine any correlation between perioperative pain and the outcome of VPT. Significance was set at ($P<0.05$). The main outcome variable for this study was success or failure. Data was analyzed using the "R" function "glm" for generalized linear model with family (success/failure) as "binomial". Data was also examined for association between selected perioperative predictors and post treatment pain. For size of the exposure, the data was log

transformed and linear regression was fit with the predictor and outcome variable. All the statistical

analysis was performed in R statistical software (version 3.2.3, www.**cran.r-project.org**).

Section 1.3 Results:

This study enrolled subjects who had scheduled appointments in all undergraduate and

graduate clinics at the University Of North Carolina School Of Dentistry, Chapel Hill, NC. A total of 70

subjects consented to participate in the study. Of the 70 subjects, 69/70 were reached for information

about pain at 24 hours, 68/70 were reached for information about pain at 1 week, and 54/62 were

reached for information about pain at 3 months. 50 subjects are currently eligible for a 6 month follow-

up examination.

The current data shows that of the full gambit of participants, 25 were male and 45 were female

(Figure 1). When gender was analyzed for any correlation to perioperative pain, no statistical difference

was found. The age of subjects ranged from 15-78 years old with the median being 45. Distribution of

data based on age is displayed in categories by decade in Figure 2. Distribution of data based on tooth

type, shown in Figure 3, is displayed in categories by region of the mouth the tooth is located. There was

no correlation between tooth type and perioperative pain. Likewise, there was no correlation between

tooth type and the outcome of VPT. Data on presence of postoperative pain is displayed in Figure 4 with

each time interval included. Distribution of intensity of pain was tallied after patient used the numeric

pain rating scale to assess their pain experience in Figure 5.

Analgesic intake postoperatively is shown in Figure 6. The study population took a wide variety

of analgesics to manage their postoperative pain after VPT. Variations of over-the-counter ibuprofen

(Motrin, Aleve, Advil), Tylenol, and some narcotics such as hydrocodone and Tylenol #3 were consumed

at each of the three time periods. Dosage of ibuprofen ranged from 200 mg – 800 mg depending on any

given subject. Of the 4 subjects that took Tylenol, all of them took 500 mg at a time. Hydrocodone was

taken with acetaminophen in a 5mg/325 combination by 1 patient at the 24 hour time point. Tylenol #3

was taken by 1 patient, also at the 24 hour time period. Analgesic intake decreased in a time-dependent manner from 30% to 19% to 9% at the 24 hour, 1 week, and 3 month time points, respectively.

Majority of patients in this study did not have pain at the 3 month follow-up period. In total, of the 54 that were contacted at 3 months, only 9 experienced pain at this time. Of those 9, 3 experienced pain at the 24 hour time period as well, while 6 did not experience any pain at 24 hours.

This study had a success rate of 78% for patients who had undergone VPT and followed up for six months (Figure 7). Using the generalized linear model with predictors, (pain at 24 hours, pain at 1 week, pain at 3 months, tooth type, and patient' age), pain at 3 months was found to be significantly associated with failure (p=0.028). On analyzing the data for an association between exposure size and post treatment pain, a marginal significance (p=o.0596) was noted between exposure size and pain at 24 hours.
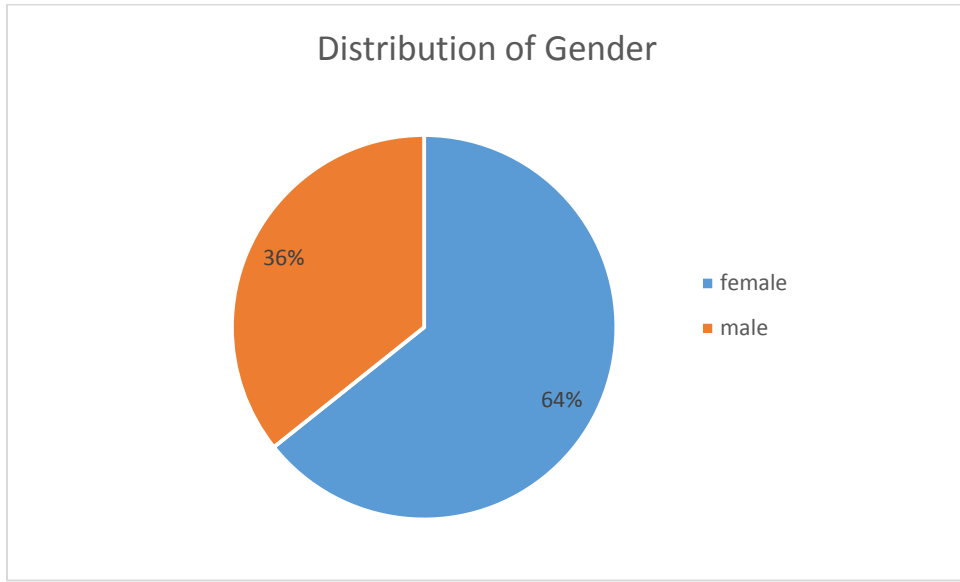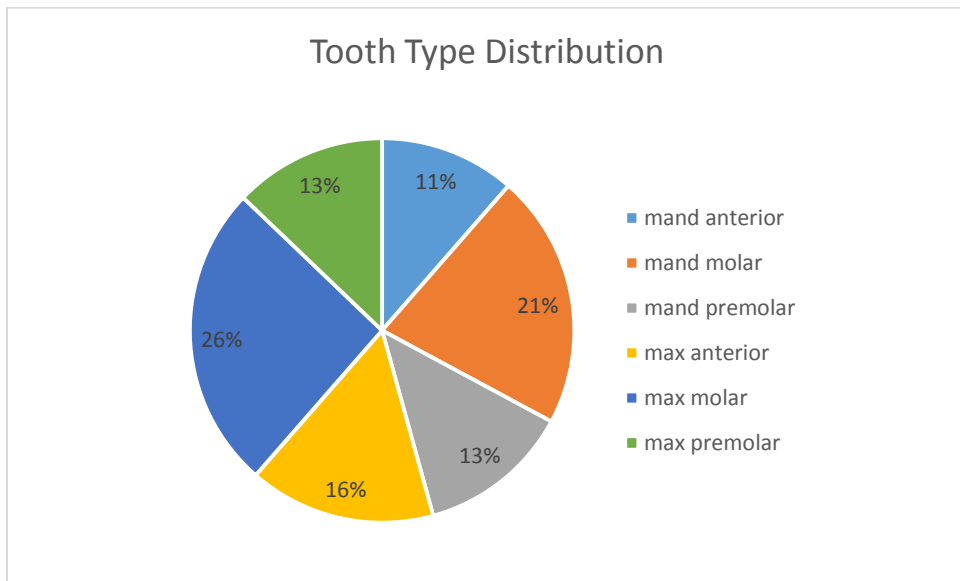
F**igure 1: Distribution of Gender.** Of the 70 subjects in this study, 25 were men and 45 were women.
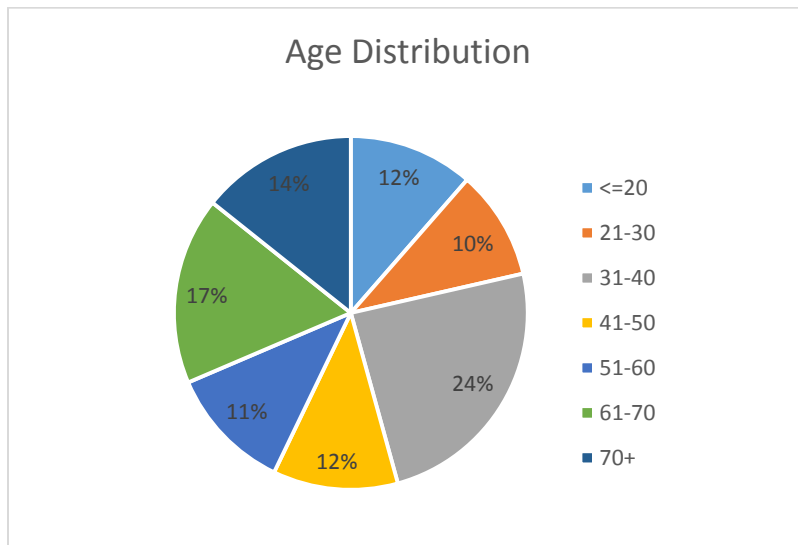
Figure 2: Distribution by Age. There were 8 subjects who were aged less than 20, 7 subjects from 21-30, 17 subjects from 31-40, 8 subjects from 41-50, 8 subjects from 51-60, 12 subjects from 61-70, and 10 subjects greater than 70 years old

Figure 3: Distribution by Tooth Type. 11 maxillary anteriors, 9 maxillary premolars, 18 maxillary molars, 8 mandibular anteriors, 9 mandibular premolars, and 15 mandibular molars were enrolled in this study.
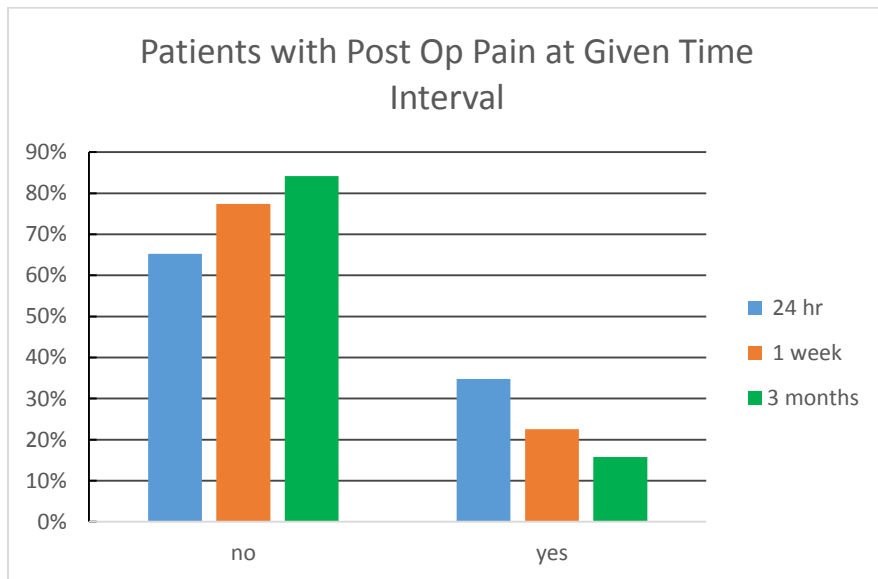
Figure 4: Presence of Postoperative Pain at Three Different Time Periods.
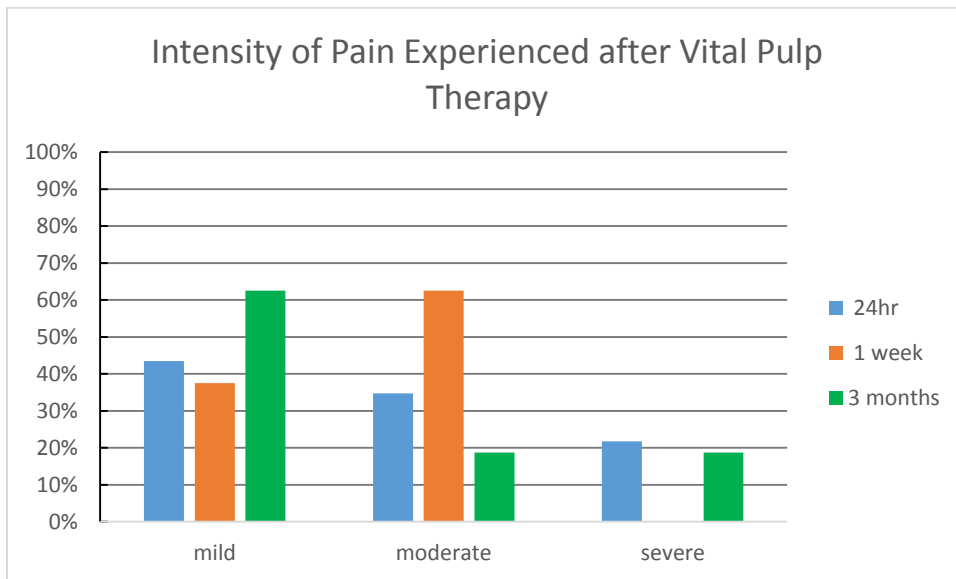
Figure 5: Intensity of Pain at Three Different Time Periods. Numeric pain rating scale, 0-10, was used to obtain postoperative pain experience of patients after VPT. Graph shows, of those patients that experienced pain at the indicated time, what percentage were of the given intensity.
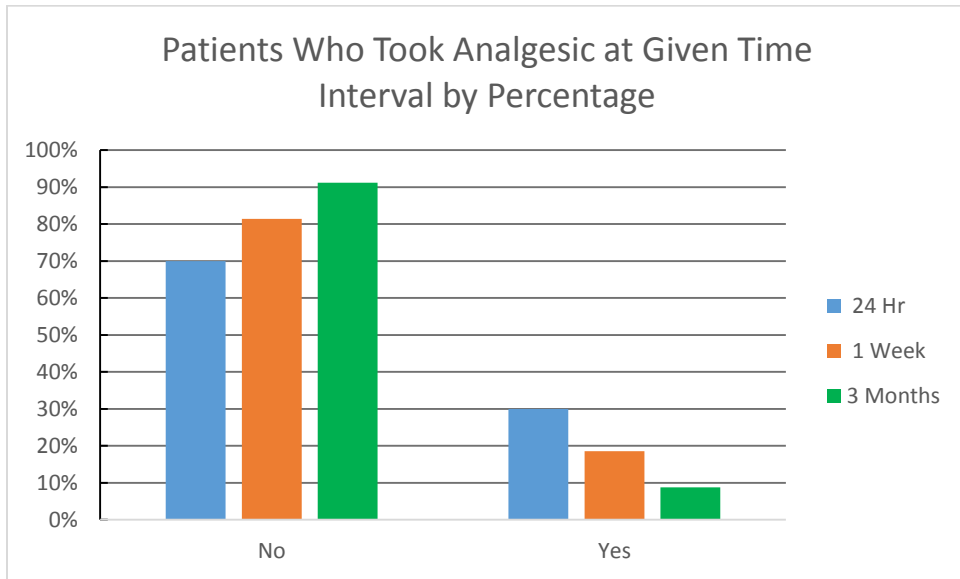
Figure 6: Analgesic Intake Postoperatively after VPT at Three Different Time Periods.
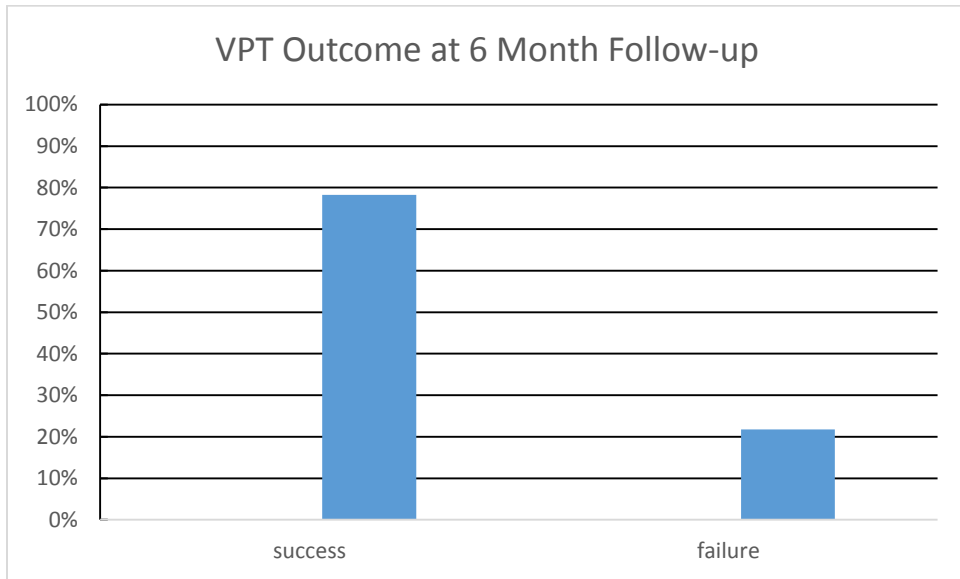
Figure 7: Distribution of Success vs. Failure of VPT after 6 Month Follow-up. 78% success rate was obtained in this study based on standardized radiographic and clinical examinations.

Section 1.4 Discussion:

The results of this study show that VPT performed with this specific protocol is 78% successful, which is consistent with previous literature on outcome of VPT (39–41,43,45). Since this was a standardized, prospective study, the protocol was well controlled and allowed for less variation or bias within the methods themselves. The study was specifically designed in a prospective manner so that confounding of variables, which was a major problem with previous research, were not such in this clinical investigation. This was necessary in order to isolate variables or factors that truly may influence the outcome of VPT.

Much of the newer research done on VPT uses MTA as its preferred pulp capping agent. This study continued that trend based off of the clear evidence that MTA results in higher success compared to calcium hydroxide (43,44). Much of the more recent literature on VPT with MTA shows success rates above 90% (42,47–49) while pulps capped with CH show success rates in the 60s to low 80% (39–42). Calcium hydroxide is better known among dental practitioners as a whole, and may still even be considered the "gold standard", however according to the data presented in the past 15 years, MTA is becoming the new "gold standard" for VPT as a capping agent and was the material of choice for this study.

The results from the pain data set show interesting trends within that clinicians can use when treating patients with VPT. This research shows that about one-third of patients who undergo the procedure will experience some sort of postoperative pain. Postoperative pain after VPT is usually experienced in the first 24 hours and resolves completely after 1 week. If a patient is going to experience pain, they are more likely to experience it in the earlier follow-up periods, such as 24 hours or 1 week after treatment. The data clearly demonstrates that pain resolves in a time-dependent manner. The data also shows that patients can experience mild to moderate pain in the immediate postoperative time period and still have a successful outcome of treatment. Not only can this pain be intense, but it

can also be either spontaneous or evoked pain. Lastly, most patients did not feel the need to take

analgesics after VPT, but if they did, they mostly needed them in the earlier periods after the procedure.

This is valuable information for a clinician performing and patient undergoing VPT.

`The clinician now has data to support postoperative instructions detailing to the patient the

relatively high likelihood that they may encounter pain and how long that pain might last for.

Reassurance to the patient that this pain experienced is normal and to not seek any emergency care or

additional endodontic treatment is imperative. Based on the data from this study, as long as the patient

is not experiencing severe pain after 1 week, the pain can be managed with analgesics with a high

chance of successful outcome. To maximally benefit the patient, the data also suggests the provider

should specify an analgesic regimen for up to 1 week so that pain experienced can be dampened,

especially in cases of moderate or severe intensity. Clinically relevant decisions by dental providers can

be gleaned from this research in order to educate their patients on what to expect after VPT.

With a p-value of 0.028, there is a significant correlation between pain at the 3 month time

point and the outcome of VPT. This is important because it can give the provider a specific follow-up

time so they can re-evaluate if the patient still has complaints of pain. Re-evaluation of the prognosis at

3 months can also give an indication to the patient if they should proceed with any additional restorative

or prosthetic treatment on the tooth that had VPT performed. This information coincides with a

previous study that showed prognosis of VPT from month 3 to month 18 is about the same (40). Thus,

the dentist and patient can confidently proceed with additional treatment if, at 3 months, the tooth still

exhibits lack of clinical and radiographic pathology, while also being asymptomatic.

With a p-value of 0.059, there is a marginally significant correlation between the maximum size

of the pulp exposure in its greatest dimension and pain at 24 hours. The clinician can also confidently

inform patients with large pulp exposures about the higher likelihood they will have pain at the 24 hour

time point.

It is important to note that this particular study used mostly dental students to perform the caries excavation, the VPT, and subsequently the restoration used for the coronal seal. This is evidence that even the least experienced practitioners can achieve a relatively high level of success, such as the 78% obtained in this study. Some of the previous studies that obtained success above 90% used highly experienced practitioners with one operator (45,48,49). From this study, general practitioners can be confident of performing this procedure with high success on a patient population in need of saving not only the teeth themselves, but the vitality of the teeth. As VPT becomes more frequently performed, it can also help patients who are less inclined to financially afford RCT and, in the past, opted for extraction. The one caveat for dental practitioners is that this procedure should only be performed in those patients who meet a strict preoperative clinical scenario, with the main entity being the absence of any previous spontaneous pain or other signs of irreversible pulpitis.

This is the first prospective, observational study looking at the association between perioperative pain and the outcome of VPT. Even though this study is well designed, there are several ways in which future research can improve upon it. One strategy would be to obtain more detailed preoperative data, such as a better history of preoperative pain and diagnostic testing on the tooth of interest. Another way would be to standardize postoperative analgesic use to rule out how different types and doses of analgesics might influence perception of pain. Future research may also want to examine outcome with longer follow-up times and can even collect biological samples or markers from the pulp upon exposure for any correlation with outcome of VPT.

Conclusion:

There is no direct correlation between the presence and quality of perioperative pain and the outcome of vital pulp therapy up to 1 week after treatment, however, if pain persists at 3 months postoperatively, VPT is likely to fail. Additionally, if VPT is performed based on strict case selection and

using the mentioned protocol, postoperative pain after VPT can be confidently managed by the provider

using information learned from this study.

DISCUSSION

Though this study was not intended to evaluate success of VPT alone, the results show that VPT performed with this specific protocol is 78% successful, which is consistent with previous studies (39,41,43,45). Since this was a standardized, prospective study, the protocol was well controlled and allowed for less variation or bias within the methods themselves. The study was specifically designed in a prospective manner so that confounding of variables, which was a major problem with previous studies, were not such in this clinical investigation. This was necessary in order to isolate variables or factors that truly may influence the outcome of VPT.

Prospective investigations are especially important compared to their counterpart: retrospective research. Even though retrospective studies are more easily done due to relatively lower costs and easier data collection, they have a greater chance for bias. In addition, they often times have missing data. Prospective studies have greater accuracy of data collection with regard to exposures, confounders, and endpoints, but this is realized at the cost of an inevitable loss of efficiency, for this design is both expensive and time-consuming. Vice versa, the retrospective design is very time-efficient but one has no choice other than to work with what has been measured in the past, often for another purpose than the one under investigation. The prospective design for this study made pain data collection easier and more accurate than if it were retrospective. Several studies have shown that recollection of pain postoperatively for a procedure, dental or medical, has less precision than if obtained at the time of evaluation (56,57). For these reasons, a standardized, prospective study was crucial to the novelty of this examination because this is the first that evaluates perioperative pain and its association with outcome of VPT.

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One of the critical decisions in designing this study was choosing which pulp capping agent to use. Calcium hydroxide has been studied extensively as a pulp capping material (20,30,41,43,44) and was considered the "gold standard" for VPT. However, newer publications on tricalcium silicates are supplanting calcium hydroxide as the preferred material. Products such as Biodentine (Septodont, Saint Maur des Faussés, France), Bioaggregate (BA; Innovative Bioceramix, Vancouver, BC, Canada), Bioceramic putty iRoot BP Plus (Innovative BioCeramix Inc.,Vancouver, Canada), and different MTA formulations have been shown to have potential applications for VPT. However, MTA is the first of all the tricalcium silicate cements to be FDA approved and most of the research on VPT and tricalcium silicates is based on MTA. There is clear and extensive evidence that MTA results in higher success compared to calcium hydroxide (43,44) with reported success rates above 90% (42,47–49). According to the data presented in the past 15 years, MTA is becoming the new "gold standard" for VPT as a capping agent and that was the rationale for choosing the material for this study.

MTA Angelus (Angelus, Londrina, PR, Brazil) was the material of choice for this study for several reasons. MTA Angelus has a faster setting time than other variations of MTA (58). It also has much easier handling characteristics due to its particle size compared to other formulations (37). Even though MTA Angelus has a slightly different chemical composition (less iron oxide and calcium sulfate compared to traditional gray MTA), the current evidence doesn't show any difference in the qualitative characteristics of each product (59–62). For these reasons, MTA Angelus was chosen to be the pulp capping agent in this study.

The results from the pain data set provide evidence that can be clinically applicable when treating patients with vital pulp therapy. This study shows that about one-third of patients who undergo the procedure experienced some postoperative pain. This pain was usually experienced in the first 24 hours and resolved completely after 1 week. The data clearly demonstrates that pain after VPT resolves in a time-dependent manner. The data also shows that patients can experience mild to moderate pain in

the immediate postoperative time period and still have a successful outcome of treatment. Not only can this pain be intense, but it can also be either spontaneous or evoked pain. Lastly, most patients did not feel the need to take analgesics after VPT, but if they did, they mostly needed them in the earlier periods after the procedure. This is valuable information for both clinicians and patients.

With the information obtained from this study, the clinician now has data to support postoperative instructions detailing to the patient the relatively high likelihood that they may encounter pain and how long that pain might last for. Reassurance to the patient that the pain experienced is normal and to not seek any emergency care or additional endodontic treatment is imperative. Based on the data from this study, as long as the patient is not experiencing severe pain after 1 week, the pain can be managed with analgesics with a high chance of successful outcome. Even though the current results from the pain data set do not support a correlation between the presence of perioperative pain and the outcome of VPT up to 1 week after treatment, clinically based decisions by dental providers can be gleaned from this research in order to educate their patients on what to expect after VPT. If patients are experiencing pain 3 months after treatment, the clinician likely should see the patient for an additional in-person clinical exam to assess the success of the treatment.

With a p-value of 0.028, there is a significant correlation between pain at the 3 month time point and the outcome of VPT. This is important because it can give the provider a specific follow-up time so they can re-evaluate if the patient still has complaints of pain. Re-evaluation of the prognosis at 3 months can also give an indication to the patient if they should proceed with any additional restorative or prosthetic treatment on the tooth that had VPT performed. This information coincides with a previous study that showed prognosis of VPT from month 3 to month 18 is about the same (40). Thus, the dentist and patient can confidently proceed with additional treatment if, at 3 months, the tooth still exhibits lack of clinical and radiographic pathology, while also being asymptomatic.

With a p-value of 0.059, there is a marginally significant correlation between the maximum size of the pulp exposure in its greatest dimension and pain at 24 hours. The clinician can use this evidence to confidently inform patients with large pulp exposures about the higher likelihood they will have pain at the 24 hour time point. Having advised the patient of any postoperative symptoms before they occur, the dental practitioner can wisely save the patient from any fearful moments or distrust of the procedure performed. It can also save time for both the patient and dental provider by curtailing any unnecessary subsequent contact such as phone calls or in-person consultations due to postoperative pain.

Pain data, in this study, was collected through a standardized telephone questionnaire that has inherent advantages and disadvantages. The telephone questionnaire was specifically crafted to ask as many closed-ended questions as possible with a specific algorithm for follow-up inquiries and obtaining more detail to certain answers. Questions were either open-ended, dichotomously closed-ended, or multichotomously closed-ended. Open-ended questions have the advantage of offering a variety of answers that help to accurately portray what the participant wants, while not using pre-determined responses that may impact the result of the question. On the down-side, replies are often problematic to assess and tend to contrast in transparency and complexity. Dichotomous questions are used for questions with two opposing outcomes. They tend to be less intricate for the participant and require less effort when interpreting the results; they can also be directly compared to answers by other respondent. Multichotomous questions offer a range of possible answers. These, too, can be easier on the respondent and equally on the interpreter later on (63). However, closed-ended questions do not offer the interpreter the opportunity to ask follow-up questions and clarify answers of participants. In this study, it was attempted to create the questionnaire in such a way that pertinent follow-up questions were standardized.

It is important to note that this particular study used mostly dental students to perform the caries excavation, the VPT, and subsequently the restoration used for the coronal seal. This is evidence that even the least experienced practitioners can achieve a relatively high level of success, such as the 78% obtained in this study. Some of the previous studies that obtained success above 90% used highly experienced practitioners with a single operator (45,48,49). From this study, general practitioners can be confident of performing this procedure with high success on a patient population in need of saving not only the teeth, but also the vitality of the pulps. As VPT becomes more frequently performed, it can also help patients who are unable to afford the treatment and, in the past, opted for extraction. The one caveat for dental practitioners is that this procedure should only be performed in those patients who meet a strict preoperative clinical scenario, with the main entity being the absence of any previous spontaneous pain.

This study continues the influx of new data on the relatively high success rate of VPT and how this new paradigm is changing the standards of clinical dentistry for mature teeth with carious pulp exposures. As mentioned before, traditional treatment for a mature tooth with a carious pulpal exposure has been root canal therapy but this study confirms that there is a viable treatment option for teeth with these strict case criteria. Performing this treatment accomplishes the goals of conventional RCT, but additionally, the pulp remains vital. One may argue that there needs to be a different way of thinking for teeth that might qualify for VPT in that not every carious pulp exposure should undergo RCT. This also may require a new definition for "asymptomatic irreversible pulpitis" or, at least, a paradigm shift in how teeth are treated in this classification. Performing VPT instead of RCT is cheaper, maintains vitality, and requires less chair time which all equates to being in the best interest of the patient. At this point, VPT is less predictable than RCT, but with this study and future ones of this nature, factors predicting the outcome of success will become much more apparent.

Though the study was designed well, there are several ways it could have been more thorough in order to correlate perioperative pain with outcome of VPT. One way in which this could have been achieved is by noting an accurate history of preoperative pain symptoms. Even though one of the exclusion criteria was history of spontaneous pain on the tooth of interest, it would be helpful to ascertain any other history or type of pain the patient experienced preoperatively with that tooth. With a quality and detailed history of pain experienced before the procedure, analysis of that data may be used to inquire about a correlation with intensity, type, and duration of preoperative pain with postoperative pain and preoperative pain with outcome of VPT.

Another amendment to the study that would have improved upon the already strict case selection process would have been to perform endodontic diagnostic testing before the procedure occurred. Not only would diagnostic testing help determine more succinctly any pain symptoms, but we would also obtain a preoperative diagnosis. A preoperative diagnosis would be another interesting piece of information to investigate in how it relates to the patients' experience of perioperative pain and also if there is any correlation of diagnosis with outcome of VPT.

As mentioned previously, data was collected on analgesic use postoperatively, however, this pain management was not standardized and it is possible it could have affected their experience of pain. It is known that different types of analgesics in different doses can mask pain (64–66). It is very possible that those patients taking analgesics postoperative, whether due to pain from the tooth or otherwise, had a varying perception of pain based on their specific analgesic and its dose. Future studies should standardize postoperative analgesic use in type, dose, and duration so as not to confound the pain experience.

There are several other adjustments that can be made to future experiments for a more complete study. For instance, this study mainly obtained six month follow-ups, however, longer recalls, up to 5 years, would be beneficial to determine the longevity of VPT success. Another way to improve

the study would be to increase the sample size in order to determine if outcome is influenced based on

spontaneous versus evoked pain or based on intensity of pain that would require many more subjects to

analyze. Future studies would also do well to analyze, at the time of pulp exposure, any biological

samples or markers to see if there was any correlation between them and the outcome of VPT.

Conclusion:

There is no direct correlation between the presence and quality of perioperative pain up to 1

week and the outcome of vital pulp therapy, however, if pain persists up to 3 months, an additional

evaluation should be performed due to the increased likelihood it will fail in this scenario. Evidence from

this data will give clinicians appropriate knowledge of how to manage VPT patients postoperatively.

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