UNIVERSIDADE FEDERAL DE SANTA MARIA CENTRO DE CIÊNCIAS DA SAÚDE PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS ODONTOLÓGICAS

Davi Faria Lopes

INFLUÊNCIA DA PROTEÇÃO SUPERFICIAL NA LIBERAÇÃO DE FLÚOR E PROPRIEDADES MECÂNICAS DE CIMENTOS DE IONÔMERO DE VIDRO: REVISÃO SISTEMÁTICA E META-ANÁLISE

Santa Maria, RS 2021 **Davi Faria Lopes**

INFLUÊNCIA DA PROTEÇÃO SUPERFICIAL NA LIBERAÇÃO DE FLÚOR E PROPRIEDADES MECÂNICAS DE CIMENTOS DE IONÔMERO DE VIDRO: REVISÃO SISTEMÁTICA E META-ANÁLISE

Dissertação apresentada ao Programa de Pós-Graduação em Ciências Odontológicas, Área de Concentração em Odontologia, ênfase em Odontopediatria, da Universidade Federal de Santa Maria (UFSM, RS), como requisito parcial para a obtenção do título de **Mestre em Ciências Odontológicas.**

Orientador: Profa. Dra. Rachel de Oliveira Rocha

Santa Maria, RS 2021 This study was financied in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001

Lopes, Davi Faria INFLUÊNCIA DA PROTEÇÃO SUPERFICIAL NA LIBERAÇÃO DE FLÚOR E PROPRIEDADES MECÂNICAS DE CIMENTOS DE IONÔMERO DE VIDRO: REVISÃO SISTEMÁTICA E META-ANÁLISE / Davi Faria Lopes.- 2021. 53 p.; 30 cm Orientadora: Rachel de Oliveira Rocha Dissertação (mestrado) - Universidade Federal de Santa Maria, Centro de Ciências da Saúde, Programa de Pós Graduação em Ciências Odontológicas, RS, 2021 1. Cimento de ionômero de vidro 2. Testes mecânicos 3. Flúor 4. Testes de dureza I. de Oliveira Rocha, Rachel II. Título.

Sistema de geração automática de ficha catalográfica da UFSM. Dados fornecidos pelo autor(a). Sob supervisão da Direção da Divisão de Processos Técnicos da Biblioteca Central. Bibliotecária responsável Paula Schoenfeldt Patta CRB 10/1728.

Declaro, DAVI FARIA LOPES, para os devidos fins e sob as penas da lei, que a pesquisa constante neste trabalho de conclusão de curso (Dissertação) foi por mim elaborada e que as informações necessárias objeto de consulta em literatura e outras fontes estão devidamente referenciadas. Declaro, ainda, que este trabalho ou parte dele não foi apresentado anteriormente para obtenção de qualquer outro grau acadêmico, estando ciente de que a inveracidade da presente declaração poderá resultar na anulação da titulação pela Universidade, entre outras consequências legais. **Davi Faria Lopes**

INFLUÊNCIA DA PROTEÇÃO SUPERFICIAL NA LIBERAÇÃO DE FLÚOR E PROPRIEDADES MECÂNICAS DE CIMENTOS DE IONÔMERO DE VIDRO: REVISÃO SISTEMÁTICA E META-ANÁLISE

Dissertação apresentada ao Programa de Pós-Graduação em Ciências Odontológicas, Área de Concentração em Odontologia, ênfase em Odontopediatria, da Universidade Federal de Santa Maria (UFSM, RS), como requisito parcial para a obtenção do título de Mestre em Ciências Odontológicas.

Aprovado em 30 de setembro de 2021:

Las Harrent

Rache de Oliveira Rocha, Dr. (UFSM) (Presidente da Banca/Orientadora)

Fernanda Riffo Ortiz Fernanda Ruffo Ortiz, Dra. (UFSM)

Graziela Botton, Dra. (CEOM)

Santa Maria, RS 2021

DEDICATÓRIA

Dedico essa dissertação de mestrado para à minha mãe, principal responsável por minhas conquistas. Minha maior influência em educação, respeito e amor ao próximo. Exala boas energias, por isso as atrai no mesmo nível. Ela é uma pétala, só que de ferro. Delicada, mas forte, muito forte. Não duvide. Mulher batalhadora, uma grande professora, educadora e pedagoga, musa para todos que estão a sua volta.

AGRADECIMENTOS

O meu desejo é agradecer à todas as pessoas que fizeram parte dessa caminhada junto comigo, por isso primeiramente agradeço à todos que estiveram ao meu lado de alguma forma nesse tempo.

Quero agradecer principalmente à três mulheres que fazem parte da minha vida e foram importantíssimas nessa jornada, minha mãe **Hugélia Santos Faria**, irmã **Dandara Faria Lopes** e namorada **Rafaela Piaia Basso**, pelo o apoio incondicional durante esse tempo, enfrentaram junto comigo todos os momentos desafiadores que o curso de pósgraduação possui e sempre instigaram a minha melhor versão. Obrigado por serem únicas e me fazerem sentir amado, protegido e confiante a todo momento.

Agradeço a Universidade Federal de Santa Maria, à todos os funcionários das clínicas, secretária e limpeza. Mais precisamente agradeço ao Programa de Pós-Graduação em Ciências Odontológicas, ao seu corpo docente que transmitiram o seu conhecimento com muito profissionalismo e sabedoria. Com relevância agradeço todos os colegas que fizeram parte da minha turma de pós-graduação por compartilharem seus conhecimentos, ideias, informações, novidades das diversas áreas dentro da nossa profissão e também fora dela.

Agradeço pela contribuição da banca de exame de qualificação e pela participação dos membros da banca examinadora da defesa.

Meus sinceros agradecimentos a professora **Rachel de Oliveira Rocha**, por todo o apoio, suporte emocional e técnico-científico que passou durante esse tempo dentro da pósgraduação. A pessoa que me inspira a todo o momento, seja pelo seu lado profissional, de educadora e principalmente humano. Sou grato por todos os ensinamentos passados durante esse tempo de orientação dentro da clínica, desde a graduação, e dentro da Academia é a principal responsável a encorajar conhecer o lado da pesquisa e inspirar na docência, mostrando que o conhecimento prático está sempre atrelado ao científico. Obrigado por ser essa orientadora ímpar, insubstituível, com certeza sempre lembrarei com amor e admiração.

RESUMO

INFLUÊNCIA DA PROTEÇÃO SUPERFICIAL NA LIBERAÇÃO DE FLÚOR E PROPRIEDADES MECÂNICAS DE CIMENTOS DE IONÔMERO DE VIDRO: REVISÃO SISTEMÁTICA E META-ANÁLISE

AUTOR: Davi Faria Lopes ORIENTADORA: Dra. Rachel de Oliveira Rocha

O cimento de ionômero de vidro (CIV) tem sido amplamente utilizado em Odontopediatria como material restaurador definitivo em razão das suas propriedades principais de adesão química ao esmalte e a dentina e liberação de flúor. Devido ao longo tempo de presa e sensibilidade à perda (sinérese) e ganho de água (embebição) durante esse período, tem-se sugerido o uso de materiais para proteção da superfície das restaurações, isolando-as do contato com a saliva até a presa final do CIV. No entanto, ainda não está claro na literatura se o efeito do uso destes agentes de proteção superficial nas propriedades dos CIVs. Deste modo, esta revisão sistemática de estudos laboratoriais teve como objetivo avaliar o efeito dos agentes de proteção superficial na libertação de flúor, microdureza e resistência dos cimentos de ionômero de vidro convencionais. Os estudos foram identificados a partir de uma busca sistemática nas bases de dados PubMed, Web of Science e Scopus. Dois revisores, de forma independente, seleccionaram os estudos, um revisor extraiu os dados, e avaliou o risco de viés. Os dados resultantes foram meta-analisados utilizando um modelo de efeitos aleatórios, com um nível de significância de p < 0.05. A heterogeneidade (I²) foi avaliada através do teste Q de Cochran. Dos 1595 estudos potenciais, 26 estudos elegíveis foram identificados com dados de liberação de flúor, microdureza ou resistência. Os agentes de proteção superficial reduziram significativamente a liberação de flúor (Z=9,62; p<0,00001) e a microdureza (Z = 2,77; p=0,006), e não tiveram efeito sobre a resistência (Z=0,91; p=0,36). A maioria dos estudos apresentou alto risco de viés. Com base nos resultados encontrados, pode-se concluir que o emprego de agentes de proteção superficial não melhoram as propriedades mecânicas do cimento de ionômero de vidro e prejudicam a libertação de flúor.

Palavras-chave: Cimentos de ionômero de vidro. Testes mecânicos. Flúor. Testes de dureza.

ABSTRACT

INFLUENCE OF SURFACE PROTECTION ON FLUORIDE RELEASE AND MECHANICAL PROPERTIES OF GLASS IONOMER CEMENTS: SYSTEMATIC REVIEW AND META-ANALYSIS

AUTHOR: Davi Faria Lopes ADVISOR: Dra. Rachel de Oliveira Rocha

Glass ionomer cement (GIC) has been widely used in pediatric dentistry as a definitive restorative material due to its main properties of chemical bonding to enamel and dentin and fluoride release. Due to the long setting time and sensitivity to water loss (syneresis) and gain (imbibition) during this period, surface coating agents have been suggested to isolate restorations from contact with saliva until the final setting of the GIC. However, it is still unclear in the literature whether the effect of using these surface coating agents on the properties of GICs. Thus, this systematic review of laboratory studies aimed to evaluate the effect of surface coating agents on fluoride release, microhardness, and strength of conventional glass ionomer cements. Studies were identified from a systematic search in PubMed, Web of Science, and Scopus databases. Two reviewers independently selected the studies; one reviewer extracted the data and assessed the risk of bias. The resulting data were meta-analyzed using a randomeffects model, with a significance level of p < 0.05. Heterogeneity (I2) was assessed using Cochran's Q test. Of the 1595 potential studies, 26 eligible studies were identified with fluoride release, microhardness, or strength data. Surface coating agents significantly reduced the fluoride release (Z=9.62; p<0.00001) and microhardness (Z = 2.77; p=0.006), and had no effect on strength (Z=0.91; p=0.36). Most of the studies presented a high risk of bias. Based on the results found, it can be concluded that surface coating agents do not improve the mechanical properties of glass ionomer cement and impair fluoride release.

Keywords: Glass ionomer cements. Mechanical tests. Fluoride. Hardness tests.

SUMÁRIO

1 INTRODUÇÃO	10
2 ARTIGO - INFLUENCE OF SURFACE COATING AGENTS ON FLU	
LEASE AND MECHANICAL PROPERTIES OF CONVENTIONAL G	LASS IONO-
MER CEMENTS: SYSTEMATIC REVIEW AND META-ANALYSIS	12
3 CONCLUSÃO	
REFERÊNCIAS	40
ANEXO 1	41
ANEXO 2	52

1 INTRODUÇÃO

O cimento de ionômero de vidro (CIV) é um dos materiais mais versáteis na Odontologia, devido às suas excelentes propriedades, como a biocompatibilidade, adesão química e coeficiente de expansão térmica semelhante à estrutura dentária. Além disso, o CIV funciona como um reservatório de liberação de flúor exercendo um efeito preventivo e terapêutico contra a cárie (DE AMORIM, LEAL, FRENCKEN, 2012). Em razão destas características, o CIV tem sido amplamente utilizado em Odontopediatria como material restaurador definitivo.

Porém, o CIV apresenta algumas peculiaridades que devem ser respeitadas para garantir suas melhores propriedades. Essencialmente, o cimento de ionômero vidro é composto por partículas de vidro de silicato de alumínio/cálcio e fluoreto de cálcio, que é misturado com uma solução aquosa de ácido policarboxílicos (ácidos poliacrílico – principal componente, itacônico e tartárico) resultando em uma matriz de policarboxilato de cálcio e alumínio. A reação de presa do cimento ocorre na presença de água, pois os ácidos policarboxílicos precisam desse meio para liberar prótons, iniciando a reação ácido-base e solidificando o material. Esta reação é, no entanto, lenta, podendo se estender por até 24 horas após a mistura do material e, durante este período, o cimento é sensível a perda (sinérese) ou ganho (embebição) de água, que pode interferir na formação da matriz, com consequente comprometimento das propriedades mecânicas do material. (SIDHU, NICHOLSON, 2016). Assim, o uso de CIV para restaurações dentárias de longa duração exige o emprego de materiais para proteção da superfície das restaurações, isolando-as do contato com a saliva, ou seja, que evitem os fenômenos de sinérese e embebição até a presa final do CIV.

Os materiais empregados mais comumente empregados para esse fim são os vernizes cavitários, sistemas adesivos, esmalte cosmético incolor, manteiga de cacau e vaselina sólida, além de produtos específicos comercializados para esse fim. A vaselina é considerada uma boa opção devido à sua segurança e biocompatibilidade, além de baixo custo; no entanto, pode ser facilmente removida e assim, um material protetor de superfície mais duradouro é desejado, sem que comprometa a liberação de flúor (ULUSOY, TUNC, BAYRAK, 2007).

HESSE et al., 2018 ao avaliarem o desgaste clínico de restaurações de CIV em molares decíduos ao longo de três anos, observaram um menor desgaste das restaurações protegidas por um sistema adesivo nanoparticulado quando comparadas as revestidas com vaselina sólida. Já no estudo de JAFARPOUR et al., 2019, as restaurações de CIV protegidas com material resinoso (*resin-based coating*) apresentaram menor sorção e solubilidade comparadas as que não foram protegidas. Entretanto, a propriedade de liberação de flúor parece ser comprometida com o emprego de materiais resinosos para proteção superficial de restaurações de CIV (KAMATHAM, REDDY, 2013).

Assim, os resultados não consensuais de estudos que avaliaram diferentes materiais para proteção superficial de restaurações de CIV fazem com que a sistematização dos resultados dos estudos existentes, de forma a auxiliar a decisão de escolha do melhor material para essa finalidade seja necessária. Assim, o presente estudo tem como objetivo revisar sistematicamente a literatura de estudos laboratoriais a fim de identificar o melhor material para proteção superficial de restaurações de cimento de ionômero de vidro.

2 ARTIGO - INFLUENCE OF SURFACE COATING AGENTS ON FLUORIDE RELEASE AND MECHANICAL PROPERTIES OF CONVENTIONAL GLASS IONOMER CEMENTS: SYSTEMATIC REVIEW AND META-ANALYSIS.

O presente trabalho está apresentado na forma artigo, redigido conforme as normas do periódico International Journal of Paediatric Dentistry (ISSN 1365-263X); Qualis CAPES Quadriênio 2013-2016 - A1.

Article type: Systematic review

Influence of surface coating agents on fluoride release and mechanical properties of conventional glass ionomer cements: Systematic review and Meta-analysis.

Davi Faria Lopes^a, Fabio Zovico Maxnuck Soares^b, Rachel de Oliveira Rocha^c

^A Dental Science Graduate Program, Federal University of Santa Maria, Santa Maria, RS, Brazil
 ^B Department of Restorative Dentistry, Federal University of Santa Maria, Santa Maria, RS, Brazil
 ^C Department of Stomatology, Federal University of Santa Maria, Santa Maria, RS, Brazil

Author contributions:

ROR conceived the idea and study design. DFL and ROR performed the literature search.

ROR performed the extraction of data and the meta-analysis. DFL wrote the manuscript. ROR

and FZMS contributed substantially to discussion and proofread the manuscript before its submission.

Running title: Surface coating of glass ionomer cements

Correspondence address:

Dr. Rachel de Oliveira Rocha

Department of Stomatology, Pediatric Dentistry

Federal University of Santa Maria, Santa Maria, RS, Brazil

Av. Roraima, 1000 Prédio 26 F, Cidade Universitária, Santa Maria, RS, Brazil

Phone: +55 55 3220 9266 e-mail: rachelrocha@smail.ufsm.br

Word count: 4181

Influence of surface coating agents on fluoride release and mechanical properties of conventional glass ionomer cements: Systematic review and Meta-analysis.

ABSTRACT

Background: The effect of surface coating agents on glass ionomer cements' properties is unclear.

Aim: This systematic review of laboratory studies aimed to assess the effect of surface coating agents on fluoride release, microhardness, and strength of conventional glass ionomer cements.

Design: Studies were identified from a systematic search across the electronic databases PubMed, Web of Science, and Scopus. Two reviewers independently selected the studies; one reviewer extracted the data and evaluated the risk of bias. The outcome data were metaanalyzed using a random-effects model, with a significance level of p < 0.05. Heterogeneity (I²) was assessed by the Cochran Q test.

Results: From 1595 screened studies, 26 eligible studies were identified with fluoride release, microhardness, or strength data. Surface coating agents significantly impaired the fluoride release (Z=9.62; p<0.00001) and microhardness (Z=2.77; p=0.006), and had no effect on strength (Z=0.91; p=0.36). Most of the studies presented a high risk of bias.

Conclusion: This systematic review and meta-analysis evidence that surface coating agents do not improve the mechanical properties of glass ionomer cement and impair the fluoride release.

Keywords: glass ionomer cement; systematic review; dentin; surface coating, fluoride release.

1. INTRODUCTION

Over the years, glass ionomer cements have had their properties improved to enable to be used in long-term restorations. The advantageous glass ionomer properties, including fluoride release, chemical adhesion, and biological compatibility,¹ contribute to its wide use in dentistry and, in particular, in pediatric dentistry. However, the prolonged setting reaction and moisture sensitivity² are concerns as early water contamination or prolonged dehydration can compromise the mechanical properties^{3,4} and the restorations clinical performance.⁵ To maintain the water balance during the setting reaction, the use of surface coating agents has been suggested,⁶⁻⁸ including petroleum jelly, waterproof varnish, and light cure resins.^{9,10}

According to previously published studies,^{6,8} the ideal characteristics of a surface coating agent include protecting the glass ionomer cement during the maturation of material before the restoration be exposed to the oral environment (at least for 1 hour).^{3,4} Longer protection times are also associated with improving mechanical^{9,11,12} and physical properties of glass ionomer cements.¹³

Nevertheless, there seems to be no consensus about the best surface coating agent and, more importantly, whether it is even necessary. Fluoride releasing from coated glass ionomer cements seems to be severely impaired¹⁴ by surface coating agents. Moreover, the influence of surface coating agents on mechanical properties seems to be material-dependent. Leiskar et al.,¹⁵ pointed out that there is no need for coating agents over Fuji IX (GC Corporation) restorations to improve the strength. A similar trend was also found for other brands of glass ionomer cement and surface coating agents.^{10,16,17} The effectiveness of surface coating in increase the microhardness of conventional glass ionomer cements is also unclear, as some studies pointed out some benefits^{6,9} and other no effect of coating agents.^{16,18,19}

Thus, considering the importance of laboratory studies as a means of evaluating

materials and, to some extent, predicting their clinical performance, and the role of systematic review in the decision-making process; the aim of this systematic review of laboratory studies was to assess the effect of surface coating agents on fluoride release, microhardness and strength of conventional glass ionomer cements. The tested null hypothesis was that surface coating agents do not influence the considered properties of glass ionomer cements.

2. MATERIALS AND METHODS

This systematic review was conducted and reported according to the Cochrane Handbook²⁰ and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).²¹ The research PICO question was: "Are surface coating agents on glass ionomer cement really necessary to obtain better properties?"; in which the conventional glass ionomer cement was the 'population'; surface coating agents were the 'intervention'; uncoated was the 'control, and fluoride release, hardness, and shear punch or flexural strength were the 'outcomes'.

2.1 Search strategy

Three electronic databases PubMed/MEDLINE, SCOPUS, and ISI Web of Science, were searched to identify potential studies related to the research question. A search strategy was developed for PubMed/MEDLINE by combining controlled vocabulary (Mesh terms) and free terms as follow: ((((((glass ionomer cements[MeSH Terms]) OR (glass ionomer cements)) OR (glass ionomer)) OR (glass-ionomer)) OR (ionomer)) OR (ionomeric)) AND (((((((((petrolatum[MeSH Terms]) OR (vaseline))) OR (surface coating)) OR (surface coat)) OR (coating)) OR (coat)) OR (surface protective agents)) OR (surface protective)) OR (surface protection)) OR (petroleum jelly)). An adapted strategy was developed for SCOPUS

ISI of Science and for Web considering the terms (ALL ("glass ionomer") AND ALL ("surface coating" OR "surface protection")) and (GLASS IONOMER) AND (SURFACE COATING), respectively. No language or publication date restrictions were considered in the search. Search results up June 2021 were collected in an electronic spreadsheet (Numbers 11.1, Apple Inc, Cupertino, CA, USA) and manually crosschecked to eliminate duplicates.

2.2 Study selection, inclusion, and exclusion criteria

The title and abstracts of each study were independently screened by two calibrated reviewers (D.F.L. and R.O.R) (Kappa= 0.82) according to the eligibility criteria: compared any surface coating agent with a control (uncoated) on conventional glass ionomer cements considering the properties: fluoride release, hardness, or strength. A third reviewer (F.Z.M.S.) was consulted to solve, by consensus, disagreements between examiners.

The selected studies were full-text retrieved and reviewed by the two reviewers and studies that not compared the same surface coating agent with a control using the same glass ionomer cement; and not presented the outcome presented as means and standard deviation were excluded.

The reference lists of the selected studies were manually screened to identify studies not registered in the search databases. Studies reporting the same bond strength data were considered only once.

2.3 Data extraction

A predefining collection form (Numbers 11.1, Apple Inc, Cupertino, CA, USA) was used to register the extracted data from the included studies, including first author name, year of publication, country of the first author, glass ionomer cement commercial brand name, coating agent, methodology, sample size and evaluation time.

2.4 Assessment of risk of bias

The risk of bias criteria was adapted from a previous systematic review of in vitro studies,²² considering the items: sample size calculation, random sequence for specimens allocation, complete description of specimens preparation, a single operator responsible for specimens preparation, glass ionomer cement used according to the manufacturer's instructions, outcome assessment clearly described and blinding of the operator responsible for undescribed or unclear item, a 'NO' was attributed. Low risk of bias was considered for those studies with 6 or 7 'YES', moderate risk of bias was considered for studies that received 1 to 3 'YES' were considered as high risk of bias.

2.5 Data analysis

Meta-analysis was undertaken separately for fluoride release, hardness, strength. The inverse of variances (Z test) with a random-effects model was used for all analyses, considering a significance level of 5%. A predefined formula²⁰ was used to obtain a grouped mean and standard deviation for the studies that considered more than one glass ionomer cement or coating agent. Subgroup analyses were performed considering the evaluation time (after specimens storage). A grouped mean and standard deviation was also obtained for evaluation time when only a few studies considered a specific period.

Heterogeneity among studies was assessed using Cochran's Q statistic and I² statistics. I² values higher than 50% were considered heterogeneous.20 All analyses were performed using Review Manager software (RevMan version 5.3; Cochrane Collaboration, London, UK).

3. RESULTS

3.1 Study selection

The study selection process as a PRISMA flowchart is shown in Figure 1. From the searched database, 1856 records were identified (1158 from PubMed, 487 from Scopus, 202 from Web of Science, and 9 from free search on Google Scholar). After subtraction of duplicates (261 records), the title and abstract of 1595 studies were reviewed, and 1551 studies were not included because they were not relevant. Thus, the full text of 44 studies was assessed, and eighteen studies were excluded. The remaining twenty-six studies were included in the systematic review and meta-analysis.

3.2 Study characteristics

Table 1 presents the data of descriptive analysis. The twenty-six studies were from fifteen countries, almost equally distributed. Croatia,²³⁻²⁵ India,^{14,26,27} Iran^{16,19,28} and Turkey²⁰⁻³¹ contributed with 3 studies each, Brazil,^{32,33} and United States^{34, 35} with two studies each, and the other countries with one study each. All studies were published in English. Studies were published between 1994 and 2021.

Despite a significant variation in glass ionomer brand description, Fuji IX's most evaluated material (12 studies),^{10,15,18,19,25,28-31,33,36,37} whereas G-Coat and Equia were the most evaluated coating agents, considered in 11 studies,^{10,16,17,19,26-31,36} and 5 studies,^{9,18,23,24,38} respectively. One single surface coating agent was compared with a control (uncoated) in twelve studies,^{9,10,15,19,25,27-31,36,38} and the others fourteen studies compared two or more coating agents. Nine studies evaluated the effect of coating on glass ionomer microhardness,^{6,9,16,18,19,28,32,33,39} 8 studies evaluated the fluoride release,^{14,23,25-27,29,34,40} 11 studies evaluated the strength,^{10,15,19,24,28,30,31,35-38} 5 studies evaluated flexural

strength,^{10,24,28,30,38} 3 studies shear punch strength,^{15,19,37} 2 studies evaluated diametral tensile strength,^{35,36} and 1 study evaluated compressive strength.³¹

3.3 Risk of bias assessment

The risk of bias assessment for the included studies is displayed in Table 2. Five studies were judged as moderate risk of bias,^{10,14,33,38,40} and the remaining eighteen as high risk⁻ Unclear or absence of information about sample size calculation, a single operator responsible for specimens preparation, and blinding the operator responsible for the outcome analysis were observed in most studies.

3.4 Meta-analysis

Twenty-six included studies were considered in the meta-analysis. For the first analysis (fluoride release) (Figure 2), coated vs. control (uncoated), the overall effect was statistically significant (Z = 9.62; p < 0.00001), i.e., the use of coated material impairs the fluoride release from glass ionomer cement. A similar effect was found for subgroup analysis considering the evaluation time (after 7, 14, 21, 28 or 30, and more than 60 days). High heterogeneity was found (95%).

The overall meta-analysis considering microhardness (Figure 3) also show a statistically significant effect (Z = 2.77; p = 0.006) of coat reducing the mechanical property, with a heterogeneity parameter (I^2) of 92%. However, a subgroup analysis, considering immediate and 28 or 30 days evaluation did not show this negative effect (Z = 1.11; p = 0.27, and Z = 1.38; p = 0.17, respectively).

The third meta-analysis considering the strength data is depicted in Figure 4. The overall and subgroup analysis for the different evaluation times (immediate, 28/35 days, 8 weeks, 6, and 12 months) did not show a significant coated effect on glass ionomer cement

strength. The overall meta-analysis resulted in high heterogeneity ($I^2=86\%$).

4. DISCUSSION

This meta-analysis set out to examine the effects of surface coating agents on glass ionomer cement properties. Pooled effect sizes across all considered glass ionomer properties outcomes showed that coating agents do not improve mechanical properties (strength) and impair the fluoride release and surface microhardness.

Glass ionomer cement has been considered an option to restore primary and permanent teeth because of its advantageous properties as adhesion to enamel and dentin, biocompatibility, and fluoride release. However, the long setting time,³⁶ and water sensitivity during the setting reaction can compromise the adequate maturation, impairing mechanical properties, and as a consequence, reducing the longevity of the restorations. Several surface coating agents have been suggested to protect the glass ionomer during the hardening and maturation process,³¹ increasing the mechanical properties and clinical performance.^{41,42} At the moment, there is no consensus regarding the best surface coating agent or even if it is really necessary, as there is no consensus about it.

The ability to release fluoride is considered a primary property of glass ionomer,⁴² on account of caries inhibitory effect adjacent to restorations. A recent panel on the threshold properties for the clinical use of glass ionomer considered that higher fluoride release values with no significant erosion are desirable.⁴² Eight studies identified in this review assessed the fluoride release of glass ionomer coated or uncoated.^{14,23,25-27,29,34,40} The pooled effect size found significantly higher fluoride release values for uncoated groups, regardless of the evaluation time (immediate to more than 60 days). Higher fluoride release values of uncoated glass ionomer were expected as the setting reaction may extend for 24 hours.^{23,25,26} During

this period, the immature glass ionomer is more soluble, and high levels of fluoride release are observed due to the wash-off effect.²⁶ The use of surface coating agents could inhibit the superficial wash-off effect,^{14,26} reducing fluoride release. However, there was substantial heterogeneity among studies regarding specimens preparation, glass ionomer brands, storage media, and fluoride release evaluation method.

A similar trend was observed regarding the effect of coating agents on glass ionomer microhardness. Although no effect had been observed on immediate and 28/30 days, an adverse effect of coating agents on microhardness values was observed on overall and subgroup meta-analysis, considering the evaluation time +56 days. High heterogeneity was also observed, probably related to microhardness test parameters (Vickers and Knoop indenter and applied load), different surface coating agents evaluated, including petroleum jelly, nail varnish, and resinous coating agents. The poor hardness properties of coating agents because of the absence or low amount of fillers can explain the observed result. However, even after a longer storage time, coated agents could not able to improve glass ionomer microhardness. Microhardness is directly related to the compressive strength of a restorative material,⁴³ and both are considered as primary mechanical properties for glass ionomer restorations.⁴² In the present systematic review, only one study evaluated compressive strength.³¹ Another 10 studies evaluated flexural,^{10,24,28,30,38} shear punch,^{15,19,37} and diametral tensile strength.^{35,36} Even so, no significant effect was observed for coating agents on glass ionomer strength, regardless of the evaluation time.

The included studies compared several surface coating agents, including petroleum jelly, nail varnish, adhesive systems, and light-cured resinous coat. G-Coat Plus (GC Corporation) and petroleum jelly were the most evaluated coated. Despite the differences in composition, no subgroup meta-analysis was performed considering the coating agents, whereas the considered control group was uncoated glass ionomer. Furthermore, subgroups

meta-analysis considering the longer evaluation time resulted in the same trend of immediate evaluation, confirming the absence of effect on strength or negative effect on fluoride release and microhardness, of surface coating agents compared to control.

Fuji IX (GC Corporation) was the most evaluated glass ionomer cement among the various cements used in the included studies. The diversity of glass ionomer cements, surface coating agents, and mainly, the non-standardized testing protocols are probably responsible for heterogeneity found for all overall meta-analyses. High heterogeneity is usual in a metaanalysis of laboratory studies,²² and for this reason, the meta-analyses were performed using the random effect model. Furthermore, only five studies^{10,14,33,38,40} presented a moderate risk of bias; the others presented a high risk of bias. The sample size calculation, random sequence of specimens allocation, a single operator responsible for specimens preparation, and blinded operator responsible for the outcome analysis were the most undescribed or unclear parameters considered in the risk of bias. The heterogeneity and the high risk of bias of the included studies also represent a limitation of this systematic review; thus, the results should be interpreted with caution. Nevertheless, the number of included studies, from several research groups, publication years, evaluating several glass ionomer cements, and coating agents available in the market, can provide a good overview of the research question. Even so, high-quality laboratory and clinical studies are needed to confirm the obtained results. Whereas laboratory studies can predict the clinical performance of glass ionomer restorations,⁴² the results of this systematic review showed that surface coating agents may not be needed to obtain the best properties of glass ionomer cements, and may even impair the fluoride release.

5. CONCLUSION

The available evidence from laboratory studies indicates that surface coating agents do

not improve the mechanical properties of glass ionomer cement and impair the fluoride release. Our data suggest that surface coating on glass ionomer cements is not necessary.

Why this paper is important to pediatric dentists

Surface coating can not be used in clinical practice with no detrimental effect on glass ionomer cements.

The use of surface coating agents can jeopardize the fluoride release from glass ionomer cements.

Figure legends

Figure 1. Flow diagram for studies' search and inclusion according to PRISMA 2020.

Figure 2. Overall meta-analysis comparing the fluoride release from coated *vs* uncoated glass ionomer cements.

Figure 3. Forest plot for microhardness values comparing coated *vs* uncoated glass ionomer cements.

Figure 4. Forest plot for strength values comparing coated *vs* uncoated glass ionomer cements.

REFERENCES

1. Wiegand A, Buchalla W, Attin T. *Review on fluoride-releasing restorative materialsfluoride release and uptake characteristics, antibacterial activity and influence on caries formation.* Dent Mater 2007;23:343–362.

2. Garoushi S, Vallittu PK, Lassila L. *Characterization of fluoride releasing restorative dental materials*. Dent Mater J 2018;37:293–300.

3. Causton BE. *The physico-mechanical consequences of exposing glass ionomer cements to water during setting*. Biomaterials 1982;2:112-115.

4. Mount GJ, Makinson OF. *Glass-ionomer restorative cements: Clinical implication of the setting reaction.* Oper Dent 1982;7:134-141.

5. Wilson AD. Developments in glass-ionomer cements. Int J Prosthodont 1989; 2:438–46.

6. Hotta M, Hirukawa H. Abrasion resistance of restorative glass-ionomer cements with a light-cured surface coating. Oper Dent 1994;19:42-46.

7. Ribeiro APG, Serra MC, Paulillo LAMS, Rodrigues AL. *Effectiveness of surface protection for resin-modified glass-ionomer materials*. Quintessence Int 1999;30:427-431.

8. Serra MC, Navarro MF, Freitas SF, Carvalho RM, Cury JA, Retief DH. *Glass ionomer cement surface protection*. Am J Dent 1994;7:203-206.

9. Handoko MW, Tjandrawinata R. *The effect of nano filled resin coating on the hardness of glass ionomer cement*. Scientific Dent J 2020;4:97-100.

10. Bonifacio CC, Werner A, Kleverlaan CJ. *Coating glass-ionomer cements with a nanofilled resin.* Acta Odontol Scand 2012;70:471–477.

11. Bagheri R, Azar MR, Burrow MF, Tyas MJ. *The effect of aging on the fracture toughness of aesthetic restorative materials*. Am J Dent 2010;23:142–146.

12. Miyazak M, Moore BK, Onose H. *Effect of surface coatings on flexural properties of glass ionomers*. Eur J Oral Sci 1996;104:600–604.

13. Jafarpour D, Mese A, Ferooz M, Bagheri R. *The effects of nanofilled resin-based coatings* on the physical properties of glass ionomer cement restorative materials. J Dent 2019;89:103177.

14. Kamatham R, Reddy SJ. Surface coatings on glass ionomer restorations in Pediatric dentistry-Worthy or not? J Indian Soc Pedod Prev Dent 2013;31:229-233.

15. Leirskar J, Nordbø H, Mount GJ, Ngo H. *The influence of resin coating on the shear punch strength of a high strength auto-cure glass ionomer.* Dent Mater 2003;19:87-91.

16. Faraji F, Heshmat H, Banava S. *Effect of protective coating on microhardness of a new glass ionomer cement: Nanofilled coating versus unfilled resin.* J Conserv Dent 2017;20:260-263.

17. Pilo R, Ben-Amar A, Barnea A, Blasbalg Y, Levartovsky S. *The effect of resin coating on the shear punch strength of restorative glass ionomer cements*. Clin Oral Investig 2017;21:1079-1086.

18. RyuW, Park H, Lee J, Seo H. *Effect of Nano-filled Protective Coating on Microhardness* and wear resistance of glass-ionomer cements. J Korean Acad Pediatr Dent 2019;46:226-232.

19. Bagheri R, Taha NA, Azar MR, Burrow MF. *Effect of G-Coat Plus on the mechanical properties of glass-ionomer cements*. Aust Dent J 2013;58:448-453.

20. Higgins J, Green S, editors. *Cochrane handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011. Available from www.cochranehandbook.org

21. Liberati A, Altman DG, Tetzlaff J, et al. *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* PLoS Med 2009;6:e1000100.

22. Sarkis-Onofre R, Skupien JA, Cenci MS, Moraes RR, Pereira-Cenci T. *The role of resin cement on bond strength of glass-fiber posts luted into root canals: a systematic review and meta-analysis of in vitro studies.* Oper Dent 2014;39:E31–E44.

23. Brzović-Rajić V, Miletić I, Gurgan S, Peroš K, Verzak Ž, Ivanišević-Malčić A. *Fluoride* release from glass ionomer with nano filled coat and varnish. Acta Stomatol Croat 2018;52:307-313.

24. Gorseta K, Glavina D, Skrinjaric T, Czarnecka B, Nicholson JW. *The effect of petroleum jelly, light-cured varnish and different storage media on the flexural strength of glass ionomer dental cements.* Acta Biomater Odontol Scand 2016;2:55-59.

25. Kelić K, Par M, Peroš K, Šutej I, Tarle Z. *Fluoride-Releasing Restorative Materials: The Effect of a Resinous Coat on Ion Release.* Acta Stomatol Croat 2020;54:371-381.

26. Kishore G, Sai-Sankar AJ, Pratap-Gowd M, Sridhar M, Pranitha K, Sai-Krishna VS. *Comparative Evaluation of Fluoride Releasing Ability of Various Restorative Materials after the Application of Surface Coating Agents - An In-vitro Study.* J Clin Diagn Res 2016;10:ZC38-ZC41.

27. Tiwari S, Nandlal B. *Effect of nano-filled surface coating agent on fluoride release from conventional glass ionomer cement: an in vitro trial.* J Indian Soc Pedod Prev Dent 2013;31:91-5.

28. Bagheri R, Palamara J, Mese A, Manton DJ. *Effect of a self-adhesive coating on the loadbearing capacity of tooth-coloured restorative materials*. Aust Dent J 2017;62:71-78.

29. Ugurlu M. *Effect of the polishing procedure and surface sealant application on fluoride release*. Braz Dent Sci 2021;24:1-10.

30. Ugurlu M. *Effects of surface coating on the flexural strength of fluoridereleasing restorative materials after water aging for one year.* Eur Oral Res 2020;54:62-68.

31. Ugurlu M. *How do the surface coating and one-year water aging affect the properties of fluoride-releasing restorative materials?* Niger J Clin Pract 2020;23:720-728.

32. Brito CR, Velasco LG, Bonini GA, Imparato JC, Raggio DP. *Glass ionomer cement hardness after different materials for surface protection*. J Biomed Mater Res A 2010;93:243-246.

33. Shintome LK, Nagayassu MP, Di Nicoló R, Myaki SI. *Microhardness of glass ionomer cements indicated for the ART technique according to surface protection treatment and storage time*. Braz Oral Res 2009;23:439-445.

34. Castro GW, Gray SE, Buikema DJ, Reagan SE. *The effect of various surface coatings on fluoride release from glass-ionomer cement*. Oper Dent 1994;19:194-198.

35. Cho E, Kopel H, White SN. *Moisture susceptibility of resin-modified glass-ionomer materials*. Quintessence Int 1995;26:351-358.

36. Novrizal A, Soufyan A, Irawan B, Matram N. *In vitro application of a nano-filled coating agent to improve the diametral tensile strength of glass ionomer cement.* J Physics Conference Series 2018;1073:062025.

37. Pilo R, Ben-Amar A, Barnea A, Blasbalg Y, Levartovsky S. *The effect of resin coating on the shear punch strength of restorative glass ionomer cements*. Clin Oral Investig 2017;21:1079-1086.

38. Thongbai-on N, Banomyong D. *Flexural strengths and porosities of coated or uncoated, high powder-liquid and resin-modified glass ionomer cements.* J Dent Sci 2020;15:433–436.

39. Fatima N, Ali Abidi SY, Qazi FU, Jat SA. *Effectiveness of commonly available surface protecting agents in maintaining microhardness of two cements*. J Coll Physicians Surg Pak 2013;23:315-318.

40. Habib SI. Fluoride Releasing/Recharging Ability of Bulk-Fill and Resin Modified Glass Ionomer Cements After the Application of Different Surface Coating Agents: An In -Vitro Study. Adv Dent J 2020;2:1-13.

41. Diem VT, Tyas MJ, Ngo HC, Phuong LH, Khanh ND. The effect of a nano-filled resin

coating on the 3-year clinical performance of a conventional high-viscosity glass-ionomer cement. Clin Oral Investig 2014;18:753-759.

42. Lohbauer U, Krämer N, Siedschlag G, Schubert EW, Lauerer B, Müller FA, et al. Strength and wear resistance of a dental glass-ionomer cement with a novel nanofilled resin

coating. Am J Dent 2011;24:124-8.

42. de Lima Navarro MF, Pascotto RC, Borges AFS, Soares CJ, Raggio DP, Rios D, et al. *Consensus on glass-ionomer cement thresholds for restorative indications*. J Dent. 2021 Apr;107:103609.

43. de Moraes RR, Marimon JL, Schneider LF, Sinhoreti MA, Correr-Sobrinho L, Bueno M, et al. *Effects of 6 months of aging in water on hardness and surface roughness of two microhybrid dental composites.* J Prosthodont. 2008;17:323–6.

Author	Country	Glass ionomer cement*	Coat*	Metodology	Sample size	Evaluation time
Bagheri et al., 2013 ¹⁹	Iran	Fuji IX (GC Corporation)	G-Coat Plus (GC Corporation)	Shear punch strength Vickers microhardness	N = 6 N = 3	24 hours 4 and 8 weeks
Bagheri et al., 2017 ²⁸	Iran	Fuji IX Fast (GC Corporation) Riva Self Cure (SDI)	G-Coat Plus (GC Corporation)	Flexural strength Vickers microhardness	N = 5 N = 3	24 hours 1, 3 and 6 months
Bonifácio et al., 2011 ¹⁰	Netherlands	GC Fuji IX GP Extra (GC Europe) Ketac Molar (Aplicap) (3M ESPE)	G-Coat Plus (GC Europe)	Flexural strength	N = 10	24 hours
Brito et al., 2009 ³²	Brazil	Ketac Molar Easy Mix (3M ESPE)	Cavitine (SS White) Magic Bond (Vigodent) Adper Single Bond (3M ESPE) Nail varnish (Colorama) Solid petroleum jelly**	Knoop microhardness	N = 10	24 hours
Brzovic-Rajic ²³	Croatia	Equia Fort (GC)	Equia Forte Coat (GC) Fuji varnish (GC)	Fluoride release	N = 6	24 hours 4, 30 and 60 days
Castro et al., 1994 ³⁴	United States	Ketac Fil Aplicap (ESPE Premier)	Ketac varnish Visiobond (ESPE Premier) Scotchbond II LC (3M Dental Products)	Fluoride release	N = 5	7, 14, 21 and 28 days
Cho et al., 1995 ³⁵	United States	Ketac-Bond Aplicap (ESPE)	Petroleum jelly (Vaseline, Chesebrough Ponds) Delton (Johnson a& Johnson)	Diametral tensile strength	N = 10	24 hours
Faraji et al., 2017 ¹⁶	Iran	Equia GI (GC America)	G-Coat (GC America) Margin Bond (Coltene/Whaledent)	Vickers microhardness	N = 20	24 hours 3 and 6 months
Fatima et al., 2013 ³⁹	Paquistan	Vitrofil (DFL)	Petroleum jelly Varnish ^{**} Nail varnish ^{**}	Vickers microhardness	N = 18	24 hours

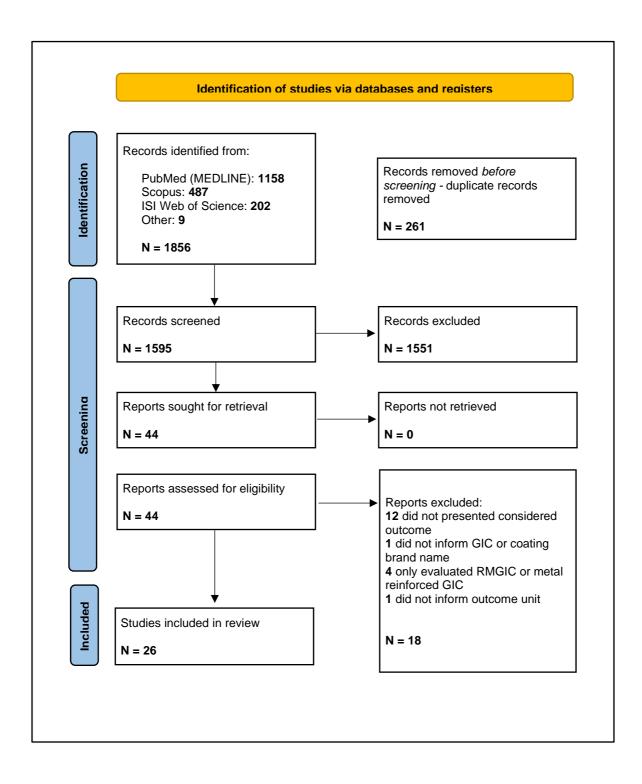
Table 1. Descriptive data of included studies

Gorseta et al., 2016 ²⁴	Croatia	Fuji Equia Fil Ketac Molar Apli- cap	Petroleum jelly (Vaseli- neVR, Uniliver) EquiaCoat VR (GC)	Flexural strength	N = 6	24 hours
Habib et al., 2020 ⁴⁰	Egypt	Equia Forte Fill (GC Corporation)	Equia Forte Coat (GC) Single Bond Universal (3M ESPE) Petroleum jelly (Hindustan Lever Ltd, Unilever)	Fluoride release	N = 6	24 hours 7, 14, 21, 28, 35, 42, 49, 56 and 63 days
Handoko et al. 2020 ⁹	Indonesia	Equia Forte Fill (GC)	Equia Forte Coat (GC)	Vickers microhardness	N = 10	24 hours
Hotta, Hirukawa, 1994 ⁶	Japan	Fuji Ionomer (GC Corp) Chelon-Fill (ESPE) Chemfil II (De Trey)	Occlusin (ICI) Bellfeel Brightener (Kanebo)	Knoop microhardness	N = 10	24 hours 7 days
Kamatham, Reddy, 2013 ¹⁴	India	Fuji II (GC Corporation)	Namuvar cavity varnish (Ratnagiri) Petroleum jelly (Vaseline, Hindustan lever ltd.)	Fluoride release	N = 10	24 hours 7 and 14 days
Kélic et al., 2020 ²⁵	Croatia	Fuji IX Extra (GC Europe)	GC Fuji Coat LC (GC Europe)	Fluoride release	N = 6	24 hours 7, 28, 84 and 168 days
Kishore et al., 2016 ²⁶	India	Fuji II (GC Corporation)	G-Coat Plus (GC corpo- ration) Petroleum jelly (Vaseline, Hindustan Lever Ltd.)	Fluoride release	N = 10	24 hours 7 and 14 days
Leiskar et al., 2013 ¹⁵	Norway	Fuji IX GP Capsule (GC Corporation)	Fuji Coat LC (GC Corporation)	Shear punch strength	N = 16	24 hours 7, 15, 35 and 54 days
Novrizal et al., 2018 ³⁶	Indonesia	Fuji IX GP Extra (GC Corporation)	GC Coat Plus (GC Corporation)	Diametral tensile strength	N - 6	24 hours 1 week
Pilo et al., 2017 ³⁷	Israel	Ketac Molar (3M ESPE) Riva Self Cure (SDI) Ionofil Molar AC (VOCO) Fuji IX GP Fast (GC Corp)	Ketac Glaze (3M ESPE) Riva Coat LC (SDI) Final Varnish LC (VOCO) G-Coat Plus (GC Corp)	Shear punch strength	N = 15	24 hours 1 and 8 weeks

Ryu et al., 2019 ¹⁸	Korea	Fuji IX Extra (GC Europe)	Equia Coat (GC America) Adper Scotchbond Multi-Purpose adhesive (3M ESPE)	Vickers microhardness	N = 10	24 hours
Shintone et al., 2009 ³³	Brazil	Vidrion R (SS White) Fuji IX (GC Corp.) Magic Glass ART (Vigodent) Maxxion R (FGM) Chem-Flex (Dentsply)	Nail varnish ^{**} Varnish recommended by the manufacturer	Vickers microhardness	N = 12	24 hours 7 and 30 days
Thongbai-on, Banomyoungm 2020 ³⁸	Thailand	Equia Forte Fill (GC)	Equia Forte Coat (GC)	Flexural strength	N = 6	24 hours
Tiwari, Nandlal, 2013 ²⁷	India	GC Gold Level (GC Corporation)	G-Coat Plus (GC Corporation)	Fluoride release	N = 10	24 hours 7, 14 and 21 days
Ugurlu, 2021 ²⁹	Turkey	Fuji IX GP Capsule (GC)	G-Coat Plus (GC)	Fluoride release	N = 15	24 hours 7, 15, 21 and 28 days
Ugurlu, 2020 (a) ³⁰	Turkey	Fuji IX GP Capsule (GC)	G-Coat Plus (GC)	Flexural strength	N = 10	24 hours 1 year
Ugurlu, 2020 (b) ³¹	Turkey	Fuji IX GP Capsule (GC)	G-Coat Plus (GC)	Flexural strength ^s Compressive strength	N = 10	24 hours 1 year

^{\$} Data published previously. Not considered in the meta-analysis.

Author	Sample size calculation	Random sequence	Specimen preparation	Single operator	Manufactors' instructions	Outcome clearly described	Blinded operator	Risk of bias
Bagheri et al., 2013 ¹⁹	Ν	Y	Y	Ν	Ν	Y	Ν	High
Bagheri et al., 2017 ²⁸	Ν	Y	Y	Ν	Ν	Y	Ν	High
Bonifácio et al., 2011 ¹⁰	Ν	Y	Y	Ν	Y	Y	Ν	Moderate
Brito et al., 2009 ³²	Ν	Ν	Y	Ν	Ν	Y	Ν	High
Brzovic-Rajic et al., 2018 ²³	Ν	Ν	Y	Ν	Y	Y	Ν	High
Castro et al., 1994 ³⁴	Ν	Ν	Y	Ν	Ν	Y	Ν	High
Cho et al., 1995 ³⁵	Ν	Ν	Y	Ν	Ν	Y	Ν	High
Faraji et al., 2017 ¹⁶	Y	Ν	Y	Ν	Ν	Ν	Ν	High
Fatima et al., 2013 ³⁹	Ν	Ν	Y	Ν	Y	Y	Ν	High
Gorseta et al., 2016 ²⁴	Ν	Ν	Y	Ν	Ν	Y	Ν	High
Habib et al., 2020 ⁴⁰	Y	Y	Y	Ν	Y	Y	Ν	Moderate
Handoko et al. 2020 ⁹	Ν	Ν	Y	Ν	Ν	Y	Ν	High
Hotta, Hirukawa, 19946	Ν	Ν	Y	Ν	Y	Ν	Ν	High
Kamatham, Reddy, 2013 ¹⁴	Ν	Y	Y	Ν	Y	Y	Ν	Moderate
Kélic et al., 2020 ²⁵	Ν	Ν	Y	Ν	Ν	Y	Ν	High
Kishore et al., 2016 ²⁶	Ν	Ν	Y	Ν	Y	Y	Ν	High
Leiskar et al., 2013 ¹⁵	Ν	Ν	Y	Ν	Ν	Y	Ν	High
Novrizal et al., 2018 ³⁶	Ν	Ν	Y	Ν	Y	Y	Ν	High
Pilo et al., 2017 ³⁷	Ν	Y	Y	Ν	Ν	Y	Ν	High
Ryu et al., 2019 ¹⁸	Ν	Ν	Y	Ν	Y	Y	Ν	High
Shintone et al., 2009 ³³	Ν	Y	Y	Ν	Y	Y	Ν	Moderate
Thongbai-on, Banomyoung 2020 ³⁸	Ν	Y	Y	Y	Y	Y	Ν	Moderate
Tiwari, Nandlal, 2013 ²⁷	Ν	Ν	Ν	Ν	Ν	Ν	Ν	High
Ugurlu, 2021 ²⁹	Ν	Y	Y	Ν	Ν	Y	Ν	High
Ugurlu, 2020 (a) ³⁰	Ν	Y	Y	Ν	Ν	Y	Ν	High
Ugurlu, 2020 (b) ³¹	Ν	Y	Y	Ν	Ν	Y	Ν	High



	Contro	l (uncoa	ted)	C	oated			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
1.1.1 Immediate										
Kamatham, Reddy, 2013	13.04	0.06	10	5.37	503	20	4.4%	0.02 [-0.74, 0.78]	2013	+
Tiwari, Nandlal, 2013	7.2	0.24	40	3.21	0.27	40	3.5%	15.47 [12.97, 17.97]		
Kishore et al., 2016	2.9	0.158		0.425	0.02	20	1.3%	26.44 [19.22, 33.66]		
Brzovic-Rajic et al. 2018	75.95	17.9	6	56.27		12	4.3%	0.89 [-0.14, 1.92]		L
	2.95	0.5	6	0.18	0.06	6	2.8%	7.18 [3.50, 10.86]		
Kélic et al., 2020										
Habib, 2020	43.85	3.85	6	2.57	1.21	18	1.7%	18.79 [12.90, 24.68]		
Ugurlu, 2021	15.74	1.42		15.95	1.36	15	4.4%	-0.15 [-0.86, 0.57]	2021	
Subtotal (95% CI)			93			131	22.4%	8.16 [4.73, 11.58]		
Heterogeneity: Tau ² = 18.22 Test for overall effect: Z = 4.	-		lf = 6 (P	< 0.000	01); I* =	97%				
1.1.2 7 days										
Castro et al., 1994	158.6	16.5	5	41.43	12.49	15	3.2%	8.32 [5.27, 11.37]	1994	
Tiwari, Nandlal, 2013	1.08	0.89	40	0.15	0.21	40	4.5%	1.42 [0.93, 1.92]	2013	-
Kamatham, Reddy, 2013	3.16	0.09	10	1.32	1.28	20	4.4%	1.70 [0.81, 2.58]		
Kishore et al., 2016	0.4	0.016		0.285	0.16	20	4.4%	0.85 [0.05, 1.64]		
Habib, 2020	19.87	2.57		2.24	1.39	18	3.1%	9.84 [6.66, 13.02]		
Kélic et al., 2020	14.5	0.56	6	0.61	0.23	6	0.4%	29.95 [15.29, 44.62]		
Subtotal (95% CI)	14.0	0.00	77	0.01	0.25	119	19.9%	3.94 [2.12, 5.75]	2020	
Heterogeneity: Tau ² = 3.54;				0.00001); i² = 92		13.370	5.54 [2.12, 5.15]		
Test for overall effect: Z = 4.	24 (r < U	.0001)								
1.1.3 14 days										
Castro et al., 1994	17.4	1.9	5	8.6	2.27	15	4.0%	3.84 [2.17, 5.51]	1994	
Kamatham, Reddy, 2013	1.96	0.03	10	0.835	0.81	20	4.4%	1.64 [0.76, 2.52]	2013	
Tiwari, Nandlal, 2013	0.48	0.23	40	0.009	0.001	40	4.4%	2.87 [2.24, 3.50]	2013	
Kishore et al., 2016	0.22	0.016	10	0.16	0.08	20	4.4%	0.88 [0.08, 1.67]		
Habib, 2020	18.55	2.7	6	1.5	0.79	18	2.8%	11.26 [7.65, 14.86]		
					0.10				2020	
Subtotal (95% CI)	0.67-44	10 46	71	00004		113	20.0 %	3.22 [1.64, 4.80]		-
Subtotal (95% CI) Heterogeneity: Tau² = 2.64; Test for overall effect: Z = 3.).00001)); I² = 91		20.0%	3.22 [1.64, 4.80]		•
Subtotal (95% Cl) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days	99 (P < 0	.0001)	4 (P < (%				
Subtotal (95% Cl) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994	99 (P < 0 18.9	.0001) 1.7	4 (P < (5	10.4	2.09	% 15	4.0%	4.05 [2.32, 5.78]		
Subtotal (95% Cl) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days	99 (P < 0	.0001)	4 (P < (2.09	%				
Subtotal (95% Cl) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994	99 (P < 0 18.9	.0001) 1.7	4 (P < (5	10.4	2.09	% 15	4.0%	4.05 [2.32, 5.78]	2013	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013	99 (P < 0 18.9 0.007	.0001) 1.7 0.001	:4 (P < (5 40	10.4 0.005	2.09 0.001	% 15 40	4.0% 4.5%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52]	2013	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020	99 (P < 0 18.9 0.007 18.45 Chi² = 22	.0001) 1.7 0.001 1.6 2.00, df=	4 (P < 0 5 40 6 51	10.4 0.005 3.75	2.09 0.001 1.95	% 15 40 18 73	4.0% 4.5% 3.5%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08]	2013	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86;	99 (P < 0 18.9 0.007 18.45 Chi² = 22	.0001) 1.7 0.001 1.6 2.00, df=	4 (P < 0 5 40 6 51	10.4 0.005 3.75	2.09 0.001 1.95	% 15 40 18 73	4.0% 4.5% 3.5%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08]	2013	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2:	99 (P < 0 18.9 0.007 18.45 Chi² = 22	.0001) 1.7 0.001 1.6 2.00, df=	4 (P < 0 5 40 6 51	10.4 0.005 3.75	2.09 0.001 1.95	% 15 40 18 73	4.0% 4.5% 3.5%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08]	2013 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2.	99 (P < 0 18.9 0.007 18.45 Chi² = 22 90 (P = 0	.0001) 1.7 0.001 1.6 2.00, df= .004)	:4 (P < (5 40 6 51 :2 (P < (5	10.4 0.005 3.75).0001);	2.09 0.001 1.95 ² = 919	% 15 40 18 73 %	4.0% 4.5% 3.5% 11.9 %	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23]	2013 2020 1994	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2. 1.1.5 28/30 days Castro et al., 1994	99 (P < 0 18.9 0.007 18.45 Chi [≠] = 22 90 (P = 0 13.5	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1	:4 (P < (5 40 6 51 :2 (P < (5	10.4 0.005 3.75).0001); 7.27	2.09 0.001 1.95 I ² = 919 1.66	% 15 40 18 73 %	4.0% 4.5% 3.5% 11.9%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51]	2013 2020 1994 2018	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Titwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2: 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020	99 (P < 0 18.9 0.007 18.45 Chi ² = 22 90 (P = 0 13.5 39.16 22.49	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 11.5 1.16	:4 (P < (5 40 6 51 :2 (P < (5 6 6	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97	2.09 0.001 1.95 I ² = 919 1.66 8.7 0.33	% 15 40 18 73 % 15 12 6	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72]	2013 2020 1994 2018 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2: 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020	99 (P < 0 18.9 0.007 18.45 Chi ² = 22 90 (P = 0 13.5 39.16	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 11.5	:4 (P < (5 40 6 51 :2 (P < (5 6	10.4 0.005 3.75).0001); 7.27 12.61	2.09 0.001 1.95 I ² = 919 1.66 8.7	% 15 40 18 73 % 15 12	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67]	2013 2020 1994 2018 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Titwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2: 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020	99 (P < 0 18.9 0.007 18.45 Chi [≠] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [≠] = 21	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 11.5 1.16 3.71 1.71, df=	:4 (P < (5 40 6 51 :2 (P < (5 6 6 8 23	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83	2.09 0.001 1.95 I ^z = 919 1.66 8.7 0.33 0.92	% 15 40 18 73 % 15 12 6 18 18 51	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72]	2013 2020 1994 2018 2020	
Subtotal (95% Cl) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% Cl) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2: 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Habib, 2020 Subtotal (95% Cl) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3:	99 (P < 0 18.9 0.007 18.45 Chi [≠] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [≠] = 21	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 11.5 1.16 3.71 1.71, df=	:4 (P < (5 40 6 51 :2 (P < (5 6 6 8 23	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83	2.09 0.001 1.95 I ^z = 919 1.66 8.7 0.33 0.92	% 15 40 18 73 % 15 12 6 18 18 51	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67]	2013 2020 1994 2018 2020	
Subtotal (95% Cl) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% Cl) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2: 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Subtotal (95% Cl) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3: 1.1.6 + 60 days	99 (P < 0 18.9 0.007 18.45 Chi [≠] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [≠] = 21 50 (P = 0	.0001) 1.7 0.001 1.6 2.00, df = .004) 1.1 11.5 1.16 3.71 .71, df = .0005)	5 40 6 51 2 (P < (5 6 6 8 23 3 (P < (10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83 0.0001);	2.09 0.001 1.95 ² = 919 1.66 8.7 0.33 0.92 ² = 869	% 15 40 18 73 % 15 12 6 18 51 %	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3 %	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81]	2013 2020 1994 2018 2020 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2: 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3: 1.1.6 + 60 days Brzovic-Rajic et al. 2018	99 (P < 0 18.9 0.007 18.45 Chi [≠] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [≠] = 21 50 (P = 0 10.15	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 11.5 1.16 3.71 1.71, df= .0005) 14.6	:4 (P < (5 40 6 51 :2 (P < (5 6 6 23 :3 (P < (6	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83 0.0001); 5.7	2.09 0.001 1.95 1.66 8.7 0.33 0.92 1 ² = 869 5.71	% 40 18 73 % 15 12 6 18 51 %	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3 %	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81] 0.45 [-0.54, 1.44]	2013 2020 1994 2018 2020 2020 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2. 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3. 1.1.6 + 60 days Brzovic-Rajic et al. 2018 Habib, 2020	99 (P < 0 18.9 0.007 18.45 Chi [≠] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [≠] = 21 50 (P = 0 10.15 10.4	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 1.15 1.16 3.71 .71, df= .0005) 14.6 0.95	:4 (P < (5 40 5 1 :2 (P < (6 6 2 3 :3 (P < (6 6 6	10.4 0.005 3.75).0001); 7.27 12.61 0.97 1.83).0001); 5.7 0.73	2.09 0.001 1.95 1.66 8.7 0.33 0.92 I ² = 869 5.71 0.4	% 15 40 73 % 51 12 6 18 51 51 12 12 18	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3% 4.3% 2.0%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81] 0.45 [-0.54, 1.44] 16.28 [11.16, 21.41]	2013 2020 1994 2018 2020 2020 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2. 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3. 1.1.6 + 60 days Brzovic-Rajic et al. 2018 Habib, 2020 Kélic et al., 2020	99 (P < 0 18.9 0.007 18.45 Chi [≠] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [≠] = 21 50 (P = 0 10.15 10.4 50.6	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 11.5 1.16 3.71 .71, df= .0005) 14.6 0.95 5.68	:4 (P < (5 40 5 1 :2 (P < (5 6 6 6 8 2 3 :3 (P < (6 6 12	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83 0.0001); 5.7 0.73 1.51	2.09 0.001 1.95 1.66 8.7 0.33 0.92 1 ² = 869 5.71 0.4 0.56	% 15 40 73 % 15 12 6 18 51 %	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3 % 4.3% 2.0% 2.8%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81] 0.45 [-0.54, 1.44] 16.28 [11.16, 21.41] 11.74 [8.02, 15.47]	2013 2020 1994 2018 2020 2020 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2. 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3. 1.1.6 + 60 days Brzovic-Rajic et al. 2018 Habib, 2020 Kélic et al., 2020 Ugurlu, 2021	99 (P < 0 18.9 0.007 18.45 Chi [≠] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [≠] = 21 50 (P = 0 10.15 10.4	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 1.15 1.16 3.71 .71, df= .0005) 14.6 0.95	4 (P < (5 40 6 51 2 (P < (3 (P < (6 6 12 10	10.4 0.005 3.75).0001); 7.27 12.61 0.97 1.83).0001); 5.7 0.73	2.09 0.001 1.95 1.66 8.7 0.33 0.92 I ² = 869 5.71 0.4	% 15 40 18 73 % 15 12 6 18 51 % 12 18 51 %	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3% 4.3% 2.0% 2.8% 4.3%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81] 0.45 [-0.54, 1.44] 16.28 [11.16, 21.41] 11.74 [8.02, 15.47] -0.72 [-1.63, 0.19]	2013 2020 1994 2018 2020 2020 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2: 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3: 1.1.6 + 60 days Brzovic-Rajic et al. 2018 Habib, 2020 Kélic et al., 2020 Kélic et al., 2020 Ugurlu, 2021 Subtotal (95% CI) Heterogeneity: Tau ² = 15.568	99 (P < 0 18.9 0.007 18.45 Chi [₹] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [₹] = 21 50 (P = 0 10.15 10.4 50.6 45.27 3; Chi [₹] = 7	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 1.15 1.16 3.71 .71, df= .0005) 14.6 0.95 5.68 4.46 '8.42, df	4 (P < (5 40 6 51 2 (P < (5 6 6 23 3 (P < (6 6 12 10 34	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83 0.0001); 6.7 0.73 1.51 48.27	2.09 0.001 1.95 ² = 919 1.66 8.7 0.33 0.92 ² = 869 5.71 0.4 0.56 3.46	% 15 40 18 73 % 15 12 6 18 51 % 12 18 12 18 12 18 12 10 52	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3 % 4.3% 2.0% 2.8%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81] 0.45 [-0.54, 1.44] 16.28 [11.16, 21.41] 11.74 [8.02, 15.47] -0.72 [-1.63, 0.19]	2013 2020 1994 2018 2020 2020 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2. 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3. 1.1.6 + 60 days Brzovic-Rajic et al. 2018 Habib, 2020 Kélic et al., 2020 Ugurlu, 2021 Subtotal (95% CI)	99 (P < 0 18.9 0.007 18.45 Chi [₹] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [₹] = 21 50 (P = 0 10.15 10.4 50.6 45.27 3; Chi [₹] = 7	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 1.15 1.16 3.71 .71, df= .0005) 14.6 0.95 5.68 4.46 '8.42, df	4 (P < (5 40 6 51 2 (P < (5 6 6 23 3 (P < (6 6 12 10 34	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83 0.0001); 6.7 0.73 1.51 48.27	2.09 0.001 1.95 ² = 919 1.66 8.7 0.33 0.92 ² = 869 5.71 0.4 0.56 3.46	% 15 40 18 73 % 15 12 6 18 51 % 12 18 12 18 12 18 12 10 52	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3% 4.3% 2.0% 2.8% 4.3%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81] 0.45 [-0.54, 1.44] 16.28 [11.16, 21.41] 11.74 [8.02, 15.47] -0.72 [-1.63, 0.19]	2013 2020 1994 2018 2020 2020 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3: 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2: 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3: 1.1.6 + 60 days Brzovic-Rajic et al. 2018 Habib, 2020 Kélic et al., 2020 Kélic et al., 2020 Ugurlu, 2021 Subtotal (95% CI) Heterogeneity: Tau ² = 15.568	99 (P < 0 18.9 0.007 18.45 Chi [₹] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [₹] = 21 50 (P = 0 10.15 10.4 50.6 45.27 3; Chi [₹] = 7	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 1.15 1.16 3.71 .71, df= .0005) 14.6 0.95 5.68 4.46 '8.42, df	4 (P < (5 40 6 51 2 (P < (5 6 6 23 3 (P < (6 6 12 10 34	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83 0.0001); 6.7 0.73 1.51 48.27	2.09 0.001 1.95 ² = 919 1.66 8.7 0.33 0.92 ² = 869 5.71 0.4 0.56 3.46	% 15 40 73 % 51 12 6 18 51 12 6 8 51 12 18 12 18 12 10 52 96%	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3% 4.3% 2.0% 2.8% 4.3%	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81] 0.45 [-0.54, 1.44] 16.28 [11.16, 21.41] 11.74 [8.02, 15.47] -0.72 [-1.63, 0.19]	2013 2020 1994 2018 2020 2020 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2. 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3. 1.1.6 + 60 days Brzovic-Rajic et al. 2018 Habib, 2020 Kélic et al., 2020 Ugurlu, 2021 Subtotal (95% CI) Heterogeneity: Tau ² = 15.568 Test for overall effect: Z = 2.	99 (P < 0 18.9 0.007 18.45 Chi [#] = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi [#] = 21 50 (P = 0 10.15 10.4 50.6 45.27 3; Chi [#] = 7 80 (P = 0	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 11.5 1.16 3.71 .71, df= .0005) 14.6 0.95 5.68 4.46 78.42, df .005)	4 (P < (5 40 5 5 1 2 (P < (6 6 6 6 23 34 10 34 = 3 (P <	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83 0.0001); 5.7 0.73 1.51 48.27 0.0000	2.09 0.001 1.95 1.66 8.7 0.33 0.92 1 ² = 869 5.71 0.4 0.56 3.46 1); 1 ² = 9	% 15 40 73 % 15 12 6 8 51 12 18 12 18 12 10 52 16% 539	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3% 4.3% 2.8% 4.3% 13.5 %	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81] 0.45 [-0.54, 1.44] 16.28 [11.16, 21.41] 11.74 [8.02, 15.47] -0.72 [-1.63, 0.19] 5.92 [1.77, 10.07]	2013 2020 1994 2018 2020 2020 2020	
Subtotal (95% CI) Heterogeneity: Tau ² = 2.64; Test for overall effect: Z = 3. 1.1.4 21 days Castro et al., 1994 Tiwari, Nandlal, 2013 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 5.86; Test for overall effect: Z = 2. 1.1.5 28/30 days Castro et al., 1994 Brzovic-Rajic et al. 2018 Kélic et al., 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3. 1.1.6 + 60 days Brzovic-Rajic et al. 2018 Habib, 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 7.45; Test for overall effect: Z = 3. 1.1.6 + 60 days Brzovic-Rajic et al. 2018 Habib, 2020 Kélic et al., 2020 Ugurlu, 2021 Subtotal (95% CI) Heterogeneity: Tau ² = 15.58 Test for overall effect: Z = 2.	99 (P < 0 18.9 0.007 18.45 Chi² = 22 90 (P = 0 13.5 39.16 22.49 16.42 Chi² = 21 50 (P = 0 10.15 10.4 50.6 45.27 3; Chi² = 7 80 (P = 0 Chi² = 52	.0001) 1.7 0.001 1.6 2.00, df= .004) 1.1 11.5 1.16 3.71 .71, df= .0005) 14.6 0.95 5.68 4.46 78.42, df .005)	4 (P < (5 40 5 5 1 2 (P < (6 6 6 6 23 34 10 34 = 3 (P <	10.4 0.005 3.75 0.0001); 7.27 12.61 0.97 1.83 0.0001); 5.7 0.73 1.51 48.27 0.0000	2.09 0.001 1.95 1.66 8.7 0.33 0.92 1 ² = 869 5.71 0.4 0.56 3.46 1); 1 ² = 9	% 15 40 73 % 15 12 6 8 51 12 18 12 18 12 10 52 16% 539	4.0% 4.5% 3.5% 11.9% 4.0% 4.2% 0.6% 3.5% 12.3% 4.3% 2.8% 4.3% 13.5 %	4.05 [2.32, 5.78] 1.98 [1.44, 2.52] 7.56 [5.05, 10.08] 4.31 [1.40, 7.23] 3.84 [2.17, 5.51] 2.62 [1.24, 3.99] 23.29 [11.87, 34.72] 7.24 [4.82, 9.67] 5.65 [2.49, 8.81] 0.45 [-0.54, 1.44] 16.28 [11.16, 21.41] 11.74 [8.02, 15.47] -0.72 [-1.63, 0.19] 5.92 [1.77, 10.07]	2013 2020 1994 2018 2020 2020 2020	-10 -5 Coated Control (uncoated)

	Control (uncoated)			C	oated		9	Std. Mean Difference		Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl		
1.2.1 Immediate												
Hotta, Hirukawa, 1994	13.13	7.81	60	20.75	15.3	60	8.8%	-0.62 [-0.99, -0.26]	1994	+		
Shintome et al., 2009	58.15	18.75	60	57.28	17.87	120	8.8%	0.05 [-0.26, 0.36]	2009	+		
Brito et al., 2009	77.5	37.7	10	84.76	34.65	50	8.3%	-0.20 [-0.88, 0.48]	2009			
Fatima et al., 2013	19.05	87,515	18	25.87	5.34	54	8.5%	-0.00 [-0.53, 0.53]	2013	+		
Bagheri et al., 2013	15.5	0.5	3	15.4	0.5	3	6.0%	0.16 [-1.45, 1.77]	2013			
Faraji et al., 2017	53.64	8.51	10	10.86	7.22	20	5.9%	5.44 [3.78, 7.09]	2017	_ _		
Bagheri et al., 2017	68.55	10.97	6	41.2	11.22	6	6.0%	2.28 [0.69, 3.86]	2017	│ ─ · ─		
Ryu et al., 2019	21.35	1.93	10	14.53	3.71	20	7.7%	2.04 [1.10, 2.98]	2019			
Handoko et al., 2020 Subtotal (95% Cl)	13.56	4.28	10 187	131.14	36.15	10 343	5.6% 65.6 %	-4.37 [-6.12, -2.63] 0.47 [-0.36, 1.29]	2020	•		
Heterogeneity: Tau ² = 1.3 Test for overall effect: Z =			df = 8 (P	< 0.000	01); I²=	92%						
1.2.2 28/30 days												
Shintome et al., 2009	66.5	21.06	60	68.46	18.75	120	8.8%	-0.10 [-0.41, 0.21]	2009	-		
Bagheri et al., 2013	11.8	0.7	3	7.3	0.3	3	0.9%	6.69 [0.03, 13.34]	2013			
Bagheri et al., 2017 Subtotal (95% CI)	89.65	12.83	6 69	47.2	10.41	6 129	5.1% 14.9 %	3.35 [1.36, 5.34] 2.34 [-0.99, 5.67]	2017			
Heterogeneity: Tau ² = 6.3 Test for overall effect: Z =			f = 2 (P =	= 0.0005)); I² = 87	%						
1.2.3 + 56 days												
Bagheri et al., 2013	13.2	1.7	3	8.2	1.8	3	3.7%	2.28 [-0.44, 5.01]	2013	+		
Faraji et al., 2017	32.48	4.29	20	14.56	7.32	40	8.1%	2.73 [1.99, 3.46]	2017	-		
Bagheri et al., 2017 Subtotal (95% Cl)	80.27	10.22	12 35	59.22	15.08	12 55	7.7% 19.5 %	1.58 [0.64, 2.52] 2.22 [1.34, 3.09]	2017			
Heterogeneity: Tau ² = 0.: Test for overall effect: Z =				0.17); l²÷	= 44%							
Total (95% CI)			291			527	100.0%	0.96 [0.28, 1.64]		◆		
Heterogeneity: Tau ² = 1.3 Test for overall effect: Z = Test for subgroup differe	= 2.77 (P =	= 0.006)								-10 -5 0 5 10 Coated Control (uncoated)		

1.4.1 mmediate Bagheri et al, 2013 1.3.2 1.7 6 8.2 1.8 6 3.6% 2.64 [0.92, 4.35] Bagheri et al, 2017 1.3 3.20 10 16.5 3.3 10 5.3% -0.96 [-1.92, -0.04] Bonfaice et al, 2011 3.215 13.16 20 3.55 6.13 20 6.0% -0.32 [-0.40, 0.30] Gorest et al, 2016 1.59 11.43 12 45.55 25.65 24 5.6% -1.46 [2.24, 0.08] Leiskar et al, 2017 50.65 0.6 1.6 5.7% -0.57 [-1.0.56] Nowrizal et al, 2017 50.65 7.06 60 44 9.49 -0.57 [-1.40, 0.59] Nourizal et al, 2017 50.65 7.06 60 44 -0.32 [-0.43, 0.30] -0.32 [-0.43, 0.30] Upurlu, 2020b 15.42 1.8 1.4.7 0.89 6 0.2% -1.26 [-2.4, -0.28] Upurlu, 2020b 15.46 18.05 10 5.4% -0.56 [-1.46, 0.03] -0.32 [-0.5, 0.46] Heterogeneity, Tau* = 2.1.5; Chi# = 78.16, df = 10 (P < 0.00001); P = 87% 52 <th></th> <th colspan="3">Control (uncoated)</th> <th colspan="3">Coated</th> <th></th> <th>Std. Mean Difference</th> <th colspan="2">Std. Mean Difference</th>		Control (uncoated)			Coated				Std. Mean Difference	Std. Mean Difference	
Bagheri et al., 2013 Bagheri et al., 2017 13.1 3.28 Bagheri et al., 2017 13.1 3.28 10.5 13.8 10.5	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
Bagher et al., 2017 Bagher et al., 2017 Bagher et al., 2017 Bagher et al., 2013 Bagher et al., 2017 Bagher Bagher et al., 2017 Bagher Bagher et al.,	1.4.1 Immediate										
Boinfactor et al., 2011 32.16 13.16 20 35.5 6.13 20 6.0% $-0.32(0.94, 0.00)$ Cho et al., 1995 20 39 10 1151 344 20 57% $0.50(0.27, 127)$ Gorseta et al., 2016 15.9 11.43 12 46.56 23.65 24 5.6% $-1.46(2.24, 0.68)$ Leiskar et al., 2013 75.7 6.8 16 67.1 84 16 5.7% $1.10(0.35, 1.85)$ Norwizal et al., 2017 0.056 7.06 60 48 4.72 60 6.4% $0.44(0.08)$ Pino et al., 2017 0.056 7.06 60 48 4.72 60 6.4% $0.44(0.80)$ Dyuru, 2020b 15.22 1.15 6 4.147 0.89 6 0.2% -32.46 [53.49, -11.96] 4 Uguru, 2020b 15.44 51 857 10 17.92 18.98 10 4.9% $-1.93[3.03, 0.03]$ Subtoal (95% C) 154.45 18.57 10 17.92 18.98 10 5.2% $-1.93[3.23, -0.36]$ Eagherie tal., 2013 35.9 3.8 6 42.56 3 6 4.2% $-1.80[-3.23, -0.36]$ Leiskar et al., 2013 35.9 3.8 6 42.56 3 6 4.2% $-1.80[-3.23, -0.36]$ Eagherie tal., 2013 35.9 3.8 6 42.56 3 6 4.2% $-1.80[-3.23, -0.36]$ Leiskar et al., 2020 87.2 9 16 7.3 7.5 16 5.6% $1.64(0.82, 2.45]$ Test for overall effect Z = 0.87 (P = 0.38) 1.4.2 2805 days Eagherie tal., 2013 35.9 3.8 6 42.56 3 6 4.2% $-1.80[-3.23, -0.36]$ Leiskar et al., 2020 87.2 9 16 7.3 7.5 16 5.6% $1.64(0.82, 2.45]$ Test for overall effect Z = 0.18 (P = 22.12, df = 2 (P < 0.0001); P = 81% Test for overall effect Z = 0.18 (P = 22.12, df = 2 (P < 0.0001); P = 91% Test for overall effect Z = 0.18 (P = 22.12, df = 2 (P < 0.0001); P = 92% Test for overall effect Z = 0.12 (P = 2.0001) 1.4.6 and 12 months Bagherie tal., 2017 1.5.3 3.59 10 1.5.5 3.58 10 5.4% $-0.05[0.93, 0.82]$ Uguru, 2020a 4.52.7 4.46 10 49.27 3.46 10 5.4% $-0.05[0.93, 0.82]$ Uguru, 2020a 4.52.7 4.46 10 49.27 3.46 10 5.4% $-0.02[0.93, 0.82]$ Uguru, 2020a 4.52.7 4.46 10 49.27 3.46 10 5.4% $-0.29[0.80, 0.22]$ Test for overall effect Z = 0.17 (P = 0.53); P = 0% Test for overall effect Z = 0.17 (P = 0.53); P = 0% Test for overall effect Z = 0.10 (P = 0.27) Total (95% C1) 310 32 100.3% $-0.22[0.71, 0.26]$ Heterogeneity, Tau" = 0.92; ChP = 131.36, df = 19 (P < 0.00001); P = 86% Test for overall effect Z = 0.11 (P = 0.53); P = 0.63); P = 0.80 Test for overall ef	Bagheri et al., 2013	13.2	1.7	6	8.2	1.8	6	3.6%	2.64 [0.92, 4.35]		
Cho et al., 1995 20 3.9 10 1816 3.44 20 6.7% 0.50 1.027 , 127 Gorsta et al., 2016 15.9 11.43 12 46.55 23.65 24 5.6% 1.46 $[2.24, -0.68]$ Leikar et al., 2013 75.7 6.8 16 67.1 8.4 16 5.7% 0.44 $[0.06, 0.027]$, 127 Dive tal., 2017 05.05 7.06 60 44 4.72 60 6.4% 0.44 $[0.06, 0.08]$ Throngbai-On, Banomyong, 2020 15.32 1.15 6 41.47 0.89 6 0.2% -23.46 $[3.49, -1.93]$, 13.90 (4) Ugurlu, 2020 154.45 18.57 10 179.2 18.98 10 5.2% 1.93 $[1.93, -0.38]$ Ugurlu, 2020 154.45 18.57 10 179.2 18.98 10 5.2% 1.93 $[1.93, -0.38]$ Ugurlu, 2020 154.45 18.57 10 179.2 18.98 10 5.2% 1.93 $[1.93, -0.38]$ Ugurlu, 2020 154.45 18.57 10 179.2 18.98 10 5.2% 1.93 $[1.95, 0.40]$ Heterogeneity: Tau ² = 1.15; Chi ² = 28.16, df = 10 ($P < 0.00001$); $P = 87\%$ Test for overall effect Z = 0.87 ($P = 0.38$) 1.4.2 28/35 days Bagheri et al., 2013 35.9 38 6 42.56 3 6 4.2% 1.80 $[3.33, -0.36]$ Bagheri et al., 2013 35.9 32 15.1% 0.18 $[2.12, 1.76]$ Heterogeneity: Tau ² = 2.41; Chi ² = 2.12, df = 2 ($P < 0.0001$); $P = 91\%$ Test for overall effect Z = 0.18 ($P = 0.86$) 1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 $[4.57, -1.02]$ Leiskar et al., 2013 59.9 6.2 7 7.39 60 6.4% 0.06 $[-0.30, 0.42]$ 32 15.1% 0.018 $[2.12, 1.76]$ Heterogeneity: Tau ² = 2.04; Chi ² = 2.27, dif = 2 ($P < 0.00001$); $P = 92\%$ Test for overall effect Z = 0.12 ($P = 0.36$) 1.4.3 8 weeks Bagheri et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 $[-0.30, 0.42]$ 30 16.2% 0.026 $[-0.32, 0.22]$ Heterogeneity: Tau ² = 0.20; Chi ² = 1.27, df = 2 ($P = 0.53$); $P = 0\%$ Test for overall effect Z = 0.12 ($P = 0.36$) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 $[-0.33, 0.82]$ Ugurlu, 2020 4 55.27 4.46 10 48.27 3.46 10 5.4% -0.026 $[-0.38, 0.22]$ Heterogeneity: Tau ² = 0.02, Chi ² = 1.37, df = 2 ($P = 0.53$); $P = 0\%$ Test for overall effect Z = 0.12 ($P = 0.36$) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.22 $[-0.38, 0.22]$ 32 100.0% 4.5.27 	Bagheri et al., 2017	13.1	3.28	10	16.5	3.38	10	5.3%	-0.98 [-1.92, -0.04]	- _	
Divise tai al., 2016 Leiskar et al., 2003 T5.7 6.8 Leiskar et al., 2003 T5.7 6.8 1.3 1.3 1.3 1.3 1.3 1.3 1.3 1.3	Bonifácio et al., 2011	32.15	13.16	20	35.5	6.13	20	6.0%	-0.32 [-0.94, 0.30]	+	
Leiskaretal. 2003 Torophal-On, Banomyong, 2020 Thongbal-On, Banomyong, 2020 The Heterogeneity, Tau" = 2.64; Chi ^m = 2.212, dif = 2 ($P < 0.00001$); $P = 91\%$ Testfor overall effect Z = 0.18 ($P = 0.36$) The stal, 2017 Thong 2.578, dif = 2 ($P < 0.00001$); $P = 91\%$ Testfor overall effect Z = 0.12 ($P = 0.0000$ The stal, 2017 Thong 2.578, dif = 2 ($P < 0.00001$); $P = 92\%$ Testfor overall effect Z = 0.12 ($P = 0.0000$ The stal, 2017 Thong 2.578, dif = 2 ($P < 0.00001$); $P = 92\%$ Testfor overall effect Z = 0.12 ($P = 0.0000$ The stal, 2017 Thong 2.578, dif = 2 ($P = 0.53$); $P = 0\%$ Testfor overall effect Z = 0.10; $P = 2.57$; $P = 0\%$ Testfor overall effect Z = 0.10; $P = 131.36$, dif = 19 ($P < 0.00001$); $P = 92\%$ Testfor overall effect Z = 0.10; $P = 0.35$; $P = 0\%$ Testfor overall effect Z = 0.10; $P = 0.30$; $P = 0\%$ Testfor overall effect Z = 0.10; $P = 0.30$; $P = 0.5$;	Choetal., 1995	20	3.9	10	18.15	3.44	20	5.7%	0.50 [-0.27, 1.27]	+	
Nowrize teal, 2018 13.79 3.43 6 15.66 2.15 6 4.88 -0.57 [1.74, 0.59] Pilo et al., 2017 50.65 7.06 60 48 4.72 60 6.4% 0.44 [0.08,0.80] Pilo et al., 2017 15.22 1.15 6 41.47 0.89 6 0.2% -23.48 [34.99, 11.96] 4 Ugurlu, 2020b 15.44 5 10.5 1.82 5.48 10 4.9% -1.93 [1.303, 0.83] Ugurlu, 2020b 15.44 5 18.57 10 17.92 1.8.98 10 52.8 -1.28 [2.24, 0.28] Subtotal (95% CI)	Gorseta et al., 2016	15.9	11.43	12	46.55	23.65	24	5.6%	-1.46 [-2.24, -0.68]		
Pilo et al., 2017 50.65 7.06 60 48 4.72 60 6.4% 0.4% 0.4% 10.05 (0.80) Thongbai-On, Banormyong, 2020 15.32 1.15 6 41.47 0.89 6 0.2% -23.48 [-34.99, -11.96] 4 Uguriu, 2020b 154.45 18.57 10 179.2 18.99 10 5.2% -1.26 [-2.24, -0.28] Subtotal (95% CI) 164.45 18.57 10 179.2 18.99 10 5.2% -1.26 [-2.24, -0.28] Subtotal (95% CI) 164.45 10 ($P < 0.00001$); $P = 87\%$ Test for overall effect Z = 0.87 ($P = 0.38$) 1.4.2 28/35 days Bagheni et al., 2013 35.9 3.8 6 42.56 3 6 4.2% -1.80 [-3.23, -0.36] Bagheni et al., 2013 35.9 3.8 6 42.56 3 6 4.2% -1.80 [-3.23, -0.36] Bagheni et al., 2013 35.9 3.8 6 42.56 3 6 4.2% -1.80 [-3.23, -0.36] Bagheni et al., 2013 36.2 10 15.5 4.58 10 5.4% -0.66 [-1.46, 0.33] Leiskar et al., 2003 87.2 9 16 7.33 7.5 16 5.56% 1.46 (0.33] Leiskar et al., 2003 87.2 9 36 7.3 7.5 16 5.55% 1.26 [0.90, 0.61] Heterogeneity: Tau ² = 2.64; Ch ² = 22.12, df = 2 ($P < 0.0001$); $P = 91\%$ Test for overall effect Z = 0.18 ($P = 0.86$) 1.4.3 8 weeks Bagheni et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.26 [0.90, 0.62] Subtotal (95% CI) 82 82 82 15.4% -0.016 [-0.30, 0.62] Subtotal (95% CI) 82 82 82 15.4% -0.017 [-1.87, 1.65] Heterogeneity. Tau ² = 2.1, 2 ($P = 0.00001$); $P = 92\%$ Test for overall effect Z = 0.12 ($P = 0.90$) 1.4.4 6 and 12 months Bagheni et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Uguriu, 2020 4 55.77 4.46 10 48.27 3.46 10 5.4% -0.025 [-0.93, 0.82] Uguriu, 2020 4 55.77 4.46 10 48.27 3.46 10 5.4% -0.02 [-0.80, 0.22] Heterogeneity. Tau ² = 0.00, Ch ² = 1.27, df = 2 ($P = 0.00001$); $P = 92\%$ Test for overall effect Z = 0.12 ($P = 0.53$); $P = 0\%$ Test for overall effect Z = 0.12 ($P = 0.53$); $P = 0\%$ Test for overall effect Z = 0.91 ($P = 0.36$) Test for overall effect Z = 0.91 ($P = 0.36$) Test for overall effect Z = 0.91 ($P = 0.36$) Test for overall effect Z = 0.91 ($P = 0.36$)	Leiskar et al., 2003	75.7	6.8	16	67.1	8.4	16	5.7%	1.10 [0.35, 1.85]	_ 	
Throngbai-On, Banomyong, 2020 15.32 1.15 6 41.47 0.89 6 0.2% -23.48 [34.99, -11.86] 4 Ugurlu, 2020 41.29 4.95 10 51.92 5.48 10 4.9% -1.93 [3.03, 0.63] Subtotal (95% C) 154.45 18.57 10 179.2 18.98 10 5.2% -1.26 [2.24, 0.28] Subtotal (95% C) 154.45 18.57 10 179.2 18.98 10 5.2% -1.26 [2.24, 0.28] Subtotal (95% C) 154.45 18.57 10 179.2 18.98 10 5.2% -1.26 [2.24, 0.28] Subtotal (95% C) 154.57 10 179.2 18.98 10 5.2% -1.26 [2.24, 0.28] Bagheri et al., 2013 35.9 3.8 6 42.56 3 6 4.2% -1.80 [3.23, -0.36] Bagheri et al., 2013 35.9 3.8 6 42.56 3 6 4.2% -0.56 [-1.46, 0.33] Leiskaret al., 2003 87.2 9 16 73.3 7.5 16 5.6% 1.64 [0.82, 2.45] Subtotal (95% C) 32 15.1% -0.18 [-2.12, 1.76] Heterogeneity, Tau ² = 2.64; Ch ² = 22.12, df = 2 (P < 0.0001); P = 81% Test for overall effect Z = 0.18 (P = 0.86) 14.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskaret al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 (0.98, 2.66] Heterogeneity, Tau ² = 2.11; Ch ² = 25.78, df = 2 (P < 0.00001); P = 92% Test for overall effect Z = 0.12 (P = 0.58); P ² = 0.82 14.4 6 and 12 months Bagheri et al., 2017 60.27 11.51 80 29.88 17.31 10 5.4% -0.05 [-0.83, 0.82] Ugurlu, 2020 45.27 4.46 10 48.27 3.46 10 5.4% -0.05 [-0.83, 0.82] Ugurlu, 2020 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [+1.60, 0.18] Subtotal (95% C) 30 30 16.2% -0.22 [-0.71, 0.26] Heterogeneity, Tau ² = 0.00; Ch ² = 1.27, df = 2 (P < 0.00001); P = 92% Test for overall effect Z = 1.10 (P = 0.53); P = 0% Test for overall effect Z = 0.31 (P = 0.53); P = 0% Test for overall effect Z = 0.31 (P = 0.53); P = 0% Test for overall effect Z = 0.31 (P = 0.53); P = 0% Test for overall effect Z = 0.31 (P = 0.53); P = 0% Test for overall effect Z = 0.31 (P = 0.36); P = 0.53; P = 0% Test for overall effect Z = 0.31 (P = 0.36); P = 0.53; P = 0% Test for overall effect Z = 0.31 (P = 0.36); P = 0.53; P = 0% Test for overall effect Z = 0.31 (P = 0.36); P = 0.53; P = 0.54% Test for overall effect Z = 0.31 (P = 0.36); P = 0.53; P = 0.54% Tes	Novrizal et al., 2018	13.79	3.43	6	15.56	2.15	6	4.8%	-0.57 [-1.74, 0.59]		
Ugunu, 2020a 41.29 4.95 10 51.20 5.48 10 4.9% -1.93 F.30.3.0.83] Ugunu, 2020b 154.45 18.57 10 179.2 18.98 10 5.2% -1.26 F.2.4.0.28] Subtotal (95% CI) -1.15; Ch ^{III} = 78.16, df = 10 ($P < 0.00001$); $P = 87\%$ Testfor overall effect $Z = 0.87$ ($P = 0.38$) 1.4.2 28/35 days Bagheri et al., 2013 3.5.9 3.8 6 42.56 3 6 4.2% -1.80 [-3.23, -0.36] Bagheri et al., 2013 3.5.9 3.8 6 42.56 3 6 4.2% -1.80 [-3.23, -0.36] Bagheri et al., 2013 3.5.9 3.8 6 42.56 3 6 4.2% -1.80 [-3.23, -0.36] Bagheri et al., 2013 3.5.9 3.8 6 42.56 3 6 4.2% -1.80 [-3.23, -0.36] Bagheri et al., 2013 3.5.9 3.8 6 42.56 3 6 4.2% -0.56 [-1.46, 0.33] Heterogeneity. Tau ² = 2.64; Ch ^{III} = 2.212, df = 2 ($P < 0.0001$); $P = 91\%$ Test for overall effect $Z = 0.18$ ($P = 0.86$) 1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.68] Heterogeneity. Tau ² = 2.11; Ch ^{III} = 25.78, df = 2 ($P < 0.00001$); $P = 92\%$ Test for overall effect $Z = 0.12$ ($P = 0.30$) 1.4.4 6 and 12 months Bagheri et al., 2017 1.5.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.39, 0.82] Ugunu, 2020 4 45.27 4.46 10 48.27 3.46 10 5.4% -0.075 [-0.83, 0.82] Ugunu, 2020 4 55.77, df = 2 ($P < 0.00001$); $P = 92\%$ Test for overall effect $Z = 0.12$ ($P = 0.53$); $P = 0\%$ Test for overall effect $Z = 0.12$ ($P = 0.53$); $P = 0\%$ Test for overall effect $Z = 0.30$ ($P = 0.25$); $P = 0\%$ Test for overall effect $Z = 0.30$ ($P = 0.25$); $P = 0\%$ Test for overall effect $Z = 0.31$ ($P = 0.25$); $P = 0\%$ Test for overall effect $Z = 0.31$ ($P = 0.25$); $P = 0\%$ Test for overall effect $Z = 0.31$ ($P = 0.25$); $P = 0\%$ Test for overall effect $Z = 0.31$ ($P = 0.25$); $P = 0\%$ Test for overall effect $Z = 0.31$ ($P = 0.35$); $P = 0\%$ Test for overall effect $Z = 0.31$ ($P = 0.36$) Test for overall effect $Z = 0.31$ ($P = 0.35$); $P = 0\%$ Test for overall effect $Z = 0.31$ ($P = 0.35$); $P = 0\%$ Test for overall effect $Z = 0.31$ ($P = 0.35$); $P = 0\%$ Test for overall e	Pilo et al., 2017	50.65	7.06	60	48	4.72	60	6.4%	0.44 [0.08, 0.80]		
Ugunty 2020b 154.45 18.57 10 179.2 18.98 10 5.2% $-1.26[-2.24] - 0.29]$ Subtotal (95% CI) 166 178.2 188 53.3% $-0.32[-1.05, 0.40]$ Heterogeneity. Tau ² = 1.15; Chi ² = 78.16, df = 10 (P < 0.00001); P = 87% Testfor overall effect Z = 0.87 (P = 0.38) 1.4.2 28/35 days Bagheri et al., 2013 35.9 3.8 6 42.56 3 6 4.2% $-1.80[-3.23, -0.36]$ Bagheri et al., 2017 13.3 2.62 10 15.5 4.58 10 5.4% $-0.56[-1.46, 0.33]$ Leiskar et al., 2003 87.2 9 16 73.3 7.5 16 5.6% 1.64 [0.82, 2.45] Subtotal (95% CI) 32 32 32 15.1% $-0.18[-2.12, 1.76]$ Heterogeneity. Tau ² = 2.64; Chi ² = 2.212, df = 2 (P < 0.0001); P = 91% Testfor overall effect Z = 0.18 (P = 0.86) 1.4.3 8weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% $-2.80[+4.57, -1.02]$ Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.66] Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% $0.06[-0.30, 0.42]$ Subtotal (95% CI) 82 82 15.4% $-0.11[-1.87, 1.65]$ Heterogeneity. Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); P = 92% Testfor overall effect Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% $-0.05 [-0.33, 0.82]$ Ugunty, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% $-0.05 [-0.33, 0.82]$ Ugunty, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% $-0.02 [-0.80, 0.22]$ Heterogeneity. Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); P = 0% Testfor overall effect Z = 1.10 (P = 0.27) Total (95% CI) 30 332 100.0% $-0.22 [-0.71, 0.26]$ Heterogeneity. Tau ² = 0.92; Chi ² = 13.16, df = 19 (P < 0.00001); P = 86% Testfor overall effect Z = 0.91 (P = 0.35); P = 0% Testfor overall effect Z = 0.92; Chi ² = 13.16, df = 19 (P < 0.00001); P = 86% Testfor overall effect Z = 0.91 (P = 0.35); P = 0% Testfor overall effect Z = 0.91 (P = 0.35); P = 0% Testfor overall effect Z = 0.91 (P = 0.35); P = 0% Testfor overall effect Z = 0.91 (P = 0.35); P = 0% Testfor overall effect Z = 0.92; Chi ² = 13.16, df = 19 (P < 0.00001); P = 86%	Thongbai-On, Banomyong, 2020	15.32	1.15	6	41.47	0.89	6	0.2%	-23.48 [-34.99, -11.96] 4		
Subtorial (95% C) Heterogeneity: Tau ² = 1.15; Ch ² = 78.16, df = 10 (P < 0.00001); P = 87% Test for overall effect Z = 0.87 (P = 0.38) 1.4.2 28/35 days Bagheri et al., 2013 35.9 3.8 6 42.56 3 6 4.2% -1.80 [-3.23, -0.36] Bagheri et al., 2017 13.3 2.62 10 15.5 4.58 10 5.4% -0.65 [+1.46, 0.33] Leiskar et al., 2003 87.2 9 16 73.3 7.5 16 5.6% 16.4 (D.82, 2.45] Subtotal (95% C) 32 32 15.1% -0.18 [-2.12, 1.76] Heterogeneity: Tau ² = 2.64; Ch ² = 22.12, df = 2 (P < 0.0001); P = 91% Test for overall effect Z = 0.18 (P = 0.86) 1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 18.2 [0.98, 2.66] Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 [-0.30, 0.42] Subtotal (95% C) 82 82 15.4% -0.11 [-1.87, 1.65] Heterogeneity: Tau ² = 2.11; Ch ² = 25.78, df = 2 (P < 0.00001); P = 92% Test for overall effect Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurtu, 2020 156.68 17.17 10 156.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% C) 30 30 16.2% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.00; Ch ² = 1.27, df = 2 (P = 0.53); P = 0% Test for overall effect Z = 1.10 (P = 0.27) Total (95% C) 310 32 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Ch ² = 131.36, df = 19 (P < 0.00001); P = 86%	Ugurlu, 2020a	41.29	4.95	10	51.82	5.48	10	4.9%	-1.93 [-3.03, -0.83]		
Heterogeneity: Tau ² = 1.15; Ch ² = 78.16, df = 10 (P < 0.00001); P = 87% Test for overall effect Z = 0.87 (P = 0.38) 1.4.2 28/35 days Bagheri et al., 2013 3.6.9 3.8 6 42.56 3 6 4.2% -1.80 [-3.23, -0.36] Bagheri et al., 2017 13.3 2.62 10 15.5 4.58 10 5.4% -0.56 [-1.46, 0.33] Leiskar et al., 2003 87.2 9 16 7.33 7.5 16 5.6% 1.64 [0.82, 2.45] Subtotal (95% CI) 32 Heterogeneity: Tau ² = 2.64; Ch ² = 22.12, df = 2 (P < 0.0001); P = 91% Test for overall effect Z = 0.18 (P = 0.86) 1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.66] Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 [-0.30, 0.42] Subtotal (95% CI) 82 Heterogeneity: Tau ² = 2.11; Ch ² = 25.78, df = 2 (P < 0.00001); P = 92% Test for overall effect Z = 0.12 (P = 0.50) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurdu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurdu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.72 [-1.63, 0.19] Ugurdu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Ch ² = 1.27, df = 2 (P = 0.53); P = 0% Test for overall effect Z = 0.12 (P = 0.53); P = 0% Test for overall effect Z = 0.12 (P = 0.53); P = 0% Test for overall effect Z = 0.92; Ch ² = 131.36, df = 19 (P < 0.00001); P = 86% Test for overall effect Z = 0.91 (P = 0.36)	Ugurlu, 2020b	154.45	18.57	10	179.2	18.98	10	5.2%	-1.26 [-2.24, -0.28]		
Test for overall effect $Z = 0.87$ (P = 0.38) 1.4.2 28/35 days Bagheri et al., 2013 35.9 3.8 6 42.56 3 6 42.% -1.80 [-3.23, -0.36] Bagheri et al., 2017 13.3 2.62 10 15.5 4.58 10 5.4% -0.56 [-1.46, 0.33] Leiskar et al., 2003 87.2 9 16 73.3 7.5 16 5.6% 1.84 [0.82, 2.45] Subtotal (95% CI) 32 32 32 15.1% -0.18 [-2.12, 1.76] Heterogeneity: Tau ² = 2.64; Chi ² = 22.12, df = 2 (P < 0.0001); P = 91% Test for overall effect $Z = 0.18$ (P = 0.86) 1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.66] Subtotal (95% CI) 82 82 15.4% -0.016 [-3.04] Subtotal (95% CI) 82 82 15.4% -0.01 [-1.87, 1.65] Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); P = 92% Test for overall effect $Z = 0.12$ (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% CI) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); P = 0% Test for overall effect $Z = 1.10$ (P = 0.27) Total (95% CI) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); I ² = 86% Test for overall effect $Z = 0.91$ (P = 0.36)	Subtotal (95% CI)			166			188	53.3%	-0.32 [-1.05, 0.40]		
1.4.2 28/35 days Bagheri et al., 2013 35.9 3.8 6 42.56 3 6 42.% $-1.80 [-3.23, -0.36]$ Bagheri et al., 2017 13.3 2.62 10 15.5 4.58 10 5.4% $-0.56 [-1.46, 0.33]$ Leiskar et al., 2003 87.2 9 16 73.3 7.5 16 5.6% $1.64 [0.82, 2.45]$ Subtotal (95% CI) 32 32 15.1% $-0.18 [-2.12, 1.76]$ Heterogeneity: Tau ² = 2.64; Chi ² = 22.12, df = 2 ($P < 0.0001$); $P = 91\%$ Test for overall effect $Z = 0.18 (P = 0.86)$ 1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% $-2.80 [-4.57, -1.02]$ Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% $1.82 [0.98, 2.66]$ Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% $0.06 [-0.30, 0.42]$ Subtotal (95% CI) 82 82 15.4% $-0.11 [-1.87, 1.65]$ Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 ($P < 0.00001$); $P = 92\%$ Test for overall effect $Z = 0.12 (P = 0.90)$ 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% $-0.05 [-0.93, 0.82]$ Ugurtu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% $-0.12 [-1.63, 0.19]$ Ugurtu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% $-0.12 [-1.63, 0.19]$ Subtotal (95% CI) 30 30 16.2% $-0.29 [-0.80, 0.22]$ Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 ($P = 0.53$); $P = 0\%$ Test for overall effect $Z = 1.10 (P = 0.27)$ Total (95% CI) 310 332 100.0% $-0.22 [-0.71, 0.26]$ Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 ($P < 0.00001$); $P = 88\%$ Test for overall effect $Z = 0.91 (P = 0.36)$			10 (P <	0.00001); I ^z = 87	%					
Bagheri et al., 2013 35.9 3.8 6 42.56 3 6 42.% $-1.80 [-3.23, -0.36]$ Bagheri et al., 2017 13.3 2.62 10 15.5 4.58 10 5.4% $-0.56 [+1.46, 0.33]$ Leiskar et al., 2003 87.2 9 16 73.3 7.5 16 5.6% $1.64 [0.82, 2.45]$ Subtotal (95% CI) 32 32 15.1% $-0.18 [-2.12, 1.76]$ Heterogeneity: Tau ² = 2.64; Ch ² = 22.12, df = 2 (P < 0.0001); P = 91% Test for overall effect Z = 0.18 (P = 0.86) 14.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% $-2.80 [-4.57, -1.02]$ Leiskar et al., 2013 91.3 7.4 16 77.3 7.6 16 5.5% $1.82 [0.98, 2.66]$ Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% $0.06 [-0.30, 0.42]$ Subtotal (95% CI) 82 82 15.4% $-0.11 [-1.87, 1.65]$ Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); P = 92% Test for overall effect Z = 0.12 (P = 0.90) 14.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% $-0.05 [-0.93, 0.82]$ Ugurtu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% $-0.72 [-1.63, 0.19]$ Ugurtu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% $-0.72 [-1.63, 0.19]$ Ugurtu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% $-0.29 [-0.80, 0.22]$ Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); P = 0% Test for overall effect Z = 0.91 (P = 0.27) Total (95% CI) 310 332 100.0% $-0.22 [-0.71, 0.26]$ Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); P = 86% Test for overall effect Z = 0.91 (P = 0.36)	Test for overall effect: Z = 0.87 (P =	0.38)									
Bagheri et al., 2017 13.3 2.62 10 15.5 4.58 10 5.4% -0.56 [+1.46, 0.33] Leiskar et al., 2003 87.2 9 16 73.3 7.5 16 5.6% 1.64 [0.82, 2.45] Juitotal (95% CI) 32 32 15.1% -0.18 [-2.12, 1.76] Heterogeneity: Tau ² = 2.64; Chi ² = 22.12, df = 2 (P < 0.0001); P = 91% Test for overall effect Z = 0.18 (P = 0.86) 1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.66] Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% -0.06 [-0.30, 0.42] Subtotal (95% CI) 82 82 15.4% -0.11 [-1.87, 1.65] Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); P = 92% Test for overall effect Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.025 [-0.93, 0.82] Ugurlu, 2020 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% CI) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); P = 0% Test for overall effect Z = 1.10 (P = 0.27) Total (95% CI) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); P = 86% Test for overall effect Z = 0.91 (P = 0.36)	1.4.2 28/35 days										
Leiskar et al., 2003 87.2 9 16 73.3 7.5 16 5.6% 1.64 $[0.82, 2.45]$ Subtotal (95% CI) 32 32 15.1% -0.18 $[-2.12, 1.76]$ Heterogeneity. Tau ² = 2.64; Chi ² = 22.12, df = 2 (P < 0.0001); P = 91% Test for overall effect Z = 0.18 (P = 0.86) 1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 $[-4.57, -1.02]$ Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 $[0.98, 2.66]$ Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 $[-0.30, 0.42]$ Subtotal (95% CI) 82 82 15.4% -0.11 $[-1.87, 1.65]$ Heterogeneity. Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); P = 92% Test for overall effect Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.69 10 15.5 3.58 10 5.4% -0.05 $[-0.93, 0.82]$ Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.012 $[-1.63, 0.19]$ Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.02 $[-0.80, 0.22]$ Heterogeneity. Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); P = 0% Test for overall effect Z = 0.10; Chi ² = 1.27, df = 2 (P = 0.00001); P = 86% Test for overall effect Z = 0.91 (P = 0.36)	Bagheri et al., 2013	35.9	3.8	6	42.56	3	6	4.2%	-1.80 [-3.23, -0.36]		
Subtotal (95% CI) 32 32 15.1% -0.18 [-2.12, 1.76] Heterogeneity: Tau ² = 2.64; Chi ² = 22.12, df = 2 (P < 0.0001); I ² = 91% Test for overall effect: Z = 0.18 (P = 0.86) 1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.66] Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 [-0.30, 0.42] Subtotal (95% CI) 82 82 15.4% -0.11 [-1.87, 1.65] Heterogeneity: Tau ² = 2.11; Chi ² = 2.578, df = 2 (P < 0.00001); I ² = 92% Test for overall effect: Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% CI) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); I ² = 0% Test for overall effect: Z = 0.91 (P = 0.36) Test for overall effect: Z = 0.91 (P = 0.36)	Bagheri et al., 2017	13.3	2.62	10	15.5	4.58	10	5.4%	-0.56 [-1.46, 0.33]	— — —	
Heterogeneity: Tau ² = 2.64; Chi ² = 22.12, df = 2 (P < 0.0001); I ² = 91% Test for overall effect: Z = 0.18 (P = 0.86) 1.4.38 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.66] Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 [-0.30, 0.42] Subtotal (95% CI) 82 82 15.4% -0.11 [-1.87, 1.65] Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); I ² = 92% Test for overall effect: Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% CI) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); I ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% CI) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); I ² = 86% Test for overall effect: Z = 0.91 (P = 0.36)	Leiskar et al., 2003	87.2	9		73.3	7.5					
Test for overall effect: Z = 0.18 (P = 0.86) 1.4.38 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.66] Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 [-0.30, 0.42] Subtotal (95% CI) 82 82 15.4% -0.11 [-1.87, 1.65] Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); P = 92% Test for overall effect: Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% CI) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); P = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% CI) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); P = 86% Test for overall effect: Z = 0.91 (P = 0.36)	Subtotal (95% CI)			32			32	15.1%	-0.18 [-2.12, 1.76]		
1.4.3 8 weeks Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.66] Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 [-0.30, 0.42] Subtotal (95% CI) 82 82 15.4% -0.11 [-1.87, 1.65] Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); I ² = 92% Test for overall effect Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% CI) 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); I ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% CI) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); I ² = 86% Test for overall effect: Z = 0.91 (P = 0.36)			2 (P < 0.	.0001); F	²= 91%						
Bagheri et al., 2013 59.9 6.2 6 76.2 4.4 6 3.5% -2.80 [-4.57, -1.02] Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% 1.82 [0.98, 2.66] Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 [-0.30, 0.42] Subtotal (95% CI) 82 82 15.4% -0.11 [-1.87, 1.65] Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); P = 92% Test for overall effect: Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); P = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% CI) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); I ² = 86% Test for overall effect: Z = 0.91 (P = 0.36)		0.00)									
Leiskar et al., 2003 91.3 7.4 16 77.3 7.6 16 5.5% $1.82 [0.98, 2.66]$ Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% $0.06 [-0.30, 0.42]$ Subtotal (95% CI) 82 82 82 15.4% $-0.11 [-1.87, 1.65]$ Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); I ² = 92% Test for overall effect: Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheni et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% $-0.05 [-0.93, 0.82]$ Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% $-0.72 [-1.63, 0.19]$ Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% $-0.12 [-1.00, 0.76]$ Subtotal (95% CI) 30 16.2% $-0.29 [-0.80, 0.22]$ Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); I ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% CI) 310 332 100.0% $-0.22 [-0.71, 0.26]$ Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); I ² = 86% Test for overall effect: Z = 0.91 (P = 0.36)	1.4.3 8 weeks										
Pilo et al., 2017 60.27 11.51 60 59.67 7.39 60 6.4% 0.06 $[-0.30, 0.42]$ Subtotal (95% Ct) 82 82 15.4% -0.11 $[-1.87, 1.65]$ Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); I ² = 92% Test for overall effect: Z = 0.12 (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 $[-0.93, 0.82]$ Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 $[-1.63, 0.19]$ Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 $[-1.00, 0.76]$ Subtotal (95% Ct) 30 16.2% -0.29 $[-0.80, 0.22]$ Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); I ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% Ct) 310 332 100.0% -0.22 $[-0.71, 0.26]$ Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); I ² = 86% Test for overall effect: Z = 0.91 (P = 0.36)	Bagheri et al., 2013	59.9		6		4.4	6		-2.80 [-4.57, -1.02]		
Subtotal (95% Cl) 82 82 15.4% -0.11 [-1.87, 1.65] Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); P = 92%	Leiskar et al., 2003	91.3	7.4								
Heterogeneity: Tau ² = 2.11; Chi ² = 25.78, df = 2 (P < 0.00001); I ² = 92% Test for overall effect: $Z = 0.12$ (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% Cl) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); I ² = 0% Test for overall effect: $Z = 1.10$ (P = 0.27) Total (95% Cl) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); I ² = 86% Test for overall effect: $Z = 0.91$ (P = 0.36)		60.27	11.51		59.67	7.39				+	
Test for overall effect: $Z = 0.12$ (P = 0.90) 1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% Cl) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); i ² = 0% Test for overall effect: $Z = 1.10$ (P = 0.27) Total (95% Cl) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); i ² = 86% Test for overall effect: $Z = 0.91$ (P = 0.36)							82	15.4%	-0.11 [-1.87, 1.65]		
1.4.4 6 and 12 months Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% $-0.05 [-0.93, 0.82]$ Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% $-0.72 [-1.63, 0.19]$ Ugurlu, 2020b 156.68 17.17 10 158.88 10 5.4% $-0.72 [-1.03, 0.19]$ Subtotal (95% CI) 30 30 16.2% $-0.29 [-0.80, 0.22]$ Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); l ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% CI) 310 332 100.0% $-0.22 [-0.71, 0.26]$ Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); l ² = 86% -2 0 2 Test for overall effect: Z = 0.91 (P = 0.36) Coated Control (uncoated) Coated			2 (P < 0.	.00001);	I² = 92%	ò					
Bagheri et al., 2017 15.3 3.59 10 15.5 3.58 10 5.4% -0.05 [-0.93, 0.82] Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% Cl) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); i ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% Cl) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); i ² = 86% Test for overall effect: Z = 0.91 (P = 0.36)		0.30)									
Ugurlu, 2020a 45.27 4.46 10 48.27 3.46 10 5.4% -0.72 [-1.63, 0.19] Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% Cl) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); i ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% Cl) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); i ² = 86% Test for overall effect: Z = 0.91 (P = 0.36)	1.4.4 6 and 12 months										
Ugurlu, 2020b 156.68 17.17 10 158.88 17.31 10 5.4% -0.12 [-1.00, 0.76] Subtotal (95% Cl) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); l ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% Cl) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); l ² = 86% Test for overall effect: Z = 0.91 (P = 0.36) -4 -2 0 2 4 Coated Control (uncoated)										-+-	
Subtotal (95% Cl) 30 30 16.2% -0.29 [-0.80, 0.22] Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); l ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% Cl) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); l ² = 86% -0.22 [-0.71, 0.26] Test for overall effect: Z = 0.91 (P = 0.36) -2 0 2											
Heterogeneity: Tau ² = 0.00; Chi ² = 1.27, df = 2 (P = 0.53); i ² = 0% Test for overall effect: Z = 1.10 (P = 0.27) Total (95% Cl) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); i ² = 86% Test for overall effect: Z = 0.91 (P = 0.36)	Ugurlu, 2020b	156.68	17.17		158.88	17.31					
Test for overall effect: Z = 1.10 (P = 0.27) Total (95% CI) 310 332 100.0% -0.22 [-0.71, 0.26] Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); I ² = 86% Test for overall effect: Z = 0.91 (P = 0.36)							30	16.2%	-0.29 [-0.80, 0.22]	-	
Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); l ² = 86% Test for overall effect: Z = 0.91 (P = 0.36) Coated Control (uncoated)			? (P = 0.5	(3); I* = C	1%						
Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); l ² = 86% Test for overall effect: Z = 0.91 (P = 0.36) Coated Control (uncoated)	Total (95% CI)			310			332	100.0%	-0.22 [-0.71, 0.26]	•	
Test for overall effect: Z = 0.91 (P = 0.36)	Heterogeneity: Tau ² = 0.92; Chi ² = 131.36, df = 19 (P < 0.00001); i ² = 86%										
	Tect for everall effect: 7 = 0.04 (P = 0.26)4 -2 U 2 4										

3. CONCLUSÃO

Por meio da revisão sistemática e meta-análise realizada pode-se concluir que o uso de agentes de proteção superficial reduz as propriedades de liberação de flúor e dureza dos cimentos de ionômero de vidro sem proporcionar benefícios na resistência do material. Diante disso, pode-se sugerir que o emprego dos agentes de proteção superficial não é necessário na prática clínica.

REFERÊNCIAS

DE AMORIM, R.G.; LEAL, S.C.; FRENCKEN, J.E. Survival of atraumatic restorative treatment (ART) sealants and restorations: A meta-analysis. **Clinical Oral Investigation**, v.16, p. 429–441, 2012.

HESSE, D.; *et al.* Bilayer technique and nano-filled coating increase success of approximal ART restorations: A randomized clinical trial. **International Journal of Paediatric Dentistry**, v. 26, n. 3, p. 231–239, 2016.

JAFARPOUR, D. *et al.* The effects of nanofilled resin-based coatings on the physical properties of glass ionomer cement restorative materials. **Journal of Dentistry**, v. 89, p. 103177, 2019.

KAMATHAM, R.; REDDY, S.J. Surface coatings on glass ionomer restorations in Pediatric dentistry-Worthy or not? **Journal of Indian Society of Pedodontics and Preventive Dentistry**, v. 31, n. 4, p. 229 - 233, Oct./Dec., 2012.

SIDHU S.; NICHOLSON J.; A review of glass-ionomer cements for clinical dentistry. **Journal of Functional Biomaterials,** v. 7, n. 3, p. E16, 2016.

ULUSOY AT.; TUNC ES.; BAYRAK Ş. Clinical performance of a glass ionomer sealant protected with two different resin-based agents over a 2-year follow-up period. **European Journal of Paediatric Dentistry**, v. 18, n. 1, p. 10 - 14, 2017.

ANEXO 1

Author Guidelines

Sections
1. Submission
2. Aims and Scope
3. Manuscript Categories and Requirements
4. Preparing the Submission
5. Editorial Policies and Ethical Considerations
6. Author Licensing
7. Publication Process After Acceptance
8. Post Publication
9. Editorial Office Contact Details

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at https://mc.manuscriptcentral.com/ijpd

Click here for more details on how to use ScholarOne.

Data protection

By submitting a manuscript to or reviewing for this publication, your name, email address, and affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognize the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at

https://authorservices.wiley.com/statements/data-protection-policy.html.

Preprint policy

Please find the Wiley preprint policy here.

This journal accepts articles previously published on preprint servers.

International Journal of Paediatric Dentistry will consider for review articles previously available as preprints. Authors may also post the submitted version of a manuscript to a preprint server at any time. Authors are requested to update any pre-publication versions with a link to the final published article.

For help with submissions, please contact: IJPDedoffice@wiley.com

2. AIMS AND SCOPE

International Journal of Paediatric Dentistry publishes papers on all aspects of paediatric dentistry including: growth and development, behaviour management, diagnosis, prevention, restorative treatment and issue relating to medically compromised children or those with disabilities. This peer-reviewed journal features scientific articles, reviews, case reports, short communications and abstracts of current paediatric dental research. Analytical studies with a scientific novelty value are preferred to descriptive studies. Case reports illustrating unusual conditions and clinically relevant observations are acceptable but must be of sufficiently high quality to be considered for publication; particularly the illustrative material must be of the highest quality.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

i. Original Articles

Divided into: Summary, Introduction, Material and methods, Results, Discussion, Bullet points, Acknowledgements, References, Figure legends, Tables and Figures arranged in this order.

• **Summary** should be structured using the following subheadings: Background, Hypothesis or Aim, Design, Results, and Conclusions and should be less than 200 words.

• **Introduction** should be brief and end with a statement of the aim of the study or hypotheses tested. Describe and cite only the most relevant earlier studies. Avoid presentation of an extensive review of the field.

• **Material and methods** should be clearly described and provide enough detail so that the observations can be critically evaluated and, if necessary repeated. Use section subheadings in a logical order to title each category or method. Use this order also in the results section. Authors should have considered the ethical aspects of their research and should ensure that the project was approved by an appropriate ethical committee, which should be stated. Type of statistical analysis must be described clearly and carefully.

• **Results** should clearly and concisely report the findings, and division using subheadings is encouraged. Double documentation of data in text, tables or figures is not acceptable. Tables and figures should not include data that can be given in the text in one or two sentences.

• **Discussion** section presents the interpretation of the findings. This is the only proper section for subjective comments and reference to previous literature. Avoid repetition of results, do not use subheadings or reference to tables in the results section.

• **Bullet Points:** Authors will need to provide no more than 3 'key points 'that summarise the key messages of their paper to be published with their article. The key points should be written with a practitioner audience in mind under the heading:

• *Why this paper is important to paediatric dentists. References: Maximum 30.

ii. Review Articles

May be invited by the Editor.

iii. Systematic reviews

We consider publishing systematic reviews if the manuscript has comprehensive and unbiased sampling of literature and covering topics related to Paediatric Dentistry.

References: Maximum 30.

Articles for the *International Journal of Paediatric Dentistry* should include: a) description of search strategy of relevant literature (search terms and databases), b) inclusion criteria (language, type of studies i.e. randomized controlled trial or other, duration of studies and chosen endpoints, c) evaluation of papers and level of evidence. For examples see:

Twetman S, Axelsson S, Dahlgren H et al. Caries-preventive effect of fluoride toothpaste: a systematic review. Acta Odontologica Scandivica 2003; 61: 347-355.

Paulsson L, Bondemark L, Söderfeldt B. A systematic review of the consequences of premature birth on palatal morphology, dental occlusion, tooth-crown dimensions, and tooth maturity and eruption. Angle Orthodontist 2004; 74: 269-279.

iv. Short Communications

Brief scientific articles or short case reports may be submitted, which should be no longer than three pages of double-spaced text and include a maximum of three illustrations. They should contain important, new, definitive information of sufficient significance to warrant publication. They should not be divided into different parts and summaries are not required. References: Maximum 30.

v. Brief Clinical Reports/Case Reports

Short papers not exceeding 800 words, including a maximum of three illustrations and five references may be accepted for publication if they serve to promote communication between clinicians and researchers. If the paper describes a genetic disorder, the OMIM unique six-digit number should be provided for online cross reference (Online Mendelian Inheritance in Man).

A paper submitted as a Brief Clinical/Case Report should include the following:

- a short Introduction (avoid lengthy reviews of literature);
- the **Case report** itself (a brief description of the patient/s, presenting condition, any special

investigations and outcomes);

• a **Discussion** which should highlight specific aspects of the case(s), explain/interpret the main findings and provide a scientific appraisal of any previously reported work in the field.

• **Bullet Points:** Authors will need to provide no more than 3 'key points 'that summarise the key messages of their paper to be published with their article. The key points should be written with a practitioner audience in mind under the heading:

• *Why this paper is important to paediatric dentists.

vi. Letters to the Editor

Letters should be no more than 1,500 words, with no more than 10 references. There should be no abstract, tables or figures.

4. PREPARING THE SUBMISSION

Cover Letters

Cover letters are not mandatory; however, they may be supplied at the author's discretion.

Parts of the Manuscript

The manuscript should be submitted in separate files: title page; main text file; figures.

Title page

The title page should contain:

i. A short informative title that contains the major key words. The title should not contain abbreviations (see Wiley's **best practice SEO tips**);

ii. A short running title of less than 50 characters;

iii. The full names of the authors and a statement of author contributions, e.g.

Author contributions: A.S. and K.J. conceived the ideas; K.J. and R.L.M. collected the data; R.L.M. and P.A.K. analysed the data; and A.S. and K.J. led the writing;

iv. The author's institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted;

v. Acknowledgments;

vi. Word count (excluding tables)

Authorship

Please refer to the journal's authorship policy the Editorial Policies and Ethical Considerations section for details on eligibility for author listing.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

Conflict of Interest Statement

Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the section 'Conflict of Interest 'in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

Main Text File

As papers are double-blind peer reviewed the main text file should not include any information that might identify the authors.

The main text file should be presented in the following order:

- i. Title, abstract and key words;
- ii. Main text;
- iii. References;
- iv. Tables (each table complete with title and footnotes);
- v. Figure legends;
- vi. Appendices (if relevant).

Figures and supporting information should be supplied as separate files.

Abstract

Abstracts and keywords are required for some manuscript types. For details on manuscript types that require abstracts, please refer to the 'Manuscript Types and Criteria 'section.

Keywords

Please provide 3-6 keywords. Keywords should be taken from the list provided at submission in ScholarOne.

Main Text

• As papers are double-blind peer reviewed, the main text file should not include any information that might identify the authors.

• The journal uses British spelling; however, authors may submit using either option, as spelling of accepted papers is converted during the production process.

References

All references should be numbered consecutively in order of appearance and should be as complete as possible. In text citations should cite references in consecutive order using Arabic superscript numerals. For more information about AMA reference style please consult the <u>AMA Manual of Style</u> Sample references follow:

Journal article

1. King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. J Comp Neurol 1998;390:537-551.

Book

2. Voet D, Voet JG. Biochemistry. New York: John Wiley & Sons; 1990. 1223 p.

Internet document

3. American Cancer Society. Cancer Facts & Figures 2003. http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf Accessed March 3, 2003

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figure Legends

Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Figures

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted.

<u>Click here</u> for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

In the text, please reference figures as for instance 'Figure 1', 'Figure 2' to match the tag name you choose for the individual figure files uploaded.

Colour Figures. Figures submitted in colour may be reproduced in colour online free of charge. Please note, however, that it is preferable that line figures (e.g. graphs and charts) are supplied in black and white so that they are legible if printed by a reader in black and white.

Data Citation

Please review Wiley's data citation policy here.

Additional Files

Appendices

Appendices will be published after the references. For submission they should be supplied as separate files but referred to in the text.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc.

<u>Click here</u> for Wiley's FAQs on supporting information.

Note: if data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

Submission of Revised Manuscripts

Revised manuscripts must be uploaded within 2 months of authors being notified of conditional acceptance pending satisfactory revision. Locate your manuscript under 'Manuscripts with Decisions' and click on 'Submit a Revision' to submit your revised manuscript. Please remember to delete any old files uploaded when you upload your revised manuscript. All revisions must be accompanied by a cover letter to the editor.

Authors should supply their response to reviewers in the field provided for this at the beginning of their submission. The replies should include a) detail on a point-by-point basis the author's response to each of the referee's comments, and b) a revised manuscript highlighting exactly what has been changed in the manuscript after revision.

Resource Identification Initiative

The journal supports the <u>Resource Identification Initiative</u>, which aims to promote research resource identification, discovery, and reuse. This initiative, led by the <u>Neuroscience Information</u> <u>Framework</u> and the <u>Oregon Health & Science University Library</u>, provides unique identifiers for antibodies, model organisms, cell lines, and tools including software and databases. These IDs, called Research Resource Identifiers (RRIDs), are machine-readable and can be used to search for all papers where a particular resource was used and to increase access to critical data to help researchers identify suitable reagents and tools.

Authors are asked to use RRIDs to cite the resources used in their research where applicable in the text, similar to a regular citation or Genbank Accession number. For antibodies, authors should include in the citation the vendor, catalogue number, and RRID both in the text upon first mention in the Methods section. For software tools and databases, please provide the name of the resource followed by the resource website, if available, and the RRID. For model organisms, the RRID alone is sufficient. Additionally, authors must include the RRIDs in the list of keywords associated with the manuscript.

To Obtain Research Resource Identifiers (RRIDs)

- 1. Use the Resource Identification Portal, created by the Resource Identification Initiative Working Group.
- 2. Search for the research resource (please see the section titled "Search Features and Tips" for more information).
- 3. Click on the "Cite This" button to obtain the citation and insert the citation into the manuscript text.

If there is a resource that is not found within the **Resource Identification Portal**, authors are asked to register the resource with the appropriate resource authority. Information on how to do this is provided in the "Resource Citation Guidelines" section of the Portal.

If any difficulties in obtaining identifiers arise, please contact <u>rii-help@scicrunch.org</u> for assistance.

Example Citations

Antibodies: "Wnt3 was localized using a rabbit polyclonal antibody C64F2 against Wnt3 (Cell Signaling Technology, Cat# 2721S, RRID: AB_2215411)"

Model Organisms: "Experiments were conducted in c. elegans strain SP304 (RRID:CGC_SP304)" Cell lines: "Experiments were conducted in PC12 CLS cells (CLS Cat# 500311/p701_PC-12, RRID:CVCL_0481)"

Tools, Software, and Databases: "Image analysis was conducted with CellProfiler Image Analysis

Software, V2.0 (http://www.cellprofiler.org, RRID:nif-0000-00280)"

Wiley Author Resources

Manuscript Preparation Tips: Wiley has a range of resources for authors preparing manuscripts for submission available <u>here</u>. In particular, authors may benefit from referring to Wiley's best practice tips on <u>Writing for Search Engine Optimization</u>.

Article Preparation Support: Wiley Editing Services offers expert help with English Language Editing, as well as translation, manuscript formatting, figure illustration, figure formatting, and graphical abstract design – so you can submit your manuscript with confidence. Also, check out our resources for **Preparing Your Article** for general guidance about writing and preparing your manuscript.

Guidelines for Cover Submissions: If you would like to send suggestions for artwork related to your manuscript to be considered to appear on the cover of the journal, please follow these <u>general</u> <u>guidelines</u>.

5. EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Peer Review and Acceptance

The acceptance criteria for all papers are the quality and originality of the research and its significance to journal readership. Manuscripts are double-blind peer reviewed. Papers will only be sent to review if the Editor-in-Chief determines that the paper meets the appropriate quality and relevance requirements.

Wiley's policy on the confidentiality of the review process is available here.

Human Studies and Subjects

For manuscripts reporting medical studies that involve human participants, a statement identifying the ethics committee that approved the study and confirmation that the study conforms to recognized standards is required, for example: <u>Declaration of Helsinki</u>; <u>US Federal Policy for the Protection of Human Subjects</u>; or <u>European Medicines Agency Guidelines for Good Clinical Practice</u>. It should also state clearly in the text that all persons gave their informed consent prior to their inclusion in the study.

Patient anonymity should be preserved. When detailed descriptions, photographs, or videos of faces or identifiable body parts are used that may allow identification, authors should obtain the individual's free prior informed consent. Authors do not need to provide a copy of the consent form to the publisher; however, in signing the author license to publish, authors are required to confirm that consent has been obtained. Wiley has a <u>standard patient consent form</u> available for use. Where photographs are used they need to be cropped sufficiently to prevent human subjects being recognized; black eye bars should not be used as they do not sufficiently protect an individual's identity).

Animal Studies

A statement indicating that the protocol and procedures employed were ethically reviewed and approved, as well as the name of the body giving approval, must be included in the Methods section of the manuscript. Authors are encouraged to adhere to animal research reporting standards, for example the <u>ARRIVE guidelines</u> for reporting study design and statistical analysis; experimental procedures; experimental animals and housing and husbandry. Authors should also state whether experiments were performed in accordance with relevant institutional and national guidelines for the care and use of laboratory animals:

• US authors should cite compliance with the <u>US National Research Council's Guide for the</u> <u>Care and Use of Laboratory Animals</u>, the <u>US Public Health Service's Policy on Humane Care and Use</u> of Laboratory Animals, and Guide for the Care and Use of Laboratory Animals.

• UK authors should conform to UK legislation under the <u>Animals (Scientific Procedures) Act</u> 1986 Amendment Regulations (SI 2012/3039).

• European authors outside the UK should conform to Directive 2010/63/EU.

Clinical Trial Registration

Clinical trials should be reported using the CONSORT guidelines available at www.consort-

statement.org. A CONSORT checklist should also be included in the submission material under "Supplementary Files for Review".

If your study is a randomized clinical trial, you will need to fill in all sections of the CONSORT Checklist. If your study is not a randomized trial, not all sections of the checklist might apply to your manuscript, in which case you simply fill in N/A.

All prospective clinical trials which have a commencement date after the 31st January 2017 must be registered with a public trials registry: <u>www.clinicaltrials.gov</u>,

http://clinicaltrials.ifpma.org/clinicaltrials/, http://isrctn.org/. The clinical trial registration number and name of the trial register will then be published with the paper.

Research Reporting Guidelines

Accurate and complete reporting enables readers to fully appraise research, replicate it, and use it. The guidelines listed below should be followed where appropriate and where applicable, checklists, and flow diagrams uploaded with your submission; these may be published alongside the final version of your paper.

• Observational studies : STROBE checklists for cohort, case-control, and cross-sectional studies,

- either individual or combined
- Systematic reviews : PRISMA
- Meta-analyses of observational studies: MOOSE
- <u>Case reports</u> CARE
- In vitro studies: CRIS
- Qualitative research : COREQ
- Diagnostic / prognostic studies : STARD
- Quality improvement studies : SQUIRE
- Economic evaluations : CHEERS
- <u>Animal pre-clinical studies : ARRIVE</u>
- Study protocols : SPIRIT
- <u>Clinical practice guidelines : AGREE</u>

The <u>Equator Network</u> (Enhancing the Quality and Transparency Of Health Research) provides a comprehensive list of reporting guidelines.

We also encourage authors to refer to and follow guidelines from:

- Future of Research Communications and e-Scholarship (FORCE11)
- National Research Council's Institute for Laboratory Animal Research guidelines
- The Gold Standard Publication Checklist from Hooijmans and colleagues
- Minimum Information Guidelines from Diverse Bioscience Communities (MIBBI) website
- FAIRsharing website

Sequence Data

Nucleotide sequence data can be submitted in electronic form to any of the three major collaborative databases: DDBJ, EMBL, or GenBank. It is only necessary to submit to one database as data are exchanged between DDBJ, EMBL, and GenBank on a daily basis. The suggested wording for referring to accession-number information is: 'These sequence data have been submitted to the DDBJ/EMBL/GenBank databases under accession number U12345'. Addresses are as follows:

- DNA Data Bank of Japan (DDBJ): www.ddbj.nig.ac.jp
- EMBL Nucleotide Archive: ebi.ac.uk/ena
- GenBank: <u>www.ncbi.nlm.nih.gov/genbank</u>

Proteins sequence data should be submitted to either of the following repositories:

- Protein Information Resource (PIR): pir.georgetown.edu
- SWISS-PROT: <u>expasy.ch/sprot/sprot-top</u>

Structural Data

For papers describing structural data, atomic coordinates and the associated experimental data should be deposited in the appropriate databank (see below). Please note that the data in databanks must be released, at the latest, upon publication of the article. We trust in the cooperation of our authors to ensure that atomic coordinates and experimental data are released on time.

• Organic and organometallic compounds: Crystallographic data should not be sent as Supporting Information, but should be deposited with the *Cambridge Crystallographic Data Centre* (CCDC) at ccdc.cam.ac.uk/services/structure%5Fdeposit.

- Inorganic compounds: Fachinformationszentrum Karlsruhe (FIZ; fiz-karlsruhe.de).
- Proteins and nucleic acids: Protein Data Bank (rcsb.org/pdb).
- NMR spectroscopy data: BioMagResBank (bmrb.wisc.edu).

Conflict of Interest

The journal requires that all authors disclose any potential sources of conflict of interest. Any interest or relationship, financial or otherwise that might be perceived as influencing an author's objectivity is considered a potential source of conflict of interest. These must be disclosed when directly relevant or directly related to the work that the authors describe in their manuscript. Potential sources of conflict of interest include, but are not limited to: patent or stock ownership, membership of a company board of directors, membership of an advisory board or committee for a company, and consultancy for or receipt of speaker's fees from a company. The existence of a conflict of interest does not preclude publication. If the authors have no conflict of interest to declare, they must also state this at submission. It is the responsibility of the corresponding author to review this policy with all authors and collectively to disclose with the submission ALL pertinent commercial and other relationships. It is the responsibility of the corresponding author to have all authors of a manuscript fill out a conflict of interest disclosure form, and to upload all forms together with the manuscript on submission. Please find the form below:

Conflict of Interest Disclosure Form

The form above does not display correctly in the browsers. If you see an error message starting with "Please wait...", we recommend that you download the file to your computer. Saving a local copy on your computer should allow the form to work properly.

Funding

Authors should list all funding sources in the Acknowledgments section. Authors are responsible for the accuracy of their funder designation. If in doubt, please check the Open Funder Registry for the correct nomenclature: <u>https://www.crossref.org/services/funder-registry/</u>

Authorship

The list of authors should accurately illustrate who contributed to the work and how. All those listed as authors should qualify for authorship according to the following criteria:

- 1. Have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and
- 2. Been involved in drafting the manuscript or revising it critically for important intellectual content; and
- 3. Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and
- 4. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section (for example, to recognize contributions from people who provided technical help, collation of data, writing assistance, acquisition of funding, or a department chairperson who provided general support). Prior to submitting the article all authors should agree on the order in which their names will be listed in the manuscript.

Additional Authorship Options. Joint first or senior authorship: In the case of joint first authorship, a footnote should be added to the author listing, e.g. 'X and Y should be considered joint first author 'or 'X and Y should be considered joint senior author.'

Data Sharing and Data Accessibility

<u>Please review Wiley's policy here</u>. This journal encourages and peer review data sharing. The journal encourages authors to share the data and other artefacts supporting the results in the paper by archiving it in an appropriate public repository. Authors should include a data

accessibility statement, including a link to the repository they have used, in order that this statement can be published alongside their paper.

All accepted manuscripts may elect to publish a data availability statement to confirm the presence or absence of shared data. If you have shared data, this statement will describe how the data can be accessed, and include a persistent identifier (e.g., a DOI for the data, or an accession number) from the repository where you shared the data. <u>Sample statements</u> <u>are available here</u>. If published, statements will be placed in the heading of your manuscript.

Human subject information in databases. The journal refers to the <u>World Health Medical</u> <u>Association Declaration of Taipei on Ethical Considerations Regarding Health</u> <u>Databases and Biobanks</u>.

Publication Ethics

This journal is a member of the **Committee on Publication Ethics (COPE).** Note this journal uses iThenticate's CrossCheck software to detect instances of overlapping and similar text in submitted manuscripts. Read Wiley'sTop 10 Publishing Ethics Tips for Authors <u>here</u>. Wiley's Publication Ethics Guidelines can be found <u>here</u>.

ORCID

As part of the journal's commitment to supporting authors at every step of the publishing process, the journal requires the submitting author (only) to provide an ORCID iD when submitting a manuscript. This takes around 2 minutes to complete. Find more information here.

6. AUTHOR LICENSING

If your paper is accepted, the author identified as the formal corresponding author will receive an email prompting them to log in to Author Services, where via the Wiley Author Licensing Service (WALS) they will be required to complete a copyright license agreement on behalf of all authors of the paper.

Authors may choose to publish under the terms of the journal's standard copyright agreement, or **Open Access** under the terms of a Creative Commons License. General information regarding licensing and copyright is available <u>here</u>. To review the Creative Commons License options offered under Open Access, please <u>click here</u>. (Note that certain funders mandate that a particular type of CC license has to be used; to check this please click <u>here</u>.)

Self-Archiving definitions and policies. Note that the journal's standard copyright agreement allows for self-archiving of different versions of the article under specific conditions. Please <u>click here</u> for more detailed information about self-archiving definitions and policies.

Open Access fees: If you choose to publish using Open Access you will be charged a fee. A list of Article Publication Charges for Wiley journals is available <u>here</u>.

Funder Open Access: Please click <u>here</u> for more information on Wiley's compliance with specific Funder Open Access Policies.

Reproduction of Copyright Material: If excerpts from copyrighted works owned by third parties are included, credit must be shown in the contribution. It is the author's responsibility to also obtain written permission for reproduction from the copyright owners. For more information visit Wiley's Copyright Terms & Conditions FAQ at http://exchanges.wiley.com/authors/fags---copyright-terms--conditions 301.html

7. PUBLICATION PROCESS AFTER ACCEPTANCE

Accepted article received in production

When an accepted article is received by Wiley's production team, the corresponding author will receive an email asking them to login or register with <u>Wiley Author Services.</u> The author will be asked to sign a publication license at this point.

Accepted Articles

The journal offers Wiley's Accepted Articles service for all manuscripts. This service ensures that accepted 'in press 'manuscripts are published online shortly after acceptance, prior to copy-editing or typesetting. Accepted Articles are published online a few days after final acceptance and appear in PDF format only. They are given a Digital Object Identifier (DOI), which allows them to be cited and tracked and are indexed by PubMed. After the final version article is published (the article of record), the DOI remains valid and can still be used to cite and access the article.

Accepted Articles will be indexed by PubMed; submitting authors should therefore carefully check the names and affiliations of all authors provided in the cover page of the manuscript so it is accurate for indexing. Subsequently, the final copyedited and proofed articles will appear in an issue on Wiley Online Library; the link to the article in PubMed will update automatically.

Proofs

Authors will receive an e-mail notification with a link and instructions for accessing HTML page proofs online. Page proofs should be carefully proofread for any copyediting or typesetting errors. Online guidelines are provided within the system. No special software is required, most common browsers are supported. Authors should also make sure that any renumbered tables, figures, or references match text citations and that figure legends correspond with text citations and actual figures. Proofs must be returned within 48 hours of receipt of the email. Return of proofs via e-mail is possible in the event that the online system cannot be used or accessed.

Early View

The journal offers rapid speed to publication via Wiley's Early View service. **Early View** (Online Version of Record) articles are published on Wiley Online Library before inclusion in an issue. Note there may be a delay after corrections are received before the article appears online, as Editors also need to review proofs. Once the article is published on Early View, no further changes to the article are possible. The Early View article is fully citable and carries an online publication date and DOI for citations.

8. POST PUBLICATION

Access and sharing

When the article is published online:

- The author receives an email alert (if requested).
- The link to the published article can be shared through social media.
- The author will have free access to the paper (after accepting the Terms & Conditions of use, they can view the article).
- The corresponding author and co-authors can nominate up to ten colleagues to receive a publication alert and free online access to the article.

Promoting the Article

To find out how to best promote an article, click here.

Article Promotion Support

<u>Wiley Editing Services</u> offers professional video, design, and writing services to create shareable video abstracts, infographics, conference posters, lay summaries, and research

news stories for your research – so you can help your research get the attention it deserves.

Measuring the Impact of an Article

Wiley also helps authors measure the impact of their research through specialist partnerships with <u>Kudos</u> and <u>Altmetric</u>.

Wiley's Author Name Change Policy

In cases where authors wish to change their name following publication, Wiley will update and republish the paper and redeliver the updated metadata to indexing services. Our editorial and production teams will use discretion in recognizing that name changes may be of a sensitive and private nature for various reasons including (but not limited to) alignment with gender identity, or as a result of marriage, divorce, or religious conversion. Accordingly, to protect the author's privacy, we will not publish a correction notice to the paper, and we will not notify co-authors of the change. Authors should contact the journal's Editorial Office with their name change request.

9. EDITORIAL OFFICE CONTACT DETAILS

For queries about submissions, please contact IJPDedoffice@wiley.com

Author Guidelines Updated 08 February 2021

ANEXO 2

PRISMA CHECK LIST

Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE	4	Identify the report on a systematic review	Daga 11
Title ABSTRACT	1	Identify the report as a systematic review.	Page 11
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 13
INTRODUCTIO			1 age 10
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 14, 15
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 15
METHODS			-
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the synthe- ses.	Page 16
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 15
Search strat- egy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 15
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 16
Data collec- tion process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pages 16, 17
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compati- ble with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 15, 16
	10b	List and define all other variables for which data were sought (e.g. participant and intervention character- istics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assess- ment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 17
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 17
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 17
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 17
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 17
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta- analysis was performed, describe the model(s), method(s) to identify the presence and extent of statisti- cal heterogeneity, and software package(s) used.	Page 17
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. sub- group analysis, meta-regression).	Page 17
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 17
Reporting bias assess- ment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 17

Section and Topic	ltem #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS	1		
Study selec- tion	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 18
Study charac- teristics	17	Cite each included study and present its characteristics.	Page 18
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 19
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 2 a 4, Page 19
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Figures 2 a 4, Page 19
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figures 2 a 4, Page 19
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figures 2 a 4, Page 19
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figures 2 a 4, Page 19
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each syn- thesis assessed.	Table 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION	•		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 20, 21
	23b	Discuss any limitations of the evidence included in the review.	Pages 20, 21
	23c	Discuss any limitations of the review processes used.	Page 22
	23d	Discuss implications of the results for practice, policy, and future research.	Page 22
OTHER INFOR	MATIO	Ν	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or spon- sors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collec- tion forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-