



UNIVERSIDADE
FERNANDO
PESSOA

LONG TERM EFFECTS OF THE ICON TECHNIQUE ON PATIENTS WITH ENAMEL HYPOMINERALIZATION. A SYSTEMATIC REVIEW

[Efeitos a longo prazo da técnica ICON em pacientes com hipomineralização do esmalte. Uma
revisão sistemática]

Dissertação de Mestrado

[Mestrado Integrado de Medicina Dentária]

Sacha Abraham Benguigui

Orientador:

Professor Carlos Palmeira

Coorientador:

Dra. Maria João Begonha

Julho 2024

LONG TERM EFFECTS OF THE ICON TECHNIQUE ON PATIENTS WITH ENAMEL HYPOMINERALIZATION. A SYSTEMATIC REVIEW

[Efeitos a longo prazo da técnica ICON em pacientes com hipomineralização do esmalte.
Uma revisão sistemática]

Dissertação de Mestrado

[Mestrado Integrado de Medicina Dentária]

Sacha Abraham Benguigui

Orientador:

Professor Carlos Palmeira

Coorientador:

Dra. Maria João Begonha

Julho 2024

À mes parents, Georges et Nathalie

A mes frères et sœurs, Harry Alexia et Johanna

À mes amis

THANKS

Merci à mes professeurs de thèse, Professeur Carlos Palmeira et Docteur Marie Joao Begonha, pour votre précieux soutien tout au long de ma thèse. Je vous remercie pour vos conseils, votre disponibilité et vos connaissances qui ont pu m'orienter tout au long de mes recherches, tout ça dans un environnement bienveillant me poussant à dépasser mes limites.

Merci à la Professeure Sandra Soares pour ses conseils vis-à-vis de la structure de ma dissertation. Merci pour votre réactivité et votre patience.

Merci à l'Université Fernando Pessoa pour ces 5 années d'études qui m'ont permis de m'accomplir personnellement et de m'avoir donné toutes les cartes en main pour me réaliser dans cette nouvelle profession.

À mes parents, Nathalie et Georges, pour leur générosité, leur soutien intellectuel tant qu'émotionnel, leurs sacrifices, leur amour et tant d'autres choses qui m'ont permises de m'épanouir et d'accéder à cette profession que je m'appête à entreprendre. Merci d'avoir cru en moi. Je vous aime.

À Harry et Alexia, mon frère et ma sœur qui ont partagé le même parcours scolaire que moi. Vous qui avez répondu à tous mes questionnements avec patience durant ces 5 ans d'étude et qui m'avez accompagné et répondu à chacun de mes doutes. Merci de votre caractère bien trempé et de votre voix bien portante pour animer tous ces moments en famille.

À Johanna, ma grande sœur bien aimée, pour ta gentille, ton soutien et ton calme dans cette famille très animée. Merci d'exister et de m'avoir rendu tonton pour la première fois.

Merci mes grands-parents, Simone et Hubert pour votre amour inconditionnel et votre soutien. J'espère vous avoir le plus longtemps possible près de moi.

À mes autres grands-parents, André et Marcel, vous qui m'observez de là-haut et qui veillent sur moi, je ne vous oublie pas. Je vous aime.

À Eva, mon binôme durant ces 2 années de clinique. Arrivée en cours de route dans cette Université un an après moi, tu m'as tout de même accompagnée durant ce parcours, faisant passer ton amitié en critère numéro un dans toutes tes relations. Tes connaissances, ton dévouement et ta persévérance ont enrichi chaque aspect de notre travail commun. Merci d'avoir été là quand il fallait.

À Arthur, mon meilleur ami, mon frère d'une autre mère, mon ancien coloc de 3 mois, qui m'accompagne depuis maintenant 10 ans dans toutes mes aventures. Même si finalement la voie de dentaire ne t'a pas choisi, tu trouveras la tienne j'en suis sûre.

À Jordan, pour ta joie de vivre, ta maturité, ta compétitivité qui me pousse toujours à bout. Merci de m'accompagner dans ma vie le plus longtemps possible je l'espère.

À Lana, mon artère de la veine du côlon irritable, ma meilleure amie depuis toutes ces années et jusqu'au lendemain, je n'en doute pas. Merci de me faire rire comme personne.

À Élixa, Sacha, La Ploum Family (Mayane et Alex), Isaac, Abi, Shanna et Carla x2 qui m'ont accompagné durant ces 5 ans, depuis le début ou attrapés en cours de route. J'ai passé des moments extraordinaires avec chacun d'entre vous et je vous remercie pour ça. On se revoit en France mes copains pour la vie.

Merci à toutes ces incroyables rencontres que j'ai pu faire en 5 ans ici, vous faites à présent tous partie de ma vie et de mon cœur.

À la ville de Porto, mes nombreux déménagements dans chacun de tes appartements, mes soirs de semaines au Norte Shopping, mes après-midis à Praia da Luz, mes soirées de bar en bar aux Galerias, mes allers-retours dans le parc Arca D'Água, merci de m'avoir accueilli pendant toute la durée de mes études. Obrigado, O Porto.

RESUMO

A hipomineralização do esmalte, comumente chamada de hipomineralização molar-incisivo (MIH), é um defeito do desenvolvimento na mineralização do esmalte dentário. É uma alteração que afeta principalmente os primeiros molares e incisivos centrais permanentes e causa o aparecimento de manchas mais ou menos escuras nos dentes afetados, o que torna estes dentes menos estéticos e mais suscetíveis a patologias. As consequências são múltiplas para o paciente e incluem a hipersensibilidade, aumento da ocorrência de lesões de cárie, diminuição da durabilidade das restaurações dentárias, diminuição da resistência do esmalte à mastigação ou aos ataques ácidos e ainda alterações estéticas, causando problemas psicológicos e comportamentais nas crianças afetadas. A técnica ICON, que consiste em infiltrar a mancha com resina após uma abrasão superficial realizada com ácido clorídrico, é um dos tratamentos disponíveis.

O objetivo principal deste trabalho é comparar e avaliar os efeitos a longo prazo da técnica ICON em pacientes afetados com MIH. Para isso, foi realizada uma pesquisa bibliográfica nas bases de dados: PubMed, Science Direct e Scielo. A triagem dos artigos encontrados foi realizada com base nos critérios PRISMA, utilizando critérios de inclusão e exclusão. A qualidade metodológica foi avaliada por meio da ferramenta Joanna Briggs Institute para séries de casos, coortes e ensaios clínicos randomizados. Combinamos dados da literatura teórica e empírica, a fim de comparar e sintetizar os resultados das diversas pesquisas sobre o tema proposto.

A análise dos estudos incluídos neste trabalho sobre a infiltração de resina ICON destaca os seus resultados positivos consistentes em termos de melhoria da estética, da hipersensibilidade dentária e da integridade estrutural dos dentes. Estas notáveis melhorias da estética, da redução da dor no pós-tratamento e da diminuição do risco de fratura do esmalte sugerem a durabilidade do tratamento e a sua potencialidade como uma solução a longo prazo no tratamento da MIH. Apesar destes resultados, limitações como as variações nos parâmetros de estudo enfatizam a necessidade de mais pesquisas de forma a estabelecer completamente a eficácia do ICON comparativamente a tratamentos alternativos. No geral, a infiltração com esta resina surge como uma opção promissora e minimamente invasiva para tratar hipomineralizações dentárias, devendo ser garantida a investigação contínua da sua aplicação clínica.

Palavras-chave: « Resin infiltration », « Molar Incisor Hypomineralization », « Enamel Microabrasions » e « Icon Infiltrant »

ABSTRACT

Enamel hypomineralization, commonly called molar-incisor hypomineralization (MIH), is a developmental defect in the mineralization of tooth enamel. It is a disorder that mainly affects the first permanent molars and central incisors and causes the appearance of more or less dark stains on the affected teeth, which makes them less aesthetic and more susceptible to pathologies. The consequences for the patient are multiple and include hypersensitivity, increased occurrence of caries lesions, decreased durability of dental restorations, decreased enamel resistance to chewing or acid attacks, and even aesthetic changes, causing psychological and behavioural problems in affected children. The ICON technique, which consists of infiltrating the stain with resin after superficial abrasion with hydrochloric acid, is one of the available treatments.

The main objective of this study is to compare and evaluate the long-term effects of the ICON technique in patients affected by MIH. To achieve that, a bibliographic search was carried out in the following databases: PubMed, Science Direct and Scielo. The articles found were screened based on the PRISMA criteria, using inclusion and exclusion criteria. Methodological quality was assessed using the Joanna Briggs Institute tool for case series, cohorts and randomized clinical trials. We combined data from the theoretical and empirical literature in order to compare and synthesize the results of the various studies on the proposed topic.

The analysis of the studies included in this work on ICON resin infiltration highlights its consistent positive results in terms of improving aesthetics, dental hypersensitivity and structural integrity of the teeth. These notable improvements in aesthetics, reduction of post-treatment pain and reduction in the risk of enamel fracture, suggest the durability of the treatment and its potential as a long-term solution in the treatment of MIH. Despite these results, limitations such as variations in study parameters emphasize the need for further research in order to fully establish the efficacy of ICON compared to alternative treatments. Overall, infiltration with this resin appears to be a promising and minimally invasive option for treating dental hypomineralization, and continued investigation into its clinical application should be ensured.

Keywords: « Resin infiltration », « Molar Incisor Hypomineralization », « Enamel Microabrasions » and « Icon Infiltrant »

GENERAL INDEX

FIGURE INDEX.....	XV
TABLES INDEX	XVII
ATTACHMENTS INDEX	XIX
LIST OF ACRONYMS AND ABBREVIATIONS.....	XXI
1. INTRODUCTION	1
2. METHODOLOGY	5
3. RESULTS	7
3.1. Altan & Yilmaz, 2023.....	16
3.2. Brescia et al., 2022.....	17
3.3. Giannetti et al., 2018.....	19
3.4. Mazur et al., 2022.....	21
3.5. Nogueira et al., 2021.....	22
4. DISCUSSION	25
4.1. General Aesthetic Appearance Results.....	25
4.2. General Dentinal Hypersensitivity Results.....	27
4.3. General Structural Integrity Results.....	27
4.4. Patient and Observer Satisfaction.....	28
5. CONCLUSION	31
6. BIBLIOGRAPHY	33
7. ANNEXES	35

FIGURES INDEX

Figure 1. Flow Diagram <i>PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)</i>	8
Figure 2. Percentage of distribution by the type of study.....	10

TABLES INDEX

Table 1: Utilization of the PIO strategy to define research elements and formulate the clinical question.	5
Table 2. Critical Methodological Evaluation for Case Series.....	9
Table 3. Critical Methodological Evaluation for Case Control Studies.....	9
Table 4. Critical Methodological Evaluation for Randomized Controlled Trials.....	9
Table 5. General Characteristics of Included Studies.....	11
Table 6. Criteria Evaluated, Type of Evaluation Scale and Comparison Technique.....	12
Table 7. Results and Conclusions.....	13
Table 8. A summary of the follow-up outcome evaluation with ICON technique treatment.....	15

ATTACHMENTS INDEX

<i>Annex 1. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Case Series.....</i>	<i>35</i>
<i>Annex 2. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Case Control Studies.....</i>	<i>36</i>
<i>Annex 3. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Randomized Controlled Trial.....</i>	<i>37</i>

LIST OF ACRONYMS AND ABBREVIATIONS

CIE: International Commission on Illumination

CP: Carlos Palmeira

DDE: Developmental Defects of Enamel

DMFT: Decayed, Missing, and Filled Primary Teeth index.

FDI: Fédération Dentaire Internationale

FV: Fluoride Varnish

FV+ etch: Fluoride Varnish + Phosphoric Acid Pre-treatment

IC: Central Incisor

L*: Brightness of the colour

MAB-Re: Microabrasion- remineralization

MeSH: Medical Subject Headings

MIH: Molar Incisor Hypomineralization

MJB: Maria João Begonha

M:F: Male:Female

N: Number of patients

N: Number of dental elements

NA: Not Applicable

OR: Odds Ratios

PEB: Post-eruptive enamel breakdown

PICO: Population; Intervention; Comparison; Outcomes

PIO: Population; Intervention; Outcomes

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RI: Refractive Index

RI: Resin Infiltration

SAB: Sacha Abraham Benguigui

TEGMA: Triethylene Glycol Dimethacrylate

VPI: Visible Plaque Index

WSL : White Spot Lesions

ΔE : Overall colour change

ΔL : Lightness

1. INTRODUCTION

The dental enamel, a calcified tissue, serves as the outer shield for the anatomical crown of a tooth. Once developed, enamel lacks the ability to undergo biological repair or replacement (Farooq & Bugshan, 2020). The enamel is composed of a massive mineral part (more than 98%), an organic matrix (less than 2%) and other elements like water (Shah et al., 2023). Sometimes, a perturbation can occur during the enamel development which can cause some anomalies such as amelogenesis imperfecta, fluorosis, or Molar Incisor Hypomineralization (MIH) (Altan & Yilmaz, 2023).

Molar Incisor Hypomineralization represents one of the most common defects in tooth crowns (Giannetti et al., 2018). It has been clearly defined at the beginning of the century as a demarcated enamel qualitative developmental defect affecting at least 1 permanent molar (Nogueira et al., 2021). This defect is due to a perturbation in the calcification phase during the dental development because of an insufficient deposition of minerals that leads to an incomplete removal of proteins in the enamel matrix (Temudo et al., 2022). This happens when the ameloblasts, which are responsible for enamel formation, are damaged during the maturation phase and fail to secrete the organic matrix effectively (Altan & Yilmaz, 2023). Compared to the enamel hypoplasia which can be confused, this defect occurs during the secretion phase. The enamel hypoplasia is a quantitative defect whereas the enamel hypomineralization is a qualitative defect of the enamel (Shah et al., 2023).

Although the exact cause of MIH is uncertain, it is theorized that fluctuations in the pH of the matrix during enamel maturation could contribute to its development (Altan & Yilmaz, 2023). About the aetiology, it has been demonstrated that MIH might not have one specific factor and can be linked to the pre-, peri- and post-natal periods with interactions between environmental factors and genetics. Systemic medical conditions like perinatal hypoxia, prematurity, and other perinatal issues associated with hypoxia, including caesarean section, seem to increase the likelihood of MIH.

MIH is also frequently associated with permanent incisors and can be identified by opacities well demarcated that can lead to aesthetic, functional, psychological, and behavioural problems in children (Almulhim, 2021). More specifically, MIH might manifest as alterations in tooth colour, presenting as white, yellow, or brownish patches.

Additionally, the enamel structure can be compromised, leading to the formation of grooves and depressions on the tooth surface (Temudo et al., 2022) and can lead to a modification of the tooth's aesthetic features, such as opacity, translucency, and fluorescence. The borders are well-demarcated, and the surface is porous. The cervical third is normally not affected contrary to the 2 other thirds (Altan & Yilmaz, 2023). Teeth affected by MIH commonly exhibit dentin sensitivity, post-eruptive enamel breakdown, inflammation of the pulp, dental pain, and the need for early tooth extraction (Altan & Yilmaz, 2023).

The pooled prevalence of MIH is 13.5% with at least 1 affected incisor in 36.6% of the cases with no continental differences (Lopes et al., 2021).

One significant aspect in the initial phases of MIH is the aesthetic impact, characterized by mottling or discoloration in the front teeth. A certain insecurity from these individuals experiencing these changes can refrain them from smiling due to embarrassment about their teeth's appearance. Particularly among young people, this issue can lead to depressive symptoms and withdrawal from social activities (Bulanda et al., 2022). Due to an understanding concern for aesthetics, patients often seek treatments to address these enamel defects. Various options are available, including crowns/veneers, conventional restorative procedures, micro abrasion, whitening, remineralizing agents, and infiltration techniques (Giannetti et al., 2018). This study will be concentrated on this latter, and more specifically on the ICON.

This new microinvasive treatment method was proposed for the management of white spot lesions and demineralized enamel lesions through resin infiltration. Introduced in 2009, Paris and Meyer-Lueckel from the University of Kiel in Germany modified the composition of conventional adhesive resins and introduced the ICON Resin Infiltrant containing 99% triethylene glycol dimethacrylate (TEGDMA) along with initiators and stabilizers. This new formulation was specifically designed to improve the depth of penetration for the treatment of white spot lesions (WSLs). Additionally, ICON helps prevent further progression of initial enamel caries by occluding the microporosities within the enamel lesion due to its low viscosity and minimal intervention on the demineralized enamel. The goal of the ICON resin infiltration technique is to create a diffusion barrier within the body of the lesion rather than on its surface (Srikumar et al., 2024). Indeed, it uses a 15% hydrochloric acid etchant to remove the surface layer of the

decalcified area due to its penetration depth. This process exposes the lesion body, allowing the resin to fill the pores. The resin makes the lesion body watertight, with a refractive index (RI ICON = 1.44) close to that of healthy enamel (RI = 1.63). This helps stop acid diffusion by creating a barrier within the lesion rather than on the surface (Kannan & Padmanabhan, 2019). This application halts the progression of caries and conceals the chalky white appearance of the white spot lesions, thus enhancing the aesthetic appearance (Arjomand et al., 2021).

The protocol is simple; the teeth are first isolated using a rubber dam, followed by cleaning the enamel surface with prophylaxis paste and a slow rubbing motion using a rubber cup. Next, a 15% hydrochloric acid gel (ICON-Etch) is applied for 120 seconds, then thoroughly rinsed off for 30 seconds. Ethanol lesion desiccation (ICON-Dry) is carried out for 30 seconds, followed by drying. The lesion is then infiltrated with resin (ICON-Infiltrate) for 3 minutes. Subsequently, any remaining material is cleaned with a cotton swab before drying. A 40-second light curing process is performed, followed by another round of infiltration (Shah et al., 2023). All the other protocols are very similar with some minor differences.

Therefore, the aim of this systematic review is to gather the information available in the literature to understand whether:

- resin infiltration using the ICON technique is an effective treatment for patients with enamel hypomineralization, specifically in terms of aesthetic results, structural integrity and tooth hypersensitivity;
- and whether its effect is maintained over long periods of time, in other words, a long-term effect

2. METHODOLOGY

For the research of the clinical question's formulation to which this work pretends to respond, it was used the criteria PIO (*Population; Intervention; Outcomes*). Normally, it is the criteria PICO that normally used, but, in the present case, the Comparison (The C in PICO) is not applicable because there is no comparison between a patient without MIH and a patient with MIH treated with the ICON technique; there is just an evaluation of the effectiveness of this technique comparing the different studies on the same technique with all the patients with MIH.

Table 1: Utilization of the PIO strategy to define research elements and formulate the clinical question.

Parameters	Evaluation
P (Population)	Patients with enamel hypomineralization
I (Intervention)	Application of the ICON technique on the teeth affected with MIH
O (Outcomes)	Different scale of colour on long term; Possible hypersensitivity; Structural Integrity

A bibliographical search was carried out in the online databases such as PubMed, Science Direct, Scielo and articles published from 2013 until 2023, written in English, French and Portuguese, were considered.

The following MeSH terms will be used as a strategy of research on the platform PubMed: « Resin infiltration », « Molar Incisor Hypomineralization », « Enamel Microabrasions » and « Icon Infiltrant » combined with each other using the term AND. This search strategy was adapted to the remaining databases used.

Inclusion criteria will be defined, such as the article's languages that will only be in Portuguese, English or French, articles from the last 10 years and without restricted access. Only articles based on patients diagnosed with Enamel Hypomineralization, independent of gender and socio-economic status.

Exclusion criteria also were defined such as articles that doesn't respond to the criteria of inclusion, articles that doesn't respect the thematic, articles that are not fully disponible, articles that doesn't include this specific pathology (MIH), animal and *in vitro* studies and articles where there is not the resin infiltration solution (ICON) included.

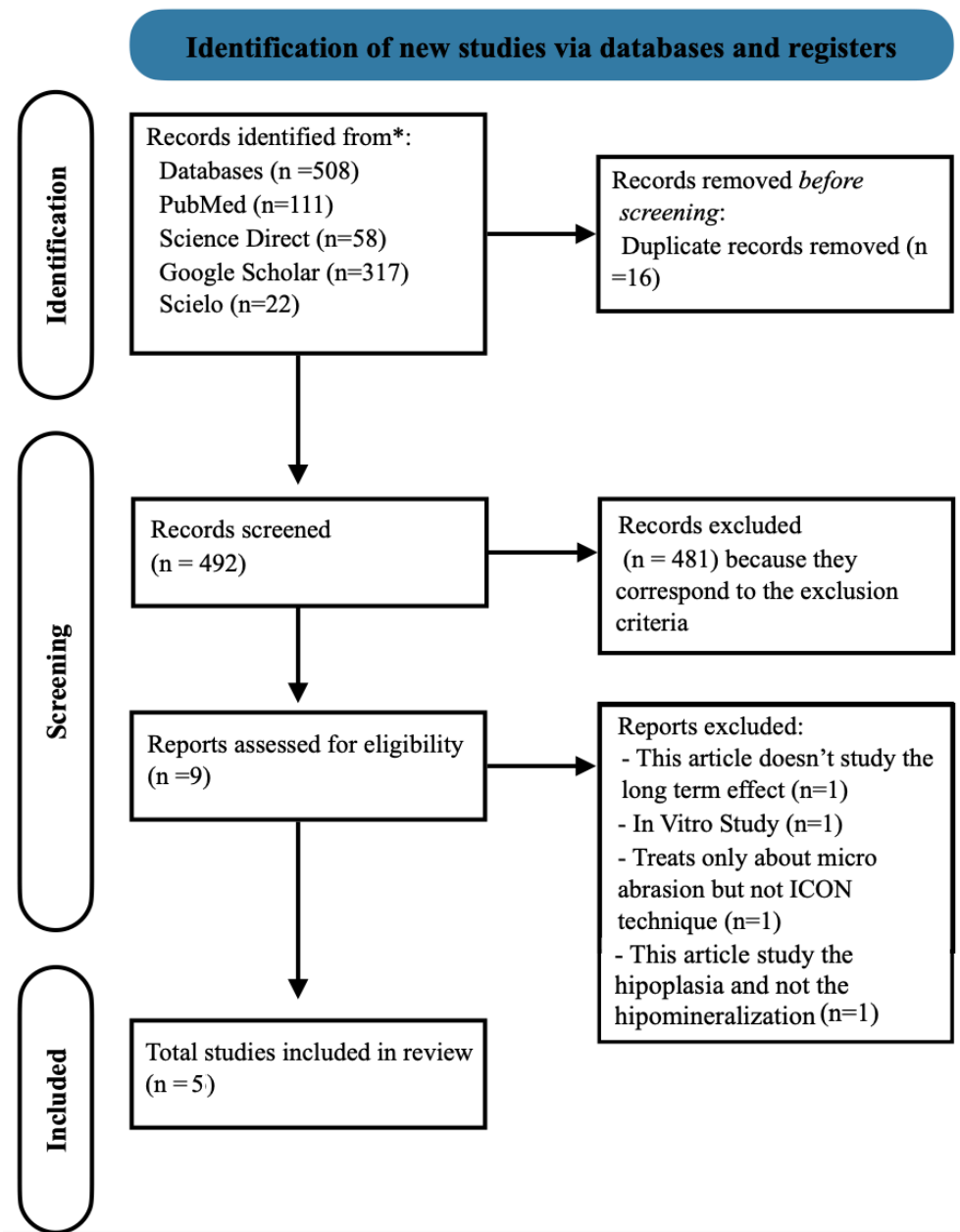
The PRISMA methodology applicated to the JBI criteria corresponding to each article were used to evaluate the quality and the bias recorded.

3. RESULTS

A total of 508 articles were identified in the different databases. Then, a total of 16 articles that were duplicates were identified and removed. After applying this process, a total of 492 articles remained. The title and summary of these were read and evaluated and a total of 481 were eliminated, corresponding to the exclusion criteria.

For full reading, a total of 9 remained, 1 being eliminated because it was an in-vitro study, 1 because it doesn't include a long-term effect and a last one was removed because it treated about micro abrasion but not specifically the ICON method. A total of 6 articles were included in this review, 3 Case Series, 1 Case Control Study and 2 Randomized Controlled Trials, totalling 213 samples/participants. The screening process is defined in the following PRISMA diagram (figure 1):

Figure 1. Flow Diagram PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).



A critical evaluation of the methodological quality of all the included articles was carried out by two reviewers (SAB and CP), using three tools developed by the Joanna Briggs Institute: “Checklist for Case Series” for serial cases studies, “Checklist for Case Control Studies” for case control studies and “Checklist for Randomized Controlled Trials” for randomized controlled trials studies. The tools consist, respectively, of 10, 10 and 13 parameters, which lead examiners to go through all the articles, with the aim of filling in each of the parameters with “Yes”, in cases where the article has all the evaluation

information; “No”, when the article does not have any references to the information under evaluation, “Unclear”, in cases where the information under evaluation is only partially mentioned and, finally, “Not applicable”, when the parameter is not applicable to be applied to the article under evaluation due to methodological determinants. A third reviewer (MJB) was consulted in the event of a disagreement until an agreement was reached. The result of this evaluation is shown in the following tables:

Table 2. Critical Methodological Evaluation for Case Series.

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
(Brescia et al., 2022)	Yes	Yes	Yes	Yes	Unclear	NA	Yes	Yes	NA	Yes
(Giannetti et al., 2018)	No	Unclear	Unclear	Yes	Unclear	Yes	No	Yes	NA	NA
(Mazur et al., 2022)	Unclear	Yes	Yes	Yes	Yes	NA	No	Yes	NA	Yes

Table 3. Critical Methodological Evaluation for Case Control Studies.

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
(Altan et Yilmaz, 2023)	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes

Table 4. Critical Methodological Evaluation for Randomized Controlled Trials.

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
(Nogueira et al., 2021)	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear

Caption:

Yes: Has all the evaluation information

No: Does not have any references to the information under evaluation

Unclear: The information under evaluation is only partially mentioned

NA: Not applicable to be applied to the article under evaluation due to methodological determinants

After the reading and the integrative analysis of the results obtained, 6 articles were selected which constitute the results of this systematic review.

We conclude this phase of bibliographical research of the articles relevant corresponding to the long-term effectiveness of the ICON technique on teeth affected with MIH with 6 articles that can be used for this study. We will analyse the 3 Case Series (Brescia et al., 2022; Giannetti et al., 2018; Mazur et al., 2022), the 1 Case Control Study (Altan & Yilmaz, 2023) and the last 1 Randomized Controlled Trials (Nogueira et al., 2021) (cf Figure 2).

Figure 2. Percentage of distribution by the type of study.

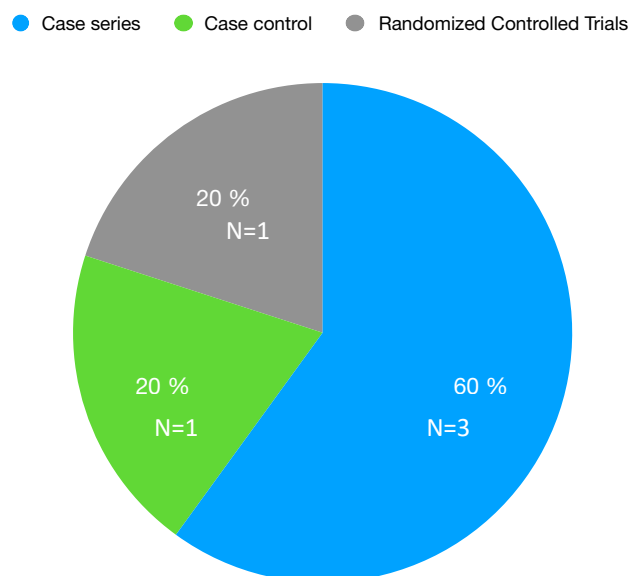


Table 5. General Characteristics of Included Studies

Authors and year	Type of study	Country	Objective	N (number of patients)	n (number of dental elements)	Age range (in years) and Gender (M:F)	Follow-up
1 Altan & Yilmaz, 2023	Non-randomized Clinical Trial (Classified in the Case Control Study category by FDI)	Turkey	Quantitatively and qualitatively evaluate the masking effect of ICON on MIH lesions on permanent incisor teeth before treatment; immediately after treatment and in follow-up.	N=37 (N=34 because 3 patients lost during the follow-up)	n=116	8-14 16:21	1; 3; 6 months
2 Brescia et al., 2022	Retrospective Clinical Trial (Classified in the Case Series category by FDI)	Italy	Evaluate the clinical efficacy of a superficial infiltration with ICON to treat the white enamel defects on the anterior sector associated with MIH. They analyse the aesthetic results and his stability over time also as the reduction of hypersensitivity, if present.	N= 33 N= 24 com MIH	n=144 (The exact number of dental elements for MIH were not documented)	10.4-11.6 (Mean 11) 18:15	T1 at 12 months and T2 at 24 months
3 Giannetti et al., 2018	Clinical Trial (Classified in the Case Series category by FDI)	Italy	Evaluate the effectiveness of the superficial infiltration treatment with ICON on different types of white defects of enamel (MIH, Fluorosis, Post-orthodontic defects and Post-trauma).	N=17	n=38 (n=9 teeth affected with MIH)	8-26 (Mean 14.7) 7:10	1; 12 months
4 Mazur et al., 2022	Prospective Clinical Trial (Classified in the Case Series category by FDI)	Italy	Evaluate the subjective and objective colour stability after ICON treatment in patients with MIH lesion treated 6 years ago.	N=15 patients less 1 lost during the follow up	n=76 (less 2 dental elements that were lost during the follow-up)	12-17 4:10	T1 at 12 months and T2 at 6 years
5 Nogueira et al., 2021	Randomized Controlled Clinical Trial (Classified in the Randomized Controlled Trials category by FDI)	Brazil	Evaluate the influence of fluoride varnish therapies or resin infiltration (RI) to maintain the structural integrity of Molar Incisor Hypo-mineralization (MIH).	N=51 (54 patients with 3 patients who withdrew their participation)	n=235 teeth (82 with Resin Infiltration)	6-12 (Mean 8.1) 49.1%: 50.9%	1; 3; 6; 12; 18 months

Table 6. Criteria Evaluated, Type of Evaluation Scale and Comparison Technique

Authors and Year	Criteria Evaluated	Type of Evaluation Scale	Comparison Technique
1 Altan & Yilmaz, 2023	Enamel Lesion, Aesthetic Appearance (colour changes and colour difference)	- DIAGNOdent Pen Value - CIE Scale (L) - ΔE value	Measurements performed before, immediately after, and 1;3;6 months after the treatment by the DIAGNOdent Pen at 3 different parts of each tooth with MIH. The colour was determined with a spectrophotometer (VITA EasyShare) and the changes were evaluated at the same time as above. They obtained intra-oral photography using the Cross-polarization technique with a ring flash Yongnuo YN-14EX TTL, China attached to the camera Canon EOS 700D, Tokyo-Japan at the same time as above. These images were then analysed using Image J software. Measurements were repeated 2 times at different times and their averages were taken as the final result, if agreed.
2 Brescia et al., 2022	Aesthetic Appearance and Dentinal Hypersensitivity	- FDI-colour matching criteria - Shiff Air Index - Wong-Baker Faces Pain Rating Scale	Digital Photographs comparisons using Nikon D80, Nikon AF-S Micro Nikkor 105 mm 1:2:8 G lens and Nikon Wireless Remote SB-R200 speedlight flash before and after the treatment. Comparison of the aesthetic appearance by 3 observers with « Colour Matching Criteria » approved by the FDI [a scale from 1 (Clinically excellent/very good) to 5 (Clinically poor)]. After that they calculate the difference of colour variation at T0, T1 and T2.
3 Giannetti et al., 2018	Aesthetic Appearance	- Scale from 0 to 2	Comparison of photographs taken at T0 (before treatment); T1 (directly afterwards); T2 (1 month); T3 (12 months later) by a NikonD70000 fitted with lens Nikon AF Micro Nikkor 105mm (1:2.8D) and ring flash Nikon Macro Speedlight. Two qualified dentists evaluate these photographs, and a grade was given from 0 (no degree of attenuation achieved) to 2 (impossible to distinguish the defect from the healthy enamel).
4 Mazur et al., 2022	Aesthetic Appearance	- FDI-colour matching criteria - CIEDE2000 colour differences	Two methods were used: - A qualitative visual evaluation using Digital Photographs comparisons with Nikon D7100, 105 mm Macro lens, R1C1 Macro flash with shutter speed 1/80 and aperture settings f32 at T0 (baseline), T1 (1 year after treatment) and T2 (6 years after treatment). The differences were observed and interpreted with the FDI-colour matching and translucency criteria evaluation scale [from 1 (Clinically excellent/very good) to 5 (Clinically poor)]. - A quantitative spectrophotometric evaluation and measurements on the enamel surface measuring the lightness from 0 to 100, the redness, the greenness, yellowness, and blueness. It calculates at 2 points the colour stability by the CIEDE2000 colorimetric at T0 (after treatment), T1 (1 year after treatment) and T2 (6 years after treatment).
5 Nogueira et al., 2021	Structural Integrity	- VPI - DMFT index	The teeth were photographs and enamel structural integrity compared at each follow-up consultation. VPI and DMFT were fully blinded re-evaluated at each follow-up appointment by the researcher.

The results and the conclusions of all the studies are summarized in table 7:

Table 7. Results and Conclusions.

Authors and Year	Results	Conclusion
1 Altan & Yilmaz, 2023	<p>For the DIAGNOdent Pen value:</p> <ul style="list-style-type: none"> - In the control group there was no significant differences between before the treatment vs directly and 3 months after. The values after 1 and 6 months were higher than the initial value. - In the ICON group, values before the treatment were higher than values directly after, 1, 3 and 6 months after the treatment. - Statistically difference at all times between the values of the 2 groups. <p>For the CIE Scale (L value):</p> <ul style="list-style-type: none"> - In the control group, no significant difference between before the treatment and immediately after and 1 month after. A significant decrease was observed after 3 and 6 months. - In the ICON group, no significant difference between before and directly after the treatment. The value was lower at 1, 3 and 6 months after the treatment. - Statistically difference at all times between the L value of the 2 groups. <p>For the ΔE value (colour difference):</p> <ul style="list-style-type: none"> - In the control group, no significant difference between ΔE value before the treatment and directly after, 1, 3 and 6 months after the treatment. - In the ICON group, no significant difference between ΔE value before the treatment and directly after, 1, 3 and 6 months after the application. - The ΔE value of both groups are statistically significantly different at all times. 	<p>With a consistent decrease in values observed with the DIAGNOdent Pen in teeth treated, it indicates a uniform infiltration of the resin into the lesion.</p> <p>With a decline of the L value during the follow-up (at 1, 3 and 6 months), it indicates a darkening of the colour of hypomineralized lesions bringing them closer to the natural colour of the tooth.</p> <p>With a ΔE values indicating no significant colour difference at all times it is a proof of a successful effect in masking the MIH on the affected teeth with the ICON resin infiltration.</p> <p>The ICON treatment is effective and works as a minimally invasive approach for managing anterior teeth with MIH lesions.</p>
2 Brescia et al., 2022	<ul style="list-style-type: none"> - Mean FDI score of 4.18 (clinically unsatisfactory) before the treatment. - Mean FDI score of 1.72 (clinically excellent) after the treatment. - "Clinically excellent" in 60.6% of cases, 18.2% as "clinically good," 6.1% as "clinically sufficient," and 15.1% as "clinically unsatisfactory". - The aesthetic results remained stable over the 2 years period, with some cases showing further improvement. 	<p>For the aesthetic appearance, on a 2-year period, the ICON technique shows the better results on patients affected with moderate MIH compared to patients affected with moderate Fluorosis and with Post-trauma Hypomineralization.</p> <p>In all the cases it effectively attenuated opacities even if the result was not considered optimal in some cases.</p> <p>For the improvement of the dentinal hypersensitivity, the results are considered satisfactory with 100% of the patients with a Wong-Baker Faces Pain Rating Scale of less than 2 after 12</p>

	<p>Patients with MIH shows the greatest results with 66.67% rated as "clinically excellent," 20.83% as "clinically good," 8.3% as "clinically sufficient," and 4.2% as "clinically insufficient."</p> <p>At T0, 24.3% of the patients with a Wong-Baker Faces Pain Rating Scale between 6 and 10.</p> <p>At T1, 90.9% of the patients with a Wong-Baker Faces Pain Rating Scale of less than 2.</p> <p>At T2, 100% of the patients with a Wong-Baker Faces Pain Rating Scale of less than 2.</p> <p>Before the treatment, 33.4% of the patients has an index of 2 and 3 on the Shiff Air scale.</p> <p>At T1, 6.1% responded over or equal to 2.</p> <p>At T2 all the patients responded with a Shiff Air value less or equal to 1 over 3.</p>	<p>months follow-up (MIH patients especially), and with 100% of the patients with a Shiff Air value less or equal to 1 over 3.</p>
<p>3</p> <p>Giannetti et al., 2018</p>	<ul style="list-style-type: none"> - For the caries defects, 4 teeth over 4 were completely hidden after 12 months follow-up. - For the post-orthodontic defects, over 11 teeth, 6 defects disappeared and 5 were attenuated after 12 months follow-up. - For the fluorosis defects, over 6 teeth, 4 out of 6 disappeared and 2 were attenuated after 12 months follow-up. - For the post-trauma defects, over 8 teeth, 2 disappeared and 6 were partially hidden after 12 months follow-up. - For the MIH defects, over 9 teeth, 1 disappeared and 8 were partially attenuated after 12 months follow-up. 	<p>This study proves a massive difference on the aetiology's role results with the same technique (ICON resin infiltration). The effectiveness is, from the better to the less effective, in that order: the caries defects (100%), post-trauma defects (75%), fluorosis defects (66.67%), post-orthodontic defects (54.55%) and MIH defect (11.11%). Even if in every case there was a partially attenuated results, it is admittable that the ICON technique is less effective on patients with MIH aetiology compared to the 4 other aetiologies studied. But, in all the cases there was an improvement so this technique can be considered effective but without a totally masking effect for patients with MIH.</p>
<p>4</p> <p>Mazur et al., 2022</p>	<p>FDI score at:</p> <ul style="list-style-type: none"> - T0= 13.5% - T1= 90.6% - T2= 93.2% <p>CIEDE2000 color differences score:</p> <ul style="list-style-type: none"> - At T0, ΔE_{00} was assessed at 6.8 (SD:3.8) - Between T0 and T1, ΔE_{00} decreased to 5.8 (SD:3.1) - Between T1 and T2, ΔE_{00} reduced to 1.3 (SD: 0.6) 	<p>For the FDI Score, there is a considerable difference between T0 before treatment and T2 after 6 years of 80%, which prove a massive improvement of the aesthetic of the defect.</p> <p>For the CIEDE2000 colour difference score, they show us a result greater than 3.3 at T0 and between T0 and T1 which indicates a clearly detectable visual colour difference. Between T1 and T2, the result is between a ΔE_{00} of 3.3 and 1.1 which indicates a perceptible but acceptable difference, which explain that after 6 years there is a little improvement but not as massive as after the treatment itself.</p> <p>This technique can be effective as a short- or long-term period with great results that stays in time.</p>

5	Nogueira et al., 2021	<p>The failure rates were 17.9% for FV, 17.3% for FV+etch, and 6.10% for RI. Failures were predominantly observed in molars.</p>						
		<p>The survival rates at 6 months were significantly lower for FV and FV+etch treatments compared to RI, with an increased risk of failure of 3.1 (OR) and 3.0 (OR), respectively ($p < 0.05$).</p>						
		<p>Some factors are significantly correlated with failure, including DMFT, opacity colour, tooth surface, and age. Among participants aged 6–9 years with DMFT >3, brown opacities, and cusp involvement, the lowest survival rates were observed across all follow-up periods, particularly at 18 months (FV: 10.7%; FV+etch: 10.4%; and RI: 20.2%). Additionally, the application of ICON infiltration, as opposed to FV, was associated with a decreased likelihood of failure in cases of yellow and brown opacities related to MIH.</p>						
		<p>Notably, teeth treated with resin infiltration exhibited no signs of caries development, irrespective of post-eruptive breakdown (PEB).</p>						
		<p>RI shows a significant lower rate with 93.9% of the case were there was no failure. Indeed, the failure rate is much lower for RI compared to FV and FV+etch.</p> <p>RI demonstrated a 20.2% survival rate at 18 months, while FV and FV+etch exhibited lower survival rates of 10.7% and 10.4%, respectively which shows the potential efficacy of resin infiltration treatment in reducing the risk of failure in yellow and/or brown MIH defects.</p>						

Table 8. A summary of the follow-up outcome evaluation with ICON technique treatment

Author	Directly after	1 Month	3 months	6 months	12 months	18 months	2 years	6 years
1 Altan & Yilmaz, 2023	Improved aesthetic appearance	Improved aesthetic appearance	Improved aesthetic appearance	Improved aesthetic appearance				
2 Brescia et al., 2022	Improved aesthetic appearance. Maintain of the dentinal hypersensitivity				Improved aesthetic appearance. Reduction of the dentinal hypersensitivity		Improved aesthetic appearance. Reduction of the dentinal hypersensitivity	
3 Giannetti et al., 2018	Little improvement in aesthetic appearance	Improved (better) aesthetic appearance			Improved (better) aesthetic appearance			
4 Mazur et al., 2022					Improved aesthetic appearance			Improved aesthetic appearance
5 Nogueira et al., 2021					Better Structural Integrity	Even better Structural Integrity (especially on occlusal/incisal surfaces)		

3.1 Altan and Yilmaz, 2023

This first article studied is a Non-randomized Clinical Trial (Classified in the Case Control Study category by FDI) conducted in 2023 in Turkey is composed of 37 patients (including 3 patients lost during the follow-up) from 8 to 14 years old including 16 boys and 21 girls. A total of 116 teeth (and especially 116 permanent Central Incisor with or without MIH) has been studied. The 116 dental elements of the 37 same patients have been separated in 2 different groups: the first group (Group I) composed of 58 permanent IC with MIH which has been treated with resin infiltration ICON and the second group (Group II, considered like the control group) composed of 58 healthy permanent CI, which has not been treated with anything and has been evaluated such as the Group I. The authors have evaluated the changes before the treatment by different methods, directly after and 1, 3 and 6 months after the procedure. The DIAGNOdent Pen has been used at 3 different parts of each tooth, the mechanism of which is based on different absorption and scattering of laser fluorescence radiation of the carious lesion compared to the surrounding healthy tissue; a spectrophotometer has been used to determine the colour changes and they have evaluated the lesion areas by using intra-oral cross-polarization photography.

The author showed that in the treatment group, the DIAGNOdent Pen values before treatment were 21.96 ± 15 and that directly after the treatment it decreased to 12.98 ± 9.95 . Subsequently, after 1, 3 and 6 months, the values stagnated from 13.12 ± 9.82 to 13.44 ± 9.69 . Comparing with the control group, they observe that the DIAGNOdent Pen values before treatment were 2.6 ± 0.57 , which is much less than the group suffering from MIH before treatment. The values directly after the treatment and 3 months afterwards are very similar to the values before treatment, but the values 1 month and 6 months afterwards are significantly higher than the initial values. By simply evaluating the values of the DIAGNOdent Pen on the treated group, it is noticeable a significant change in the enamel of hypomineralized teeth treated with ICON (the statistically significantly difference is indicated with different lower-case letters).

By observing the spectrophotometer data, they can evaluate the measured colour changes (L values). In the treated group, there was no significant colour change between before and directly after treatment, but during the follow-up part, after 1, 3 and 6 months, they observed an L value significantly lower than the initial value which represents a decrease

in colour brightness. In the control group, which was not treated, there was no colour change between before, directly after and 1 month after the treatment. However, 3 and 6 months after the treatment they noticed a reduction in the brightness of the colour (L) as well as a darkening of the colour of the teeth. Comparing the control cases to the treated teeth, however, they noticed a significant difference at all times.

Then, by evaluating the ΔE values (depict the change between colours) of the treated group and the control group, they notice in the treated group that the difference between each consultation is not significantly different from each other. It is also the case for the control group. However, they still notice a significant difference at all times between the ΔE values of the treated and untreated groups.

Finally, by relatively evaluating the lesion areas using cross-polarization photography, they observed that in the group treated before treatment a value of 4.9 ± 3 was registered, which, compared to the values directly after treatment and 1, 3 and 6 months afterwards, is significantly different. Indeed, they observe a reduction in the lesion area which remains relatively stable over time.

With all these results, including a consistent decrease in values observed with the DIAGNOdent Pen in teeth treated followed by stable readings over a 6-month period which may indicate an uniform infiltration of the resin into the lesion; a notable decline of the L value during the follow-up (at 1, 3 and 6 months) indicates a darkening of the colour of hypomineralized lesions bringing them closer to the natural colour of the tooth; and the ΔE values indicating no significant colour difference at all time; it is for the author a proof of a successful effect in masking the MIH on the affected teeth with the ICON resin infiltration. The resin infiltration treatment (ICON) demonstrated effectiveness as a minimally invasive approach for managing anterior teeth with MIH lesions.

3.2 Brescia et al., 2022

This article highlights a Retrospective Clinical Trial (Classified in the Case Series category by FDI) that recruited 33 participants (18 boys and 15 girls) that has been treated with resin infiltration ICON in Italy between January 2020 and July 2020 and retrieved from their database 12 months (T1) and 24 months (T2) afterwards to verify the stability of the aesthetic result obtained. It is also the only article that evaluate the reduction of

dentinal hypersensitivity, if present. The participants were 33 children from 10.4 to 11.6 years old (mean 11) comprising 114 dental elements that has been treated with the exact same superficial infiltration technique following the same protocol. The children can be classified in different DDE type composed of 24 children (72.7%) with moderate or low-grade MIH, 5 children (15.2%) with moderate or low-grade Fluorosis and 4 children (12.1%) with Traumatic hypomineralization. After 2 years, 3 observers were recruited to evaluate the aesthetic appearance of the teeth at T0, T1 and T2 using the FDI colour match criteria to standardize the diagnostic-therapeutic procedures. They calculated the difference of colour variation in a scale from 1 corresponding to "Clinically excellent/very good" to 5 corresponding to "Clinically poor" between the different appointment sessions. The different observers also check for the dentinal hypersensitivity with the Shiff Air Index checking the perception of discomfort after the application of air and the Wong-Baker Faces Pain Rating-Scale to characterize the pain from 0 (no pain) to 10 (very strong pain).

For the qualitative visual evaluation, according to the FDI colour match criteria, the pre-treatment quality assessment was deemed "clinically unsatisfactory" with a mean FDI score of 4.18. However, after the infiltration technique, the evaluation improved significantly to "clinically excellent" with a mean FDI score of 1.72. This improvement was observed in 60.6% of cases, with 18.2% rated as "clinically good," 6.1% as "clinically sufficient," and 15.1% as "clinically unsatisfactory." The aesthetic results remained stable over the 24-month follow-up period, with some cases showing further improvement. The success rate of the infiltrative treatment was calculated specifically for patients with MIH, with 66.67% rated as "clinically excellent," 20.83% as "clinically good," 8.3% as "clinically sufficient," and 4.2% as "clinically insufficient." Overall, all patients were satisfied with the treatment outcome, as it effectively attenuated opacities even if the result was not considered optimal in some cases. The author refer that they can clearly see the mild MIH before the treatment but after 24-months of follow up it is impossible to distinguish the hypomineralization defect. The author refer that they can see that the aesthetic improvement at T1 and the stability of the results at T2 is significantly greater in patients with MIH and fluorosis than in patients with trauma. The predicted FDI value for patients diagnosed with MIH decreases from 4.0 at the initial assessment (T0) to 1.5 after treatment (T1), and remains nearly constant at T2, with a value of 1.46.

Talking now about the dentinal hypersensitivity part, it has been noticed at the beginning of the study that 24.3% of patients reported discomfort ranging from "strong" to "very strong" on the Wong–Baker Faces Pain Rating Scale. After the treatment at T1, 90.9% of patients reported a pain rating of less than 2 over 10, indicating significant improvement. After 24 months at T2, all patients reported a pain rating equal to or less than 2 over 10. This improvement was consistent across all patients, particularly those with MIH, indicating a significant reduction in dentinal hypersensitivity. About the Shiff Air Index, it shows some similarities with the Wong Scale. Before the treatment, it was reported 33.4% of the patients with an index of 2 and 3 on the scale from 0 to 3. At T1, only 6.1% responded over or equal to 2 and, at T2 after 24 months, all the patients responded with a Shiff Air value less or equal to 1 over 3.

Consequently, each patient considered the treatment outcome satisfactory, attributing it to both the reduction in opacities and the decrease of the dentinal hypersensitivity. It gives very satisfactory results in all the cases of MIH and in instances where a "clinically sufficient" outcome wasn't initially achieved, there was still noticeable improvement during follow-up, likely attributed to the ongoing infiltration of fluid resin within the enamel structure over time. Furthermore, a certain stability of the achieved results was noted at the 2-year follow-up. The ICON technique presents itself as a viable alternative to conventional methods, particularly for the enamel opacities associated with mild or moderate fluorosis and mild cases of MIH achieving a satisfactory aesthetic outcome in a single session. However, it is not possible to predict the aesthetic results which represent the only limit observable, according to the authors.

3.3 Giannetti et al., 2018

This Clinical Trial (Classified in the Case Series category by FDI) that took place at the University of Modena and Reggio Emilia in Italy during the year 2017 choose to evaluate the effectiveness of the ICON treatment on different types of white defects of with a follow up of 1 and 12 months afterwards. It is distinguishable in this study 5 different groups: 1 composed of MIH patients, 1 with post-orthodontic defects, 1 composed of patients with fluorosis, 1 with incipient caries defects and the last one post-trauma. For that, the study recruited 17 participants in total (with an unknow number of patients

affected with MIH) aged from 8 to 26 years. Nine teeth with MIH were studied, 11 with post-orthodontic defects, 6 with fluorosis, 4 with incipient caries and 8 teeth with post-trauma defects for a total of 38 teeth with defects on enamel. The 38 teeth were all treated with the same infiltration resin ICON, following the same exact protocol, and were analysed and evaluated afterwards by 2 qualified dentists. They have compared the photographs taken at 4 different time of the study (before the treatment at T0, directly after the treatment at T1, 1 month afterwards at T2 and 12 months afterwards at T3) at the same Dental Clinic with the same photograph's parameters and material, by assigning a value of 0 if no degree of attenuation was achieved, a value of 1 if they observed a partial attenuation (with improvement less extended or less contrasted with the surrounding healthy enamel) and a value of 2 if it was impossible to distinguish the defect from the healthy enamel.

Talking about the results now, they class them in each category of white defects:

- Early caries defects were completely hidden. 4 teeth were treated, and from the initial step to the 12-month follow-up, there was complete resolution of the defect.
- For the post-orthodontic defects, it disappeared in 6 cases and were attenuated in 5. Eleven teeth were treated, and from the first step to the 12-month follow-up, there was complete resolution of the defect in 6 cases.
- For cases of fluorosis, 4 out of 6 disappeared. Six teeth were treated, and from the first application to the 12-month follow-up, there was complete resolution of the defect in 3 cases.
- Regarding post-trauma cases, 6 were partially attenuated and 2 disappeared. Eight teeth were treated, and from the first application to the 12-month follow-up, there was complete resolution of the defect in 2 cases.
- The part that interests the present work is the teeth suffering from MIH. It showed partial attenuation in 8 cases, and only in 1 case the defect disappears. Nine teeth were treated, and at the first check-up, there was no complete resolution of any defect. Eight teeth were partially attenuated, and 2 had no attenuation at all. After 1 month, 1 defect was totally attenuated. After 12 months, 2 more teeth were partially attenuated.

Comparing the different results, the teeth affected with MIH confronted to all the other defects it is the one which shows the least total attenuation, explained by a histological difference of the lesions. By only evaluating the MIH's treated results, even if the resin

infiltration process is not completely effective in all the cases, it obviously permits to attenuate partially in every case the aesthetic defect and add a therapeutic possibility of treating the MIH patients with a less invasive treatment.

3.4 Mazur et al., 2022

This Prospective Clinical Trial (Classified in the Case Series category by FDI) published in 2022 took place in “Sapienza” University of Rome in Italy in 2021, 6 years after the initial treatment in 2015. This long-term follow-up study recalled patients from a previously published work (Mazur et al., 2018), concerning 76 teeth treated with the ICON technique because they were affected with MIH.

A qualitative and a quantitative comparison were performed; The first one using Digital Photographs that were observed and interpreted with the FDI-colour matching and translucency criteria evaluation scale from 1 (Clinically excellent/very good) to 5 (Clinically poor) and a quantitative spectrophotometric evaluation and measurements on the enamel surface measuring the lightness from 0 to 100, the redness, the greenness, yellowness and blueness calculating at 2 points the colour stability by the CIEDE2000 colorimetric. These data were collected at T0 (baseline) T1 (1 year after treatment) and T2 (6 years after treatment). A correlation between the 2 data were done afterwards.

After 6 years, the 15 patients of the initial study were recalled, with 1 patient lost in the follow-up. Indeed 74 permanent teeth were studied in total.

Comparing the FDI scores results for the qualitative visual evaluation at T0, T1 and T2, they obtained an augmentation of the Clinically excellent and clinically good results (1 and 2 on the FDI-scale) from 13.5% before treatment to 90.6% at T1 and 93.2% at T2 with a difference between the first and the last of approximately 80%. These results indicate a massive improvement of the aesthetic of the defect directly after treatment and further improved 6 years afterwards.

Comparing the quantitative spectrophotometric evaluation results, ΔE_{00} was assessed at 6.8 (SD:3.8) at T0. Between T0 and T1, ΔE_{00} decreased to 5.8 (SD:3.1), and further reduced to 1.3 (SD: 0.6) between T1 and T2. At time point T0 and between T0 and T1, it has been observed a result surpassing 3.3, indicating a distinctly noticeable colour discrepancy. Between T1 and T2, the outcome ranges from a ΔE_{00} of 3.3 to 1.1,

signifying a perceptible yet manageable distinction. This elucidates that after 6 years, there is some minor enhancement, but not as remarkable as immediately following the treatment.

A correlation between the qualitative and quantitative evaluation is workable; $\Delta E00$ between T1 and T0 and all 3 FDI results correspond. This correlation explains that in patients with higher FDI results, there is a larger colour difference ($\Delta E00$). However, the correlation between T1 and T2 is negative which says that a larger difference of colour at the T1-T0 stage is more likely associated with smaller FDI scores (Clinically excellent and clinically good). There was no significant correlation observed between $\Delta E00$ at T2 and T1 and FDI scores at T0, T1, and T2.

As a conclusion of this article, after 6 years, the mean colour difference $\Delta E00$ (T2-T1) was 1.261 ± 0.637 . This result confirms an excellent long-term colour stability. Talking about the FDI score, this one was given a score of 1 or 2 (clinically excellent and clinically good) by more than 92% of the patients which reflect an aesthetic outcome of the colour stability. In addition, no dental or soft tissue hypersensitivity, loss of vitality, discoloration or gingival changes were observed after treatment. Like the qualitative evaluation, the quantitative results shows that the ICON technique is obviously durable over time and can be considered a good aesthetic and minimally invasive solution on a long-term period for patients suffering from MIH's aesthetic defects.

3.5 Nogueira et al., 2021

This research shows some relative differences compared to the other articles included in this review, namely the fact that aesthetic results of the ICON technique is not specifically evaluated. The authors are more concentrated on the risk of enamel breakdown on the long-term. Considered a Randomized Controlled Clinical Trial (Classified in the same way by FDI), this study was realized in Brazil, studying 54 children (comprising 3 patients who withdrew their participation) from 6 to 12 years old selected them if they had a routine treatment in the Paediatric Clinic of the Araraquara School of Dentistry from September 2016 to January 2017. All were affected with MIH opacities on at least 1 incisor and 1 first pre-molar and the study followed them for 18 months to assess the impact of Fluoride Varnish treatments or resin infiltration to preserve the structural

integrity of Molar Incisor Hypomineralization. The 51 patients (comporting in total 235 teeth) were randomly distributed in 3 different groups: 1 group has been treated with the ICON resin infiltration technique (RI), the second one with Fluoride Varnish (Duraphat) (FV) and the last one with the same Fluoride Varnish in addition to an enamel etching with phosphoric acid 37% (FV+etch). Considering only the children who followed the follow-up until the end, there was in the FV group 45 molars and 33 incisors (78 teeth); in the FV+etch group 43 molars and 32 incisors (75 teeth); and in the RI group 47 molars and 35 incisors (82 teeth).

Each teeth affected was photographed at the different appointment at 1, 3, 6, 12 and 18 months and VPI and DMFT were fully blinded re-evaluated at each follow-up timepoint by the researcher to compare the enamel structural integrity throughout this evaluation.

Analysing the results, following the 18-month assessments, the failure rates were 17.9% for FV, 17.3% for FV+etch, and 6.10% for RI, showing a significantly lower rate for this last one which makes it possible to refer, according with the authors, that in 93.9% of the cases there was no failure. Failures were predominantly observed in molars, which can be explained by the fact that molar teeth are exposed to greater mechanical stress than incisors. Survival analysis indicated that the FV and FV+etch treatments had significantly lower survival rates compared to RI at 6 months with an increased risk of failure of 3.1 (OR) and 3.0 (OR), respectively ($p < 0.05$). DMFT, opacity colour, tooth surface, and age were significantly correlated with failure (Fisher's Exact Test; $p < 0.05$). Participants aged 6–9 years with DMFT > 3 , brown opacities, and cusp involvement showed the lowest survival rates across all follow-up periods, particularly at 18 months (FV: 10.7%; FV+etch: 10.4%; and RI: 20.2%).

The application of ICON infiltration, in contrast to FV, was shown to decrease the likelihood of failure in yellow and brown opacities associated with MIH. Notably, teeth treated with resin infiltration showed no signs of caries development independent of post-eruptive breakdown (PEB). Only 6.1% of teeth treated with RI experienced failure after 18 months, a significantly lower rate compared to those treated with FV and FV+etch. The principal limitation of the infiltration technique lies in its unpredictable nature regarding pore obliteration and penetration depth within the opacities, necessitating further exploration.

Teeth with cusp or incisal involvement were found to have significantly higher failure risks (15.25 OR) compared to those with only free surface involvement. Additionally, brown opacities exhibited nearly 3 times higher failure risks than yellow opacities. Age also emerged as a significant factor, with a higher likelihood of PEB occurrence observed in patients aged 6–8 years compared to those aged 9–12 years. In addition to age, MIH patients with DMFT >3 were more susceptible to developing PEB due to the MIH condition itself. Survival rates declined over time, reaching their lowest point at 18 months post-intervention for all groups characterized by DMFT >3, brown opacities, cusp involvement, and age between 6–8 years. However, RI demonstrated a 20.2% survival rate for these characteristics at 18 months, while FV and FV+etch exhibited lower survival rates of 10.7% and 10.4%, respectively. These findings highlight the potential efficacy of resin infiltration treatment in mitigating the risk of failure in yellow and/or brown MIH defects, although it's crucial to acknowledge that a 20.2% survival rate implies a 79.8% rate of PEB.

Despite the constraints of this study, resin infiltration demonstrated effectiveness as an intervention for reducing post-eruptive breakdown in teeth affected by MIH and exerted a positive impact on maintaining the structural integrity of MIH-affected teeth, resulting in a reduced risk of enamel breakdown observed over an 18-month follow-up period.

4. DISCUSSION

This systematic review made it possible to compile the information available in the literature on the effectiveness of MIH treatment using the ICON technique, a treatment proposed for the management of white spot lesions and demineralized enamel lesions through resin infiltration. This effectiveness of this treatment was evaluated in relation to three parameters: aesthetics, structural integrity and dentinal hypersensitivity.

The first topic was the most studied among the evaluated articles and was easily compared between the different articles because 4 out of 5 studies addressed it. The drawback is that almost every study used a different aesthetic scale, making numerical comparisons difficult. The second and third parameters studied have fewer elements for comparison between articles, making them less conclusive compared to the first point. However, the results obtained in both parameters will be indicated, considering the lack of studies on the subject. Additionally, this work seeks to verify whether the treatment effectiveness only occurs after IR or whether it is maintained over time. Since all studies have different follow-up periods ranging from 1 month to 6 years, these differences must be considered when comparing the results from the three outcome parameters studied.

4.1. General Aesthetic Appearance Results

As already mentioned, the aesthetic appearance was the topic most discussed in this review. This may be due to the impact of this parameter in the quality of life of affected patients. As mentioned before, aesthetic changes lead to a decrease in the patient's-esteem, namely by inhibiting the act of smiling, which can lead to depressive symptoms and social isolation.

The attention was focused on the results obtained regarding the appearance of anterior teeth affected by MIH using ICON resin infiltration. In fact, 4 of the 5 articles shows positive results from partial attenuation in a large majority (Giannetti et al., 2018) to excellent long-term colour stability (Mazur et al., 2022).

In Mazur et al. (2022), results were obtained directly after the application of ICON resin infiltration. In Altan & Yilmaz (2023), they obtained good results such as a uniform

infiltration of the resin into the lesion, a darkening of the colour of hypomineralized lesions bringing them closer to the natural colour of the tooth and no significant colour difference at all time. For the authors, this was a proof of a successful effect in masking the MIH on the affected teeth with the ICON resin infiltration. Compared with a case-control study, Altan and Yilmaz (2023) indicated uniform infiltration of the resin into the lesion and a closer resemblance to the natural tooth color.

Sometimes, the aesthetic results can even improve over time. Brescia et al. (2022) and Mazur et al. (2022) obtained better aesthetic improvements a certain period after the treatment compared to immediately after it. In all the articles studied, no evaluation of aesthetic appearance during follow-up revealed less satisfactory results compared to the evaluation immediately after treatment. In all cases, the aesthetic results were maintained or even improved. These results suggest that ICON resin, in addition to being effective, it may mask better the defect over a long period of at least 6 years without a decrease over time, and even with improvement. Of course, some studies only deal with follow-ups of at least 6 months compared to others that investigate on much longer periods. That's why, this improvement in results should, be interpreted with caution, as the number of articles is small and the follow-up time varies.

Regarding the different etiologies for the white spot lesions and the application of the RI technique, there is divergence between the articles. In fact, in the different articles observed, there were various etiologies causing enamel defects. For example, Giannetti et al. (2018) evaluated the same RI technique on patients with MIH, post-traumatic defects, and post-orthodontic defects. Similarly, Brescia et al. (2022) showed results on patients with MIH, moderate fluorosis, and post-traumatic hypomineralization. In Brescia et al. (2022), over the longest term, the ICON technique showed better results in patients with moderate MIH compared to those with moderate fluorosis and post-traumatic hypomineralization. In contrast, Giannetti et al. (2018) reported less effective aesthetic results in patients with MIH compared to other etiologies. This difference can be explained by the smaller number of patients in Giannetti et al. (2018) (17 in total) compared to Brescia et al. (2022) (33 patients in total), making the former less relevant. Additionally, the scale used in Giannetti et al. (2018) is smaller and not universal compared to the FDI score used in Brescia et al. (2022) and Mazur et al. (2022). Even if less effective, Giannetti et al. (2018) still showed improvement in all cases, indicating

that ICON RI cannot have a negative effect on aesthetic aspects. Comparing the effectiveness of this technique with patients affected by other enamel defects similar to MIH is essential for comprehensive understanding.

In conclusion, the ICON technique has been effective in every case but to varying degrees of improvement. This can be explained by differences in the study period, proper application of the technique, the operator, the observer, and most likely the differences between the various aesthetic scales.

4.2. General Dentinal Hypersensitivity Results

Regarding dentinal hypersensitivity, before treatment, Nogueira et al. (2021) states that patients with MIH frequently present structural loss and hypersensitivity. After RI, only Brescia et al. (2022) studied hypersensitivity seriously, using two different and universal pain scales. They obtained positive results, with 100% of patients after 2 years experiencing no pain or very little pain on both the Shiff Air Index and the Wong-Baker Faces Pain Rating Scale. Before treatment, 24.3% and 33.4% of patients respectively reported pain. Although not studied in Mazur et al. (2022), these results are supported by the absence of hypersensitivity as a side effect, as well as the absence of loss of vitality, discoloration, or gingival changes after treatment. With only one article studying hypersensitivity, it cannot be definitively affirmed that RI reduces it without any doubt. However, the fact that the authors assessed this parameter with two different methods adds relevance, although more research is needed. This may suggest that tooth hypersensitivity reduces over time after the application of ICON, with good results even directly after treatment, though this should be interpreted cautiously pending further research.

4.3. General Structural Integrity Results

Finally, concerning structural integrity, as with hypersensitivity, only a few articles show results that can be discussed. Nogueira et al. (2021) reported a clear decrease in the risk of enamel breakdown before versus after treatment compared to FV and FV+etch techniques, where 6.1% of cases experienced failure, almost three times more than with FV and FV+etch. The survival rate of the teeth was almost double after one and a half

years in patients treated with ICON. They also showed better results in anterior teeth compared to molars, which are subject to greater mechanical stress, and better results in MIH yellow opacities, where brown opacities have almost three times more risk of failure. This study is supported by Altan & Yilmaz (2023), with higher values of enamel lesions in the control group between the initial value and 6 months after treatment compared to a reduction of enamel lesions after 1, 3, and 6 months in the ICON group. Despite the limited number of articles on the subject, it could be suggested that tooth resistance increases and the risk of failure decreases with the application of RI, even after 18 months of follow-up, demonstrating its longevity.

4.4. Patient and Observer Satisfaction

Furthermore, Brescia et al. (2022) also questioned the satisfactory results from the perspective of the patients themselves. In conclusion, all patients were satisfied, even if in some cases the results weren't optimal, thanks to both the attenuation of opacities and the improvement of dentinal hypersensitivity, showing a significant improvement compared to the initial condition.

Regarding the satisfaction of patients and observers in Altan & Yilmaz (2023), Giannetti et al. (2018), Mazur et al. (2022), and Nogueira et al. (2021), no specific information was found concerning their satisfaction after ICON resin infiltration treatment. However, given that the results perceived by patients and dentists show significant improvements in aesthetics, hypersensitivity, and structural integrity, it is reasonable to assume their satisfaction is undeniable.

Although all the results obtained show considerable improvement in all aspects, it is necessary to remain cautious about the limitations encountered. The difference in studied etiology, follow-up time, and the number of patients in each study are limitations to note, requiring a cautious interpretation of our results. A new study considering specifically the satisfaction of the patients and observers should be performed in order to respond better to the satisfaction part.

Lastly, it's important to note that ICON treatment is not only cost-effective due to its minimal number of sessions for achieving good results compared to other methods like fixed prostheses, but it also has an easy-to-follow and well-established protocol. This

accessibility means that general dentists, rather than just specialists, can successfully incorporate ICON into their practices, with a good knowledge of the different steps to follow and some training.

5. CONCLUSION

In conclusion, the comprehensive analysis of various studies on the efficacy of ICON resin infiltration reveals a consistent positive trend across multiple parameters over the long term, even with variations in effectiveness. The 3 key aspects investigated, namely, aesthetic appearance, structural integrity of teeth, and dentinal hypersensitivity, each demonstrate promising outcomes.

Aesthetic enhancement, the most extensively studied aspect, showcases significant improvement across most cases, although comparison is hindered by the varied aesthetic scales used. The potential for continued improvement in aesthetics over time underscores the durability of the ICON resin.

Regarding dentinal hypersensitivity, preliminary findings suggest a reduction in pain post-treatment, as indicated by a notable decrease in discomfort levels on the different scales studied.

In terms of structural integrity, limited but promising data suggest a decrease in the risk of enamel breakdown and an increase in tooth survival rates following ICON resin infiltration.

The conclusion of this study is made by affirming that the ICON technique is a good alternative on a long-term period to invasive solutions by proposing a minimal invasive treatment for patients affected with molar-incisal hypomineralization and even for other enamel defects from different aetiologies.

However, it is crucial to acknowledge the study's limitations, including variations in aetiology, follow-up duration, and sample sizes across studies. These constraints necessitate a cautious interpretation of the results and highlight the need for further research to elucidate the full scope of ICON resin infiltration's efficacy and its comparative effectiveness against alternative treatments.

Finally, it's worth mentioning that the fact that this treatment with ICON requires only a few sessions makes it cheaper than other techniques (such as fixed prostheses and others). In addition, it is an easy technique with a well-established protocol, which allows all dentists, not just specialists, to use it in their practice.

6. BIBLIOGRAPHY

- Almulhim, B. (2021). Molar and incisor hypomineralization. In *Journal of the Nepal Medical Association* (Vol. 59, Issue 235, pp. 295–302). Nepal Medical Association. <https://doi.org/10.31729/jnma.6343>
- Altan, H., & Yilmaz, R. E. (2023). Clinical evaluation of resin infiltration treatment masking effect on hypomineralised enamel surfaces. *BMC Oral Health*, 23(1). <https://doi.org/10.1186/s12903-023-03140-6>
- Arjomand, M. E., Ganjkar, M. H., & Ghamari, R. (2021). Effect of tea on color stability of enamel lesions treated with resin infiltrant. *Frontiers in Dentistry*, 18. <https://doi.org/10.18502/fid.v18i4.5434>
- Brescia, A. V., Montesani, L., Fusaroli, D., Docimo, R., & Di Gennaro, G. (2022). Management of Enamel Defects with Resin Infiltration Techniques: Two Years Follow Up Retrospective Study. *Children*, 9(9). <https://doi.org/10.3390/children9091365>
- Bulanda, S., Ilczuk-Rypuła, D., Dybek, A., Pietraszewska, D., Skucha-Nowak, M., & Postek-Stefańska, L. (2022). Management of Teeth Affected by Molar Incisor Hypomineralization Using a Resin Infiltration Technique—A Systematic Review. In *Coatings* (Vol. 12, Issue 7). MDPI. <https://doi.org/10.3390/coatings12070964>
- Farooq, I., & Bugshan, A. (2020). The role of salivary contents and modern technologies in the remineralization of dental enamel: A review. *F1000Research*, 9. <https://doi.org/10.12688/f1000research.22499.1>
- Srikumar GPV, Megha Ghosh, A. Arvind Kumar, Siddharth Bardia, Akansha Wasule, & J. S. Beautlin. (2024). An in vitro evaluation of Icon resin infiltrant penetration into demineralized enamel lesions using an indirect staining technique with confocal laser scanning microscope analysis in dual fluorescence mode. doi: 10.4103/JCDE.JCDE_3_24
- Giannetti, L. (2018). "Superficial infiltration to treat white hypomineralized defects of enamel: clinical trial with 12-month follow-up. In *Article in Journal of Biological Regulators and Homeostatic Agents*. <https://www.researchgate.net/publication/328402869>
- Kannan, A., & Padmanabhan, S. (2019). Comparative evaluation of Icon® resin infiltration and Clinpro™ XT varnish on colour and fluorescence changes of white spot lesions: a randomized controlled trial. *Progress in Orthodontics*, 20(1). <https://doi.org/10.1186/s40510-019-0276-y>
- Lopes, L. B., Machado, V., Mascarenhas, P., Mendes, J. J., & Botelho, J. (2021). The prevalence of molar-incisor hypomineralization: a systematic review and meta-analysis. *Scientific Reports*, 11(1). <https://doi.org/10.1038/s41598-021-01541-7>
- M. Mazur, S. Westland, D. Corridore, M. Vichi, F. Guerra, A. Maruotti, G.M. Nardi, & L. Ottolenghi. (2018). Objective and subjective aesthetic performance of icon® treatment for enamel hypomineralization lesions in young adolescents: a retrospective single center study. *J. Dent.* 68, 104–108.

- Mazur, M., Westland, S., Ndokaj, A., Nardi, G. M., Guerra, F., & Ottolenghi, L. (2022). In-vivo colour stability of enamel after ICON® treatment at 6 years of follow-up: A prospective single center study. *Journal of Dentistry*, 122. <https://doi.org/10.1016/j.jdent.2021.103943>
- Nogueira, V. K. C., Mendes Soares, I. P., Fragelli, C. M. B., Boldieri, T., Manton, D. J., Bussaneli, D. G., & Cordeiro, R. de C. L. (2021). Structural integrity of MIH-affected teeth after treatment with fluoride varnish or resin infiltration: An 18-Month randomized clinical trial. *Journal of Dentistry*, 105. <https://doi.org/10.1016/j.jdent.2020.103570>
- Paris S, Meyer-Lueckel H. Masking of labial enamel white spot lesions by resin infiltration--a clinical report. *Quintessence Int.* 2009 Oct;40(9):713-8. PMID: 19862396.
- Shah, Y., Deshpande, A., Jain, A., Jaiswal, V., & Andharia, M. (2023). Effectiveness of resin infiltration (ICON) and microabrasion-remineralization technique with two remineralizing agents (Tooth Mousse and Toothmin) on permanent incisor hypoplasia - A randomized clinical trial. *Journal of Indian Society of Pedodontics and Preventive Dentistry*, 41(3), 204–215. https://doi.org/10.4103/jisppd.jisppd_245_23
- Temudo, R., Neves, P., Ventura, I., & Lopes, L. (2022). A conservative approach to rehabilitate a molar-incisor hypomineralization case. *RGO - Revista Gaúcha de Odontologia*, 70. <https://doi.org/10.1590/1981-86372022001020200140>

7. ANNEXES

Annex 1. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Case Series.

JBI Critical Appraisal Checklist for Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Was the condition measured in a standard, reliable way for all participants included in the case series?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Were valid methods used for identification of the condition for all participants included in the case series?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Did the case series have consecutive inclusion of participants?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Did the case series have complete inclusion of participants?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Was there clear reporting of the demographics of the participants in the study?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Was there clear reporting of clinical information of the participants?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Were the outcomes or follow up results of cases clearly reported?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Was statistical analysis appropriate?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal: Include Exclude Seek further info

Comments (Including reason for exclusion)

Annex 2. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Case Control Studies.

JBI CRITICAL APPRAISAL CHECKLIST FOR CASE CONTROL STUDIES

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not applicable
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Were cases and controls matched appropriately?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Were the same criteria used for identification of cases and controls?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Was exposure measured in a standard, valid and reliable way?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Was exposure measured in the same way for cases and controls?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Were confounding factors identified?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Were strategies to deal with confounding factors stated?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Was the exposure period of interest long enough to be meaningful?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Was appropriate statistical analysis used?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal: Include Exclude Seek further info

Comments (Including reason for exclusion)

Annex 3. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Randomized Controlled Trials.

Assessor:	Date of Appraisal:	Record Number:
Study Author:	Study Title:	Study Year:

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	Was true randomization used for assignment of participants to treatment		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Was allocation to treatment groups concealed?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Were treatment groups similar at the baseline?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to administration of intervention/exposure						
4	Were participants blind to treatment assignment?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Were those delivering the treatment blind to treatment assignment?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	Were treatment groups treated identically other than the intervention		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to assessment, detection and measurement of the outcome						
7	Were outcome assessors blind to treatment assignment?		Yes	No	Unclear	N/A
	Outcome 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 7		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	Were outcomes measured in the same way for treatment groups?		Yes	No	Unclear	N/A
	Outcome 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 7		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

9	Were outcomes measured in a reliable		Yes	No	Unclea	N/A
	Outcome 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 7		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Bias related to participant retention

10	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described					
	Outcome 1		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Outcome 7		Yes	No	Unclea	N/A
Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Statistical Conclusion Validity

1	Were participants analysed in the groups to which they were randomized?				
1					
	Outcome 1	Yes	No	Unclea	N/A
	Result 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2	Yes	No	Unclea	N/A
	Result 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3	Yes	No	Unclea	N/A
	Result 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4	Yes	No	Unclea	N/A
	Result 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5	Yes	No	Unclea	N/A
	Result 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6	Yes	No	Unclea	N/A
	Result 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 7	Yes	No	Unclea	N/A
	Result 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

1	Was appropriate statistical analysis used?					
	Outcome 1		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6		Yes	No	Unclea	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Outcome 7		Yes	No	Unclea	N/A	
Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Result 2		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Result 3		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

		Yes	No	Unclea	N/A
1	Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3 Overall Include: Exclude: Seek Further Info:

Comments: