STUDY PROTOCOL (last updated: 15 March 2020)

Study Title: Silver Diamine Fluoride and Papain-Based Gel for Management of MIH-affected Molar in Paediatric Patients

Study Summary:

This randomised controlled trial of MIH affected first permanent molar requiring interim restorative treatment (ITR) aim to determine the clinical outcome of additional usage of Silver Diamine Fluoride (SDF) with and without papain-based gel on MIH molars at 12 months duration. SDF and Papain-based gel are the additional to the conventional Glass Ionomer Cement ITR.

Study Description:

Rationale

Molar Incisor Hypomineralization (MIH) is a systemic origin, qualitative developmental defect of enamel affecting one to four first permanent molars and frequently involving incisors (Weerheijm, 2001). Lesion presented as well-demarcated discolouration of the enamel, or enamel destruction due to breakdown or dental caries with a global prevalence was estimated around 14.2% (Schwendicke F et al, 2018). MIH teeth presented with various clinical problem including increase susceptibility of caries and post eruptive breakdown, inferior bonding to composite restoration, recurrent restorative failure, hypersensitivity, and difficulty to achieve anaesthesia. Extraction of the MIH affected first permanent molar is an option and require comprehensive evaluation and 'ideal' time. Currently, acceptance to invasive restorative treatment and extraction is a significant challenge in children. Hence, a less-invasive treatment using glass ionomer cement (GIC) with remineralisation and desensitising agents that comply with principle of Minimal Intervention Dentistry (MID) has gained attention as interim therapeutic restoration in moderate to severe MIH affected tooth to prevent progression of disease. Silver Diamine is a high concentration topical fluoride agent has shown superior performance for remineralization and caries arrest (Gao et al., 2016). Papain based gel is a chemomechanical caries removal and deprotenizing agent assist to remove debris and protein without the need of rotary instrument(Deng et a., 2018). There is a paucity in the published literature regarding the effect of SDF and papain-based gel on MIH-affected teeth. To date, no study has been done to evaluate the clinical outcome of MIH-affected molars treated with papain-based gel as deproteinising agent and SDF followed by interim therapeutic restoration with GIC. It is hoped that findings obtained from this study will give new insight into managing MIH-affected molars in children

Objective:

The aim of the study is to determine the clinical outcome of additional SDF with and without papain-based gel on MIH molars versus HVGIC alone as interim therapeutic restoration at 6 and 12 months. Specifically, the objective of this study is

1. To determine and compare the clinical outcome determine as success and failure of treatment related to pulpal health, structural integrity and hypersensitivity on MIH molars treated with GIC alone or with or without the use of SDF and papain-based gel at 6 and 12 months

Methodology:

Study Design: This study is a single centre, three arms, parallel randomised controlled trial (RCT) on MIH molars in children aged 5 to 15-year-old presented with at least one molar tooth diagnosed as MIH. RCT was opted as it allows comparison of data with the conventional management using GIC which is a common interim therapeutic restorative material of choice.

Research Subject and Participant: MIH screening and diagnosis of the first permanent molar will be done using the European Academy of Paediatric Dentist (EAPD) MIH index by Ghanim et al., 2015, ICDAS caries assessment, clinical assessment, and radiographic evaluation. The inclusion criteria of the participant and molar include.

1. Children aged 5 – 15 years old
2. Healthy with no medical problem
3. Subject presented with at least one MIH FPM with:
    a. Post eruptive breakdown (PEB)
    b. Unsatisfactory atypical restoration
    c. Atypical caries without pulp involvement

The exclusion criteria of the participant and molars include

1. Children with difficulty comprehending instruction
2. Children with inability to perform oral hygiene care independently
3. Known allergy to silver
4. Affected FPM with
    a. Non MIH defect (Fluorosis, Amelogenesis Imperfecta)
    b. No PEB and carious lesion
    c. Lesion into the pulp

d. Intact restoration
e. Extensive coronal breakdown requiring extraction

Upon obtained of informed consent, based on the tooth as the unit, it will then be randomised (1:1:1 via blocks) to either intervention arms by an independent collaborator based on the allocation sequence. The collaborator will not be involved in the study and was responsible for keeping the randomisation list. The randomisation allocation sequence will be generated using computer software.

Intervention: Intervention will be carried out by single investigator who is not involved in assignment of the samples. Group 1 will receive High Viscous Glass Ionomer Cement (HVGIC) restoration; Group 2 will be treated with 38% SDF (RivaStar®) and restored with HVGIC, and Group 3 will receive papain-based gel, Papacarie Duo™ followed by 38% SDF application and HVGIC restoration. In this study, 38% SDF by the RivaStar was the only SDF available and marketed in Malaysia. It is approved by the Malaysia Device Authority and U.S Food and Drug Administration (FDA) in 2014. In addition, the papain base gel (Papacarie Duo™) was obtained from the manufacturer and has been used in many clinical studies as chemomechanical caries removal agent as well as deproteinizing agent to improve adhesion of composite (Goyal et al., 2015, Pithon et al., 2016, Bottega et al. 2018)

Observation: At 6- and 12-months follow-ups, the findings for this study will be assessed by a blinded assessor who was not involved in recruitment and intervention. The clinical parameters recorded include presence of pain, swelling, tenderness, abscess, enamel breakdown, restoration quality, presence of caries associated with the tooth and Schiff Cold Air Sensitivity Scale (SCASS). This clinical outcome of the molar; success or failure will then be determined based on the clinical parameters.

Table 1: Description of the clinical outcome

Outcome	Description
Success	• Absence of pain related to the treated tooth • Absence of tenderness to percussion • No evidence of swelling or presence of a sinus tract • Absence of enamel breakdown and caries along margin of restoration • No hypersensitivity (SCASS 0 or 1)
Major failure	• Presence of spontaneous throbbing or persistent pain • Presence of tenderness to percussion • Evidence of swelling and sinus
Minor failure	• Presence of new carious lesion or enamel breakdown at the margin of restoration • Presence of hypersensitivity (SCASS 2 or 3)

Sample size: The sample size is calculated based on Grossi et al., who reported that the clinical success of GIC (Equia Forte) restoration using ART technique in MIH affected permanent molars was 98.3% (Grossi et al., 2018). Since there was no literature reporting on the clinical success of Silver Diamine Fluoride and papain-based gel on MIH-affected molars, the success rate was assumed to be 50%. With an estimated error of 5% and power of 90%, the minimum estimated sample size was calculated to be 14 teeth per intervention group. The sample size calculation will be performed using G-power 3.1 software that calculated the power and sample size for tests by comparing two independent binomial populations with probabilities $\pi 1$ and $\pi 2$, respectively. Pearson chi-square test was used to test the association of two binary variables (two groups and two outcomes). An additional 50% was added to compensate for the possibility of high dropout or recall failure. Hence, the number was increased to 21 teeth per group for a total of 63 teeth. The high percentage of dropout rate in this study is decided to accommodate a high need of retreatment of GIC restoration based on few published literature (Al Muallem et al., 2018; Linner et al., 2020). Besides, the high dropout rate may also be related to the higher chance of the affected molar to be extracted following advice by an orthodontist during the review phase.

Data Management and Analysis:

Data obtained will be entered and analysed using Statistical Package for the Social Sciences (SPSS) version 26.0 software. The continuous data will be checked for normality of distribution and reported accordingly. Categorical data in this study are the clinical parameters, clinical outcome, and restorative quality. Descriptive statistics of frequencies and percentages will be presented for categorical data. The primary data analysis will be done using Intention-to-treat (ITT) analysis involving all the samples recruited and randomised. The Per Protocol (PP) analysis will be done to compare the difference between treatment effects as a sensitive analysis of missing value. Comparison of categorical outcomes will be assessed using Chi-square goodness of fit test and Friedman Two-way Analysis of Variance (ANOVA) by Ranks test. Association studies such as factors affecting the outcome will be further evaluated using the Binary Logistic Regression. In all analyses, the level of significance is set at $p<0.05$. The power of the study will be calculated using G*Power Version 3.1.9.4 using the Post Hoc test of Goodness-of-Fit.

Ethical Consideration:

This study has already received approval from the Medical Ethics Committees, Faculty of Dentistry, University of Malaya (CD1912/0061/20155(P)). Patient Information Sheet (PIS) will be disseminated to parents and participated children before consenting. Written informed and verbal consent from parents and, where appropriate, the children, were obtained before intervention. Participation is based on a voluntary basis and they may decide to leave at any time of the study.

Reference:

1. Almuallem, Z. & Busuttil-Naudi, A. 2018. Molar incisor hypomineralisation (MIH) – an overview. *British Dental Journal,* 225, 601-609.
2. Bottega, F., Bussadori, S. K., Battisti, I. D. E., Vieira, E. P., Pompeo, T. S. & Winkelmann, E. R. 2018. Costs and benefits of Papacarie in pediatric dentistry: a randomized clinical trial. *Scientific Reports,* 8.
3. Deng, Y., Feng, G., Hu, B., Kuang, Y. & Song, J. 2018. Effects of Papacarie on children with dental caries in primary teeth: a systematic review and meta-analysis. *Int J Paediatr Dent,* 28, 361-372.
4. Gao, S. S., Zhang, S., Mei, M. L., Lo, E. C.-M. & Chu, C.-H. 2016. Caries remineralisation and arresting effect in children by professionally applied fluoride treatment – a systematic review. *BMC Oral Health,* 16.
5. Goyal, P. A., Kumari, R., Kannan, V. P. & Madhu, S. 2015. Efficacy and tolerance of papain gel with conventional drilling method: a clinico-microbiological study. *J Clin Pediatr Dent,* 39, 109-12.
6. Grossi, J. D. A., Cabral, R. N., Ribeiro, A. P. D., & Leal, S. C. 2018. Glass hybrid restorations as an alternative for restoring hypomineralized molars in the ART model. *BMC Oral Health, 18*(1). doi:10.1186/s12903-018-0528-0
7. Linner, T., Khazaei, Y., Bücher, K., Pfisterer, J., Hickel, R. & Kühnisch, J. 2020. Comparison of four different treatment strategies in teeth with molar-incisor hypomineralization-related enamel breakdown–A retrospective cohort study. *International Journal of Paediatric Dentistry,* 30, 597-606.
8. Pithon, M. M., Campos, M. S. & Coqueiro Rda, S. 2016. Effect of bromelain and papain gel on enamel deproteinisation before orthodontic bracket bonding. *Aust Orthod J,* 32, 23-30.
9. Schwendicke, F., Elhennawy, K., Reda, S., Bekes, K., Manton, D. J. & Krois, J. 2018. Global burden of molar incisor hypomineralization. *J Dent,* 68**,** 10-18.
10. Weerheijm, K. L., Groen, H. J., Beentjes, V. E., & Poorterman, J. H. 2001. Prevalence of cheese molars in eleven-year-old Dutch children. *ASDC J Dent Child, 68*(4), 259-262, 229.