Title

Comparative Effectiveness Research of Dentin Hypersensitivity Intervention - A Mixed Systematic Review Analysis

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Publication Date

2016

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Comparative Effectiveness Research of Dentin Hypersensitivity Intervention - A Mixed Systematic Review Analysis

A thesis submitted in partial satisfaction

of the requirements for the Master of Science

in Oral Biology

by

Nouf Abduallah A Alaskar

2016

ABSTRACT OF THE THESIS

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Master of Science in Oral Biology

University of California, Los Angeles, 2016

Professor Francesco Chiappelli, Chair

Introduction and Objective: Dentin Hypersensitivity (DH) is one of the common oral conditions that affect adult population and defined as a short, sharp pain arising from exposed dentin in response to stimuli typically thermal, evaporative, tactile, osmotic or chemical and cannot ascribe to any other form of dental pathology or disease. DH development through two distinct but interrelated phases of tooth wear and gingival recession associated with different etiological factors.

Morphological alterations in DH and intradental nerve excitability are the underlying sources that lead to disease progression, pain evocation as well as therapeutic strategies investigations to

interrupt pain transmission. Numerous treatment modalities have been used to manage DH. The interventions of DH have been classified based on the mode of delivery (in-office or professionally-applied therapy and over-the-counter (OTC) or at- home therapy). The other classification used based on the mechanism of action and could be divided into two main categories: the dentinal tubules occluding agents to block the hydrodynamic mechanism of pain stimulation and the nerve desensitizers to interrupt the neural response to pain stimuli (neural blocker). The main objective for any dentine-desensitizing agent is to produce a clinically significant reduction in clinical symptoms and minimize or abolish the symptoms of pain or discomfort associated with DH. The variety of products and techniques used for the treatment of DH indicated a doubt among dentists about the best treatment option, as well as dissatisfaction with outcomes of available treatments, which necessitate the conduction of a comparative effectiveness research and a practice analysis to provide dentists and patients with precise scientific information for comparing the effectiveness and safety of alternative treatment options in resolving DH among different available treatment. The aim of the study is to conduct a comparative effectiveness research to find out if In-office desensitizing agents with dentinal tubules occlusion mechanism of action are more effective than self-applied desensitizing toothpaste with a neural stimulus blocker mechanism of action in resolving dentin hypersensitivity.

Methods: Search for systematic reviews, randomized clinical trials and observational studies were done using the National Library of Medicine-PubMed, Cochrane's library and the American Dental Association (ADA) web Library. The relevance of the identified systematic reviews, clinical trials and observational studies to the study and PICOTS question was assessed using the inclusion and exclusion criteria. The quality of evidence and clinical relevance analysis

achieved using validated and reliable instruments by two independent readers, and all disagreements resolved by discussion after establishing the inter-rater reliability of the two readers. The revised Assessment of Multiple Systematic Reviews (R-AMSTAR) instrument utilized to assess and quantify the quality of retained systematic reviews, the quantified Risk of Bias instrument utilized to evaluate the quality of retained clinical trials and the Expansion in the Grading of Recommendations Assessment, Development and Evaluation (Ex-GRADE) was used to evaluate the clinical relevance and the strength of recommendation. Acceptable sampling analysis was done using the Friedman test statistics. Meta-analysis was done on the two highest quality and homogenous clinical trials.

Results: Three out of six systematic reviews were considered as high-quality studies and two out of thirty-one clinical trials were considered as high-quality studies. However, the bibliome was concerned with a body of literature that has a considerable heterogeneity in terms of quality of the evidence, which prevented further work toward establishing the quantitative and qualitative consensus of the best evidence. Therefore, an alternative approach for acceptable sampling was conducted. Whereby the top 20% highest scoring papers in the bibliome were accepted. So, out of thirty-one studies, seven studies included and considered as high quality studies. The results of the qualitative analysis of this review shows that 5% potassium nitrate toothpaste has inferior effectiveness in DH management as at home intervention, however, the reduction in the hypersensitivity increase with each recall that suggests the slow effectiveness that could be explained by the requisite of maintaining a high level of potassium nitrate to reach the maximum effectiveness. 5% potassium was not effective compared to in-office desensitizing intervention. Although it is difficult to prove or reach a conclusive evidence of the best treatment option, treatment approaches with resin-based composite restoration and glass ionomer liner resulted in

statistically significant reduction in sensitivity. Yet, the complicated procedure of application of these restorations might be considered in terms of time and cost in treating dentin hypersensitivity. Furthermore, it considered as technique sensitive owing to the tendency to perform an overhang at the gingival margins, which contribute to the development of gingivitis or jeopardize the biological width of the periodontal tissues. Gluma and fluoride varnishes were effective in reducing DH for up to 6 months with no reported adverse effects aside to the time and cost consideration.

Conclusion: Based on the qualitative analysis of this review, the 5% potassium nitrate toothpaste has inferior effectiveness in DH management as at home intervention, which was not effective compared to in-office desensitizing interventions. Resin-based composite restoration and glass ionomer liner as in-office interventions yielded statistically significant reduction in sensitivity. However, the complicated procedure of application of these restorations might be considered in terms of time and cost in treating dentin hypersensitivity, which suggest that Gluma and fluoride varnishes might be superior treatment options in reducing DH in terms of efficacy and effectiveness. This review highlights the extent of heterogeneity and quality inferiority of clinical trials in this field, which impact the degree of their reliability. Also, it necessitates the future conduction of well-constructed clinical trials that directed to overcome current deficiencies and weaknesses.

The thesis of Nouf Abduallah A Alaskar is approved.

Carl Maida

Reuben Kim

Francesco Chiappelli, Committee Chair

University of California, Los Angeles

2016

Dedication

To my beloved parents,

And to my sisters and brothers

Without whom none of my success would be possible.

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Acknowledgments

This thesis won't be accomplished without the assistance and guidance of several people. First and above all, I would like to thank God for providing me this opportunity and granting me the ability to proceed successfully.

I would like to express my sincere gratitude to Dr. Francesco Chiappelli for the precious guidance, continuous support, for his patience, motivation, and immense knowledge. His guidance and knowledge helped me tremendously throughout my work on the research. I could not have imagined having a better advisor and mentor for my master thesis.

I would like to thank my thesis committee: Dr. Carl Maida and Dr. Ruben Kim for their insightful comments and encouragement.

I would like to acknowledge Dr. Andre Barkhordarian and my second reader Melissa Nahcivan for their considerable contribution.

Furthermore, I would like to show my great gratitude to my family: my Mother and Father, who have continuously encouraging, and supporting me to achieve my goals. I am so grateful to my sisters and brothers Mashael, Raghad, Norah, Yazeed, Meshal and Khalid for being always there for me.

Finally, My thanks to my friends and to everyone who helped me along the way to complete this work.

Chapter 1

Introduction

1. Dentin Hypersensitivity

1.1. Definition of Dentin Hypersensitivity:

Dentin hypersensitivity (DH) defined as a short, sharp pain arising from exposed dentin in response to stimuli typically thermal, evaporative, tactile, osmotic or chemical and cannot ascribe to any other form of dental pathology or disease as proposed by Holland and later by the Canadian Advisory Board on Dentin Hypersensitivity (Holland et al. 1997, Canadian Advisory Board on Dentine Hypersensitivity 2003)

The term hypersensitive dentin is widely used, however patients recognize exposed dentin as hypersensitive due to the lack of sensation before dentin exposure (Addy 2015). Dentin is an innervated tissue that protected by enamel or cementum. Therefore, losing these protective layers will cause the feeling of sensitivity. Though, the term 'Dentin Hypersensitivity' (DH) was used within the literature to describe that condition.

1.2. Prevalence of Dentin Hypersensitivity:

Dentin Hypersensitivity (DH) is one of the common oral conditions that affect adult population. Mostly, patients with DH range from 20 to 40 years and the peak in incidence is in the late thirties (Rees et al 2000). The prevalence of dentine hypersensitivity conflictingly ranges from 1.34% (Bamise et al. 2007) to 98% (Chabanski et al 2012). This conflicting can be explained by the selection criteria used for different study samples, whether the source of data is based on

clinical evaluation or patient-based questionnaires and especially by the selected diagnostic approaches as DH diagnosed by exclusion (West et al. 2014, Gernhardt et al. 2012). Relatively some studies have reported a high incidence of DH among females (Rees et al. 2004, Taani and Awartani, 2002). This could reflect their better oral hygiene awareness and their dietary habits. Furthermore, females also tend to visit the dental clinic more often, which may result in an over-representation and, therefore, introduce a selection bias in studies samples. In addition, females eventually have more concerns about health problems than males, which may introduce a detection bias for females (Taha 2015).

DH affects the quality of life of patients as a consequence of frequent pain and discomfort, which in turn cause behavior modification. Such as restricted dietary selection, avoiding chilled food and drink or prevent optimum oral hygiene that negatively affect the oral health (Boiko et al. 2010).

1.3. Mechanism of Dentine Hypersensitivity:

Dentine is a vital tissue that acquires the ability to react to physiological and pathological stimuli (Addy et al. 2000). Histologically, odontoblasts that are the principal elements of dentine tissue located along the dentin-pulp border and comprise the outermost region of the pulp. It plays an important role in dentin formation. It composed of odontoblasts cell bodies and odontoblastic processes that extend within the dentinal tubules, which filled by dentinal fluid emerging from the blood vessels of the pulp (Thomas et al. 1979)

To explain the mechanism of DH pain the literature discusses three main theories that have been proposed to explain the mechanism of DH, these are the direct nerve stimulation theory, the odontoblast-receptor theory, and the hydrodynamic theory (Addy et al. 2000). DH has mainly

explained by the hydrodynamic theory. Which first hypothesized by Gysi as a fluid flow movement outward from the pulp along dentine tubules (West et al.2012). Then Brannstrom was able to approve it by studying the fluid movement in dentine in response to thermal, evaporative, tactile, and osmotic stimuli (Brännström et al.1962, 1966, 1967,1968,1992)

Basically, DH pain is stimulus-based pain that induced fluid flow in the dentinal tubules and consequently, alters the pressure, which activates the mechanoreceptor response located in A-beta and A-delta nerve fibers and the pulp-dentine border area. A-beta and some A-delta fibers are Intradental myelinated nerve that responds to stimuli by alteration of the fluid flow in the dentinal tubules, resulting in prominent short, sharp pain of DH (Narhi et al. 1992)

Microscopically, different studies showed the features that positively correlate with the degree of hypersensitivity (Brännström.1965, Yoshiyama et al. 1996). These features include the patency of the dentinal tubules, density, diameter and size of the open dentinal tubules. In sensitive teeth, the number of tubules per unit area is about eight times greater than the number found in non-sensitive teeth, and the tubular diameter is two times greater (Absi et al 1987). Furthermore, according to the hydrodynamic theory of dentin sensitivity, the amount of fluid flow in hypersensitive teeth should be greater than the flow in the non-sensitive teeth in response to stimuli (Absi et al 1987). The association of wider diameter of dentinal tubules with sensitive teeth has been explored compared to the non-sensitive teeth. As the flow through a capillary follows the Poiseuille's law, which states that the rate of movement is dependent on the radius of the capillary to the power four. Thus, doubling the dentinal tubule radius would increase the flow 16 times (Absi et al 1987). Additionally, Pulpal inflammation could be responsible for increasing

pain intensity and decreasing the pain threshold, thus exposed dentin become hypersensitive (Pashley, 2013).

1.4. Etiology and Predisposing Factors:

In order to develop DH, dentin must undergo two different phases. Initially, dentine exposure phase that occurred by the loss of enamel or cementum with gingival recession, which called (lesion localization phase). Next, the patent or un-occluded dentinal tubules that connect the pulp to the oral environment, which called the (lesion initiation phase). Thus, not all exposed dentin is sensitive but it has to undergo the initiation phase (Addy. 2002). Lesion initiation and dentinal tubules' patency could be due to the absence of the transient smear layer, which represents the protein and inorganic debris derived from saliva and oral environment. Additionally, the degree of dentin sclerosis and the extent of occlusion by reparative dentine (secondary dentin lay down) on the pulpal surface could play an important role in the fluid movement within the dentine tubules (Yoshiyama et al. 1996).

Basically, DH development is through these two distinct but interrelated phases associated with different etiological factors such as tooth wear and gingival recession (Olley and Bartlett 2015).

Gingival recession and migration apical to the cemento-enamel junction as well as cementum loss are highly contributed to dentinal tubules exposure and DH development (Smith. 1997). Gingival recession result from multiple factors such as the anatomy of the buccal plate of the alveolar bone (dehiscence and fenestration) or high frenal attachment, tooth anatomy, soft-tissue trauma as a result of vigorous tooth brushing or orthodontic movement, all can prompt the gingival recession. Another indirect cause of the gingival recession is the poor oral hygiene, leading to periodontal disease (Smith. 1997).

Physiologically, teeth wear considered as a normal process that advances with aging and allow

extended time for the pulp to develop a protective layer of reparative dentine. Thus, will block the fluid flow within the dentinal tubules, which explain the absence of DH in that situation (Krauser.1986). In contrast, teeth wear seen in young patients with fast progression rate will be considered as pathological teeth wear. As reported, it is associated with DH symptoms, since it leaves the dentinal tubules exposed and patent (Smith and Knight 1984). The process of teeth wear and enamel loss is an irreversible loss of dental hard tissue caused by multifactorial etiology that could be subdivided into attrition, abfraction, abrasion and erosion (Bartlett and Smith 2000).

Attrition is the wear that occurs when teeth are in direct contact and grind against each other, usually associated with the occlusal function. Excessive or parafunctional habits, such as bruxism, may result in extreme pathologic wear and increased sensitivity (Meurman and Sovari 2000).

Abrasion is the tooth wear caused by objects other than other teeth. Such as, tooth brushing including the type of toothbrush, brushing technique and toothpaste also considered as a potential abrasive factor (West et al. 1998). Moreover, its combination with other factors such as, erosion will accelerate the process of tooth wear. Actually, erosion and acid exposure play the main role of tooth wear as well as DH localization and initiation (Absi et al. 1992, West et al. 2014). Whereby the superficial demineralization of hard tissue and the chemical dissolution of the apatite crystals in enamel by the acid attack will result in tissue loss and tubular opening (Absi et al. 1992). Typical sources of intrinsic acid are the stomach acid containing hydrochloric acid (HCL) due to vomiting or gastro-esophageal reflux (Scheutzel 1996). While the typical extrinsic sources could be the dietary consumption of acidic food or beverages such as acidic citrus and other fruits, carbonated beverages, beers, herbal teas, vinegar and pickles, candies, or acidic

medication. Also, acidic exposure associated with some occupational environment (Lussi. 2006). Furthermore, Abfraction lesions, which developed near the cervical margin as a result of occlusal stress. Usually, it evolves the non-carious cervical lesions (NCCLs) and associated with DH (Addy. 2002). Generally, Abrasion and erosion are the most common etiological factors to develop dentin hypersensitivity. Also, It is considered that gingival recession is the predominant localization factor and erosion is the predominant initiation factor. While DH is frequently seen in patients with periodontitis, transient hypersensitivity may occur after periodontal procedures such as deep scaling, root planning or gingival surgery. Transient hypersensitivity also may be associated with teeth whitening and restorative procedures (Orchardson et al. 2006)

1.5. Diagnosis and Assessment Methods:

The diagnosis of dentine hypersensitivity (DH) is not an easy direct process since the pain and clinical signs of the condition are similar to other oral conditions associated with pain that are managed and treated differently, besides the absence of a decisive test for DH. Therefore, an acceptable diagnosis of DH will be possible using the differential diagnostic approach and the elimination of all dental and periodontal conditions with the same pain perception (Holland et al. 1997, Addy. 2000)

Synchronically, it is essential to obtain a comprehensive medical history and dental history, in particular, pain history alongside the presence of certain clinical features or patient's habits. For instance, the exposed dentine as a result of gingival recession or enamel wear, high acidic diet, smoking and excessive brushing, are associated with DH, and their presence or history might suggest that DH is the cause of the pain reported. Additionally, Patients with xerostomia are potentially at a higher risk of erosion leading to DH (West et al. 2012).

According to the Canadian Advisory Board on Dentin Hypersensitivity, the dental professional is

advised to follow six steps with patients suffering from hypersensitivity teeth: (Canadian Advisory Board on Dentine Hypersensitivity 2003)

- Diagnosis of DH, comprising a patient's history and a brief clinical examination.
- Identification of etiologic and predisposing factors, particularly dietary and oral hygiene habits associated with erosion and abrasion.
- Differential diagnosis, to exclude all other dental conditions with alike pain symptoms.
- If present, treatment of all conditions with symptoms similar to dentin hypersensitivity.
- Elimination of etiologic and predisposing factors through dietary advice and improved oral hygiene instruction.
- Recommendation or implementation of treatment based on individual needs.

Assessing DH and its severity are achieved by two different assessment methods. Stimulating the teeth with stimuli known to provoke a hypersensitivity response and evaluate the stimulus intensity (stimulus-based assessment). Such stimulation will cause the pain, and this must be taken into account when interpreting a patient's response as a pain threshold measurement. (Gillam et al. 1997, Holland et al. 1997, Gernhardt 2012)

The other method is to assess the pain severity following the application of a standardized stimulus (response-based assessment). It is a subjective evaluation of pain produced by a defined stimulus such as tactile, cold, and evaporative air stimuli. After the stimulation patient's response can be quantified by using a validated pain scale. Commonly used scale is the visual analog scale (VAS) in which the patient places a mark on a 100-mm line labeled from no pain to worst pain (Holland et al. 1997, Gernhardt 2012). Another method of quantification is to use a verbal descriptor scale, which uses word descriptors as a scaling technique to describe variations in pain according to the patient's spontaneous report or by the use of a validated questionnaire.

Furthermore, another scale has been used called the Schiff cold air sensitivity scale. This scale is scored as follows: (Schiff et al. 2009)

- 0 Subject does not respond to air stimulus
- 1 Subject responds to air stimulus but does not request discontinuation of stimulus.
- 2 Subject responds to air stimulus and requests discontinuation or moves from the stimulus.
- 3 Subject responds to air stimulus, considers stimulus to be painful and requests discontinuation of the stimulus.

Clinically, it is recommended to confirm DH diagnosis with at least two different hydrodynamic stimuli (Canadian Advisory Board on Dentine Hypersensitivity 2003).

1.6. Dentin Hypersensitivity Treatment:

Morphological alterations in DH and intradental nerve excitability are the underlying sources that lead to disease progression, pain evocation as well as therapeutic strategies investigation to interrupt pain transmission. Numerous treatment modalities have been used to manage DH. The management of DH has been classified based on the mode of delivery (in-office or professionally-applied therapy and over-the-counter (OTC) or at- home therapy). OTC desensitizing agents are generally based on formulations with the same active ingredients as the in-office agents, yet with a lower concentration to allow safe usage and tend to be inexpensive and can treat simultaneously generalized DH affecting many teeth (Orchardson et al. 2006). The other classification used based on the mechanism of action and could be divided into two main categories: the dentinal tubules occluding agents to block the hydrodynamic mechanism of pain stimulation and the nerve desensitizers to interrupt the neural response to pain stimuli (neural blocker) (Orchardson et al. 2006). As the foremost objective for any dentine-desensitizing agent

is to produce a clinically significant reduction in clinical symptoms and minimize or abolish the symptoms of pain or discomfort associated with DH, it is very important to start with patient counseling and education about the dietary habits, oral hygiene instruction and subsequent monitoring the condition over time as the first line of treatment in order to eliminate any etiological and predisposing factors (Canadian Advisory Board on Dentine Hypersensitivity 2003). Afterward, different treatment approaches could be prescribed based on the clinical situation, and the clinician experience. Multiple systematic reviews have been published on different treatment modalities with a different mechanism of action and mode of delivery in order to assess the evidence that support the available treatment options.

1.6.1. Nerve Desensitization (Neural Blocker)

Potassium salts containing kinds of toothpaste are the most widely used at-home treatment for DH (Orchardson et al. 1987). Potassium ions have been shown to interrupt the neural response to pain stimuli by diffusing along the tubules and raising the concentration of local extracellular potassium ions, thus blocking intradental nerve function. Accordingly, It is important to maintain the high level of extracellular potassium ions to have the desired effect, which may take longer time (Nähri et al. 1992). Potassium-containing products (nitrate, chlorine and citrate) including both toothpaste and mouthrinse formulations have been reported to be effective in reducing DH compared to placebo controls (Orchardson and Gillam 2000, Markowitz 2009). The 5 % potassium nitrate formulations have been the most extensively evaluated desensitizing agent (Rösing et al. 2009). Sensodyne toothpaste that contains 5% Potassium nitrate as an active ingredient has been accepted by the ADA Council on Scientific Affairs to receive the ADA seal as the only approved OTC desensitizing agent. Though, previous systematic review directed to

assess the effectiveness of potassium-containing toothpaste in reducing DH by including randomized control trials (RCTs) comparing potassium to non-potassium containing toothpaste which, failed to show a significant effect (Poulsen et al. 2006).

1.6.2. Dentinal Tubule Occluding Agents

The most direct approach to desensitize dentine is the alteration of fluid flow in dentinal tubules by dentinal tubules occlusion. The effectiveness of the tubular occluding agents will depend on their resistance to removal, especially in an acidic environment. There are multiple and complex techniques in which different agents and products could potentially work to partially or completely occlude tubules (Markowitz 2009, Cummins 2010)

- **Deposition of a thin-film coating layer by creating an artificial smear layer over the open tubules.**

  Typically, the polymer-based materials such as adhesive materials, restorative resins, dentin bonding agents or Glass ionomer cement, have been proposed to work by that mechanism of tubular occlusion. Several investigators have reported the application of dentin adhesive materials for relieving DH (Mehta et al. 2014, Brunton et al. 2000). Basically, it promotes a micro-mechanical interlocking through a hybridization process. Besides the presence of functional monomers, they have the potential to interact chemically with the calcium ions from the residual hydroxyapatite that remains available within the submicron hybrid layer (Pei et al. 2013).

- **Induction of protein precipitation**

  The Glutaraldehyde - based desensitizing materials aside to hydroxyethyl methacrylate will occlude the dentinal tubules by interaction with the dentinal proteins. It reacts with the serum

albumin in the dentinal fluid, resulting in precipitation of the serum albumin. This reaction also causes the polymerization of 2- hydroxyethyl methacrylate (HEMA) that block the dentinal tubules (Stewardson et al. 2004, Qin et al. 2006). Several investigators have reported the effectiveness of protein precipitation to reduce DH (Duran et al. 2005, Schmidin and Sahrmann 2012).

- **Deposition of a layer of fine particles (physical barrier)**

  Several desensitizing materials have used this technique to create a physical barrier on the exposed dentinal tubules. It distributed directly as fine abrasive particles or formed as a precipitate in situ, such as strontium, stannous fluoride, and calcium phosphate particles (Cummins 2010). Strontium has been investigated as a treatment for DH since 1956. It introduced as 25% strontium/water solution and a 75% glycerin paste (Pawlowska 1956, West 2008). Many investigations reported their effectiveness in treating DH compared to placebo controls (Kobler et al 2008). The main mode of action of strontium formulations was considered to be one of the tubular occlusion through the participation of strontium to replace calcium in hydroxyapatite (Minkoff et al. 1987).

  Fluoride compounds (stannous fluoride in a 0.4% gel or sodium fluoride in a 0.5% mouthrinse or a 1.1% gel) have a valued action as an anti-cariogenic and desensitizing treatment (Featherstone. 2000). Fluorides reduce the permeability of dentin by its ability to react with hydroxyapatite and form fluorapatite, which considered less susceptible to acid dissolution than hydroxyapatite (Morris et al 1999).

  Iontophoresis of fluoride has been used for the treatment of DH; however, its real benefit is debated. Iontophoresis has been described as a method of facilitating the transfer of ions by electrical potential into soft or hard tissues of the body for therapeutic purposes. Many studies

have found Iontophoresis a safe and effective method for treating cervical DH although some investigators consider it time-consuming and technique demanding. Many mechanisms have been proposed for its action. It may desensitize hypersensitive dentin by formation of a secondary dentin as a result of the electrical current applied or by increasing the concentration and depth of penetration of fluoride ions into dentinal tubules (precipitate calcium fluoride) thereby occluding the tubules and reducing the conduction of stimuli (Gillam et al. 1990)

- **Induction of natural mineral formation.**

  As one of the difficulties with most of the desensitizing agents using the dentinal tubules' occlusion technique is the inability to resist the chemical and mechanical challenges in the oral environment. Therefore, those necessitate the development of new technologies, which based on the stimulation of biological mineral development, such as the Pro-Argin technology, NovaMin bioactive glass and Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP). It is believed to work through their binding to the exposed dentinal tubules to mediate the formation of biological minerals (Cummins 2010).

  Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP), a milk derivative, was primarily developed for both anti-caries and enamel and dentin remineralization strategies rather than for the treatment of DH (Nongonierma and Fitzgerald. 2012). CPP is a bioactive peptide released from caseins with an enhanced binding ability to calcium. Amorphous calcium phosphate (ACP) has the ability to convert to hydroxyapatite in the presence of saliva. Accordingly, both calcium and phosphate were able to compose as a stable hydroxyapatite (Nongonierma and Fitzgerald. 2012).

  Bioactive glasses (calcium sodium phosphosilicate) which promote hydroxycarbonate apatite (HCA) participation. Investigations showed new calcium and phosphate development on dentin

surface and dentinal tubules' occlusion afterward (Litkowski and Greenspan 2010, Pradeep and Sharma 2010).

Pro-Argin, calcium carbonate and arginine complex as first formulated by Kleinberg (Kleinberg 2002). This complex developed in order to simulate the natural process of DH reduction that happens in the presence of calcium, phosphate and glycoproteins in saliva. Naturally, Arginine is an amino acid found in saliva; it acts in combination with calcium carbonate and phosphate to create a plug in dentinal tubules that prevent fluid flow (Cummins 2010). The proposed mechanism of action states that the positively charged arginine is attracted to negatively charged dentine, and the alkaline pH promotes deposition of calcium, phosphate, arginine and carbonate at the dentine surface and inside the dentine tubules (Petrou et al. 2009).

1.6.3. Lasers:

Laser therapy was first introduced as a potential method for treating dentinal hypersensitivity in 1985 (Matsumoto et al. 1985). Generally, there are two types of lasers used for the treatment of dentin: low output power (low-level) lasers [helium-neon (He-Ne) and gallium/aluminum/arsenide (GaAlAs) (diode) lasers], and middle output power lasers (Nd: YAG and CO2 lasers). Lasers work by coagulation of proteins in the dentinal fluid and hence reduce permeability (Goodis et al. 1997). They are also believed to create an amorphous sealed layer at the dentine surface, which appears to be due to partial meltdown of the surface (Kumar et al 2005). Nevertheless, lasers' efficacy and mechanism of actions are questioned, due to deficient information related to the irradiation standards and guidelines (Sgolastra et al. 2011).

Even though, various methods available to treat or manage dentin hypersensitivity, none of them considered an ideal treatment that satisfies the gold standards.

According to Holland, the ideal desensitizing agent should not irritate the pulp, should be relatively painless when applied or shortly afterward, should be easily applied, should act rapidly, should be permanently effective, should be cost-effective and should not discolor tooth structure (Holland et al. 1997).

Based on a survey conducted regarding the diagnosis and treatment of DH within Northwest Practice-Based Research Collaborative in Evidence-Based Dentistry (PRECEDENT), a practice-based dental research network. Information regarding types and frequency of use of different methods of diagnosis and treatment of DH was collected. The survey results imply that practitioners frequently use a wide variety of products and techniques to treat a patient with dentin hypersensitivity. Fluoride, glutaraldehyde / HEMA, bonding agents, potassium nitrates and restorative treatments were the common treatment and considered as a successful treatment, whereas observation, dietary and tooth brushing advice and lasers, as least successful (Cunha-Cruz et al 2010).

The variety of products and techniques used for the treatment of DH indicated a doubt among dentists about the best treatment option, as well as dissatisfaction with outcomes of available treatments. Which necessitate the conduction of a comparative effectiveness research and a practice analysis to provide dentists and patients with precise scientific information for comparing the effectiveness and safety of alternative treatment options in resolving DH among different available treatment.

2. Evidence-Based Dentistry:

Evidence-based dentistry (EBD) is systematic patient-centered researches that conducted by replicable methodologies and involve all implicate stakeholders.

The ultimate goal of these researches is to translate all the information and knowledge about the best available health-care modalities for a certain patient in a specific clinical setting. According to the concept of EBD research, the best available health care means it is cost and safely effective aside with the best efficacy (Chiappelli. 2014).

Basically, this coincides with the eventual aim of the translational effectiveness as part from the translational science. Translational science represented by two aspects; the translational research, which defined by The National Institutes of Health (NIH) as the transaction between the patient at the clinical setting and the fundamental pathobiology.

The other aspect as described by the Agency for Healthcare Research Quality (AHRQ) is the utilization, application, and implications of the best available evidence in certain clinical settings. Eventually, Translational science results from a transaction between translational research and translational effectiveness (the translational research–effectiveness transaction, TRET) (Woolf. 2008, Chiappelli. 2014)

EBD relies on a systematic process of research synthesis that aims to develop a comparative efficacy and effectiveness research, review, and analysis, for practice (CEERAP), as well as to recognize the best available evidence to support any health care modalities (Chiappelli and Danaei. 2012)

This systematic process starts from a research question (PICOTS) or a hypothesis, which defined the population of interest (P), the intervention (I), the comparator (C) and the clinical outcome (O) within a given timeline (T) and clinical setting (S).

Using the elements of the PICOTS research question to extract the related keywords and create the list of inclusion/exclusion criteria that facilitate the investigation of the entire relevant evidence (Bibliome). Then, a bibliome systematic screening is required to exclude irrelevant evidence that does not fit within the PICOTS question elements and the inclusion/exclusion criteria. Afterward, assessment of the quality and clinical relevance of evidence performed with validated reliable grading instruments intended to evaluate the strength of evidence, which are designed to quantify the quality of evidence based on recognized standards for research methodology, design, and statistical analysis (AHRQ, Methods Guide for Effectiveness and Comparative Effectiveness Reviews, 2014).

The following step is data analysis, which comprises the acceptable sampling analysis. Essentially, translating the best available evidence is the ultimate goal of comparative efficacy and effectiveness research. Therefore, it is very important to conduct the acceptable sampling analysis to retain the high quality level of evidence (Chiappelli. 2014).

Then, the systematic process of CEERAP concluded by developing an overarching statistical significance analysis between non-heterogeneous outcomes. Heterogeneity determined by the Cochran Q and I^2 statistical tests. Heterogeneity could be developed from original studies due to differences in participants, interventions, co-interventions, outcomes, measurements, settings and other factors varying within the data sets, studies, and participants. Meta-analysis conducted through two different methods based on the presence of certain extent of heterogeneity. Whereby, fixed or random model should be followed. Moreover, it is imperative to be aware of biases that may develop in the meta-analysis, which could be inherited from the primary evidence that represent variable biases within them or those that affect the overarching total body of evidence.

At the end, CEERAP produces the consensus of the best available evidence through the scientific process of research synthesis, which is reported in a scientific form as a systematic review (Chiappelli. 2014).

3. Purpose of The Study:

The aim of the study is to conduct a comparative effectiveness research to find out if In-office desensitizing agents with dentinal tubules occlusion mechanism of action are more effective than self-applied desensitizing toothpaste with the neural stimulus blocker mechanism of action in resolving dentin hypersensitivity.

This drive the following **PICOTS question**:

Population: Adult patients (age 18<), diagnosed with dentine hypersensitivity due to exposed dentine.

Intervention: In-office desensitizing agents with dentinal tubules occlusion mechanism of action.

Comparator: Self-applied desensitizing toothpaste with the neural stimulus blocker mechanism of action

Outcome: Pain and sensitivity reduction (Pain level)

Timeline: 6 weeks or more.

Setting: Any clinical practice

Chapter 2

Methodology

1. **Hypothesis:**

- **Research Hypothesis*:*** In-office desensitizing agents with dentinal tubules occlusion mechanism of action are more effective than self-applied desensitizing toothpaste with a neural stimulus blocker mechanism of action in resolving dentin hypersensitivity.
- **Null Hypothesis*:*** There is no difference in the desensitizing effect of In-office desensitizing agents with dentinal tubules occlusion mechanism of action compared to the self-applied desensitizing toothpaste with a neural stimulus blocker mechanism of action.

2. **Analytical Framework:**

The analytic framework represents relevant clinical concepts and refines the relationship between intermediate outcome measures and ultimate health outcomes. It helps in understanding the situation in which clinical decisions are made. (AHRQ, Methods Guide for Effectiveness and Comparative Effectiveness Reviews, 2014).

Analytic framework was developed and associated with following key questions:

1. Is the desensitizing agent effectiveness impacted by overall the oral environment?
2. Is DH prevalence and treatment outcome impacted by gender?
3. Is the desensitizing agent effectiveness enhanced by certain application technique?

Figure (1) shows the analytic framework.

3. Search Strategy:

The search for systematic reviews, randomized clinical trials and observational studies was done in March 2016 via electronic bibliographic databases using the following keywords:

A. Dentin sensitivity,

B. Dentin hypersensitivity,

C. Tooth sensitivity,

D. Dentin Desensitizing Agents,

E. GLUMA (Glutaraldehyde /2-hydroxyethyl methacrylate),

F. Fluoride Compounds,

G. Oxalate Product (Potassium),

H. Calcium Phosphate,

I. Arginine + Calcium Carbonate,

J. Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP) – (ACP),

K. Strontium Salts,

L. Bioactive glass,

M. Hydroxyapatites,

N. Resin and adhesives,

O. Dentin Bonding Agent,

P. GIC / Glass Ionomer Cement,

Q. Potassium Nitrate,

R. Iontophoresis,

S. Ozone.

The Medical Subject Headings (MeSH) and Text Words used to preform the search strategy:

((((("Dentin Sensitivity"[Mesh]) OR ("dentin sensitivity"[text word] OR "dentin sensitivities"[text word] OR "dentin hypersensitivity"[text word] OR "dentin hypersensitivities"[text word] OR "dentine sensitivity"[text word] OR "dentine sensitivities"[text word] OR "dentine hypersensitivity"[text word] OR "dentine hypersensitivities"[text word]))) AND ("Dentin Desensitizing Agents"[Mesh] OR "Dentin Desensitizing Agents"[text word] OR "Fluorides"[Mesh] OR fluoride*[text word] OR "Denquel"[Supplementary Concept] OR "Isodan"[Supplementary Concept] OR "potassium nitrate"[Supplementary Concept] OR "Denquel"[text word] OR "Isodan"[text word] OR "potassium nitrate"[text word] OR "casein phosphopeptide-amorphous calcium phosphate nanocomplex" [Supplementary Concept] OR "CPP-ACP"[text word] OR "tooth mousse"[text word] OR "Recaldent"[text word] OR "casein phosphopeptide-amorphous calcium phosphate nanocomplex"[text word] OR "pro-argin" [Supplementary Concept] OR "pro-argin"[text word] OR proargin[text word] OR "Calcium Carbonate"[Mesh] OR "Oxalates"[Mesh] OR oxalate*[text word] OR oxalic[text word] OR Ethanedioic[text word] OR "Calcium"[Mesh] OR calcium[text word] OR "Calcium Phosphates"[Mesh] OR "Silicates"[Mesh] OR "calcium silicate" [Supplementary Concept] OR "BioAggregate" [Supplementary Concept] OR silicate*[text word] OR "gluma desensitizer" [Supplementary Concept] OR "Gluma" [Supplementary Concept] OR "Gluma Comfort Bond and Desensitizer" [Supplementary Concept] OR "Gluma One Bond" [Supplementary Concept] OR "Gluma 2000" [Supplementary Concept] OR gluma[text word] OR (("Glass"[Mesh] OR glass[text word]) AND bioactive[text word]) OR "Dentin-Bonding Agents"[Mesh] OR "Dentin-Bonding Agents"[text word] OR "Dentin-Bonding Agent"[text word] OR "Glass Ionomer Cements"[Mesh] OR (("Glass Polyalkenoate"[text word] OR "Glass Ionomer"[text word]) AND cement*[text word]) OR "Resin Cements"[Mesh] OR "resin cement"[text word] OR "resin cements"[text word] OR "Iontophoresis"[Mesh] OR iontophores*[text word] OR "Strontium"[Mesh] OR "strontium chloride" [Supplementary Concept] OR "strontium-containing hydroxyapatite" [Supplementary Concept] OR "strontium titanium fluoride" [Supplementary Concept] OR strontium[text word])) AND (("Clinical Trial "[Publication Type] OR "Randomized Controlled Trial "[Publication Type] OR "randomized"[tiab] OR "placebo"[tiab] OR "drug therapy"[sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT ("animals"[MeSH] NOT "humans"[MeSH]))

3.1. **Search for Systematic Reviews:**

The search engines explored were:

- The National Library of Medicine-PubMed,
- Cochrane library,
- American Dental Association (ADA) web Library.

3.2. **Search for Randomized Clinical Trials:**

The search engines explored were:

- The National Library of Medicine-PubMed,
- Cochrane library,
- American Dental Association (ADA) web Library.

4. Determination of The Relevance:

The relevance of the identified systematic reviews, clinical trials and observational studies to the study and PICOTS question was assessed using the following criteria:

4.1. **Inclusion Criteria:**

- Assessment of DH using a scale for pain measurement for 6 weeks or more.
- Treatment with in-office desensitizing agents with dentinal tubules occlusion mechanism of action.
- Treatment with self-applied desensitizing toothpaste with neural stimulus blocker mechanism of action (5% Potassium Nitrate).
- English language studies.

4.2. **Exclusion Criteria:**

- Post restorative treatment tooth sensitivity
- Post-bleaching teeth sensitivity
- Patients with active periodontal disease
- Non English language papers

4.3. **Adherence to The Proposed PICOTS Question:**

The PICOTS question was applied to the methodology and results of each study in order, to filter papers after applying the inclusion and exclusion criteria and to determine the faithfulness of each identified paper in the bibliome.

5. Measurements:

The quality of evidence and clinical relevance analysis achieved using validated and reliable instruments to allow a systematic evaluation of retained evidence. As recommended by the Cochrane group, the decision was done by two independent readers trained and standardized in the critical assessment of the principles of research methodology, design and statistical analysis and all disagreements resolved by discussion. Readers' standardization and Inter-rater reliability of the two readers was evaluated by obtaining the Pearson correlation coefficient (r) and the shared variance (r^2).

- The correlation coefficient (r) between the two readers on three systematic reviews was 0.93 and the shared variance (r^2) was 0.86
- The correlation coefficient (r) between the two readers on three clinical trials was 0.92 and the shared variance (r^2) was 0.85

5.1. Quality of Systematic Reviews:

The revised Assessment of Multiple Systematic Reviews (R-AMSTAR) instrument utilized to assess and quantify the quality of retained systematic reviews (Kung et al. 2010). The R-AMSTAR includes 11 questions, which cover 37 systematic review quality domains in a quantitative approach. Each question could score from 1 to 4 by which score 4 means all the criteria are fulfilled.

- **R-AMSTAR Items**

1. Was an ‘‘a priori’’ design provided?

- A clearly focused (PICO-based) question
- Description of inclusion criteria
- Study protocol is published and/or registered in advance

2. Was there duplicate study selection and data extraction?

- At least two persons independently extracted the data, explicitly stated
- Statement of consensus procedure for disagreements
- Disagreements among extractors resolved properly as stated or implied

3. Was a comprehensive literature search performed?

- At least two electronic sources are searched
- Years and databases used are mentioned
- Key words and/or MESH terms are stated and where feasible the search strategy outline is provided
- Searches should are supplemented by consulting current contents, reviews, textbooks, registers and by reviewing the references in the studies found
- Journals are hand-searched or manual searched

4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?

- The authors state that they searched for reports regardless of their publication type.
- The authors state whether or not they excluded any reports based on their publication status, language etc.
- "Non-English papers were translated "or readers sufficiently trained in foreign language
- No language restriction or recognition of non-English articles

5. Was a list of studies (included and excluded) provided?

- List of included and excluded studies should be provided.
- Table/list/figure of included studies, a reference list does not suffice
- Table/list/figure of excluded studies either in the article or in a supplemental source
- Satisfactory/sufficient statement of the reason for exclusion of the seriously considered studies
- Reader is able to retrace the included and the excluded studies anywhere in the article bibliography, reference or supplemental source

6. Were the characteristics of the included studies provided?

- In an aggregated form such as a table, data from the original studies are provided on the participants, interventions/exposure and outcomes
- Ranges are provided of the relevant characteristics in the studies analyzed
- The information provided appears to be complete and accurate

7. Was the scientific quality of the included studies assessed and documented?

- 'A priori' methods are provided
- The scientific quality of the included studies appears to be meaningful
- Discussion/recognition/awareness of level of evidence is present

- Quality of evidence is rated/ranked base on characterized instruments

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

- The scientific quality is considered in the analysis and the conclusions of the review
- The scientific quality is explicitly stated in formulating recommendations
- Conclusions integrated/drives towards practice guidelines
- Clinical consensus statement drives toward revision or confirmation of practice guidelines

9. Were the methods used to combine the findings of studies appropriate?

- Statement of criteria that were used to decide that the studies analyzed were similar enough to be pooled
- For the pooled results, a test is done to ensure the studies were combinable, to assess their homogeneity
- Recognition of heterogeneity or lack of thereof is present
- If heterogeneity exists a 'random effects model' is used and/or the PEROSH OSH Evidence Methods AMSTAR items Criteria rationale of combining is taken into consideration
- If homogeneity exists, author state a rationale or a statistical test

10. Was the likelihood of publication bias assessed?

- Recognition of publication bias or file drawer effect
- Graphical aids (e.g. funnel plot)
- Statistical tests (e.g. Egger regression test)

11. Was the conflict of interest included?

- Statement of sources of support
- No conflict of interest. This is subjective and may require some deduction or searching.
- An awareness/statement of support or conflict of interest in the primary inclusion studies.

5.2. Quality of Clinical Trials:

The quantified Risk of Bias instrument utilized to evaluate the quality of retained clinical trials (Barkhordarian et al. 2013). Originally, the qualitative Risk of Bias developed by the AHRQ to evaluate evidence systematically in four domains: (risk of bias, consistency, directness and precision) (Viswanathan et al. 2012)

- **Quantified Risk of Bias criteria**

  i. **Risk of Bias:** Study design and study conduct for individual studies.

  Principle criteria (maximum score is 4)

  a. Bias in study design.

  b. Bias in methodology.

  c. Bias in study conduct

  ii. **Consistency:** Degree of similarity in the effect sizes of different studies within an evidence base

  Principle criteria (maximum score is 3)

  a. Inconsistent evidence bases have significant unexplained clinical statistical heterogeneity

  b. Meta-analysis should use appropriate test, Cochran's Q test or 1^2 statistics.

iii. **Directness:** Either a single direct link between the interventions of interest and the ultimate health outcome under consideration or multiple links in a casual chain. With multiple links, strength of evidence is only as strong as the weakest link.

Principle criteria (maximum score is 3)

a. A single direct link between the interventions of interest and the ultimate health outcome under consideration.
b. Reliance on multiple links, evidence of a casual chain (with multiple links, strength of evidence is only as strong as the weakest link).

iv. **Precision:** The degree of certainty for estimate of effect with respect to a specific outcome.

Principle criteria (maximum score is 4)

a. Includes statistical significance for effect estimates.
b. Includes confidence intervals for those effect estimates.
c. Include any summary estimate of effect size.

5.3. Clinical Relevance Analysis:

The Expansion in the Grading of Recommendations Assessment, Development and Evaluation (Ex-GRADE) was used to evaluate the clinical relevance and strength of recommendation. The strength of recommendation part includes 7 questions, each question could score from 1 to 4 by which score 4 means all the criteria are fulfilled (Phi et al. 2012)

- **Ex-GRADE Items**

1 Are risk and affordability considered when given the recommendation for the intervention?

Principle criteria

- Recognition of risk for the intervention is directly stated, or acknowledgement of risk can be inferred
- Recognition of possible adverse effects post-intervention is directly stated, or acknowledgement of possible adverse effects post-intervention can be inferred
- Recognition of cost for the intervention is directly stated, or approximate and/or relative cost for the intervention can be inferred
- Recognition of affordability is directly stated or can be inferred.

2. Are alternative recommendations given, if appropriate?

Principle criteria

- Alternative suggestions or recommendations were given with regards to risk during the intervention.
- Alternative suggestions or recommendations were given with regards to possible adverse effects following the intervention.
- Alternative suggestions or recommendations were given with regards to cost & affordability.
- Explicitly states that no alternative recommendations are appropriate with regards to risk during the intervention.
- Explicitly states that no alternative recommendations are appropriate with regards to possible adverse effects following the intervention.
- Explicitly states that no alternative recommendations are appropriate with regards to cost & affordability.

3. Is availability of resources for the population of interest taken into account prior to formulating the recommendation? [Is the recommendation practical for the population of interest?]

   Principle criteria

- Insurance coverage is available for the recommended intervention at hand [Some research on various insurance plans may need to be done]
- Other alternative funding aside from insurance is available for the recommended intervention at hand [Some research for alternative funding may need to be done]
- Resources in terms of equipment & supplies for the recommendation are easily accessible in clinical practice [This may require some prior knowledge of the equipment & supplies provided in the standard setting of the population of interest]

4. Is a measureable guideline provided to monitor the intended outcome(s) of the recommendation? [Was there a method provided that can measure the effectiveness of the recommendations? How did they/will they measure the outcomes or results?]

   Principle criteria

- Method of monitoring the intended outcome of the recommendation is given.
- Method of monitoring the intended outcome can produce tangible data for the researcher.
- Method of analyzing the data produced from monitoring the intended outcome is provided.

5. Are the results of the intervention statistically significant?

   Principle criteria

- Chosen methodology of the research is appropriate for the intended recommendation at hand.
- Methodology of the research (e.g. methodology of the clinical trial, methodology of the systematic review, etc.) is executed properly & accurately.

- Statistical analysis of the data shows statistical significance with $p < 0.05$.

6. Are the results clinically significant?

   Principle criteria

   For curative medicine/care, palliative medicine/care, or aesthetic/cosmetic care:

- The intervention alters the pathophysiology of the disease/issue in question
- The intervention can be realistically carried out & successfully executed in the clinical setting
- The time it takes for noticeable results to be seen post-intervention is reasonable taking into consideration the total cost of the intervention (Cost = monetary expenses & risk, both during the intervention & post-intervention)

7. Is the patient likely to comply with the suggested recommendation?

   Principle criteria

- Minimal level of invasiveness to the patient
- Minimal level of side effects after the given intervention
- Benefits of the recommendation outweigh its total cost (Cost = monetary expenses & risk, both during the intervention & post-intervention)

5.4. Acceptable Sampling Analysis

The Friedman test statistics for homogeneity of non-parametric analysis of factorial designs was done (Kung et al. 2010). Where, a significant result indicates heterogeneous scores, therefore a cut off of the low quality studies required to get more homogenous scores that represents a higher score among all evaluation domains as well as higher quality. MDAS (Medical Data Analysis System) program used for that. However, the bibliome was concerned with a body of

literature that has a considerable heterogeneity in term of quality of the evidence. Only two papers were left after the analysis, which precluded further work toward establishing the quantitative (i.e., by meta-analysis) and qualitative consensus of the best evidence. Therefore, an alternative approach for acceptable sampling was conducted. Whereby the top 20% highest scoring papers in the Bibliome were accepted by convention (Barkhordarian et al. 2013).

5.5. Overarching Statistical Significance:

Meta-analysis was done on the two highest quality and homogenous clinical trials, based on the type of outcome mean and standard deviation obtained at baseline and different timeline evaluations. As meta-analysis could be conducted through the fixed or random model based on the presence of a certain extent of heterogeneity. Whereby, the fixed model assumes that the size of the treatment effect is fixed among all studies and all studies come from a common population. That is, if the sample size in each study were infinite, then the effect size in all studies would be identical and the variation gotten between studies resulted as a part of chance. While, the random model assumes that the treatment effect is varying between studies and samples are from populations with different effect sizes. Moreover, the actual effect in the studies might differ as the patient characteristics varied from one study to the next, or because the treatment itself varied as well as the outcome measure differed among the studies (Chiappelli 2014).

Based on the fact that these two studies are included randomly from a potentially large population of studies on the topic and as a part of distribution of such studies, thus the random method used, so that the result of the meta-analysis represents one of a several possible along that random distribution.

Chapter 3

Results

1. Search Results and Determination of the Relevance:

1.1 Searches for Systematic Reviews:

The initial systematic reviews search resulted in 54 studies. After duplicate and irrelevant studies exclusion, only 6 systematic reviews studies retained as relevant to the PICOTS question:

1. Potassium containing toothpastes for dentine hypersensitivity. (Poulsen et al. 2006)
2. The effect of calcium sodium phosphosilicate on dentin hypersensitivity: a systematic review and meta-analysis. (Zhu et al. 2015)
3. Management of dentine hypersensitivity: efficacy of professionally and self-administered agents. (West et al. 2014)
4. The efficacy of strontium and potassium toothpastes in treating dentine hypersensitivity: a systematic review. (Karim and Gillam 2013)
5. In-office treatment for dentin hypersensitivity: a systematic review and network meta-analysis. (Lin et al. 2012)
6. Dentin hypersensitivity and oxalates: a systematic review. (Cunha-Cruz 2010)

Figure (2) shows the summary of systematic review studies selection process.

1.2. Search for Randomized Clinical Trials:

The initial search for randomized clinical trials, using PubMed, Cochrane central and ADA website search engines, resulted in 1272 studies. After duplicate removal, we got 611 studies. Then, 31 studies retained, as a relevant to the PICOTS question and after applying the inclusion/exclusion criteria:

1. A clinical study of the effect of calcium sodium phosphosilicate on dentin hypersensitivity (Acharya et al. 2013).
2. A clinical study comparing oral formulations containing 7.5 % calcium sodium phosphosilicate (NovaMin), 5% potassium nitrate and 0.4 % stannous fluoride for management of dentin hypersensitivity (Sharma et al 2010).
3. Biomimetic mineralization: long-term observations in patients with dentin sensitivity (Guentsch et al. 2012).
4. Treatments for hypersensitive non-carious cervical lesions: a practitioners engaged in applied research and learning (PEARL) network randomized clinical effectiveness study (Veitz-Keenan et al. 2013).
5. Clinical evaluation of a resin-modified glass-ionomer liner for cervical dentin hypersensitivity treatment (Tantbirojn et al. 2006).
6. Assessing the efficacy of three dentifrices in the treatment of dentinal hypersensitivity (Silverman et al. 1996).
7. Treating cervical dentin hypersensitivity with fluoride varnish a randomized clinical study (Ritter et al. 2006).

8. Efficacy of a dentifrice containing potassium nitrate, soluble pyrophosphate, PVM/MA copolymer, and sodium fluoride on dentinal hypersensitivity: a twelve - week clinical study (Schiff et al. 1994).
9. Randomized, placebo-controlled study of the efficacy of a calcium phosphate containing paste on dentin hypersensitivity (Mehta et al. 2015).
10. Clinical effectiveness of two agents on the treatment of tooth cervical hypersensitivity (Kakaboura et al. 2005).
11. Hydroxyapatite as an in-office agent for tooth hypersensitivity: a clinical and scanning electron microscopic study (Shetty et al. 2010).
12. Evaluation of three different agents for in-office treatment of dentinal hypersensitivity: a controlled clinical study (Patil et al. 2015).
13. Comparison of efficacy of three commercially available dentifrices on dentinal hypersensitivity: a randomized clinical trial (Pradeep et al. 2012).
14. A randomized clinical trial of the desensitizing efficacy of three dentifrices (Schiff et al. 2000).
15. Efficacy of a dentifrice containing 5% potassium nitrate and 1500 PPM sodium monofluorophosphate in a precipitated calcium carbonate base on dentinal hypersensitivity (Schiff et al. 1998).
16. Instant dentin hypersensitivity relief of a single topical application of an in-office desensitizing paste containing 8% arginine and calcium carbonate: A split-mouth, randomized-controlled study (Kapferer et al. 2012).
17. A double blind controlled trial comparing three treatment modalities for dentin hypersensitivity (Brahmbhatt et al. 2012).

18. Comparison of two desensitizing agents for the treatment of cervical dentine sensitivity (Gillam et al. 1997).
19. The long-term effectiveness of five current desensitizing products on cervical dentine sensitivity (Duran and Sengun. 2004).
20. Effects of two topical desensitizing agents and placebo on dentin hypersensitivity (Vora et al. 2012).
21. Comparison of two different forms of varnish in the treatment of dentine hypersensitivity: a subject- blind randomized clinical study (Sethna et al. 2011).
22. Efficacy of two different CHX-containing desensitizers: a controlled double-blind study (Drebenstedt et al. 2012).
23. Clinical evaluation of Prime & Bond 2.1 for treating cervical dentin hypersensitivity (Swift et al. 2001).
24. Clinical efficacy of two dentin desensitizing agents (Morris et al. 1999).
25. Efficacy of calcium sodium phosphosilicate in managing dentinal hypersensitivity (Surve et al. 2012).
26. Randomized controlled clinical trial on the efficacy of dentin desensitizing agents (Mehta et al. 2014).
27. Clinical evaluation of desensitizing treatments for cervical dentin hypersensitivity (Aranha et al. 2009).
28. Clinical evaluation of a potassium nitrate dentifrice for the treatment of dentinal hypersensitivity (Nagata et al. 1994).

29. Comparison between effectiveness of a low-viscosity glass ionomer and a resin-based glutaraldehyde containing primer in treating dentine hypersensitivity—a 25.2-month evaluation (Polderman and Frencken 2007).
30. Dentin desensitizing effects of Gluma Alternate, Health-Dent Desensitizer and Scotch bond Multi-Purpose (Dondi dall'Orologio et al. 1999).
31. Desensitizing effects of Gluma and Gluma 2000 on hypersensitive dentin (Dondi dall'Orologio et al. 1993).

Figure (3) shows the summary of Randomized Clinical Trial studies selection process.

2. Measurements and Quality Assessment:

2.1. Quality of Systematic Reviews:

The revised Assessment of Multiple Systematic Reviews (R-AMSTAR) and the EX-GRADE instruments utilized to assess the quality and clinical relevance of six systematic reviews. Mean score from both readers were entered across the eleven domains of (R-AMSTAR) tool and the eight domains of (EX-GRADE) tool, each column corresponding to a certain question of the instruments. The marginal totals, means and standard deviations (horizontal marginal value) were used to assess the consistencies and to recognize the evidence strength across all domains for each paper. As a high mean of scores and low standard deviation signified higher quality evidence. While the vertical marginal totals, means and standard deviations would represents the relative strength of each domain across the bibliome where the high mean and low standard deviation indicated strength in that domain within the bibliome. Table (1) shows the scores of each systematic review, which fell within the confidence interval set by the sample (mean± standard deviation: 53.67 ± 9.61, CI95: 49.35 - 57.99) except for the (Zhu et al. 2015) study that

scored 67 as the highest score and the (Karim & Gillam 2013**)** study that scored 37 as the lowest score. R-AMSTAR domain represented by question 10 (publication bias assessment) have low mean value (1.83 ± 1.17) indicated a relatively weak domain among the bibliome. While, the EX-GRADE domains represented by question 2 (consideration of risk and affordability) with mean value (1.67 ± 0.82) and question 3 (recommendation of alternative) with mean value (1.83 ± 0.98) indicated relatively weak domains of clinical recommendations.

2.2. Quality of Clinical Trials:

The quantified Risk of Bias and the EX-GRADE instruments utilized to evaluate the quality and clinical relevance of 31 clinical trials. Mean score from both readers were inserted across the four domains of (Risk of Bias) tool and the seven domains of (EX-GRADE) tool, each column corresponding to a certain question of the instruments. The marginal totals, means and standard deviations (horizontal marginal value) were investigated to evaluate the consistencies and to identify the evidence strength across all domains for each paper. The higher mean of scores and lower standard deviation implied higher quality evidence. While the vertical marginal totals, means and standard deviations would represents the relative strength of each domain across the bibliome where the higher mean and lower standard deviation indicated strength in that domain within the bibliome. Table (2) shows the scores of each clinical trial, which mainly fell within the confidence interval set by the sample (mean± standard deviation: 28.09 ± 3.05, CI95: 26.29 to 29.9). However, It appears that seven studies scored above the confidence interval and six studies scored below the confidence interval. The consistency domain of the risk of bias instrument appears to have low mean value (1.98 ± 0.6) indicated a relatively weak domain among the bibliome. While, the EX-GRADE domains represented by question 2 (consideration

of risk and affordability) with mean value (1.58 ± 0.85) and question 3 (recommendation of alternative) with mean value (1.09 ± 0.30) indicated relatively weak domains of clinical recommendations.

3. Data Analysis:

3.1. Acceptable Sampling (Quality of the Systematic Review):

A non-significant result of the Friedman test indicated homogeneous scores. Therefore, cut off of the low quality studies yielded only three out of six systematic reviews that considered as high quality studies:

(*Figure 4: Shows The Friedman test statistics for homogeneity for Systematic Review)*

1. Potassium containing toothpastes for dentine hypersensitivity. (Poulsen et al. 2006).
2. The effect of calcium sodium phosphosilicate on dentin hypersensitivity: a systematic review and meta-analysis. (Zhu et al. 2015).
3. Management of dentine hypersensitivity: efficacy of professionally and self-administered agents. (West et al. 2014).

3.2. Acceptable Sampling (Quality of the Clinical trials):

A non-significant result of the Friedman test indicated homogeneous scores. Thus, a cut off of the low quality studies yielded only two out of thirty-one clinical trials that considered as high quality studies:

(*Figure (5): Shows The Friedman test statistics for homogeneity for Clinical Trials)*.

1. A clinical study of the effect of calcium sodium phosphosilicate on dentin hypersensitivity (Acharya et al. 2013).

2. A clinical study comparing oral formulations containing 7.5 % calcium sodium phosphosilicate (NovaMin), 5% potassium nitrate and 0.4 % stannous fluoride for management of dentin hypersensitivity (Sharma et al 2010).

However, the bibliome was concerned with a body of literature that has a considerable heterogeneity in terms of quality of the evidence, which prevented further work toward establishing the quantitative and qualitative consensus of the best evidence. Therefore, an alternative approach for acceptable sampling was conducted. Whereby, a convention made to accept the top 20% highest scoring papers in the bibliome. So, out of thirty-one studies, a total of seven studies were accepted:

1. A clinical study of the effect of calcium sodium phosphosilicate on dentin hypersensitivity (Acharya et al. 2013).
2. A clinical study comparing oral formulations containing 7.5 % calcium sodium phosphosilicate (NovaMin), 5% potassium nitrate and 0.4 % stannous fluoride for management of dentin hypersensitivity (Sharma et al 2010).
3. Biomimetic mineralization: Long-term observations in patients with dentin sensitivity (Guentsch et al. 2012).
4. Treatments for hypersensitive non-carious cervical lesions: a practitioners engaged in applied research and learning (PEARL) network randomized clinical effectiveness study (Veitz-Keenan et al. 2013).
5. Clinical evaluation of a resin-modified glass-ionomer liner for cervical dentin hypersensitivity treatment (Tantbirojn et al. 2006).
6. Assessing the efficacy of three dentifrices in the treatment of dentinal hypersensitivity (Silverman et al. 1996).

7. Treating cervical dentin hypersensitivity with fluoride varnish a randomized clinical study (Ritter et al. 2006).

4. Data Extraction:

Data extraction was done to obtain the study name (Author and publication year), study design, sample Size (Patient/Teeth)(Age/ Sex), intervention, comparator, assessment time points, method of assessment, method of pain assessment, DH baseline and oral hygiene and dietary counseling during the clinical trial.

Table (3) shows the extracted data

5. Overarching Statistical Significance:

Based on the limited number of acceptable studies in terms of quality and the variation of interventions, including the mode of application and mechanism of action, the hydrodynamic stimuli applied, pain assessment methods used and the timeline evaluation all have contributed to the heterogeneity, which preclude their include in a single meta-analysis. Though, Meta-analysis was done on the two highest quality and homogenous clinical trials that tested the 5% potassium nitrate toothpaste compared to calcium sodium phosphsilicate toothpaste as at home interventions. Both studies reported the VAS scores to the air blast stimuli. The forest plot is presented in figure (6); a random model meta-analysis was used. “A” represents the 5% potassium nitrate group and “ B ” represents the calcium sodium phosphsilicate group. There is a significant effect in favor of B across both studies and time points. The 4 weeks time point evaluation is significantly the best indicated by both studies as shown by the forest plot in figure (7).

Chapter 4

Discussion

The overall total scores of graded evidence reveal the extent of adherence to the commonly accepted criteria of quality of research synthesis. The analysis of the marginal mean and standard deviations (horizontal marginal values) reflects the relative strength or weakness of the bibliome among all domains. The result indicates that certain domains strong and acceptable in terms of quality and clinical relevance. Whereas, other domains are weak that might threaten the clinical recommendations determined by the investigated bibliome.

1. Consensus of The Best Available Evidence:

1.1 Interpretations and Qualitative Consensus of Systematic Review:

1.1.1. Potassium containing toothpastes for dentine hypersensitivity (Poulsen et al. 2006):

This systematic review designed to evaluate the effectiveness of potassium-containing toothpaste in reducing DH. Studies that were included in the review were randomized control trials (RCTs) comparing potassium to non-potassium containing toothpaste that assessed at baseline and 6-8 weeks after the treatment. Four methods were used to assess DH: tactile, thermal, air-blast, and patient's subjective assessment of pain. The following databases were searched: Cochrane Oral Health Group Trials Register (searched until August 2005); CENTRAL (until August 2005); EMBASE/MEDLINE, PubMed, Web of Science (until September 2005). Six studies only satisfied the inclusion criteria for this review, which showed the statistically significant effect of potassium nitrate toothpaste on air blast and tactile sensitivity at the 6 to 8 weeks follow up.

However, the subjective assessment failed to show a significant effect at the 6 to 8 week assessment.

1.1.2. The effect of calcium sodium phosphosilicate on dentin hypersensitivity: a systematic review and meta-analysis (Zhu et al. 2015):

Generally, This systematic review conducted to assess the effect of using Calcium Sodium Phosphosilicate (CSPS) to treat DH compared with that of a negative (placebo) control. Five databases used for search of randomized controlled trials (RCTs) until January14, 2015: Medline (via PubMed), EMBASE, Web of Science, CENTRAL (The Cochrane Library) and the Chinese Biomedical Literature Database. DH pain was assessed by tactile, evaporative, or thermal stimuli, and reported self-assessed sensitivity. Different scales were used to quantify DH; 10-cm visual analog scale (VAS) was the most commonly used for measurements. Two of the studies included showed an advantage of a professionally applied prophylaxis paste containing 15% CSPS compared with a negative control in the management of DH immediately after prophylaxis and at 4 weeks, as determined using evaporative or tactile stimuli. The observation of adverse reactions absence during the study period mentioned in these studies, although other studies reported minor adverse response such as; soft tissue irritation gastrointestinal disorders, infections, injury, poisoning and procedural complications, and nervous system disorders. Additionally, the included studies were industry-sponsored, which may impact the outcome of studies.

1.1.3. Management of dentine hypersensitivity: efficacy of professionally and self-administered agents (West et al. 2015):

This systematic review included various treatment modalities for dentine hypersensitivity. Randomized controlled trials retained were diverse in design, study period, negative and positive controls and comparator products investigated. DH assessed with multiple stimuli: air-blast and tactile or thermal stimuli. Three databases (PubMed, Medline and Cochrane clinical trials database) and hand searches were used from 14–21 July 2014 to identify randomized controlled trials. Assessing and driving decisive statements about the treatment effectiveness were difficult due to various reasons. For instance, different active ingredients were evaluated, the presence of additional ingredients that might have an impact on the management of dentine hypersensitivity.

This review revealed limited evidence about the effectiveness of potassium salts for dentine hypersensitivity management. As the low quality of evidence doesn't support potassium being as effective as other positive control agents, or more effective than negative controls. In regard to the In-office desensitizing agents, the outcomes of the review suggest that professionally applied arginine, Calcium sodium phosphosilicate (CSPS), oxalates and resins are effective for the treatment of dentine hypersensitivity; although, available evidence weren't adequate to support these agents compared to other professionally applied agents. Generally, In-office desensitizing agents seem to be an effective approach for the treatment of dentine hypersensitivity; however, there is unsatisfactory evidence to recommend one agent compared to another.

1.2 Interpretations and Qualitative Consensus of Clinical Trials:

1.2.1. A clinical study of the effect of calcium sodium phosphosilicate on dentin hypersensitivity (Acharya, 2013):

This clinical trial conducted to assess the efficacy and safety of a desensitizing agent containing calcium sodium phosphosilicate toothpaste compared to 5% potassium nitrate containing

toothpaste. Air evaporative stimulus and visual analog scale (VAS) used to assess and measure sensitivity level. Hypersensitivity reduction observed in all treatment groups from baseline to 2, 4 and 8 weeks that increased with time of treatment. The potassium nitrate group showed a reduction in sensitivity but reduction compared with the calcium sodium phosphosilicate group was less at 2 weeks. However, it was found to be as effective as calcium sodium phosphosilicate at 8 weeks. Since calcium sodium phosphosilicate showed a greater reduction in sensitivity compared to potassium nitrate at an earlier stage, which could be explained by the fact that calcium sodium phosphosilicate act faster than potassium nitrate. Clinically, it is very important to have faster relief of dentinal hypersensitivity.

1.2.2 A clinical study comparing oral formulations containing 7.5 % calcium sodium phosphosilicate (NovaMin), 5% potassium nitrate and 0.4 % stannous fluoride for management of dentin hypersensitivity (Sharma el al 2010):

The clinical trial aimed to compare the clinical effectiveness of 7.5% calcium phosphosilicate (NovaMin), 5% potassium nitrate and 0.4% stannous fluoride for DH management. Sensitivity to cold water and air blast stimuli measured with visual analog scale (VAS) at baseline, two, four, and 12 weeks. The study concluded that potassium and stannous fluoride desensitizing agent show similar efficacy. However, compared to calcium phosphosilicate, the sensitivity reduction significantly inferior in the first two weeks and almost the same at 12-week assessment. Which explained by the fact that calcium phosphosilicate has rapid effectiveness and not sustainable compared to 5% potassium nitrate.

1.2.3. Biomimetic mineralization: long-term observations in patients with dentin sensitivity (Guentsch 2012):

This clinical trial conducted to assess the effectiveness of a biomimetic mineralization system (BIMIN) compared to Gluma Desensitizer as in-office DH treatment approach. Air blast stimuli and Visual-Analog-Scale (VAS) used to assess the sensitivity level at baseline (pre-treatment), 2 days, 4, 8 and 12 weeks, and 12 months post-treatment. The study concluded that both treatments approach resulted in statistically significant reductions in sensitivity and VAS scores through all time assessment and differences between the two approaches were statistically not significant.

1.2.4. Treatments for hypersensitive non-carious cervical lesions: a practitioners engaged in applied research and learning (PEARL) network randomized clinical effectiveness study (Veitz-Keenan et al. 2013)*:*

This clinical study designed to determine the effectiveness of three approaches for DH management: 5% potassium nitrate toothpaste as at-home approach for hypersensitivity treatment, the application of a resin-based composite restoration and sealant. Air blast stimulation and Numeric Pain Assessment Scale (NPAS) used to evaluate the sensitivity level at baseline and at one, three and six months. The study outcome showed that throughout the evolution period, both the sealant and the resin-based composite restoration treatment approaches demonstrated a comparable effectiveness in reducing hypersensitivity. Although, the complicated procedure of application of the restoration compared with the sealant might be considered in terms of time and cost in treating dentin hypersensitivity. 5% potassium nitrate toothpaste was not as effective, nevertheless, the reduction in the hypersensitivity increase with each recall that suggests the slow effectiveness of 5% potassium nitrate.

1.2.5. Clinical evaluation of a resin-modified glass-ionomer liner for cervical dentin hypersensitivity treatment (Tantbirojn et al. 2006):

The aim of this clinical trial is to evaluate the effectiveness of resin-based Gluma desensitizer and glass ionomer liner material in treating dentin hypersensitivity. Tactile stimulus and cold test used then pain level measured with visual analog scale (VAS). Sensitivity assessment was done at baseline, after treatment at 1 week, 1, 3, 6, and 12 months. The study results showed a sensitivity reduction for both treatment options up to one year; however, with glass ionomer liner was significantly superior in sensitivity reduction than Gluma. With glass ionomer liner treatment option there is a tendency to perform an overhang at the gingival margins, which contribute to the development of gingivitis. Also, the development of local burning sensation in the buccal mucosa with Gluma application reported in this clinical trial.

1.2.6. Assessing the efficacy of three dentifrices in the treatment of dentinal hypersensitivity (Silverman et al. 1996)*:*

This clinical trial aimed to evaluate the desensitizing effectiveness and safety of the 5% potassium nitrate and 0.243 % sodium fluoride formulation, 5% potassium nitrate formulation and 10 % strontium chloride compared to placebo as control and to each other. Cold-air and tactile stimuli followed by visual analog scale (VAS) sensitivity assessment used throughout baseline, two-week, four-week and eight-week study period. Additionally, an oral soft tissue examination conducted to assess the safety of the agents. Generally, the study results showed that, at eight-weeks assessment, both 5 % potassium nitrate toothpastes were significantly greater than 10% strontium chloride in DH management. In terms of safety, 5 % potassium nitrate based toothpaste provides a safe treatment approach.

1.2.7. Treating cervical dentin hypersensitivity with fluoride varnish - a randomized clinical study (Ritter et al. 2006):

This clinical trial purpose was to evaluate the immediate and 24-week efficacy of two fluoride varnishes with similar active ingredients in reducing dentin hypersensitivity. Compressed air and cold stimuli used then followed by visual analog scale (VAS) assessment. Dentinal hypersensitivity evaluated at five-time points: enrollment (six-weeks before treatment), end of the run-in period (baseline), two weeks after treatment, eight weeks after treatment and 24 weeks after treatment. The study concluded that DH reduced after single application of both types to fluoride varnishes at 24 weeks assessment with no significant differences between the desensitizing efficacy of this varnish and that of the control varnish. Moreover, the study provided evidence regarding the safety of these agents with the absence of any subjective or objective soft-tissue irritation.

2. Quantitative Consensus of Systematic Review:

The limited number of studies included in the meta-analysis prevented the founding of high power meta-analysis. Yet, we can infer that 5% potassium nitrate toothpaste has inferior effectiveness in DH management as at home intervention. 5% potassium nitrate toothpaste compared to calcium sodium phosphsilicate toothpaste as at home intervention had a very slow effectiveness. Calcium sodium phosphsilicate toothpaste at 4 weeks time point evaluation is significantly the best indicated by both studies, however, that effectiveness is not sustained beyond 4 weeks to be comparable to 5% potassium nitrate effectiveness after that.

Chapter 5

Conclusion

In conclusion, based on the qualitative analysis of this review, the 5% potassium nitrate toothpaste has inferior effectiveness in DH management as at home intervention, however, the reduction in the hypersensitivity increase with each recall that suggests the slow effectiveness that could be explained by the requisite of maintaining a high level of potassium nitrate to reach the maximum effectiveness. 5% potassium was not effective compared to in-office desensitizing intervention. Although it is difficult to prove or reach a conclusive evidence of the best treatment option, treatment approaches with resin-based composite restoration and glass ionomer liner resulted in statistically significant reduction in sensitivity. Yet, the complicated procedure of application of these restorations might be considered in terms of time and cost in treating dentin hypersensitivity. Furthermore, it considered as technique sensitive owing to the tendency to perform an overhang at the gingival margins, which contribute to the development of gingivitis or jeopardize the biological width of the periodontal tissues. Gluma and fluoride varnishes were effective in reducing DH for up to 6 months with no reported adverse effects aside to the time and cost consideration.

This review shed the light on current deficiencies and weakness in the clinical trials that conducted to evaluate DH intervention. Essentially, these necessitate the creation of efficient and comprehensive standards and guidelines for these clinical trials in order to overcome existing weakness in the field. Furthermore, considering the field weakness in the future studies will help to achieve a decisive evidence to support the best DH treatment options and increase the extent of reliability.

1. Limitation:

1.1. Study Limitation:

First of all, selection bias may have arisen, as a result of language restriction to only English publications. Also, the variation of interventions, including the mode of application and mechanism of action, the hydrodynamic stimuli applied, pain assessment methods used and the timeline evaluation all add to the deficiencies in the design and methodology of the clinical trials, which have contributed to the heterogeneity as well as in a low power for meta-analyses. Additionally, the stringent method for acceptable sampling using the Friedman test for non-parametric analysis of factorial designs contribute to the limited number of acceptable studies in terms of quality across all evaluation domains, which also prevented the founding of high power meta-analysis.

Furthermore, the quality of evidence could vary based on the instruments used for its measurement and grading. The degree of domains convergence across the measurement instruments might differ and the amount of agreement between measurement approaches for quality rating diverge. There is less or more emphasis on different criteria and inconsistency in terms of domains used to assess the evidence quality. Therefore, the use of limited measurement instruments could contribute to the presence of bias in assessing quality.

1.2. Field Limitation:

Regardless the numerous DH intervention options that are available and the conducted clinical trials to demonstrate their efficacy, it is still difficult to prove or reach a conclusive evidence of the best treatment option. This could be as a result of the subjective nature and complexity of pain. As patients' response to different stimuli might be influenced by different factors such as individualized pain perception, psychological and emotional factors. Furthermore, the influence

of placebo effect and Hawthorne effect might be involved in the complexity of DH pain measurement. Although double-blind placebo-controlled studies could help in overcoming the influence of placebo effect and Hawthorne effect, it remains a challenge in the actual clinical setting. Moreover, the clinical trials designed to evaluate DH treatment options highly contributed to the inconclusive outcome. As the diversity of stimuli methods used to provoke pain to be measured, acquire a lot of deficiencies that impacts their reproducibility and complicate pain monitoring among the trials. Additionally, lacking standardized oral hygiene instructions, including toothpaste used and brushing technique during the trials aside to the indefinite dietary regimen. All could contribute to the oral environment alteration that involved with the demineralization - remineralization cycle and biased the outcome.

Pulp and dentin tissue are vital tissues that normally react to physiological stimuli. As in some patients with dentin hypersensitivity, a self-defense mechanism by secondary dentin lay down might occur with time, in order to reduce the fluid flow within the dentinal tubules as well as sensitivity feeling. Consequently, that might contribute to the false-positive outcome during the clinical trials. Therefore, clinical trials designed to assess DH treatment must be conducted within a time frame that not exceed the dentin-pulp physiological response, which need to be determined.

Furthermore, the concern of industry-sponsored clinical trial in this field will preclude any decisive clinical recommendation regarding the treatment option and increase the risk of publication bias.

The comprehensive assessment of the clinical findings should not be one-sided and based only on the subjective-based interpretation of the patient's pain response. However, additional objective assessment methods are needed such as the hormone level assay. Several salivary

biomarkers have been identified to be associated with pain and stress including salivary amylase, cortisol, substance P, lysozyme and secretory IgA (Malamud and Rodriguez-Chavez. 2011). Furthermore, the correlation between pain responses in dental pulp and neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, neurokinin A and neurokinin P have been investigated (Malamud and Rodriguez-Chavez. 2011). A significant correlation between visual analog scale (VAS) and salivary alpha amylase was found, which suggest that this biomarker may be a suitable indicator for the objective assessment of pain intensity (Shirasaki et al. 2007). Utilizing salivary biomarker to assess hormones associated with pain has the advantage of avoiding pain and stress might cause by other invasive methods.

2. Clinical Recommendations:

It is essential to diagnose DH and identify the predisposing factors in order to effectively manage DH and improve patients' quality of life by developing a management approaches that integrate preventative and treatment aspects. Beginning with the proper oral hygiene practices including timing of tooth brushing as brushing following an acid challenge may lead to further loss of hard tissue. Additionally, it is important to provide an appropriate dietary advice based on the analysis of dietary habits. This will help providing a personalized DH treatment and prevention. As this review concluded that 5% potassium nitrate toothpaste has inferior effectiveness in DH management as at home intervention, while the reduction in the hypersensitivity increase with each recall that suggests the slow effectiveness that could be explained by the requisite of maintaining a high level of potassium nitrate to reach the maximum effectiveness, which might be impossible in the oral environment.

Though it is challenging to verify or reach a conclusive evidence of the best treatment option,

treatment approaches with resin-based composite restoration and glass ionomer liner resulted in statistically significant reduction in sensitivity. Nevertheless, time and cost consideration arise due to the complicated procedure of application of these restorations. In addition, Gluma and fluoride varnishes were effective in reducing DH for up to 6 months with no reported adverse effects beside to the time and cost consideration.

The challenges to achieve a decisive evidence to support the best DH treatment options highlight the extent of heterogeneity and quality inferiority of clinical trials in the field, which impact the degree of their reliability. These require the future conduction of well-constructed clinical trials that directed to overcome current deficiencies and weaknesses in the field.

Tables

Table (1): Systematic Reviews Grading Scores (R-AMSTAR and EX-GRADE Instruments)

	EX-GRADE											R-AMSTAR										
Systematic Review	**Q 1**	**Q 2**	**Q 3**	**Q 4**	**Q 5**	**Q 6**	**Q 7**	**Q 8**	**Q 9**	**Q 10**	**Q 11**	**Q 1**	**Q 2**	**Q 3**	**Q 4**	**Q 5**	**Q 6**	**Q 7**	**Q 8**	**Total**	**Mean**	**SD**
Zhu et al. 2015	**4**	**4**	**3**	3	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**3**	**3**	**2**	**3**	**4**	**3**	**3**	67	3.56	0.61
Poulsen et al. 2006	**4**	**3**	**4**	**4**	**4**	**3**	**4**	**4**	**3**	**2**	**1**	**3**	**1**	**1**	**2**	**4**	**2**	**3**	**3**	55	2.89	1.10
West et al. 2014	**3**	**4**	**4**	**2**	**3**	**4**	**4**	**4**	**1**	**2**	**4**	**3**	**1**	**1**	**2**	**4**	**3**	**3**	**3**	55	2.89	1.10
Cunha-Cruz 2010	**4**	**4**	**4**	**4**	**4**	**4**	**3**	**3**	**2**	**1**	**1**	**2**	**2**	**3**	**2**	**4**	**2**	**3**	**3**	55	2.89	1.04
Lin et al. 2013	**3**	**4**	**4**	**2**	**4**	**4**	**3**	**2**	**3**	**1**	**3**	**2**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	53	2.79	0.85
Karim & Gillam 2013	**3**	**4**	**3**	**2**	**4**	**4**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**1**	**1**	**3**	37	1.95	1.18
Mean	3.5	3.83	3.67	2.83	3.83	3.83	3.16	3	2.33	1.83	2.33	2.5	1.67	1.83	2	3.33	2.5	2.67	3	53.66		
SD	0.55	0.41	0.52	0.99	0.41	0.41	1.17	1.26	1.21	1.17	1.51	1.05	0.82	0.98	0	0.82	1.05	0.82	0	9.61		

Table (2): Clinical Trials Grading Scores (Risk of Bias and EX-GRADE Instruments)

Clinical Trials	Risk of Bias				EX-GRADE							Total	Mean	SD
	Risk of Bias	Consistency	Directness	Precision	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8			
Acharya et al. 2013	3	3	3	3	3	1	2	4	4	4	4	34	3.09	0.94
Sharma et al 2010	4	3	2	3	3	1	2	4	4	4	4	34	3.09	1.04
Guentsch et al. 2012	4	2	3	3	1	1	2	4	4	4	4	32	2.90	1.22
Veitz-Keenan et al. 2013	4	3	3	3	2	1	2	4	3.5	3	3	31.5	2.86	0.89
Tantbirojn et al. 2006	3	2	3	3	3	1	2	4	4	3	3	31	2.82	0.87
Siverman et al. 1996	3	2	2	3	3	1	2	4	3	4	3	30	2.73	0.90
Ritter et al. 2006	3	3	3	3	1	1	2	4	4	3	3	30	2.73	1.01
Schiff et al. 1994	2.5	2	2	2	3	1	2	4	3	4	4	29.5	2.68	1.01
Mehta et al. 2015	3	2	2	2	3	1	1	4	4	4	3	29	2.64	1.12
Kakaboura et al. 2005	3	2.5	2.5	3	1	1	2	4	4	3	3	29	2.64	1.00
Shetty et al. 2010	3	2	2	3	1	1	2	4	4	3	4	29	2.64	1.12
Patil et al. 2015	3	2	3	3	1	1	2	4	4	3	3	29	2.64	1.03
Pradeep et al. 2012	3	3	2	2	2	1	2	4	4	3	3	29	2.64	0.92

Table (2): Clinical Trials Grading Scores (Risk of Bias and EX-GRADE Instruments) *(Continue)*

Clinical Trials	Risk of Bias				EX-GRADE							Total	Mean	SD
	Risk of Bias	Consistency	Directness	Precision	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8			
Schiff et al. 2000	3	2	2	2	2	1	2	4	3.5	3	4	28.5	2.59	0.97
Schiff et al. 1998	2	2	2.5	2	1	2	2	4	3	4	4	28.5	2.59	1.02
Kapferer et al. 2013	2	2	3	3	1	1	2	4	4	3	3	28	2.54	1.04
Brahmbhatt et al. 2012	3	1	3	2	1	1	2	4	4	3	4	28	2.54	1.21
Gillam et al. 1997	2	2	2	3	1	1	2	4	4	3	4	28	2.54	1.13
Duran & Sengun. 2004	3	2	2	3	1	1	2	4	4	3	3	28	2.55	1.03
Vora et al. 2012	3	2	2	3	1	1	2	4	4	3	3	28	2.55	1.04
Sethna et al. 2011	3	2	2	2	1	2	2	4	3	4	3	28	2.55	0.93
Drebenstedt et al. 2012	3	2	2	3	1	1	2	4	3	3	3	27	2.45	0.93
Swift et al. 2001	2	1	3	3	1	1	2	4	4	3	3	27	2.45	1.13
Morris et al. 1999	2	2	2	4	1	1	2	4	3	3	3	27	2.45	1.04
Surve et al. 2012	2	1	2	2	3	1	2	3	3	4	4	27	2.45	1.04
Mehta et al. 2014	3	2	2	3	1	1	1	3	4	3	3	26	2.36	1.03
Aranha et al. 2009	2	2	2	3	1	1	2	4	3	3	3	26	2.36	0.92

Table (2): Clinical Trials Grading Scores (Risk of Bias and EX-GRADE Instruments) *(Continue)*

Clinical Trials	Risk of Bias				EX-GRADE							Total	Mean	SD
	Risk of Bias	Consistency	Directness	Precision	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8			
Nagata et al. 1994	2	2	3	2	1	1	2	3	3	2.5	3	24.5	2.23	0.75
Polderman & Frencken 2007	2	1	3	2	1	1	2	2	3	3	3	23	2.09	0.83
Dondi dall'Orologio et al. 1999	1	1	2	2	2	2	2	2	1	3	3	21	1.91	0.70
Dondi dall'Orologio et al. 1993	2	1	2	3	1	1	2	2	2	2	2.5	20.5	1.86	0.63
Mean	2.69	1.98	2.39	2.68	1.58	1.09	1.94	3.71	3.48	3.24	3.31	28.09		
SD	0.69	0.61	0.48	0.54	0.85	0.30	0.25	0.64	0.71	0.53	0.49	3.05		

Table (3): Extracted Data

Study RCT (Authors /year)	**Extracted Data**
Acharya et al. 2013	*Study design:* Randomized, double blind and parallel group clinical trial *Sample Size*: 20 Patient (18 - 65 years) *Intervention:* 5% Calcium Sodium Phosphosilicate *Comparator:* 5% Potassium Nitrate (positive control) *Assessment Time points*: Baseline, 2, 4 and 8 weeks *Method of Assessment:* Cold pack test / controlled air pressure *Method of Pain assessment:* 10 cm (VAS) *DH Baseline:* VAS > 5 cm *Oral Hygiene:* Yes *Dietary counseling:* Yes
Sharma et al. 2010	*Study design:* Single center randomized double blind parallel group design *Sample Size:* 120 Patient (20-50 years) *Intervention:* 7.5 % Calcium Sodium Phosphosilicate (NovaMin) *Comparator:* 5% Potassium Nitrate 0.4 % Stannous Fluoride *Assessment Time points:* 2, 4 and 12 weeks *Method of Assessment:* Air Blast/ cold water *Method of Pain assessment:* 10 cm (VAS) *DH Baseline:* VAS >5 cm *Oral Hygiene:* Yes *Dietary counseling:* No
Arndt et al. 2012	*Study design:* Single-blind, 2-arm trial *Sample Size:* 40 Patients (111 teeth) *Intervention:* Biomimetic mineralization system (BIMIN) *Comparator:* Gluma desensitizer *Assessment Time points:* 2 days, 4, 8, 12 weeks and 12 months *Method of Assessment:* Air stimulation / Impression *Method of Pain assessment:* 100 mm (VAS) / SEM analysis *DH Baseline:* VAS >50 mm *Oral Hygiene:* No *Dietary counseling:* No
Veitz-Keenan et al. 2013	*Study design:* Three-armed randomized clinical effectiveness study *Sample Size:* 304 patient *Intervention:* Sealant (The DBA and resin layer)/Flowable composite resin *Comparator:* 5% Potassium Nitrate and 0.2 % Sodium Fluoride *Assessment Time points:* Baseline, 1, 2 and 6 months *Method of Assessment:* Air-blast *Method of Pain assessment:* (0–10) Numeric Pain Assessment Scale Questionnaires *DH Baseline:* NPAS > 3 *Oral Hygiene:* Yes *Dietary counseling:* No

Table (3): Extracted Data *(Continue)*

Study RCT (Authors /year)	Extracted Data
Tantbirojn et al. 2006	*Study design:* Split-mouth randomized controlled clinical trial *Sample Size:* 44 Patients / 106 teeth (22-68 years) *Intervention:* (Liquid/ Paste) Resin-Modified Glass-Ionomer liner *Comparator:* Gluma *Assessment Time points:* Baseline, After Tx, 1 week, 1,3,6 and 12 months *Method of Assessment:* Tactile stimulus / cold test *Method of Pain assessment:* 10 cm (VAS) *DH Baseline:* At least 2 cm *Oral Hygiene:* No *Dietary counseling:* No
Silverman el al, 1996	*Study design:* Double-blind, parallel design clinical trial *Sample Size:* 230 patient (mean 41 years) *Intervention:* 5 % potassium nitrate: 0. 243% sodium fluoride dentifrice 5 % potassium nitrate' 10 % strontium chloride *Comparator:* Placebo *Assessment Time points: 4 and 8 weeks* *Method of Assessment:* Cold-air sensitivity /Tactile sensitivity Questionnaire examination *Method of Pain assessment:* 100 mm (VAS) / Yeaple probe *DH Baseline:* (VAS) 30 – 70 mm Probe 10 to 50 grams *Oral Hygiene:* Yes *Dietary counseling:* No
Ritter el al. 2006	*Study design:* Subject-blind randomized clinical trial *Sample Size:* 19 patient / 59 teeth *Intervention:* Fluoride varnish *Comparator:* Fluoride varnish No placebo *Assessment Time points:* (Baseline), 2, 8 and 24 weeks *Method of Assessment:* Compressed air / Cold stimulus *Method of Pain assessment:* 100 mm (VAS) *DH Baseline:* Moderate / sever. *Oral Hygiene:* Yes *Dietary counseling:* No

Figures

Figure (1): Analytic Framework

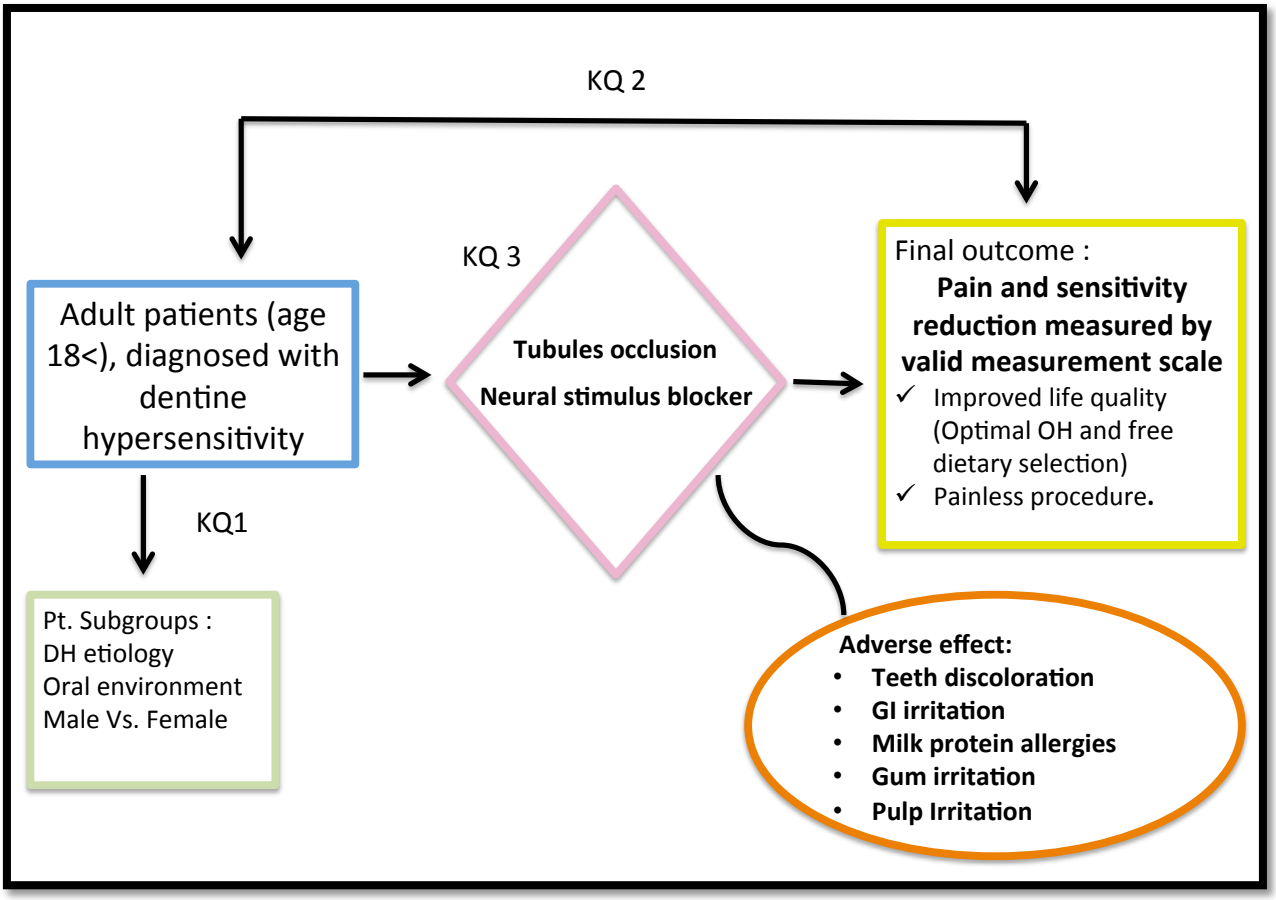


Figure (2): Summary of Systematic Review Studies Selection Process

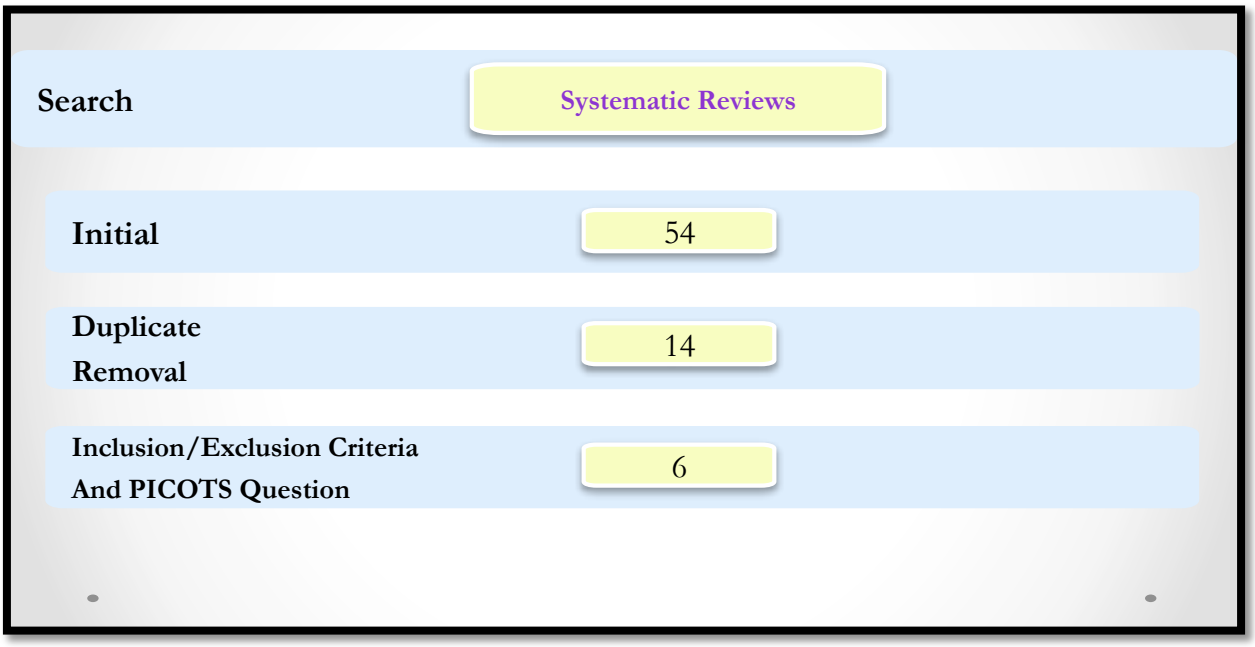


Figure (3): Summary of Randomized Clinical Trials Studies Selection Process

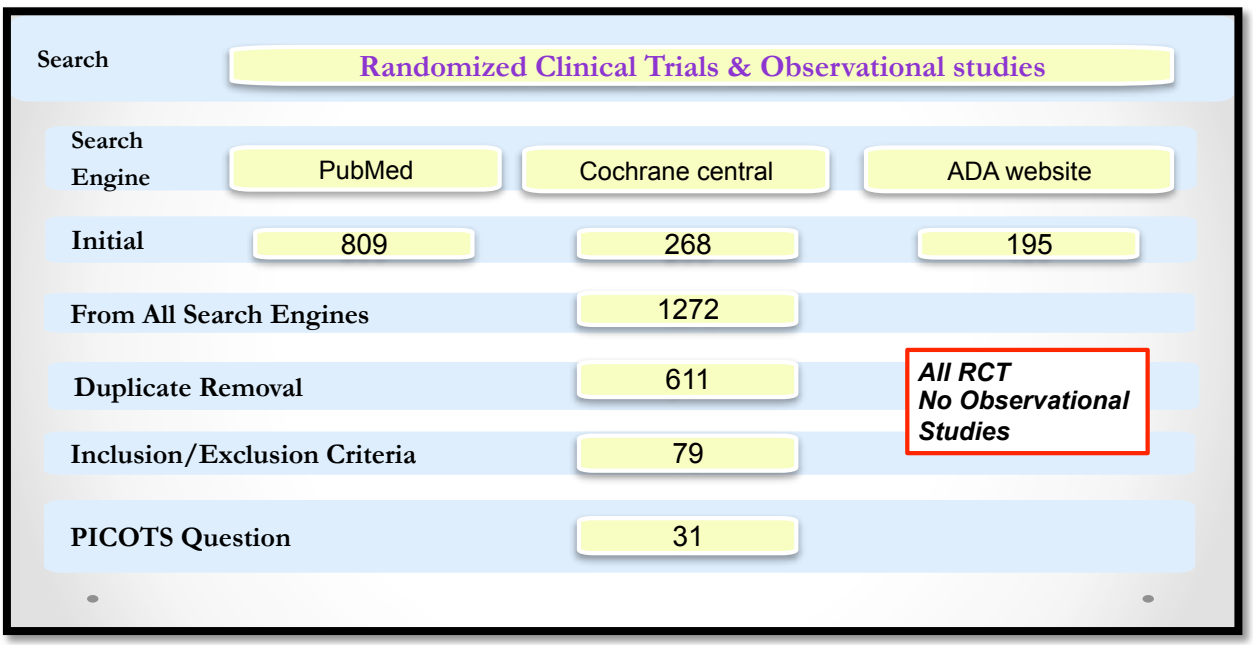


Figure (4): The Friedman Test Statistics for Homogeneity for Systematic Review.

Sample	Rank Sum	Mean Ranks	Median
1	39.5	13.1667	4
2	39.5	13.1667	4
3	37	12.3333	4
4	26	8.6667	3
5	39.5	13.1667	4
6	39.5	13.1667	4
7	46	15.3333	4
8	46	15.3333	4
9	25.5	8.5	3
10	24	8	2
11	32	10.6667	4
12	33	11	3
13	9	3	1
14	9	3	1
15	11	3.6667	2
16	37	12.3333	4
17	28.5	9.5	3
18	24	8	3
19	24	8	3
Cases: 3 Chi-Square: 24.9842 df: 18 Prob: .1254 Epsilon Squared: .0874			

Figure (5): The Friedman Test Statistics for Homogeneity for Clinical Trials

Sample	Rank Sum	Mean Ranks	Median
1	14	7	3.5
2	10	5	3
3	7.5	3.75	2.5
4	10	5	3
5	10	5	3
6	2	1	1
7	4.5	2.25	2
8	18.5	9.25	4
9	18.5	9.25	4
10	18.5	9.25	4
11	18.5	9.25	4
Cases: 2 Chi-Square: 16.4318 df: 10 Prob: .0879 Epsilon Squared: .2014			

Figure (6): Meta-Analysis and Forest Plot

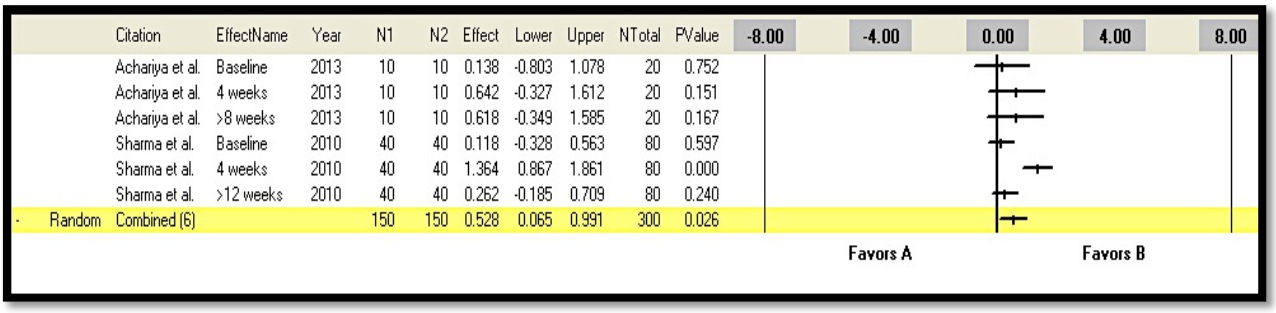
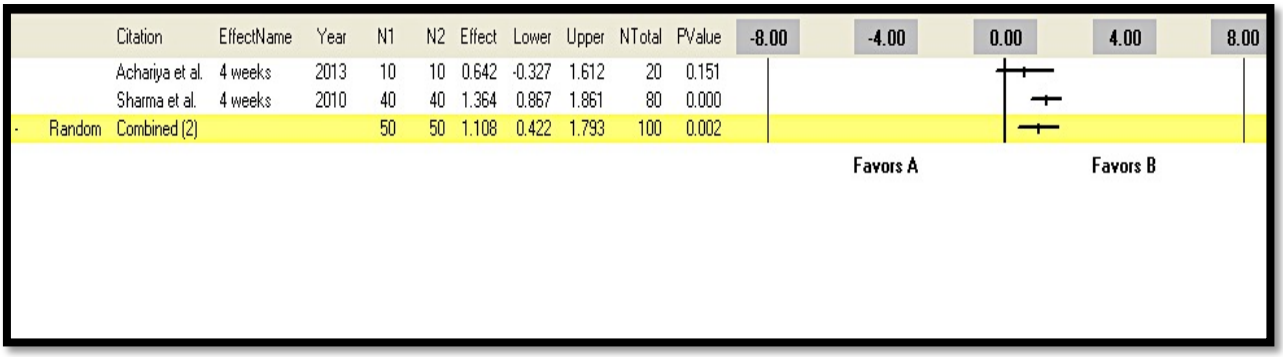


Figure (7): Meta-Analysis and Forest Plot (4 Weeks Timeline Evaluation)



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