UNIVERSIDADE ESTADUAL DE PONTA GROSSA
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA – DOUTORADO
ÁREA DE CONCENTRAÇÃO: DENTÍSTICA RESTAURADORA

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AVALIAÇÃO DE ESTRATÉGIAS ADESIVAS EM LESÕES CERVICAIS ATRAVÉS DE REVISÕES SISTEMÁTICAS E META-ANÁLISES

PONTA GROSSA
2020

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Tese apresentada como pré-requisito para obtenção do título de Doutora na Universidade Estadual de Ponta Grossa, no Programa de Pós-Graduação *Stricto Sensu* em Odontologia – Área de Concentração Dentística Restauradora. Linha de Pesquisa: Propriedades físico-químicas e biológicas dos materiais.

Orientadora: Profª. Drª. Alessandra Reis

PONTA GROSSA
2020

Dreweck, Fabiana Dias Simas
D776 Avaliação de estratégias adesivas em lesões cervicais através de revisões sistemáticas e meta-análises / Fabiana Dias Simas Dreweck. Ponta Grossa, 2020.
169 f.

Tese (Doutorado em Odontologia - Área de Concentração: Dentística Restauradora), Universidade Estadual de Ponta Grossa.

Orientadora: Profa. Dra. Alessandra Reis.

1. Agentes de união à dentina. 2. Lesões cervicais. 3. Eficácia de tratamento. 4. Revisão sistemática. 5. Meta-análise em rede. I. Reis, Alessandra. II. Universidade Estadual de Ponta Grossa. Dentística Restauradora. III.T.

CDD: 617.6

Ficha catalográfica elaborada por Maria Luzia Fernandes Bertholino dos Santos- CRB9/986

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Avaliação de estratégias adesivas em lesões cervicais através de revisões sistemáticas e meta-análises

Tese apresentada ao Programa de Pós-graduação Stricto Sensu em Odontologia da Universidade Estadual de Ponta Grossa, como requisito parcial à obtenção do título de Doutora em Odontologia, área de concentração em Dentística Restauradora, linha de Pesquisa Propriedades físico-químicas e biológicas dos materiais.

Ponta Grossa, 12 de fevereiro de 2020.

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Profª. Drª. Alessandra Reis Silva Loguercio
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Dedico este trabalho ao meu marido Marcelo, meu companheiro, melhor amigo, meu porto seguro...e ao meu filho Vinícius, minha vida, razão do meu viver.

AMO VOCÊS ALÉM DO INFINITO!

AGRADECIMENTOS

Aos meus pais **Lincoln** e **Maria do Carmo** por tudo que fizeram por mim todos estes anos, pela infância feliz ao lado da minha irmã **Vanessa,** por todo o empenho, apoio e dedicação quando saí de casa para estudar fora não deixando faltar nada durante o período da faculdade e até os dias de hoje. Posso dizer com certeza que tenho uma base familiar sólida e que sempre vocês serão meu porto seguro. Essa conquista também é de vocês, obrigada por tudo.

Ao meu filho **Vinícius**, amor maior do mundo. Faltam palavras pra descrever este amor que cresce a cada dia. Você é muito mais do que sonhei, meu companheiro, amoroso e sempre cuidadoso comigo. Me perdoe os momentos de falta de atenção, paciência e acompanhamento, muitas vezes me fazia perguntas do tipo "Mãe: Falta muito pra você terminar este trabalho?" ou "Mãe: quando você vai terminar?". Obrigada meu amor, te amo mais que tudo!

Ao meu sogro **Romeu** e minha sogra **Ana Rita** (*in memorian*) que nos deixou no meio desta jornada, mesmo nas minhas ausências sempre me apoiaram e incentivaram, cuidando também com muito amor do nosso Vini, não tenho palavras para agradecer.

A professora **Osnara**, minha primeira orientadora, sempre solícita e com uma palavra de conforto e aconchego, como uma verdadeira mãe, serei sempre grata.

A professora **Alessandra**, não apenas minha orientadora, mas um presente que ganhei no final do segundo tempo do doutorado. Poucos são tão privilegiados como eu por ter tido a sorte de conviver com uma pessoa tão generosa, dedicada e especial. A você Professora Alessandra, meu muito obrigada. Muito obrigada mesmo. Sem você este projeto não teria existido.

Ao professor **Alessandro**, pelo acolhimento logo no início do doutorado, com um projeto inicial que não "decolou", mas espero colhermos frutos mais a frente. Preciso externar minha profunda admiração e agradecer por todo o apoio, incentivo e ajuda. Você e a Alessandra são demais. Muito obrigada de coração.

A todos os **professores do PPGO**, muito obrigada pelos ensinamentos.

Aos colegas e amigos de pós-graduação, obrigada pelo convívio e troca de experiências, em especial ao **Mario Felipe**, **Andréia**, **Bianca**, **André**, **Driellen** e **Pâmela**.

A **Adrieli**, minha verdadeira amiga de todas as horas, dos choros, das risadas, dos conselhos, das trocas de ideias, sempre presente em todos os momentos. Quantos dias até altas horas extraindo dados.....espero que nossos desejos de aproveitarmos os dias sem compromissos de horário após isso tudo se concretizem. A sua amizade é muito especial para mim, desejo que você fique sempre por perto. Minha amiga irmã te desejo o mundo.

A todos os **funcionários** da UEPG, em especial a **Bianca**, em meio a tantos afazeres sempre dispostos a ajudar com palavras carinhosas.

Os meus respeitosos agradecimentos pela contribuição da **banca de exame de qualificação** e pela participação dos membros da **banca examinadora de defesa**, profissionais dos quais tenho profunda admiração.

Finalmente, faço questão de agradecer a todos que de alguma forma permitiram que este trabalho se concretizasse.

AGRADECIMENTO ESPECIAL

Meu agradecimento mais profundo só poderia ser dedicado a uma pessoa: meu marido **Marcelo.** O tempo todo ao meu lado, principalmente nos momentos mais difíceis deste último ano, em que muitas vezes ouviu eu dizer: “Não aguento mais” e ele sempre ao meu lado com palavras de conforto e sua calma presença. Toda a parte estatística deste trabalho eu devo a você, que realmente se dedicou, estudou muito e perdeu horas de sono decifrando a rede. O meu crescimento profissional e intelectual é compartilhado com você e posso dizer com toda a certeza, crescemos muito juntos e meu amor e admiração aumentam a cada dia. É isso que quero para nós e nossa família. Obrigada por tudo meu amor!

DADOS CURRICULARES

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RESUMO

Dreweck, F.D.S. **Avaliação de estratégias adesivas em lesões cervicais através de revisões sistemáticas e meta-análises.** 2020. [Tese] Doutorado em Dentística Restauradora – Universidade Estadual de Ponta Grossa. Ponta Grossa, 2020.

Objetivos: Comparar as taxas de retenção de adesivos autocondicionantes de 1-passo (1SE) e adesivos de condicionamento ácido total de 3-passos (3ER) em lesões cervicais não cariosas (LCNCs) (1), avaliar qual estratégia adesiva é mais efetiva clinicamente em LCNCs (2) e se existem diferenças nas taxas de retenção dos adesivos OptiBond FL e Clearfil SE Bond com outras marcas comerciais de adesivos (3). **Materiais e Métodos:** Para este trabalho, 3 revisões sistemáticas (RSs) foram realizadas, sendo que o estudo (2) foi uma RS em rede conduzida pela metodologia de comparação mista de tratamento (MTC). Apenas estudos clínicos randomizados (ECRs) em LCNCs de acordo com os critérios de elegibilidade foram incluídos. O vocabulário controlado e palavras-chave foram combinadas na estratégia de busca para PubMed/Medline e adaptadas para outras bases de dados bem como consulta da literatura cinzenta. O risco de viés foi avaliado usando a ferramenta de Colaboração da Cochrane (RoB) e a heterogeneidade foi avaliada pelos testes Q da Cochrane e estatística I^2. A abordagem GRADE foi utilizada para avaliar a qualidade da evidência. Meta-análises foram conduzidas para taxas de retenção, descoloração marginal e integridade marginal, nos períodos de acompanhamento de 12 a 24-meses, 24 a 36-meses e 60-meses no estudo (1) e no estudo (3) meta-análises para taxas de retenção para o adesivo OptiBond FL nos períodos de 12 a 24-meses, 36 a 48-meses, 60 a 96-meses, 108 a 156-meses e para o adesivo Clearfil SE Bond nos períodos de 12 a 24-meses e 36 a 48-meses. No estudo (2), foram realizadas as meta-análises tradicional e em rede Bayesiana para taxas de retenção nos períodos de 12 a 24-meses, 36 a 48-meses, acima de 48-meses e as estratégias adesivas foram ranqueadas pela SUCRA. **Resultados:** No estudo (1), não foram observadas diferenças significativas nas taxas de retenção entre os adesivos 1SE versus adesivos 3ER nos diferentes períodos de acompanhamento: 12 a 24-meses ($p = 0.66$), 24 a 36-meses ($p = 0.21$) e 60-meses ($p = 0.96$). Foi encontrada uma diferença significativa na integridade marginal em 12 a 24-meses ($p = 0.04$) e na descoloração marginal em 12 a 24-meses ($p = 0.003$). Na RS de MTC (2) foi encontrada uma diferença significativa no resultado da rede apenas no par 2SE vs 3ER em favor da estratégia 2SE em 12 a 24-meses (RR = 0.72; 95% CrI 0.52 to 0.99), nos demais períodos de acompanhamento não foram encontradas diferenças significativas. No artigo (3) nenhuma diferença foi observada para taxas de retenção nos períodos de 12 a 24-meses ($p = 0.97$), 36 a 48-meses ($p = 0.72$) e 108 a 156 meses ($p = 0.73$) para o OptiBond FL e 12 a 24-meses ($p = 0.10$) e 36 a 48-meses ($p = 0.17$) para o Clearfil SE Bond. Uma diferença significativa foi encontrada para o OptiBond FL em 60 a 96-meses ($p = 0.02$), mas apenas 3 estudos foram incluídos nesta meta-análise. **Conclusões:** Não existem evidências que adesivos 3ER possuem melhores taxas de retenção que adesivos 1SE em LCNCs (1). Nenhuma estratégia adesiva foi superior a outra (2) e não há evidências de que as taxas de retenção dos adesivos OptiBond FL e Clearfil SE Bond são maiores que das marcas comerciais de adesivos com as quais foram comparados (3).

Palavras-chave: Agentes de união à dentina. Lesões cervicais. Eficácia do tratamento. Revisão sistemática. Meta-análise em rede.

ABSTRACT

Dreweck, F.D.S. **Evaluation of adhesive strategies in cervical lesions through systematic reviews and meta-analysis**. 2020. [Thesis] Doctorate in Restorative Dentistry – State University of Ponta Grossa. Ponta Grossa, 2020.

Objectives: To compare the retention rates of 1-step self-etch adhesives (1SE) and 3-step etch-and-rinse adhesives in non-carious cervical lesions (NCCLs) (1), to assess which adhesive strategy is most effective clinically in NCCLs (2) e whether there are differences in retention rates for OptiBond FL and Clearfil SE Bond adhesives with other adhesive brands (3). **Material and Methods:** For this study, 3 systematic reviews (SRs) were carried out, and the study (2) was an SR conducted by the mixed treatment comparison methodology (MTC). Only randomized clinical trials (RCTs) in NCCLs according to the eligibility criteria were included. The controlled vocabulary and keywords were combined in the search strategy for PubMed/Medline and adapted to other databases as well as gray literature screening. The risk of bias was assessed using the Cochrane Collaboration tool (RoB) and the heterogeneity was assessed by Cochrane's Q test and I^2 statistics. The GRADE approach was used to assess the quality of evidence. Meta-analysis were conducted for retention rates, marginal discoloration and marginal integrity, at 12 to 24-month, 24 to 36-month and 60-month follow-up periods in the study (1) and in the study (3) meta-analysis for retention rates for OptiBond FL adhesive at 12 to 24-month, 36 to 48-month, 60 to 96-month, 108 to 156-month periods and for the Clearfil SE Bond adhesive at 12 to 24-month and 36 to 48-month.In the study (2), pairwise meta-analysis and Bayesian network meta-analysis were performed for retention rates at 12 to 24-month, 36 to 48-month, over 48-month and the adhesive strategies were rated by SUCRA. **Results:** In the study (1), no significant differences were observed in retention rates between 1SE adhesives vs 3ER adhesives in the different follow-up periods 12 to 24-month 12 to 24-month ($p = 0.66$), 24 to 36-month ($p = 0.21$) and 60-month ($p = 0.96$). A significant difference was found in marginal integrity at 12 to 24-month ($p = 0.04$) and in marginal discoloration at 12 to 24-month ($p = 0.003$). In the MTC (2) a significant difference was found in the network result only in the pair 2SE vs 3ER in favor of the strategy 2SE in 12 to 24-month (RR = 0.72; 95% CrI 0.52 to 0.99), in the other periods no significant differences were found. In study (3) no difference was observed for retention rates in the periods of 12 to 24-month ($p = 0.97$), 36 to 48-month ($p = 0.72$) and 108 to 156-month ($p = 0.73$) for OptiBond FL and 12 to 24-month ($p = 0.10$) and 36 to 48-month ($p = 0.17$) for Clearfil SE Bond. A significant difference was found for OptiBond FL at 60 to 96-month ($p = 0.02$), but only 3 studies were included in this meta-analysis. **Conclusions:** There is no evidence that 3ER adhesives have better retention rates than 1SE adhesives in LCNCs (1). No adhesive strategy was superior to another (2) and there is no evidence that the retention rates of OptiBond FL and Clearfil SE Bond adhesives are higher than those of the adhesive brands with which they were compared (3).

Keywords: Dentin-bonding agents. Cervical lesions. Clinical effectiveness. Systematic review. Network meta-analysis.

LISTA DE FIGURAS

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

ER	Adesivos de condicionamento ácido total (*etch-and-rinse*)
SE	Adesivos autocondicionantes (*self-etch*)
LCNCs	Lesões cervicais não cariosas
RSs	Revisão Sistemáticas
MTC	*Mixed Comparison Treatment*
ECRs	Ensaios Clínicos Randomizados
PubMed	Serviço da Biblioteca Nacional de Medicina dos Estados Unidos
RoB	*Risk of Bias*
I^2	Teste de Inconsistência de Higgins
GRADE	*Grading of Recommendations: Assessment, Development and Evaluation*
SUCRA	Superfície sob a Curva de Classificação Cumulativa
RR	Razão de risco ("*Risk Ratio*")
CrI	Intervalo de credibilidade
NCCLs	Non-carious cervical lesions
ADA	Associação Dentária Americana
PICO	Acrônimo da questão de pesquisa
P	População
I	Intervenção
C	Controle
O	Desfecho ("*outcome*")
S	Desenho do estudo ("*study design*")
PROSPERO	*International Prospective Register of Systematic Reviews*
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-Analysis*
BBO	Biblioteca Brasileira de Odontologia
LILACS	Literatura Latino-Americana em Ciências da Saúde
EMBASE	Banco de dados bibliográfico e farmacológico
IADR	Associação Internacional de Pesquisa Odontológica
EDTA	Ácido etilenodiaminotetracético
IC	Intervalo de confiança
ID	Identificação do estudo
RCTs	*Randomized Clinical Trials*
SIGLE	*System for Information on Grey Literature in Europe*

MeSH	*Medical Subject Headings*
CONSORT	Consolidação Padronizada de Estudos Clínicos Randomizados
USPHS	*United States Public Health Service*
FDI	*International Dental Federation*
RoB	*Cochrane Collaboration Risk of Bias Tool*
n.r	*Not reported*
SD	*Standard Deviation*
els	*Extra low shrinkage resin composite*
UEPG	Universidade Estadual de Ponta Grossa

LISTA DE SÍMBOLOS E UNIDADES

p Valor de probabilidade

% Porcentagem

pH Potencial Hidrogeniônico

> Maior

< Menor

= Igual

mth month

vs versus

Number

± Mais ou menos

SUMÁRIO

1 INTRODUÇÃO

As lesões relacionadas a perda de estrutura dental na junção cemento-esmalte sem a presença de microrganismos são denominadas lesões cervicais não cariosas (LCNCs). Clinicamente apresentam-se como depressões rasas ou profundas, de forma angulada ou arredondada e de etiologia multifatorial. Os mecanismos clínicos reconhecidos que levam a perda da integridade estrutural na região cervical são biocorrosão (degradação química, eletroquímica e bioquímica), abrasão (desgaste mecânico) ou abfração (desgaste mecânico com concentração de tensões) associados à cargas oclusais excêntricas (1, 2).

Apresentam maior prevalência na população adulta de meia-idade devido à maior exposição aos fatores etiológicos que levam a sua formação e progressão, sendo a face vestibular dos pré-molares a região mais frequentemente acometida (3, 4). As restaurações diretas em resina composta embora não tratem a etiologia das LCNCs, apresentam bons resultados pois substituem o tecido perdido recuperando a integridade do dente e a estética com baixo custo.

A Associação Dental Americana (5) recomenda que o desempenho e a efetividade de materiais restauradores sejam avaliados em estudos clínicos em LCNCs, pois normalmente estas lesões se localizam em esmalte e dentina e não apresentam retenções macromecânicas, dependendo assim exclusivamente da performance do material (6, 7). A longevidade destas restaurações é demonstrada em ensaios clínicos randomizados onde apresentaram desempenho clínico favorável (8, 9), sendo que a seleção da melhor estratégia adesiva e a eficiência de união dos sistemas adesivos contemporâneos são fatores que contribuem para o aumento da longevidade a médio e longo prazo (9-11).

Entretanto a falha ou perda da restauração na interface adesiva dente/restauração normalmente é o parâmetro de avaliação clínico mais objetivo (12), embora descoloração marginal, integridade marginal e lesões de cárie adjacentes às restaurações também sejam relatadas (13, 14). Sendo assim, o desafio dos novos materiais adesivos é proporcionar uma adesão igualmente eficaz tanto no esmalte quanto na dentina e minimizar o número de etapas envolvidas nesse processo.

Existem duas grandes categorias de sistemas adesivos que abordam diferentes estratégias adesivas, amplamente aceitas e empregadas. Van Meerbeek em 2003, sugeriu a classificação dos sistemas adesivos em duas categorias de acordo com a interação ao substrato dental: adesivos convencionais de condicionamento ácido total, conhecidos como *etch-and-*

rinse (ER) e adesivos autocondicionantes, chamados de *self-etch* (SE). A estratégia ER inclui o passo do condicionamento com ácido fosfórico em diferentes concentrações, sendo a mais comum 37% tanto no esmalte quanto na dentina. O condicionamento ácido remove a camada de *smear layer* e dissolve os cristais de hidroxiapatita que envolvem a matriz orgânica, criando uma camada de dentina desmineralizada expondo as fribrilas colágenas. A matriz de colágeno exposta em seguida é infiltrada por monômeros resinosos adesivos formando a camada híbrida. Se apresentam na forma convencional de 3-passos onde cada etapa é aplicada separadamente (ácido + *primer* + *bond*) ou simplificados de 2-passos, que combinam o *primer* e o *bond* no mesmo frasco em uma única aplicação (15).

Outra categoria são os adesivos SE, que eliminam a fase de condicionamento ácido, baseada na aplicação de monômeros acídicos que condicionam e infiltram simultaneamente a dentina, apenas modificando a *smear layer*. Consequentemente esta abordagem apresenta menor sensibilidade técnica devido ao número reduzido de etapas clínicas e ausência ou menor incidência de sensibilidade pós-operatória. Estão disponíveis comercialmente como adesivos de 1-passo onde *primer* e *bond* estão incorporados no mesmo frasco ou 2-passos em que *primer* e *bond* estão em fracos separados (16).

Frente aos diferentes tipos de abordagens e marcas comerciais disponíveis, torna-se difícil para o clínico definir qual a melhor técnica adesiva adotar na rotina clínica. Embora esta decisão deva ser baseada em altos níveis de evidência como estudos clínicos randomizados (ECRs), o grande número de estudos neste tema impede que se chegue a uma conclusão de qual estratégia é mais eficiente.

Sendo assim, revisões sistemáticas (RSs) e meta-análises são estudos complementares aos ECRS, pois agrupam os dados e ajudam a resumir o conhecimento atual disponível em saúde com o objetivo comum de buscar evidências científicas sólidas para uso na prática clínica. Mas este panorama geral se repete quando são analisadas RSs publicadas na literatura avaliando sistemas adesivos em LCNCs, não se chegando a um consenso da existência de uma estratégia superior. As principais conclusões destes estudos que avaliaram performance clínica (taxas de retenção, descoloração marginal e integridade marginal) podem ser sintetizadas a seguir:

- Adesivos 3-passos ER e 2-passos SE apresentaram desempenho clínico semelhante e os de 1-passo SE apresentaram o pior desempenho (12);
- Adesivos 3-passos ER e 2-passos SE apresentaram melhor performance clínica que as demais categorias de sistemas adesivos (17);
- Não encontraram evidências que uma estratégia adesiva seja superior a outra (18);

- Adesivos 3-passos ER foram superiores aos 2-passos ER e aos SE de pH forte e os de 1-passo de pH suave foram comparados aos de 3-passos ER (19);
- Adesivos 3-passos ER apresentaram menor risco de perda de retenção comparados aos 2-passos ER e o 2-passos SE apresentou o menor risco de perda quando comparados aos 2-passos ER. E após 3 anos não há diferença nas taxas de retenção entre 3-passos ER com 2-passos SE e 1-passo SE (13);
- Adesivos 3-passos ER e 2-passos SE devem ter preferência em relação ao 1-passo SE quando avaliada a performance clínica (20) e
- As taxas de retenção foram similares nas estratégias ER e SE e a ER apresentou menor descoloração marginal (21).

Diante do exposto, considerando que as revisões sistemáticas e meta-análises são os estudos de maior nível de evidência e podem facilitar a tomada de decisão sintetizando os resultados de múltiplas pesquisas, o objetivo desta tese de doutorado foi: (1) avaliar se os adesivos de 1-passo SE apresentam performance clínica semelhante aos adesivos de 3-passos ER em LCNCs, (2) qual é a melhor estratégia adesiva em LCNCs e (3) se as taxas de retenção de adesivos consagrados como “padrão ouro” na literatura são maiores que as obtidas por outras marcas comerciais de adesivos por meio de revisões sistemáticas.

2 PROPOSIÇÃO

2.1 ESTUDO 1

2.1.1 Proposição geral

Realizar uma RS e meta-análise da literatura com o objetivo de responder a seguinte pergunta foco no formato PICO: “Os adesivos de 1-passo SE produzem taxas de retenção semelhantes aos adesivos de 3-passos ER quando usados em restaurações de resinas compostas em LCNCs de pacientes adultos”?

2.1.2 Proposição específica

1. Avaliar se existem semelhanças baseadas em evidências nas taxas de retenção entre adesivos de 1-passo SE versus adesivos 3-passos ER quando utilizados em restaurações de resina composta em LCNCs.
2. Avaliar se existem diferenças baseadas em evidências nos desfechos secundários, descoloração marginal e integridade marginal, nas restaurações de resina composta em LCNCs quando utilizados adesivos de 1-passo SE versus adesivos 3-passos ER.

2.2 ESTUDO 2

2.2.1 Proposição geral

Realizar uma RS e meta-análise em rede com o objetivo de responder a seguinte pergunta foco no formato PICO: “Qual a eficácia comparativa das estratégias adesivas em restaurações de resinas compostas em pacientes adultos em termos de retenção e qual o ranking relativo destes tratamentos”?

2.2.2 Proposição específica

1. Avaliar as taxas de retenção entre as diferentes estratégias adesivas (3-passos ER, 2-passos ER, 2-passos SE e 1-passo SE em curto prazo (12 a 24-meses), médio prazo (36 a 48-meses) e longo prazo (acima de 48 meses) em LCNCs.

2. Determinar o ranqueamento relativo entre as estratégias adesivas avaliadas.

2.3 ESTUDO 3

2.3.1 Proposição geral

Realizar uma RS e meta-análise da literatura com o objetivo de responder a seguinte pergunta foco no formato PICO: As taxas de retenção de restaurações em resina composta em LCNCs com adesivos consagrados como "padrão ouro" na literatura são maiores que as obtidas com outras marcas comerciais de sistemas adesivos?

2.3.2 Proposição específica

1. Avaliar se existem diferenças baseadas em evidências nas taxas de retenção entre o adesivo de 3-passos ER OptiBond FL e outras marcas comerciais de adesivos em LCNCs.
2. Avaliar se existem diferenças baseadas em evidências nas taxas de retenção entre o adesivo de 2-passos SE Clearfil SE Bond e outras marcas comerciais de adesivos em LCNCs.

3 MATERIAL E MÉTODOS

Nesta sessão está descrita a metodologia de forma resumida de cada estudo, sendo que as informações detalhadas deste item podem ser encontradas nos Artigos 1, 2 e 3.

3.1 ESTUDO 1

Este protocolo de revisão sistemática e meta-análise foi registrado no banco de dados PROSPERO – CRD42016037743 (ANEXO A – p. 170). Foram seguidas as recomendações da declaração *Preferred Reporting Items for Systematic Reviews and Meta-Analisys* (PRISMA)(22) para a realização desta revisão sistemática. A metodologia detalhada deste experimento está descrita no Artigo 1 (p. 31 – 61).

3.1.1 Fontes de informação e estratégia de busca

O vocabulário controlado e palavras-chave livres na estratégia de busca foram definidos com base no acrônimo PICOS:

1. População (P): restaurações de resina composta em LCNCs em pacientes adultos;
2. Intervenção (I): adesivos SE de 1-passo;
3. Comparação (C): adesivos ER de 3-passos;
4. Desfecho (O): taxas de retenção;
5. Desenho do estudo (S): estudos clínicos randomizados

Para identificar os estudos a serem incluídos nesta revisão, foi feita uma busca nas bases de dados eletrônicas (MEDLINE via PubMed, Biblioteca Cochrane, Biblioteca Brasileira de Odontologia (BBO), Literatura Latino-Americana em Ciências da Saúde (LILACS) e bancos de dados de citações (Scopus e Web of Science), também foi realizada uma busca na literatura cinzenta e nos Registros de Estudos Clínicos. As listas das referências de todos os estudos primários foram pesquisadas manualmente para publicações relevantes adicionais. Também pesquisamos os links de artigos relacionados de cada estudo primário no banco de dados PubMed sem restrições na data de publicação ou idiomas.

3.1.2 Critérios de elegibilidade

Foram incluídos ECRs pareados ou com múltiplas restaurações por participante que comparavam a eficácia clínica (taxas de retenção, descoloração marginal e integridade marginal) de adesivos de 1-passo SE e adesivos de 3-passos ER em LCNCs.

OS ECRs foram excluídos nos casos de:

- estudos sem grupo controle e
- estudos não randomizados.

3.1.3 Seleção dos estudos e processo de coleta de dados

Inicialmente, os artigos foram selecionados pelos títulos e resumos. O texto completo dos artigos foi obtido quando o título e o resumo tinham informações suficientes para tomar uma decisão clara. Posteriormente, três revisores classificaram aqueles que preencheram os critérios de inclusão. Detalhes sobre o estudo, como métodos e os resultados foram extraídos utilizando formulários de extração personalizados.

3.1.4 Risco de viés individual dos estudos

A validade interna dos estudos incluídos foi avaliada por dois revisores independentes utilizando a ferramenta de colaboração Cochrane para avaliar o risco de viés em ECRs.

O instrumento de avaliação de validade utilizado contém os seguintes componentes: 1) viés de seleção; 2) ocultação de alocação; 3) cegamento de avaliadores; 4) desistências e abandonos; 5) confiabilidade e validade dos métodos de coleta de dados; e 6) outras possíveis fontes de viés. Os componentes são classificados como “alto”, “baixo” ou “incerto” risco de viés seguindo as recomendações do Manual Cochrane para Análises Sistemáticas de Intervenções 5.1.0(23).

3.1.5 Meta-análise

A meta-análise foi realizada em estudos classificados como “baixo” ou “incerto” risco de viés, de acordo com a classificação final dos componentes de avaliação de validade.

3.1.6 GRADE

A qualidade da evidência foi classificada para cada resultado em todos os estudos (corpo de evidência) usando a Avaliação, Desenvolvimento e Avaliação da Classificação de Recomendações (GRADE)(24).

3.2 ESTUDO 2

Este protocolo de revisão sistemática e meta-análise em rede foi registrado no banco de dados PROSPERO – CDR42018112672 (ANEXO B – p. 171). Foram seguidas as recomendações da declaração PRISMA com extensão em meta-análise em rede para a realização desta revisão sistemática. A metodologia detalhada deste estudo estará descrita no artigo 2 (p. 62 – 115).

3.2.1 Fontes de informação e estratégia de busca

O vocabulário controlado e palavras-chave livres na estratégia de busca foram definidos com base no acrônimo PICOS:

1. População (P): restaurações de resina composta em LCNCs em pacientes adultos;
2. Intervenção e Controle (I e C): estratégias adesivas (3-passos ER, 2-passos ER, 2-passos SE e 1-passo SE);
3. Desfecho (O): taxas de retenção e ranking relativo;
4. Desenho dos estudos (S): estudos clínicos randomizados.

Para identificar os estudos a serem incluídos nesta revisão, foi feita uma busca nas bases de dados eletrônicas (MEDLINE via PubMed, Biblioteca Cochrane, BBO, LILACS, EMBASE e bancos de dados de citações (Scopus e Web of Science), também foi realizada uma busca na literatura cinzenta, resumos do International Association for Dental Research (IADR) entre 2015-2019 e nos Registros de Estudos Clínicos. As listas das referências de todos os estudos primários foram pesquisadas manualmente para publicações relevantes adicionais. Também pesquisamos os links de artigos relacionados de cada estudo primário no banco de dados PubMed sem restrições na data de publicação ou idiomas.

3.2.2 Critérios de elegibilidade

Foram incluídos ECRs pareados ou com múltiplas restaurações por participante que avaliaram pelo menos duas estratégias adesivas diferentes em LCNCs. OS ECRs foram excluídos nos casos de:

- estudos que compararam dois adesivos de mesma estratégia (sem grupo controle);
- cavidades forradas com outros materiais;
- períodos de acompanhamento inferiores a 12 meses;
- estudos que empregaram o ácido fosfórico em baixas concentrações (10%);
- estudos que realizaram pré-tratamento na dentina (EDTA, clorexidina);
- adesivos de 2ª e 3ª gerações e
- cavidades em lesões cariosas.

3.2.3 Seleção dos estudos e processo de coleta de dados

Inicialmente, os artigos foram selecionados pelos títulos e resumos. O texto completo dos artigos foi obtido quando o título e o resumo tinham informações suficientes para tomar uma decisão clara. Posteriormente, três revisores (F.D.S.D., A.B., e A.R.) classificaram aqueles que preencheram os critérios de inclusão. Detalhes sobre o estudo, como métodos e os resultados foram extraídos utilizando formulários de extração personalizados.

3.2.4 Risco de viés individual dos estudos

A validade interna dos estudos incluídos foi avaliada por dois revisores independentes utilizando a ferramenta de colaboração Cochrane para avaliar o risco de viés em ECRs. O instrumento de avaliação de validade utilizado contém os seguintes componentes: 1) viés de seleção; 2) ocultação de alocação; 3) cegamento de avaliadores; 4) desistências e abandonos; 5) confiabilidade e validade dos métodos de coleta de dados; e 6) outras possíveis fontes de viés. Os componentes são classificados como “alto”, “baixo” ou “incerto” risco de viés seguindo as recomendações do Manual Cochrane para Análises Sistemáticas de Intervenções 5.1.0(23).

3.2.5 Meta-análise

A metodologia MTC (*Mixed Comparison* Treatment) foi escolhida para a análise estatística, a fim de avaliar simultaneamente os efeitos dos diferentes tratamentos, utilizando o software estatístico R(25) e a inferência Bayesiana foi realizada utilizando JAGS(26).

Neste estudo, o modelo seguido foi o de comparar simultaneamente todas as quatro estratégias adesivas. Primeiramente, foi realizada uma meta-análise tradicional da evidência direta, a partir dos estudos que compararam diferentes estratégias adesivas, derivando um risco relativo e um intervalo de confiança (IC) de 95%. A heterogeneidade foi avaliada usando o teste Q de Cochrane e estatística I^2. Subsequentemente, a meta-análise em rede foi realizada comparando simultaneamente as quatro estratégias adesivas a curto (12 a 24-meses), médio (36 a 48-meses) e longo prazo (acima de 48-meses).

No caso de diferenças entre tratamentos, uma abordagem Bayesiana usando valores de probabilidade resumida como Superfície sob a Curva de Classificação Cumulativa (SUCRA) para avaliar a probabilidade de o tratamento ter a melhor performance em relação ao desfecho retenção. Ou seja, quanto maior o valor da SUCRA, maior probabilidade de a estratégia ter as melhores taxas de retenção.

3.2.6 Avaliação da Inconsistência

A inconsistência estatística foi verificada usando gráficos posteriores e valores de p bayesianos produzidos pelo método de divisão de nós (*Split Node*), testando a concordância entre as evidências diretas e indiretas. Um valor de p igual ou superior a 0,008 foi considerado o limiar de significância, pois os mesmos dados foram utilizados em 6 comparações.

3.2.7 Efeitos de pequenos estudos e viés de publicação

A presença de efeitos de pequenos estudos foi avaliada através do desenho de um gráfico de funil ajustado por comparação que explica o fato de que diferentes estudos comparam diferentes conjuntos de intervenções.

3.2.8 GRADE

A qualidade da evidência foi classificada para cada resultado em todos os estudos (corpo de evidência) usando a Avaliação, Desenvolvimento e Avaliação da Classificação de Recomendações (GRADE)(24).

3.3 ESTUDO 3

Este protocolo de revisão sistemática e meta-análise foi registrado no banco de dados PROSPERO – ID 158813 (aguardando registro). Foram seguidas as recomendações da declaração *Preferred Reporting Items for Systematic Reviews and Meta-Analisys* (PRISMA)(22) para a realização desta RS. A metodologia detalhada está descrita no Artigo 3 (p. 116 – 154).

3.3.1 Fontes de informação e estratégia de busca

O vocabulário controlado e palavras-chave livres na estratégia de busca foram definidos com base no acrônimo PICOS:

1. População (P): restaurações de resina composta em LCNCs em pacientes adultos;
2. Intervenção (I): adesivos de outras marcas comerciais;
3. Comparação (C): adesivos “gold standard” OptiBond FL ou Clearfil SE Bond;
4. Desfecho (O): taxas de retenção;
5. Estudos (S): estudos clínicos randomizados.

Para identificar os estudos a serem incluídos nesta revisão, foi feita uma busca nas bases de dados eletrônicas (MEDLINE via PubMed, Biblioteca Cochrane, BBO, LILACS, EMBASE e bancos de dados de citações (Scopus e Web of Science), também foi realizada uma busca na literatura cinzenta, resumos do International Association for Dental Research (IADR) entre 2015-2019 e nos Registros de Estudos Clínicos. As listas das referências de todos os estudos primários foram pesquisadas manualmente para publicações relevantes adicionais. Também pesquisamos os links de artigos relacionados de cada estudo primário no banco de dados PubMed sem restrições na data de publicação ou idiomas.

3.3.2 Critérios de elegibilidade

Foram incluídos ECRs pareados ou com múltiplas restaurações por participante que compararam a eficácia clínica entre o adesivo de 3-passos ER OptiBond FL e adesivos de outras marcas comerciais e estudos que compararam o adesivo de 2-passos SE Clearfil SE Bond com adesivos de outras marcas comerciais em LCNCs. OS ECRs foram excluídos nos casos de:

- adesivos aplicados fora da especificação do fabricante;
- estudos que não avaliaram o OptiBond FL ou o Clearfil SE Bond;
- estudos sem grupo comparador;
- cavidades em lesões cariosas e
- estudos não randomizados.

3.3.3 Seleção dos estudos e processo de coleta de dados

Inicialmente, os artigos foram selecionados pelos títulos e resumos. O texto completo dos artigos foi obtido quando o título e o resumo tinham informações suficientes para tomar uma decisão clara. Posteriormente, três revisores (F.D.S.D., A.D. e A.R.) classificaram aqueles que preencheram os critérios de inclusão. Detalhes sobre o estudo, como métodos e os resultados foram extraídos utilizando formulários de extração personalizados.

3.3.4 Risco de viés individual dos estudos

A validade interna dos estudos incluídos foi avaliada por dois revisores independentes (F.D.S.D. e A.D.) utilizando a ferramenta de colaboração Cochrane para avaliar o risco de viés em ECRs.

O instrumento de avaliação de validade utilizado contém os seguintes componentes: 1) viés de seleção; 2) ocultação de alocação; 3) cegamento de avaliadores; 4) desistências e abandonos; 5) confiabilidade e validade dos métodos de coleta de dados; e 6) outras possíveis fontes de viés. Os componentes são classificados como “alto”, “baixo” ou “incerto” risco de viés seguindo as recomendações do Manual Cochrane para Análises Sistemáticas de Intervenções 5.1.0(23).

3.3.5 Meta-análise

A meta-análise foi realizada em estudos classificados como “baixo” e “incerto” risco de viés, de acordo com a classificação final dos componentes de avaliação de validade.

3.3.6 GRADE

A qualidade da evidência foi classificada para cada resultado em todos os estudos (corpo de evidência) usando a Avaliação, Desenvolvimento e Avaliação da Classificação de Recomendações (GRADE)(24).

4 ARTIGOS

4.1 ARTIGO 1: IS THERE EVIDENCE THAT THREE-STEP ETCH-AND-RINSE ADHESIVES HAVE BETTER RETENTION RATES THAN ONE-STEP SELF-ETCH ADHESIVES IN NON-CARIOUS CERVICAL LESIONS? A SYSTEMATIC REVIEW AND META-ANALYSIS

STATUS: PUBLICADO.

REVISTA: JOURNAL OF ADHESIVE DENTISTRY.

ARTIGO 1 – Is there evidence that three-step etch-and-rinse adhesives have better retention rates than one-step self-etch adhesives in non-carious cervical lesions? A systematic review and meta-analysis.

Short title: Self-etch vs. etch-and-rinse adhesives: meta-analysis.

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PROSPERO registration number: CRD42016037743.

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CONFLICT OF INTEREST: The authors declare no conflict of interest of any kind related to this study.

SOURCE OF FUNDING: This study was partially supported by the National Council for Scientific and Technological Development of the Brazilian Government under grants 304105/2013-9 and 305588/2014-1.

ABSTRACT

Purpose: A systematic review and meta-analysis was conducted to compare the retention rates of 3-step etch-and-rinse (3ER) adhesive systems with 1-step self-etch (1SE) systems in non-carious cervical lesions (NCCLs). The secondary outcomes were marginal integrity and marginal discoloration.

Materials and Methods: Only randomized clinical trials (RCTs) that compared 1SE with 3ER in NCCLs were included. Controlled vocabulary and keywords were combined in the search strategy for PubMed/Medline, LILACS, BBO, Web of Science, Cochrane Library, Grey literature and IADR abstracts (1990-2018). The Cochrane risk of bias tool (RoB) was applied to the eligible studies. Meta-analyses were conducted for retention rate and secondary outcomes at different follow-up times, using the random effects model. Heterogeneity was assessed with the Cochran Q test and I2 statistics. The GRADE approach was used to assess the quality of the evidence.

Results: After the removal of duplicates, title and abstract screening, 18 studies remained. Of these, 15 studies were used for meta-analysis. Fourteen out of these 15 were judged at "unclear" risk and 1 at "low" risk of bias. No significant differences between groups were observed in the different follow-up periods for retention rates 12 to 24-months ($p = 0.66$), 24 to 36 months ($p = 0.21$) and 60-months ($p = 0.96$). A significant difference in marginal integrity was found at 12 to 24-months ($p = 0.04$) and to marginal discoloration at 12 to 24-months ($p = 0.003$).

Conclusion: There is no evidence that 3-step ER adhesives have better retention rates than 1-step SE adhesives in NCCLs.

Clinical Significance: This systematic review and meta-analysis did not show better retention rates for 3-step etch-and-rinse systems over simplified 1-step self-etch systems in non-carious cervical lesions but did show reduced marginal discoloration and better marginal integrity.

Keywords: Dentin-bonding agents. Non-carious cervical lesions. Clinical effectiveness. Systematic Review. Meta-analysis.

INTRODUCTION

In randomized controlled trials (RCTs), the efficacy of dentin bonding agents has been evaluated in non-carious cervical lesions (NCCLs), as recommended by American Dental Association (ADA) (1). This recommendation was because adhesive restorations placed in such type of cavities remain in place by means of the micromechanical interlocking produced by adhesive infiltration. In such clinical situations, loss of retention is attributed to loss of bonding (44, 75).

Two different bonding strategies can be used in adhesive procedures. The etch-and-rinse technique (ER) requires the application of an ortho-phosphoric acid etchant (32% to 40%), followed by a primer and a bonding resin. This bonding protocol may be performed in a two-step or three-step protocol depending on whether the priming and bonding solutions are provided in a single or separate bottle. The second bonding strategy is the self-etch (SE) technique, which does not require a separate etching step and involves either a two- (acidic primer and a bonding resin) or one-step application, where both solutions are in a single bottle (75). Theoretically, SE adhesives are capable of demineralizing and infiltrating the dental substrates simultaneously with a reduced number of steps (5). As such, this strategy is claimed to be user-friendly because of its shorter application time and less sensitive technique (73).

Several adhesive systems have been used in adhesive dentistry, and type of bonding strategy has been correlated with the longevity of composite resin restorations (12, 22, 50, 51). Therefore, the choice of the adhesive system and bonding strategy is important in providing appropriate clinical guidelines.

A higher failure rate has been reported for simplified adhesives than ER systems (51, 55, 68). However, another the study reported the superiority of 1-step SE over 3-step ER adhesives (70), and other investigators have reported similar clinical performance between SE and ER adhesive systems in NCCLs (6, 8, 9, 24, 43, 67). In face of the controversy among RCTs, a systematic review is indicated to answer the following focused research question based on the PICO (P – participant; I - intervention; C – control; O – outcome) protocol: "Do one-step SE adhesives produce similar retention rates to three-step etch-and-rinse adhesives when used to bond composite resins in the NCCLs of adult patients?

MATERIAL AND METHODS

This study was designed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (39, 62).

Protocol and registration

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under the registration number CRD42016037743. The methods section followed the previously described methodology of an earlier study conducted at our university (65).

Eligibility criteria

Only randomized controlled trials (RCTs), either with paired or multiple restorations per participant that evaluated the clinical effectiveness of 3-step ER adhesive systems and 1-step SE in NCCLs were included. The following exclusion criteria were applied: (1) studies with follow-up periods lower than 12 months; (2) studies that used silorane-based adhesives; (3) studies that used glass ionomer cements or resin-modified glass ionomer cements as liner and (4) non-randomized studies.

Information sources and search strategy

A search strategy for MEDLINE/PubMed based on the concepts of participant and intervention of the focused PICO question (described at the end of the introduction section) was elaborated (Table 4.1 – 1). Within each concept, controlled vocabulary (MeSH terms) and free keywords from title and abstracts were combined using the Boolean operator OR. Then, the concepts (population and intervention) were combined with the Boolean operator "AND" and a validated filter from the PubMed website.

To increase the sensitivity of the search strategy, other electronic databases were also searched. The reference lists of all primary studies were searched for additional relevant publications as well as the first page of related article links of the PubMed database. No restrictions were placed on publication date or language.

Grey literature was inspected to minimize publication bias. Abstracts of the International Association for Dental Research (IADR) and its regional divisions (1990–2018) were searched. The database of Grey Literature in Europe (SIGLE), dissertations and theses (ProQuest Dissertations and Theses Full Text databases and the Periódicos Capes Theses database) and Google Scholar were also searched.

Unpublished and ongoing trials were searched in the following trials registries Current Controlled Trials (www.controlled-trials.com), International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), Brazilian Clinical Trials Registry (www.rebec.gov.br), ClinicalTrials.gov (www.clinicaltrials.gov) and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

Study selection and data collection process

Initially, duplicates were removed. Then, two reviewers (F.D.S.D. and D.Z.) independently evaluated the articles by title and abstracts. Full-text articles were obtained when insufficient information was available in the title and abstract to decide on the eligibility of the study.

Each eligible article received a study ID, combining first author and year of publication. Relevant information about the study design, participants, type of adhesive, resin composite per group, rubber dam, bevel enamel, dentin preparation, number of operators, number of

examiners and evaluation criteria were extracted using customized extraction forms by three authors (F.D.S.D., D.Z. and L.M.W.) independently.

Multiple reports of the same study (reports with different follow-up periods) were extracted directly into a single data collection form to avoid overlapping data. The collection form was pilot tested using a sample of study reports to ensure that the collection form was consistent with the research question.

Risk of bias in individual studies

Two independent reviewers (F.D.S.D. and L.M.W.), evaluated the RCTs using the Cochrane Collaboration Risk of Bias Tool (RoB version 1.0) (26). The RoB tool contained six domains: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. The latter domain (other possible bias) was not used in the present study. During data selection and quality assessment, any disagreements between the reviewers were solved by discussion, and, if needed, consultation with a third reviewer (A.R.).

For each domain, RoB was scored following the recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org). The judgment for each entry consisted of recording “yes” (low risk of bias), “no” (high risk of bias) or “unclear” (either lack of information or uncertainty over the potential for bias).

Two of the six domains of the RoB tool were considered the key study domains (sequence generation and allocation concealment) as they are strictly correlated with selection bias. We have not considered the other domains as key domains due to the following reasons: 1) for the primary outcome retention rate, patient and examiner blinding has little effect on the reported data; 2) incomplete outcome data was managed in this study by using different extraction process as it will be seen in the next sections and 3) selective outcome reporting is rarely observed in NCCLs. At the study level, studies were judged to be at low risk of bias if they were judged as at low risk in these key domains. If at least one of these two domains were at high risk, the study was classified as at high risk of bias. When the study was judged as “unclear” in at least one key domain, the study was at unclear risk of bias.

Summary measures and synthesis of the results

The primary outcome was retention of restorations, and the secondary outcomes were marginal integrity and marginal discoloration. As some studies reported the results at different follow-up periods, we performed different meta-analysis by grouping the studies with similar follow-up periods (12 to 24-month; 36-month and 60-month). In case more than one type of the bonding strategy (e.g., 3-step ER or 1-step SE) was investigated in the primary study, data were merged to make a single entry. In case the study reported data twice within the range described above, data were taken from the longest follow-up period.

Data were calculated using two different approaches. In approach 1 (intention-to-treat protocol), the number of events were related to the baseline data (number of placed restorations) for the retention rate. The same approach was used for marginal integrity and marginal discoloration, but in these secondary outcomes, the number of events was related to the baseline data minus the number of debonded restorations in each follow-up. In the second approach (per-protocol analysis), the number of events was related to the data at each recall (number of available restorations for evaluation). The same was used for the other secondary outcomes, but the total number of events was the number seen at each recall minus the number of debonded restorations at each follow-up period.

In the primary studies, were usually scored as Alpha, Bravo or Charlie; we dichotomized Alpha vs. Bravo/Charlie for all meta-analyses. Only studies classified at “low” or “unclear” risk of bias were meta-analyzed. Dichotomized data of all outcomes were collected, and a meta-analysis was performed to obtain a pooled estimate of the overall risk ratio (RR) with 95% confidence interval. The random-effects models were employed. Heterogeneity was assessed using the Cochran Q test and I2 statistics. All analyses were conducted using Revman 5 (Review Manager Version 5.3, The Cochrane Collaboration, Copenhagen, Denmark).

Assessment of the quality of evidence using GRADE

The quality of the evidence was graded for each outcome across studies (body of evidence) using the Grading of Recommendations: Assessment, Development and Evaluation (GRADE) (http://www.gradeworkinggroup.org/). This technique allowed determination of the overall strength of evidence for each meta-analysis (23). The GRADE grades the evidence in four levels: very low, low, moderate, and high. The “high quality” level suggests high

confidence that the true effect lies close to the estimate of the effect. At the other extreme, “very low quality” suggests very low confidence in the effect estimate, and the estimate reported can be substantially different from what was measured.

For RCTs, the GRADE approach addresses five reasons (risk of bias, imprecision, inconsistency, indirectness of evidence and publication bias) for possibly rating down the quality of the evidence by 1 or 2 levels. Each of these aspects was assessed as having “no limitation” (0); “serious limitations” (1 level downgraded) and “very serious limitations” (2 levels downgraded). The GRADEpro Guideline Development Tool, available online (www.gradepro.org), was used to create a Summary of findings table as suggested in the Cochrane Handbook for Systematic Reviews of Interventions.

RESULTS

Study selection

After database screening and the removal of duplicates, 5797 articles were identified. After removal of duplicates and title screening, 3546 articles remained. This number was reduced to 37 articles after examination of the abstracts. Of these 37, 19 were excluded (Fig. 4.1.1) because they did not compare 3-step ER adhesives with 1-step SE adhesives (4, 6, 8, 9, 15, 17, 18, 24, 29, 34-36, 42, 56, 60, 64, 67, 68) or because patients were not randomized (71).

A total of 18 articles remained (2, 3, 11, 14, 16, 19, 24, 27, 28, 30-33, 40, 47, 52, 55, 69), four of which reported the same population sample at different follow-up periods (30-32, 52). These four articles received the same study ID, which was van Landuyt et al. 2008.

Characteristics of the included articles

The characteristics of the 15 eligible studies are listed in Table 4.1.2. All studies performed multiple restorations per participant and considered them as experimental units. Among the 3-step ER systems the following commercial brands were tested:

- Adper Scotchbond Multi-Purpose [3M] (2, 11, 27, 28, 33, 46),
- Optibond FL [Kerr] (3, 14, 19, 40, 69, 74),
- Syntac Classic [IvoclarVivadent] (adhesive 4-step ER classified as 3-step ER) (24),
- Gluma Solid Bond [Kulzer] (55) and

- CFM (experimental) (16).

More commercial brands available as 1-step SE systems were used in the primary articles, and they are described below:

- Adper Easy One [3M] (2, 46),
- Tokuyama Bond Force [Tokuyama] (3),
- iBond [Kulzer] (11, 55, 69),
- Clearfil S3 Bond [Kuraray] (19, 69),
- AQ Bond [d-tech] (11),
- Optibond All-in-One [Kerr] (14, 40),
- G-Bond [GC] (16, 31, 69),
- Futurabond M [Voco] (24),
- Adper Prompt [3M] (27, 28) and
- Scotchbond Universal [3M] (33).

Most of the composite resins employed were microhybrids, nanohybrids or nanofilled. The following commercial brands were used: Gradia Direct [GC] (70) and the other studies used Filtek Z-350 XT [3M] (2), Estelite Sigma Quick [Tokuyama] (3), CeramX-Duo [Denstsply] (69), Filtek Z-250 [3M] (11), Amaris [Voco] (24), Tetric EvoCeram [Ivoclar Vivadent] (24), Denfil [Vericom] (27, 28), Clearfil AP-X [Kuraray] (19), Herculite XRV [Kerr] (40), Filtek Supreme Plus [3M] (46), Durafill VS [Kulzer] (55), Filtek Supreme Ultra [3M] (14, 33), Premise [Kerr] (3) and Gradia Direct Anterior [GC] (74).

The majority of the studies reported that no rubber dam was used (2, 16, 19, 28, 31, 40, 46). Three studies used rubber dam (14, 24, 33), other threes did not report the use (11, 27, 69) and two studies described that rubber dam was used depending on the location and access of the lesion (3, 55).

Seven studies (2, 19, 24, 28, 33, 55, 74) prepared a small enamel bevel at the incisal/occlusal margin of the lesion. Seven studies (16, 19, 24, 28, 31, 40, 55) superficially roughened the exposed dentin with a coarse diamond rotatory instrument, three studies did not perform any preparation on the dentin (14, 33, 46) and three did not report whether enamel or dentin was prepared (3, 11, 27). The number of operators ranged from 1 to 6; two papers did not report this information (3, 46).

Most of the studies used the modified USPHS criteria for restoration evaluation (2, 11, 16, 27, 28, 40, 46, 55), two studies used the USPHS (3, 69), although two studies (19, 74) applied the Vanherle Method, one of them used the FDI criteria and the modified USPHS

criteria (14), only one used the FDI criteria (24) and another one employed the Cvar e Ryge criteria (33). The follow-up periods ranged from 12 to 108 months (9 years).

Risk of bias of the included studies

The quality assessment of the RoB of included studies is presented in Figure 4.1.2. Of the fifteen eligible studies, one was considered at "low" risk of bias (14) and fourteen were considered at "unclear" risk of bias (2, 3, 11, 16, 19, 24, 27, 28, 33, 40, 46, 55, 69, 74). Studies were usually classified as at unclear risk due to lack of description of sequence generation and allocation concealment.

Meta-analysis

Approach 1 (intention-to-treat analysis)

Eleven studies were included in the meta-analysis as four studies were excluded, which were abstracts without information from the authors. The results of the meta-analysis with data extraction following the intention-to-treat protocol (approach 1) are presented in the Figures 4.1.3, 4.1.4 and 4.1.5.

Retention. No significant differences between groups were observed in the different follow-up periods (Fig. 4.1.3). The risk ratio (RR) and the 95% confidence interval at 12 to 24-months was 1.13 (0.65 to 1.98; p = 0.66), at 36-months 1.58 (0.77 to 3.25; p = 0.21) and at 60-months 0.98 (0.39 to 2.47; p = 0.96). Heterogeneity was not observed in any of the follow-up periods.

Marginal integrity. A significant difference between was found between the groups at 12-24-months (RR = 1.40; 1.02 to 1.90; p = 0.04) in favor of the 3-step ER group, but no difference at 36-months (RR = 1.07; 0.21 to 5.28; p= 0.11) and at 60-months (RR = 1.23; 0.82 to 1.83; p = 0.32) (Fig. 4.1.4). Heterogeneity was observed at the follow-up periods 12 to 24-months (p = 0.02; I2 = 55%), at 36-months (p < 0.0001; I2 = 91%) and at 60-months (p = 0.11; I2 = 61%).

Marginal discoloration. A significant difference between was found between the groups at 12 to 24-months (RR = 1.55; 1.17 to 2.06; p = 0.003) in favor of the 3-step ER group, but no difference at 36-months (RR = 2.06; 0.42 to 10.06; p = 0.37) and at 60-months (RR = 0.83; 0.34 to 2.02; p = 0.69) (Fig. 4.1.5). Heterogeneity was observed at 24 to 36-months (p = 0.0004; I2= 87%) and at 60-months (p = 0.0007; I2 = 91%).

Approach 2 (per-protocol analysis)

Retention. Like approach 1, no significant differences between groups were observed in the different follow-up periods (Table 4.1.3).

Marginal integrity. Like approach 1, a significant difference between the groups was found at 12 to 24-months (RR = 1.56; 1.19 to 2.04; p= 0.001) and differently to approach 2, a significant difference was also observed at 36-months (RR = 2.11; 1.65 to 2.70; p < 0.00001) (Table 4.1.3) in favor of the 3-step ER group.

Marginal discoloration. Like approach 1, a significant difference the groups were observed in the 12 to 24-months follow-up in favor of the 3-step ER group and a non-significant difference observed in the 36-months recall (Table 4.1.3).

Assessment of the quality of evidence (GRADE)

Short-term and long-term follow-ups for each outcome are summarized in Table 4.1.4. For the outcome retention rate, the quality of evidence for 12 to 24-month and 60-month recalls were downgraded two levels because most studies were at unclear risk of bias and because of imprecision (very wide confidence interval that does not exclude superiority or inferiority of 3-step ER over 1-step SE). For the secondary outcomes (marginal discoloration and marginal integrity), at the short-term follow-up periods, the body of evidence was downgraded two and three levels, respectively because of the unclear risk of bias of most studies, imprecision, and inconsistency. Data in the 60-month follow-up period were considered of moderate quality. One level was downgraded because of the unclear risk of bias of the majority of the studies.

DISCUSSION

Discussion

Earlier systematic reviews and meta-analysis have reported the clinical effectiveness of different types of adhesives in the same study (10, 25, 37, 50, 58). However, some of these earlier systematic reviews had flaws. In most of them, no appraisal of the risk of bias of the eligible studies was performed. Additionally, the authors failed to choose an appropriate statistical analysis (10, 50) for data management.

To combine results from multiple RCTs, meta-analysis should be performed rather than simply combining the percentages of retention rates of the multiple studies. This latter approach, which has been used in some reviews (25, 37, 51), does not give appropriate weight to the studies under comparisons. Additionally, one cannot expect that a single estimate exists in different populations, where bonding protocols are performed with different brands and operators. In such circumstances, a meta-analysis with a random effects model (7), should be performed contrary to the fixed effect models used by Santos et al. 2014 (59).

The present systematic review did not aim to evaluate all adhesive strategies, but to compare 1-step SE systems with the so-called 3-step ER adhesives. Three-step ER systems have been considered the gold standard for bonding. This belief was based on the findings of laboratory investigations reporting that the bond strength to both enamel and dentin of 3-step ER adhesives was higher than that obtained with simplified systems (13, 48, 73) and by some earlier systematic reviews that did not use appropriate statistical analysis (25, 37, 51).

After an appropriate analysis of the risk of bias of the included studies and using appropriate statistical methodology, the present study did not find that 3-step ER was superior to 1-step SE adhesive systems in terms of retention rates at follow-up periods. Primary studies presented risk ratios with 95% confidence intervals that cross the null value of 1, meaning that this finding is very consistent in primary studies.

Potential biases in the review process

Ideally, the units of randomization and analysis in the included trials should be at the individual level. In split mouth studies each trial participant should receive one tooth randomized to the intervention and another to the control group, making it possible to analyze

the paired nature of the data. However, such an approach was not used in most of the trials (20, 41, 45, 55, 70, 74), and the data were treated as if the unit of randomization was the tooth. Unfortunately, we cannot summarize data differently than reported in the primary studies. Thus, the unit of analysis in this review was the tooth and not the individual. We should recognize that the pooled estimate appears to be more precise (narrower 95% confidence interval) than it actually is, and therefore the data should be interpreted accordingly.

Failures in data reporting in the primary studies may also have induced biases in the data extraction process. In some clinical trials, events reported at the shortest follow-up periods were not carried forward to the longest follow-up periods, which may lead to reports of higher percentages of events in a short-term follow-up than in a longer one. This may give the impression that the intervention itself has a self-healing process, which is unlikely. To make this clear, a hypothetical scenario can be considered in which 10 out of 100 restorations placed at baseline failed at 12-months. In such a case, the success rate or retention rate would be 90% (90/100). At the next 24-month recall, the authors would detect five failures from a total of 90 restorations in participants that attended the recall (recall rate of 90%).

Some authors describe the success rate as being 94% (85/90), which does not represent the “truth”. In such a situation, the investigators have no way to know if the 5 failures observed at the 24-month follow-up are the same ones observed at 12 months or whether they are new failures. It would still be possible that some of these 5 restorations were failures detected at the 12-month follow-up and that others were new failures.

While extracting data for meta-analysis, the review authors attempt to guess what the authors meant to report. In the majority of the primary studies, the extraction of the total number of debonded restorations at each follow-up requires, “some detective work” to figure out hints throughout the body of the text and in the table of results as to the best match for that cell table.

In the per-protocol analysis, apart from the above limitations in data extraction, an additional limitation was found. It was not easy to determine the number of evaluated restorations at each follow-up recall. Some authors either reported an overall recall rate (not specified per group, which does not help in data extraction) or did not report it at all. To make the analysis more difficult, some authors reported the percentage of events instead of the raw number of events, without specifying whether the denominator of such percentages was the total number of placed restorations or the total number of evaluated restorations at that follow-up.

Explanation of the main study findings

Ideally, results should be reported using the intention-to-treat protocol, as it takes into account all restorations randomized at baseline. However, this is not yet the consensus, among the review authors. In this study, we observed that different conclusions for marginal integrity and marginal discoloration were reached depending on the protocol used for data extraction. This finding calls out for an urgent need for standardization of the description of the results of clinical trials conducted in NCCLs.

The primary outcome retention rate reached the same conclusions in both approaches, which makes the conclusions sufficiently robust for such variations in data extraction. However, the quality of evidence for retention rates at all three follow-ups was graded as low, because of the unclear risk of bias of the majority of the studies and the imprecise estimates gathered in the meta-analysis.

The lack of difference between clinical bonding strategies probably means that the low bond strength values achieved in laboratory evaluations with 1-step SE, are adequate to withstand the stresses in the cervical area of the teeth, given that the overall percentage of debonded restorations at all follow-up periods was low. The SE adhesive showed a debonding rate of 4.8% in the 12 to 24-month follow-up, 7.5% in the 36-month follow-up and 4.5% in the 60-month follow-up. These figures were 3.8%, 4.1% and 4.3% for the 3-step ER system.

The similarity of the results in the present investigation may be because all restorations in the primary studies were placed in a university setting with calibrated, experienced, and knowledgeable operators who could optimize any adhesive strategy. This represents an “ideal” scenario, which allow us to evaluate the material’s efficacy rather than effectiveness. The latter reflects the differences in protocol in the real practice.

Another aspect that deserves attention is that most adhesive systems, used in the primary studies included in this systematic review (Adper Easy One [pH = 2.4], Tokuyama Bond Force [pH = 2.3], Optibond All-in-One [pH = 1.7], Clearfil S3 Bond [pH = 2.7], iBond [pH = 1.6], G-Bond [pH = 2]), Scotchbond Universal [pH = 2.7] and Futurabond M [pH = 2.0] were mild and ultra-mild SE, which appears to have better bond stability than the more acidic SE adhesives(48, 53, 63).

In the intention-to-treat analysis, the clinical behavior of the 3-step ER was better for both marginal discoloration and marginal integrity. Previous reviews that investigated the

clinical performance of adhesives found less favorable clinical performance in the self-etch bonding strategies compared with an etch-and-rinse protocol corroborating this study (61, 72).

Three-step ER systems showed lower marginal discoloration and better marginal integrity than 1-step SE systems in the shortest follow-up, with the quality of evidence being graded as moderate. Although these outcomes are not critical for clinical recommendation, they are important when dealing with anterior NCCLs. In anterior restorations, aesthetic requirements have higher importance when balancing properties for selecting a material and /protocol. Indeed, laboratory investigations have reported lower bond strength of SE systems to enamel than dentin (38, 57). The etching pattern and the micromechanical interlocking of adhesives to phosphoric acid-etched enamel is better than the simple application of an SE adhesive (49) (76). The performance of SE systems in enamel can be performed by preliminary selective enamel etching (21). Indeed, a recent systematic review of literature has shown that SE adhesives applied in phosphoric acid-etched enamel show lower marginal discoloration and better marginal integrity than the sole use of SE adhesive (66).

Implications for research

This study has uncovered a need to improve the design and/or reporting of RCTs in this area, particularly in the areas of randomization, allocation concealment and blinding. A recent systematic review that evaluated the adherence of RCTs in NCCLs to the CONSORT Statement (Reis et al. 2018) (54) also identified this issue. Additionally, study authors should focus attention on the report of the study results, paying attention to the cumulative effect of the outcomes being evaluated.

Implications for practice

As the quality of evidence was graded as low for retention rates, we cannot be completely sure that the results reported here represent the “truth”. However, we may state that we still do not have enough clinical evidence to report that 3-step ER systems are better than 1-step SE in terms of retention rates. For marginal integrity and marginal discoloration, evidence gathered in this study and in an earlier systematic review (66) shows that enamel etching improves the performance of adhesives.

CONCLUSION

There is still no evidence to support the statement that 3-step ER systems are better than 1-step SE in terms of retention rates. However, 3-step ER provided lower rates of marginal discoloration and better marginal integrity than 1-step SE.

Table 4.1.1 – Electronic database and search strategy conducted on October 26, 2018.

Pubmed – n = 2615		
#1 dental restoration, permanent [MeSH Term] OR molar[MeSH Term] OR dentition, permanent[MeSH Term] OR dentition, mixed[MeSH Term] OR tooth erosion[MeSH Term] OR tooth cervix[MeSH Term] OR tooth abrasion[MeSH Term] OR bicuspid[MeSH Term] OR molar*[Title/Abstract] OR "permanent dentition"[Title/Abstract] OR "mixed dentition"[Title/Abstract] OR "tooth erosion"[Title/Abstract] OR "tooth erosions"[Title/Abstract] "tooth cervix"[Title/Abstract] OR "tooth abrasion"[Title/Abstract] OR "tooth abrasions"[Title/Abstract] OR bicuspid[Title/Abstract] OR "permanent molar"[Title/Abstract] OR premolar*[Title/Abstract] OR abfraction*[Title/Abstract] OR "cervical lesion"[Title/Abstract] OR "cervical lesions"[Title/Abstract] OR "class 5"[Title/Abstract] OR "class V"[Title/Abstract] OR "non carious cervical lesion"[Title/Abstract] OR "non carious cervical lesions"[Title/Abstract] OR NCCL*[Title/Abstract]	#2 dentin-bonding agents[Mesh Term] OR "adhesive system"[Title/Abstract] OR "adhesive systems"[Title/Abstract] OR "bonding agent"[Title/Abstract] OR "bonding agents"[Title/Abstract] OR "dental adhesive"[Title/Abstract] OR "dental adhesives"[Title/Abstract] OR "dentin bonding agent"[Title/Abstract] OR "dentin bonding agents"[Title/Abstract] OR "adhesive material"[Title/Abstract] OR "adhesive materials"[Title/Abstract] OR "etch-and-rinse adhesive"[Title/Abstract] OR "etch-and-rinse adhesives"[Title/Abstract] OR "total-etch adhesive"[Title/Abstract] OR "total-etch adhesives"[Title/Abstract] OR "self-etch adhesive"[Title/Abstract] OR "self-etching adhesive"[Title/Abstract] OR "self-etch adhesives"[Title/Abstract] OR "self-etching adhesives"[Title/Abstract] OR "all-in-one adhesive"[Title/Abstract] OR "all-in-one adhesives"[Title/Abstract] OR "one-bottle adhesive"[Title/Abstract] OR "one-bottle adhesives"[Title/Abstract] OR "single-bottle adhesive"[Title/Abstract] OR "single-bottle adhesives"[Title/Abstract] OR "one-step self-etch adhesive"[Title/Abstract] OR "one-step self-etch adhesives"[Title/Abstract] OR "one-step self-etching adhesive"[Title/Abstract] OR "one-step self-etching adhesives"[Title/Abstract]	#3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh]))
#1 AND #2 AND #3		
#23 AND #37		

Table 4.1.2 – Summary of the descriptive characteristics of the primary studies included (n=15).

Study ID	Follow-ups (mth)	Study design [setting]	Subject's ages mean ± SD [range] (years)	Groups: Type of adhesive -Adhesive brand [number of restorations per group]	Resin composite per group	Rubber dam	Enamel bevel/ Dentin prep	# of operators/ examinators	Evaluation criteria
Araújo 2013[37]	6, 12	Paired [university]	n.r. ± n.r. [23-54]	I: 3ER- Scotchbond Multi-Purpose[a] [31] II: 1SE- Adper Easy One[a] [31]	Filltek Z-350 XT[a]	No	No/Yes	01/02	Modified USPHS
Armstrong 2012[44]	6, 12	Paired [n.r.]	n.r. ± n.r. [n.r.]	I: 3ER- Optibond FL[b] [30] II: 1SE- Tokuyama Bond Force[c] [30]	I: Premise[b] II: Estelite Sigma Quick[c]	No/Yes*	n.r./n.r.	n.r/ n.r.	USPHS
Blunck 2013[52]	12, 24	Split-mouth [n.r.]	n.r. ± n.r. [n.r.]	I: 1SE- iBond[d] [58] II: 1SE- G-Bond[e] [58] III: 1SE- Clearfil S3 Bond[f] [58] IV: 3ER- Optibond FL[b] [58]	CeramX-Duo[g]	n.r.	No/No	2/n.r.	USPHS
Dall'orologio 2006[48]	Baseline, 6, 12, 18, 24, 36, 60, 72	n.r. [n.r.]	n.r. ± n.r. [30-52]	I: 1SE- iBond[d] [n.r.] II: 1SE- AQ Bond[h] [n.r.] III: 3ER- Scotchbond Multi-Purpose[a] [n.r.]	Filtek Z-250[a]	n.r.	n.r./n.r.	3/1	Modified USPHS
de Paula 2015[43]	Baseline, 6, 12	Paired [university]	n.r. ± n.r. [n.r.]	I: 3ER- Optibond FL[b] [46] IV: 1SE- Optibond All-in-One[b] [46]	Filtek Supreme Ultra[a]	Yes	No/No	04/02	FDI/Modified USPHS
Ermis 2012[62]	Baseline, 6, 12, 24	Paired [university]	50 ± 8.3 [39-79]	I: 1SE- Clearfil S3 Bond[f] [81] II: 3ER- Optibond FL[b] [80]	Clearfil AP-X[f]	No	Yes/Yes	01/02	Vanherle method
Häfer 2015[14]	Baseline, 6, 12, 24, 36	Multiple restorations [university]	46.7 ± 14.1 [18-66]	I: 1SE- Futurabond M[i] [40] III: 3ER- Syntac Classic[j]	I: Amaris[i] III: Tetric EvoCeram[j]	Yes	Yes/Yes	03/01	FDI
Kim 2009[50]	Baseline, 6, 12, 24	Paired [university]	50 ± n.r. [34-65]	I: 3ER-Scotchbond Multi-Purpose[a] [25] II: 3ER- RF + Scotchbond Multi-Purpose[a] [25] V: 1SE-Adper Prompt[a] [25] VI: 1SE- RF + Adper Prompt[a] [25]	Denfil[k]	No	Yes/Yes	01/02	Modified USPHS
Lawson 2015[51]	Baseline, 6, 12, 24	Paired [university]	60.1± n.r. [n.r.]	I: 3ER- Scotchbond Multi-Purpose[a] [42] III: 1SE- Scotchbond Universal[a] [42]	Filtek Supreme Ultra[a]	Yes	Yes/No	05/02	Cvar and Ryge
Lee 2006[49]	Baseline, 6	Paired [n.r.]	n.r. ± n.r. [n.r.]	I: 3ER- Scotchbond Multi-Purpose[a] with grooves [25] II: 3ER- Scotchbond Multi-Purpose[a] without grooves [25] V: 1SE- Adper Prompt[a] with grooves [25] VI: 1SE- Adper Prompt[a] without grooves [25]	Denfil[k]	n.r.	n.r./n.r.	01/ n.r.	Modified USPHS

Moosavi 2013[63]	Baseline, 6, 12, 18	Paired [n.r.]	n.r. ± n.r. [20-50]	I: 3ER- Optibond FL[b] [30] III: 1SE-Optibond All-in-One[b] [30]	Herculite XRV[b]	No	No/Yes	01/02	Modified USPHS
Perdigão 2012[40]	Baseline, 6, 18	Paired [n.r.]	47.6 ± n.r. [22-78]	I: 3ER- Scotchbond Multi- Purpose[a] [34] IV: 1SE- Adper Easy One Bond[a] [29]	Filltek Supreme Plus[a]	No	No/No	n.r./02	Modified USPHS
Ritter 2008[11]	Baseline, 6, 18, 36	Paired [university]	55 ± n.r. [36-77]	I: 3ER- Gluma Solid Bond[d] sclerosis 1-2 [26] II: 1SE-iBond[d] sclerosis 1-2 [28] III: 1SE- iBond[d] sclerosis 3-4 [25]	Durafill VS[d]	No/Yes*	Yes/Yes	06/02	Modified USPHS
van Dijken 2013[12]	6, 12, 18, 24, 36, 48, 60	Multiple restorations [university]	64.7 ± n.r. [39-84]	I: 1SE- G-Bond[e] [67] II: 3ER- CFM[l] [51]	I: Gradia Direct[e] III: els[l] + Gradia Direct[e]	No	No/Yes	01/03	Modified USPHS
Van Landuyt 2008,[45] 2011,[46] 2014,[41] Peumans, 2018[47]	6, 12, 24, 36, 60, 108	Paired [university]	n.r. ± n.r. [n.r.]	I: 1SE- G-Bond[e] [133] II: 3ER- Optibond FL[b] [134]	Gradia Direct Anterior[e]	No	Yes/Yes	02/02	Vanherle method

ID – identification; mth – months; # - Number; SD – standard deviation; n.r. – not reported in the study; 3ER – three-step etch-and-rinse adhesive; 1SE – one-step self-etch adhesive; USPHS – United States Public Health Service; els – extra low shrinkage resin composite; * Depending of access and location of the lesion.

[a] 3M ESPE, St. Paul, MN, USA.
[b] Kerr Corporation, Orange, USA.
[c]Tokuyama Dental, Tokyo, Japan.
[d]Kulzer, GmbH, Hanau, Germany.
[e]GC Corporation, Tokyo, Japan.
[f]Kuraray, Tokyo, Japan.
[g]Dentsply DeTrey, Konstanz, Germany.
[h]Sun Medical, Shiga, Japan.
[i]Voco GmbH, Cuxhaven, Germany.
[j]IvoclarVivadent AG, Schaan, FL.
[k]Vericom, Anyang, Korea.
[l]Saremco AG, Rebstein, Switzerland.
[m]DeTrey/Dentsply, Konstanz, Germany.

Table 4.1.3 – Data and analyses of the adhesive strategies 1-step SE and 3-step ER for approaches 1 and 2.

Outcome	Approach	Follow-up (month)	1SE (events/total)	3ER (events/total)	Test for overall effect p-value	Heterogeneity Chi-square - p-value	I^2	Difference between approaches
Retention	Intention-to-treat	12-24	29/607	21/549	0.66	0.84	0%	No
		36	22/293	10/241	0.21	0.77	0%	
		60	9/200	8/185	0.96	0.95	0%	
	Per-protocol	12-24	19/492	8/455	0.07	0.88	0%	
		36	5/207	7/178	0.48	0.76	0%	
Marginal integrity	Intention-to-treat	12-24	220/557	148/511	0.04	0.02	55%	Yes
		36	109/244	64/204	0.94	0.0001	91%	
		60	110/181	82/173	0.32	0.11	61%	
	Per-protocol	12-24	191/442	119/420	0.001	0.15	33%	
		36	104/166	47/146	0.00001	0.62	0%	
Marginal discoloration	Intention-to-treat	12-24	122/533	69/490	0.003	0.40	4%	Yes
		36	71/244	28/204	0.37	0.0004	87%	
		60	90/179	120/244	0.69	0.0007	91%	
	Per-protocol	12-24	96/442	55/420	0.06	0.21	27%	
		36	63/166	16/146	0.14	0.09	66%	

Table 4.1.4 – Summary of findings table for the intention-to-treat approach.

Patient or population: restoration of NCCLs; Setting: university
Intervention: 1-step SE; Comparison: 3-step ER

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 1-step ER	Risk difference with 3-step ER
Retention rates 12 to 24 mths - assessed with: dichotomous scale (present/absent)	578 (11 RCTs)	⊕⊕◯◯ LOW [a,b]	RR 1.13 (0.65 to 1.98)	38 per 1,000	5 fewer per 1,000 (13 fewer to 37 more)
Retention rates mean 60 mths - assessed with: dichotomous scale (present/absent)	385 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	RR 0.98 (0.39 to 2.47)	43 per 1,000	1 more per 1,000 (26 fewer to 64 more)
Marginal integrity 12 to 24 mths - assessed with: dichothomous scale (alpha vs. bravo/charlie)	1068 (10 RCTs)	⊕◯◯◯ VERY LOW [a,,b,c]	RR 1.40 (0.93 to 2.12)	290 per 1,000	116 more per 1,000 (20 fewer to 324 more)
Marginal integrity means 60 mths - assessed with: dichotomous scale (apha vs. bravo/charlie)	354 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]	RR 1.29 (1.10 to 1.52)	474 per 1,000	137 more per 1,000 (47 more to 246 more)
Marginal discoloration 12 to 24 mths - assessed with: dichotomous scale (alpha vs. bravo/charlie)	1023 (12 RCTs)	⊕⊕◯◯ LOW [a,c]	RR 1.55 (1.17 to 2.06)	141 per 1,000	77 more per 1,000 (24 more to 149 more)
Marginal discoloration - means 60 mths assessed with: dichotomous scale (alpha vs. bravo/charlie)	423 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]	RR 1.40 (1.02 to 1.90)	492 per 1,000	197 more per 1,000 (10 more to 433 more)

For GRADE assessment, it was selected the shortest and the longest-term follow-up for each outcome to comply with the Cochrane suggestion of a maximum of 7 outcomes in the summary of findings table.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
⊕⊕⊕⊕ High certainty: We are very confident that the true effect lies close to that of the estimate of the effect;
⊕⊕⊕◯ Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕◯◯◯ Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Most studies are at unclear risk of bias
b. Very wide confidence interval that does not exclude a clinically important superiority or inferiority of 3-step ER systems
c. Wide confidence interval in which boundaries include an unimportant clinical effect and an expressive superiority of 3-step ER systems
d. Unexplained heterogeneity

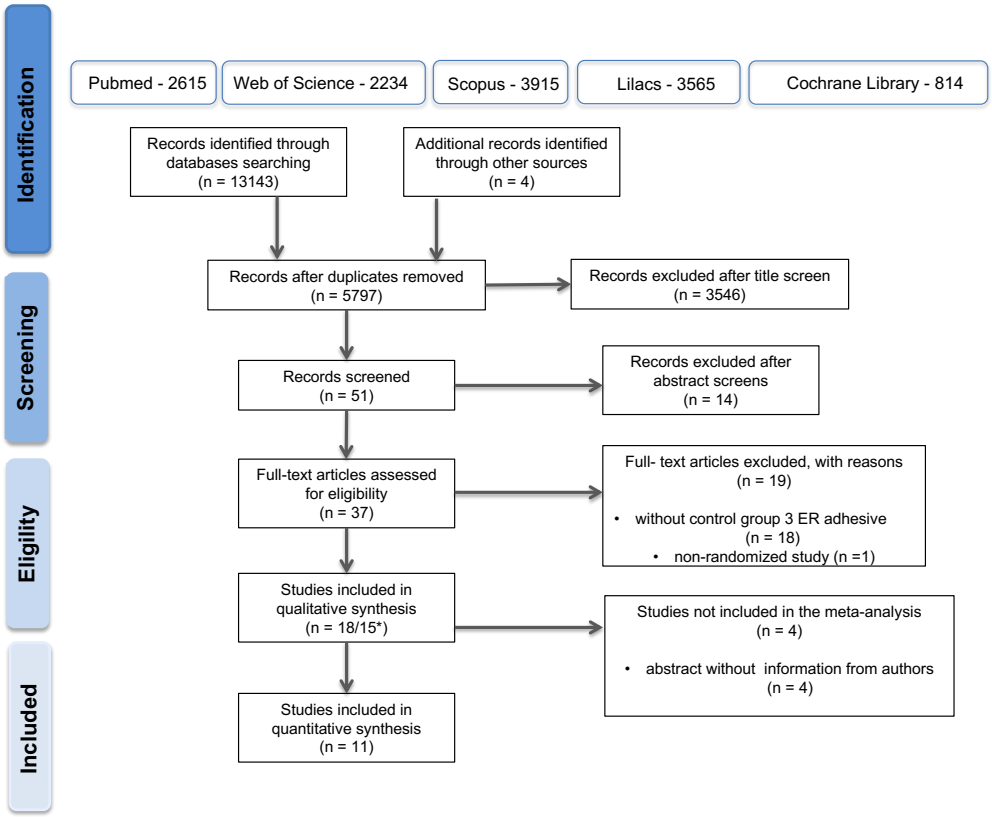
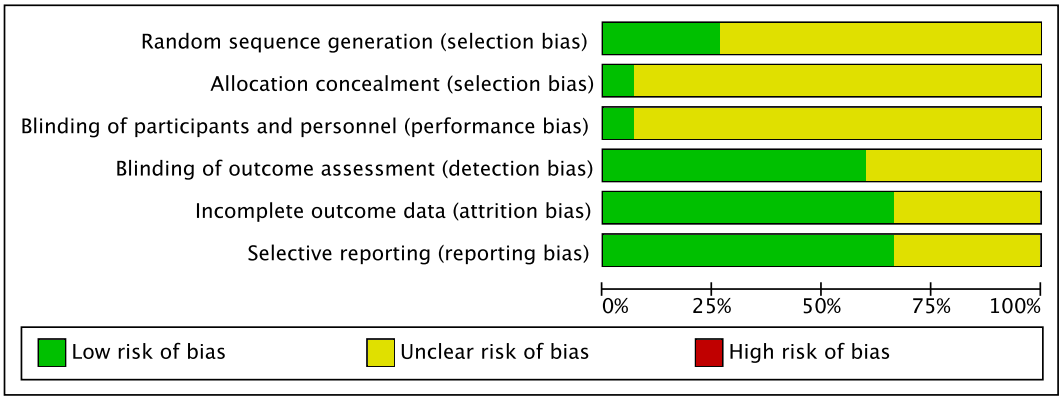


Figure 4.1.1 – Flow diagram of study.

Note: *Reports of the same study at different follow-ups.

A)



B)

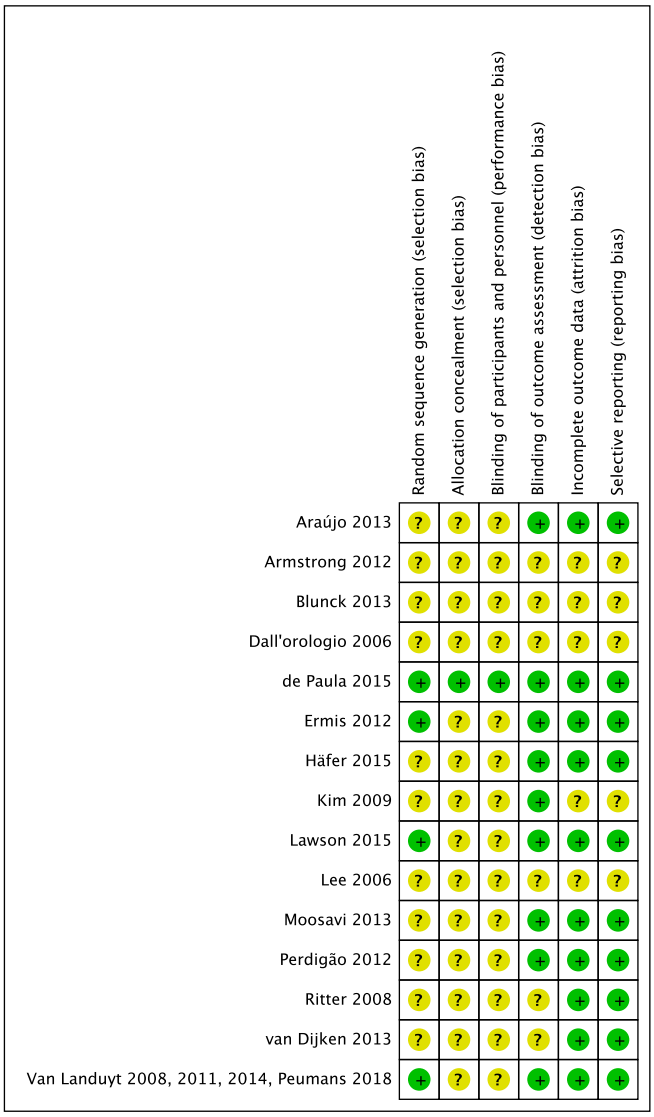
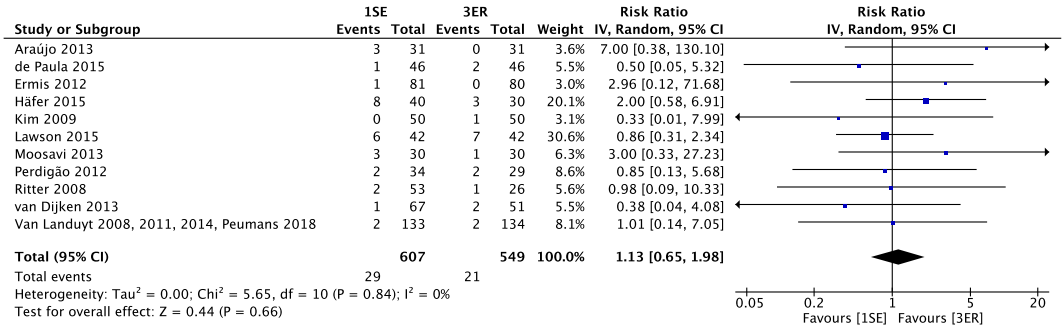
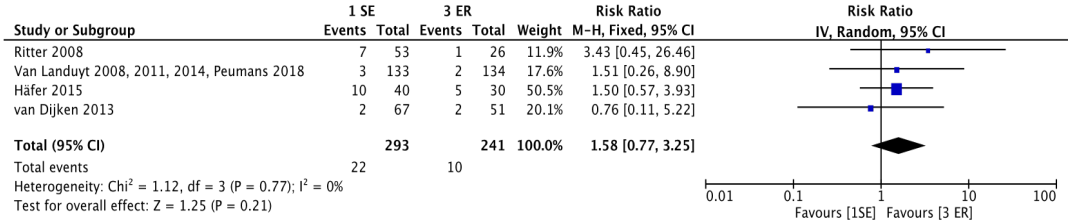


Figure 4.1.2 – A) Risk of bias graph according to the Cochrane Collaboration toll and B) Risk of bias summary.

A) At 12 to 24-month.



B) At 36-month.



C) At 60-month.

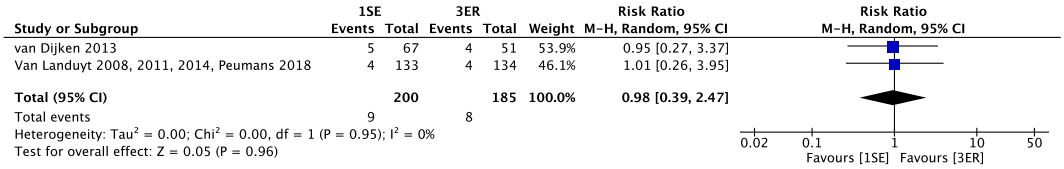
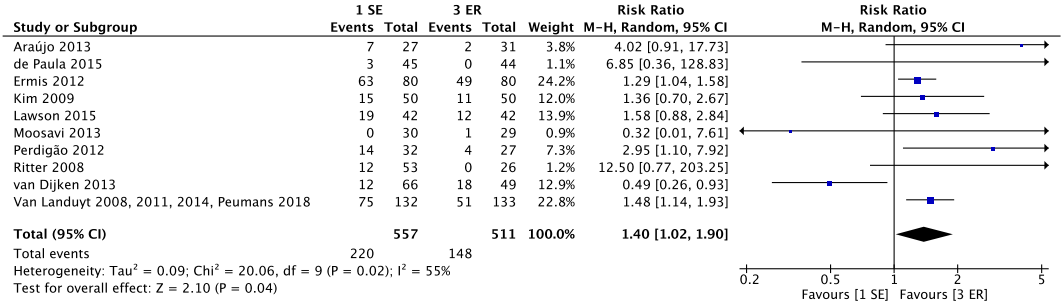
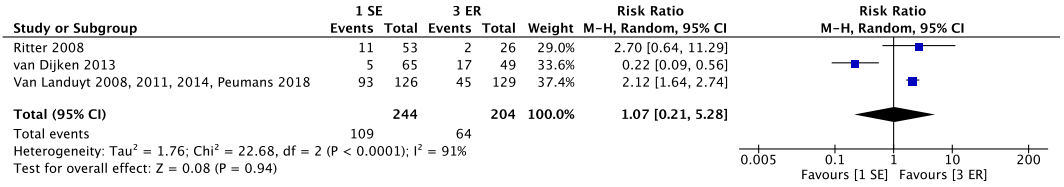


Figure 4.1.3 – Forest plot of the retention rates, approach 1, A) at 12 to 24-month, B) 36-month and C) 60-month.

A) At 12 to 24-month.



B) At 36-month.



C) At 60-month.

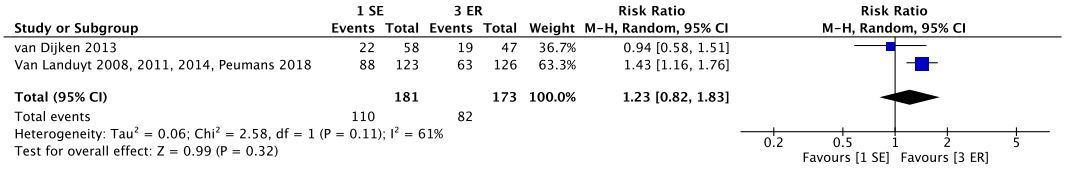
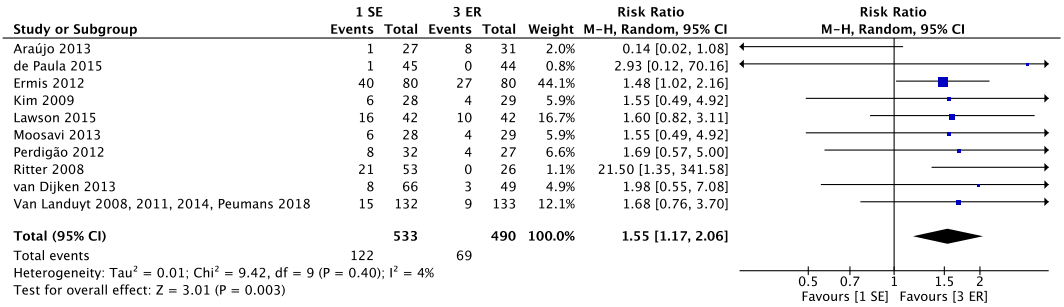
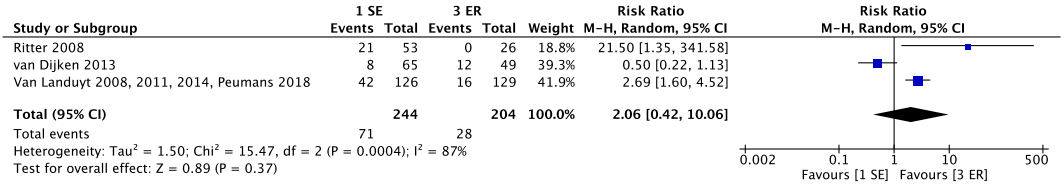


Figure 4.1.4 – Forest plot of the marginal integrity, approach 1, A) at 12 to 24-month, B) 36-month and C) 60-month.

A) At 12 to 24-month.



B) At 36-month.



C) At 60-month.

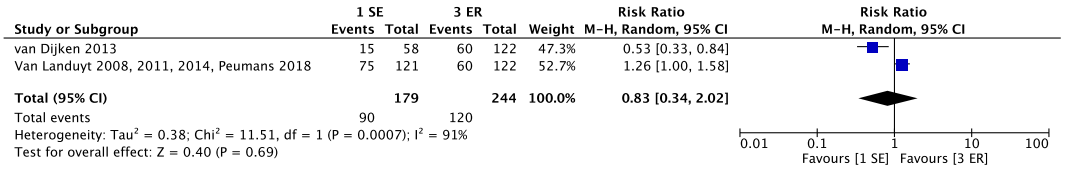


Figure 4.1.5 – Forest plot of the marginal discoloration, approach 1, A) at 12 to 24-month, B) 36-month and C) 60-month.

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4.2 ARTIGO 2: ADHESIVE STRATEGIES IN CERVICAL LESIONS: SYSTEMATIC REVIEW AND A NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

STATUS: PUBLICADO.

REVISTA: CLINICAL ORAL INVESTIGATIONS.

ARTIGO 2 – ADHESIVE STRATEGIES IN CERVICAL LESIONS: SYSTEMATIC REVIEW AND A NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Short Title: Adhesive strategies in cervical lesions: network meta-analysis

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Conflict of interest: The authors declare no conflict of interest related to this study.

Source of funding: This study was partially supported by National Council for Scientific and Technological Development of the Brazilian Government under grants 304105/2013-9 and 305588/2014-1.

ABSTRACT

Objective: A network meta-analysis (NMA) was performed to assess which adhesive strategy is most clinically effective in treating non-carious cervical lesions (NCCLs).

Methods: Studies were identified by a systematic search of electronic databases including MEDLINE via PubMed, Brazilian Library in Dentistry (BBO), Cochrane Library, EMBASE, Latin American and Caribbean Health Sciences Literature database (LILACS), Scopus, Web of Science without restrictions on publication year or language. The grey literature was also consulted. Only randomized clinical trials that compared different adhesive strategies in NCCLs in adult patients were included. The risk of bias was evaluated by using the Cochrane Collaboration tool. A random-effects Bayesian mixed treatment comparison model was used to compare adhesive strategies (3ER, 2ER, 2SE and 1SE) at different follow-up times. The surface under cumulative ranking curve (SUCRA) was estimated for each strategy. Heterogeneity was assessed by using the Cochran Q test and I2 statistics. The quality of evidence was evaluated using the GRADE approach.

Results: A total of 5058 studies were identified, 66 of which met the eligibility criteria and of these 5 were judged “low” risk of bias and 57 were meta-analyzed. We did not observe significant differences in the NMA analysis for any two pairs of adhesives, except for the shortest follow-up for 2ER vs 3ER. The adhesive 2SE ranked highest, although it differed only slightly from the other bonding strategies.
Conclusions: No bonding strategy is better than the others.

Clinical Relevance: Adhesive efficacy cannot be characterized by its bonding strategy.

Keywords: Dentin-bonding agents; dental bond; non-carious cervical lesions; clinical effectiveness; network meta-analysis.

INTRODUCTION

Although numerous laboratory investigations have measured the bond strength values of different dental adhesives in an attempt to predict their clinical outcomes,[1, 2] randomized controlled trials (RCTs) remain the most appropriate research design for assessing the clinical efficacy of any intervention.[3, 4] To evaluate the effectiveness and clinical performance of adhesive systems, the American Dental Association (ADA)[5] recommends clinical trials on non-carious cervical lesions (NCCLs), as composite resin restorations only remain bonded to these lesions by the micromechanical interlocking produced by the adhesive systems.[6] The immediate, short-term and long-term bonding performance of adhesive systems is then evaluated by retention, marginal integrity and marginal discoloration.

Ideally, the clinical decision-making process should be based on the best available evidence which encompassing RCTs; however, the increasing number of RCTs published about adhesive systems prevents an overall conclusion about the most efficient adhesive strategy. Systematic reviews can facilitate this challenge through research synthesis of multiple studies.

Systematic reviews aim to collect, appraise, and synthetize the amount of evidence in a specific domain. Although standard systematic reviews adhesive strategies have reported for dental bonding,[7-9] they present comparisons between pairs of different adhesive strategies and rarely involve multiple comparisons. When choosing adhesive systems for clinical purposes,

several competing types of adhesive strategies are available (3- and 2-step etch-and-rinse adhesives, 2- and 1-self etch adhesives, and 1-step adhesives used with selective enamel etching and universal adhesives). Thus, one of the most important questions remaining to be answered is which adhesive strategy offers the greatest benefits in terms of retention, marginal discoloration, and marginal integrity.

Clinicians who need to decide among these different strategies would benefit from a single review that includes all relevant adhesive strategies and presents their comparative efficacy. Network meta-analysis is a technique that allows for the comparison of three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies, even when there are no head-to-head trials for some of the interventions. The authors are unaware of a network meta-analysis dealing with the different adhesive strategies.

Therefore, the aim of the present systematic review and network meta-analysis was to establish a clinically meaningful hierarchy of the different adhesive approaches to bond composite resin restoration in NCCL cavities through the synthesis of available evidence from RCTs. To this end, we aimed to answer the following PICO (Population, Intervention, Comparison, and Outcome) question: What is the comparative effectiveness of adhesive strategies (I and C) for bonding composite resin restorations in adult patients (P) in terms of retention (O), and what the relative ranking of these strategies?

MATERIALS AND METHODS

Protocol and Registration

This study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO-CDR42018112672) and adhered to the recommendations of the Preferred Reporting Items for Systematic Reviews (PRISMA- NMA) guidelines and the corresponding extension for network meta-analysis.[10]

Information Sources and Search Strategy

A literature search was performed in MEDLINE/PubMed, Brazilian Library in Dentistry (BBO), Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE,

Latin American and Caribbean Health Sciences Literature database (LILACS), and in the citation databases Scopus and Web of Science, with no data or language restriction and using a predefined search strategy.

Controlled vocabulary (MeSH and Entree terms) and free keywords, defined based on the concept of population (adult patients requiring NCCL restorations) and intervention (composite restorations with adhesive systems), were combined within each concept using the Boolean operator "OR". The concepts (population and intervention) were combined with the Boolean operator "AND" and whenever possible with a validated filter from PubMed.

We hand-searched the references lists of all primary studies and the related article link of each primary study in the PubMed database. Grey Literature in Europe (SIGLE), Google Scholar and abstracts of the International Association for Dental Research (1998-2019) and ongoing and unpublished trials (Current Controlled Trials, International Clinical Trials Registry Platform, Clinical Trials.gov, Brazilian Clinical Trials Registry and EU Clinical Trials Register) were also searched.

Eligibility Criteria

We included published and unpublished RCTs with paired or multiple restorations per participant that evaluated at least two different adhesive strategies in NCCLs. Studies not adhering to the inclusion criteria were excluded. The following exclusion criteria were applied to the studies:

- adhesive 2SE used in 3ER mode;
- compared two adhesives from the same strategy (without control group);
- conducted in other types of cavities (class I, II, III, or IV);
- with follow-up less than 12 months;
- performed dentin pretreatment;
- cavities were lined with other materials;
- used 2nd and 3rd generation adhesives and
- used phosphoric acid etching at low concentrations (e.g., 10%).

Study Selection and Data Collection Process

Articles appearing in more than one database were considered only once. Subsequently, two reviewers (F.D.S.D. and A.B.) evaluated titles and abstracts to remove ineligible studies. Full-text articles were acquired from the likely eligible studies, and two reviewers classified those meeting the inclusion criteria. Each eligible article received a study ID combining first author and year of publication. Three authors from this study extracted relevant information about the study design, participants, type of adhesive, use of rubber dam, enamel bevel, dentin preparation, number of operators, number of examiners, and evaluation criteria using customized extraction forms; in cases of disagreements, a decision was reached by consensus. Multiple reports of the same study (reports with different follow-up times) were extracted directly into a previously tested, single data collection form to avoid overlapping data. The events were classified as dichotomous outcomes at the end of each follow-up.

Risk of bias within Individual Studies

Quality assessments of the selected trials were carried out by two independent reviewers using the Cochrane Collaboration Risk of Bias Tool (RoB version 1.0) for RCTs.[11] The RoB tool contained six domains: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. The last domain (other bias) was not used in the present study. During data selection and quality assessment, any disagreements between the reviewers were resolved through discussion and consultation with a third reviewer (A.R.). The judgement for each entry consisted of recording low, high, or unclear risk of bias (either lack of information or uncertainty about the potential for bias).

Summary measures and planned methods of analysis

The adhesive strategies were classified as (A) 3-step ER; (B) 2-step ER; (C) 2-step SE or (D) 1-step SE approaches. The universal adhesives were classified into the category B when used in the 2-step ER approach and into category D when used in the 1-step SE approach. Self-etch adhesives used in selective enamel etching were considered as either 1-step SE or 2-step SE. The 4-step ER Syntac adhesive (Ivoclar Vivadent) was classified as a 3-step ER adhesive.

In studies where 1-step SE adhesives were treated as a primer and coated with a hydrophobic adhesive layer, they were considered as a 2-step SE. The same was true for

universal adhesives when used in the 2-step ER mode, however, with an additional coat of a hydrophobic layer, the adhesive was classified as 3-step ER and treated as such in this study.

When trials compared more than two bonding strategies, they were included in the meta-analysis separately to provide more than one effect size. Data were extracted using intention-to-treat analysis by using the total number of failures of each treatment arm at each follow-up as the nominator and the total number of participants randomized at baseline as the denominator wherever trial reporting allowed.

The primary outcome evaluated was restoration loss. We calculated risk ratios for this binary outcome in a traditional pairwise meta-analysis, presenting their 95% confidence intervals at different follow-up periods (12 to 24 months; 36 to 48 months, and > 48 months). In case two or more adhesive systems from the same bonding strategy were investigated in the primary study, data were merged to make a single entry. In case the study reported data twice in the follow-up range described above, data from the longer follow-up was taken.

Transitivity was assumed to occur in all studies, meaning that the different sets of interventions were sufficiently similar to provide valid indirect inferences. For this purpose, we applied narrow inclusion criteria to keep population and treatments as similar as possible within and across treatment comparisons.

Statistical analysis

We performed a network meta-analysis (NMA) by using the Bayesian model with the statistical package geMTC in R (version 3.4.2). The Mixed Treatment Comparison methodology, supported by the Markov Chain Monte Carlo hierarchy, was chosen to carry out the NMA. This model allows for the simultaneous comparison of all four adhesive strategies and the incorporation of trials with three or more arms. Random effects models with the DerSimonian and Laird variance estimator and the inverse of the variance method were used. The convergence was based on the Brooks Gelman-Rubin criteria with inspection of trace plots, and 20 000 interactions were undertaken for 4 chains at a thinning interval of 10. Heterogeneity was assessed using the Cochran Q test and I2 statistics.

The results of the network meta-analysis were displayed in point estimates, 95% credible intervals (95% CrI). We also calculated the relative ranking for each intervention using the Surface Under the Cumulative Ranking curve (SUCRA), estimated within the Bayesian framework. A SUCRA value of 100% indicates the treatment is certain to be the most effective

in the network, while a value of 0% indicates it is certain to be the least effective. The larger the SUCRA value, the better the rank of an intervention in the network. All analyses were implemented using the Meta and geMTC packages of the R statistical software program.[12]

Assessment of inconsistency

A further assumption of NMA is consistency, the statistical agreement between the direct and indirect comparisons. The consistency assumption is the statistical manifestation of transitivity and depends on the statistical agreement between different sources of evidence. Statistical inconsistency was checked using posterior plots and Bayesian p-values produced by the node-splitting method of Dias et al., 2010[13] by testing the agreement between direct and indirect evidence. A p-value equal to or greater than 0.008 was considered as the threshold for significance after Bonferroni correction, as the same data were used in six multiple comparisons.

Small study effects and publication bias

Publication bias was assessed by funnel plot asymmetry. The presence of small-study effects was evaluated by drawing a comparison-adjusted funnel plot that accounts for the fact that different studies compare different sets of interventions. The null hypothesis was tested by using the Egger test in all follow-up periods at a significance level of 5%.

Assessment of the quality of evidence using Grading of Recommendations: Assessment, Development, and Evaluation

We followed the GRADE approach to appraise the confidence in estimates derived from the network meta-analysis of retention rates following the Puhan et al. approach.[14] Direct evidence from RCTs starts at high confidence and can be rated based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity) and/or publication bias, to levels of moderate, low, and very low confidence. The rating of indirect estimates starts at the lowest rating of the pairwise estimates that contribute as first-order loops to the indirect estimate but can be rated further for imprecision or intransitivity (dissimilarity between studies in terms of

clinical or methodological characteristics). If direct and indirect estimates were similar (i.e., coherent), then the higher of the ratings was assigned to the network meta-analysis estimates.

RESULTS

Study Selection

The search strategy was conducted initially on February 9, 2019 and was updated on November 20, 2019 (Supplementary Table 4.2.1). A total of 5058 studies were retrieved from electronic databases. After removal of duplicates, and title and abstract screening, 143 studies remained. Of these, 62 studies were excluded (Supplementary Table 4.2.2), which left 81 eligible randomized controlled trials. Of these, fifteen reported the same population sample at different follow-up periods and received the same study ID.[15-29] Therefore, 66 studies were included in the qualitative synthesis and 57 in the quantitative analysis. Nine studies[30-38] were excluded from the quantitative studies because they were abstracts without data description as demonstrated in the flow diagram (Supplementary Figure 4.2.8).

Characteristics of Included Articles

The characteristics of the 66 eligible studies are listed in Supplementary Table 4.2.3. Thirty-seven studies used the paired design,[30-32, 34, 36, 37, 39-69] twenty-eight studies performed multiple restorations per participant[35, 38, 70-95], and only one did not report this information.[33] The follow-up periods ranged from 3 to 108 months, and great variability was observed in the age range of participants in all the included studies (18 to 88 years). A wide variation of commercial brands of each adhesive strategy and composite resin for restoration was used in the included studies.

Among the 3-step ER, the two most tested materials were OptiBond FL (Kerr)[30, 32, 33, 50, 59, 60, 74, 75, 84, 87, 94] and Scotchbond Multi-Purpose (3M ESPE)[40, 42, 51, 52, 56, 80] used in 11 and 6 comparisons respectively. For 2-step ER and 2-step SE strategies, the adhesives Adper Single Bond (3M ESPE) and Clearfil SE Bond (Kuraray), respectively, were the most tested, and, in the 1-step SE strategy, Scotchbond Universal (3M ESPE) was the most used. In three studies, an extra layer of a hydrophobic bonding resin (Scotch Multi-Purpose- 3M ESPE) was applied as in Perdigão 2019[81] (Universal to 3ER, Universal to 2SE), Reis 2009[62] (1SE to 2SE) and Sartori 2013[64] (1SE to 2SE).

The majority of the studies used cotton rolls, retraction cords, and a saliva ejector to isolate of the operative field,[38, 40-42, 44, 45, 48, 50, 51, 59, 61, 64-69, 71, 73, 75, 77-82, 85, 86, 88-94, 96], and three reported that the use of rubber dam depended on the location and access of the lesion.[30, 83, 84]Twenty-three studies did not perform any preparation on either enamel or dentin,[32, 43-45, 48, 53, 54, 57-59, 63-65, 69, 72, 74, 77, 79, 80, 86, 88, 89, 97] twelve studies prepared both enamel and dentin[50, 51, 68, 70, 75, 76, 78, 82, 83, 87, 94, 95] and eight did not report this information.[30, 31, 33-37, 81] The number of operators ranged from 1 to 6, the number of evaluators ranged from 1 to 3, and in eight studies this information was not reported.[30, 31, 34-37, 49, 56] The most used criteria for restoration evaluation was the modified USPHS,[33, 34, 37, 38, 41-46, 48, 49, 51, 53, 56, 57, 61, 64-66, 68, 71, 73, 74, 78, 80-82, 84, 85, 87, 88, 90-93, 95, 96] but the FDI criteria and the Vanherle method were also described.

Assessment of the Risk of Bias

The RoB of the eligible studies is presented in Figure 4.2.1. With regard to the specific items of the risk of bias assessment tool by the Cochrane Collaboration, 65% of the included studies indicated an unclear risk of bias for random-sequence generation, 85% for allocation concealment, 80% for blinding of participants and personnel, 60% for blinding of outcome, 30% for incomplete data outcome, and 40% for selective reporting. Overall, most of the RCTs had an unclear risk of bias and only five studies were classified as being at low risk of bias.[55, 57, 58, 69, 74]

Evidence network

Figure 4.2.2 displays the network of the four adhesive strategies (3ER, 2ER, 2SE and 1SE) for each follow-up, where each node represents an adhesive strategy. The strategies connected by a line represent direct comparisons, with the number of pairs (from RCTs) reflected by the thickness of the edges, and the number of restorations reflected by the size of the nodes.

Fifty-seven studies were included in three independent meta-analyses for loss of retention at the different follow-up periods (12 to 24 months, 36 to 48 months and > 48 months). In all follow-ups, the 1SE bonding strategy is the one with the highest number of placed restorations. A high number of restorations are placed in the short-term follow-up and this decrease, especially in the medium and long-term periods.

In the 12- to 24-month and 36- to 48-month follow-ups, there is evidence from all possible direct pairwise comparisons. At > 48 months, some pairwise comparisons show direct evidence only (from head-to-head studies, for example, 2ER vs. 2SE), some show indirect evidence only (for example, 3ER vs. 2SE) and the other pairs show both direct and indirect evidence.

Synthesis of results of network

In the first approach, we included all studies in the network analysis. An important inconsistency was observed in the pair 1SE vs 3ER by Split node analysis (p-value = 0.0060). Heterogeneity was analyzed in the primary studies and the pair 2ER vs 3ER showed moderate heterogeneity ($\tau 2 = 0.236$; I2 = 28.80%). Both Leav-One-Out and the Baujatplot method showed that the study of Van Dijken 2000[90] was causing the heterogeneity (Supplementary Table 4.2.4 and Figure 4.2.9). The removal of this study corrected the heterogeneity of the 2ER vs. 3ER comparison and the inconsistency of the 1SE vs. 3ER comparison without altering the NMA results for the follow-up 12- to 24-month follow-up.

Loss of retention at 12 to 24-months

Traditional pairwise meta-analysis for all possible pairs can be found in Supplementary Figure 4.2.10. Figure 4.2.3 summarizes the direct, indirect, and pooled estimates for comparisons of bonding strategies. We observed a significant difference in the pair 2SE vs 3ER (RR = 0.72; 95% CrI 0.52 to 0.99) in the NMA analysis in favor of the 2SE bonding strategy. No other significant difference was found among any two pairs of bonding strategies.

P-values in Figure 4.2.3 indicate the probability that the direct and indirect evidence is consistent. The smallest Bayesian p-value found for inconsistency was equal to 0.05 (for 2ER vs 3ER) and therefore higher than the threshold of 0.008 (after Bonferroni correction), showing that we do not have evidence to reject the hypothesis of consistency. We did not observe heterogeneity (p > 0.38; I2 = 7%; Supplementary Table 4.2.5).

Loss of retention at 36 to 48-months

Traditional pairwise meta-analysis for all possible pairs can be found in Supplementary Figure 4.2.11. No significant difference in the NMA was found among any two pairs (Figure

4.2 – 4). Heterogeneity was observed ($p < 0.01$; $I2 = 72\%$; Supplementary Table 4.2.6), but inconsistency between direct and indirect evidence was not detected.

Loss of retention at > 48 months

Traditional pairwise meta-analysis for all possible pairs can be found in Supplementary Figure 4.2.12. Figure 4.2.5 summarizes the direct, indirect, and pooled estimates for the comparison 2ER vs 3ER, as this was the single comparison with both direct and indirect evidence. We found no significant difference between pairs. Only four pairs had direct comparisons: 2ER vs 1SE, 2ER vs 2SE, 3ER vs 2ER, and 3ER vs 1SE. The heterogeneity was high ($p = 0.02$; $I2 = 82\%$; Supplementary Table 4.2 – 7), but inconsistency was not detected.

SUCRA rankings for all study follow-ups

In the primary probabilistic analysis, strategies were ranked as having the higher probability of being the first, second, third and fourth at each study follow-up. Figure 6 illustrates the ranking and the SUCRA values for all study follow-ups. The probability of being the best adhesive strategy varies in the study follow-ups, but the 2SE strategy is ranked as first in two study follow-ups (12 to 48 months and > 48 months; Figure 4.2.6 A and C) and is ranked as second in the 36- to 48-month follow-up (Figure 4.2.6 B).

Small study effects and publication bias

Publication bias was not observed in any of the study follow-ups (Figure 4.2.7). Studies with high precision (high sample sizes) are plotted near the point estimate and studies with low precision (small sample sizes) are spread evenly on both sides of the point estimate, creating a roughly funnel-shaped distribution. We did not reject the null hypothesis because nonsignificant p-values were found for the Egger test in all follow-up periods [at 12 to 24 months ($p = 0.76$), at 36 to 48 months ($p = 0.08$), and at > 48 months ($p = 0.88$)].

Quality of evidence

The ratings of the quality of the direct, indirect and network evidence can be seen in the Supplementary Table 4.2.8. In general, the quality of evidence of the network meta-analysis (Figures 4.2.3, 4.2.4 and 4.2.5) was graded as low because of unclear risk of bias and imprecision.

DISCUSSION

This systematic review and network meta-analysis were conducted to allow a more comprehensive evaluation of all bonding strategies available dental bonding strategies. Previous pairwise meta-analyses have compared any two bonding strategies among all possible pairs[98-101], some with flaws in their methodology. In two of them, no appraisal of the risk of bias of the eligible studies was performed, and the authors failed to choose the appropriate statistical analysis for data management.[7, 8]

Earlier systematic reviews attempting to include all adhesive strategies did not preserve the within-trial randomization[8, 102] as they pooled single arms across studies, ignoring the comparator that was used in the primary studies and treating data as if they came from a single large, randomized trial. This type of analysis discards the benefits of within-trial randomization (Li and Dickersin, 2013)[103] and should be avoided.

Network meta-analyses (NMA) are capable of simultaneously addressing the comparative efficacy of multiple interventions by combining of direct and indirect estimates of effect. This statistical approach is adequate to evaluate multiple treatment options. Differently from an earlier NMA[104], we did not merge different follow-up periods, as failure rates seems to increase over time and merging them may lead to misleading conclusions.

In the traditional pairwise meta-analysis (Supplementary Figures 4.2.10, 4.2.11 and 4.2.12) from the present study, none of the bonding strategies was better than the other, with their point estimates (risk ratio) always crossing the null value of one. By adding indirect evidence to these direct pairwise meta-analyses, the resulting NMA did not increase precision enough to allow us to conclude that one bonding strategy is better than any other, except for a single comparison (2ER vs 3ER) in the shortest follow-up. Because of the imprecise estimate of this comparison, we cannot conclude that this significant finding did not occur by chance.

Researchers wish to provide clinicians with the best choice among available treatment options. Therefore, we determined ranks based on the Bayesian approach, by calculating the Surface Under the Cumulative Ranking Curve (SUCRA). SUCRA value is as a single numeric

presentation of the overall ranking of the materials representing the probability of a treatment ranking best. An overview of the SUCRA values in the three study follow-ups highlights that the bonding strategy that ranked best (ranked as first in two follow-ups and as second in the other) was the 2SE. This agrees with the conclusion Schwendicke et al., 2016[104] who reported that except for resin modified glass ionomer cement, 2SE was the one that was ranked first most often.

Although this result is easier to grasp compared with the other reported statistics, it should be interpreted with caution. SUCRA does not consider the magnitude of differences in effects between treatments. This means that the material ranked first may be only slightly better than the second ranked treatment. Additionally, SUCRA does not take uncertainty into account, and ranking may be based on evidence of low quality. Indeed, most of the evidence gathered in this study is of low quality because of the unclear risk of bias and imprecision.

Even if no clinically or statistically relevant differences in the efficacy of treatments are found, the difference in their ranks will imply otherwise. This indeed was observed in the present study, as all comparisons except one (2ER vs 3ER; 12 to 24 months) were similar to one another. If, indeed, 2SE is to be considered the best bonding strategy as reported by SUCRA, one may conclude that the difference between this material and the other bonding strategies is not sufficient to justify changing the adhesive systems being used by clinicians or public health systems.

Reporting that different bonding strategies have similar performance may make readers suspicious. For more than 20 years, there has been a widespread belief that 3ER systems are the best bonding strategy for restorative and luting procedures. Several laboratory studies with immediate and aged interfaces reported superior bond strength values for the 3ER systems. The authors of a recent meta-analytical review of parameters on bond strength values, De Munck et al. 2012[105], concluded that that the 3ER Optibond FL performed best.

However, we should bear in mind that laboratory and clinical findings often do not coincide. Although an earlier study byVan Meerbeek 2010[106] reported a correlation between laboratory and clinical data, this correlation could have been by chance because it was only found between ‘aged’ bond strength data and medium-term retention rates of adhesives.

The authors of the present investigation are not concluding that all dental adhesives have similar performance. There have been short-term reports of high failure rates of some adhesives when tested in some primary studies.[36, 90, 107] What is concluded is that the efficacy of adhesive systems cannot be labeled by their bonding strategy, as it depends, among other things, much

more on the balanced chemical composition of structural and functional monomers, solvents, polymerization initiators, inhibitors, or stabilizers.

In all bonding strategies, there are efficient and inefficient adhesives, and, when merged by the label of their bonding strategy, results are similar. Future studies should focus more on evaluating specific commercial brands both in short- and long-term follow-up periods.

Limitations of the present systematic review include that the authors of RCTs of bonding studies have not reported the study findings in a standardized way, and this may result in misleading conclusions. In some clinical trials, events at the shortest follow-up period were not carried forward to longest follow-up period, leading to misleading results. Additionally, as the recall rate drops drastically in long-term follow-ups, review authors may calculate the retention rates based on the number of recalled restorations and not on the total number of restorations placed at baseline.

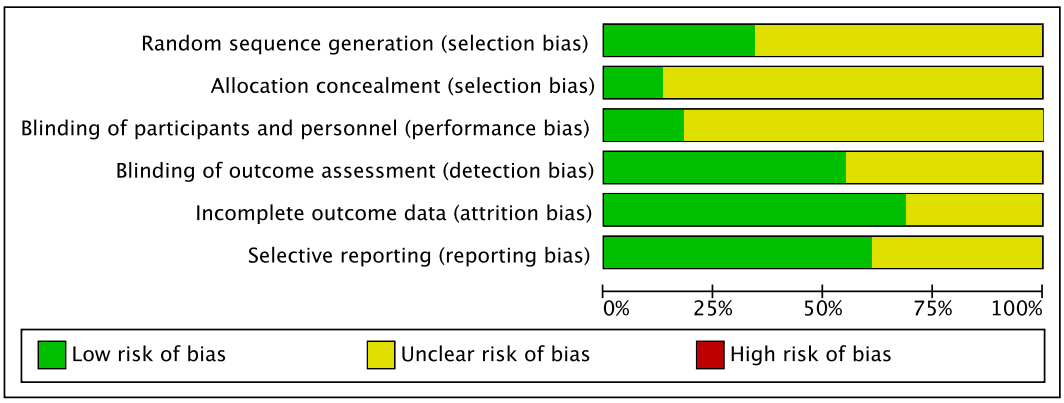
We performed data extraction from the primary studies by following the intention-to-treat analysis, always evaluating the worst-case scenario. However, there was no standardization in the primary studies regarding the reporting of events (cumulative or not) and drop-out reporting over the follow-up periods. The standardization of the collection of these data providing this information is recommended by the ADA guidelines[108], but this is not observed in most studies. All these concerns regarding data extraction indicate the urgent need to standardize the reporting conducted in NCCLs. Instead of providing retention rates per follow-up, the use of survival analysis could provide better estimates of what occurs to the adhesives over time.

Another important consideration is that most of the RCTs focused on short- and medium-term follow-ups, 12 to 48 months. In these short-term follow-ups, the number of events, e.g., debonded restorations, is low, leading to imprecise estimates. Indeed, this was one of the reasons why the quality of the evidence was downgraded.

CONCLUSION

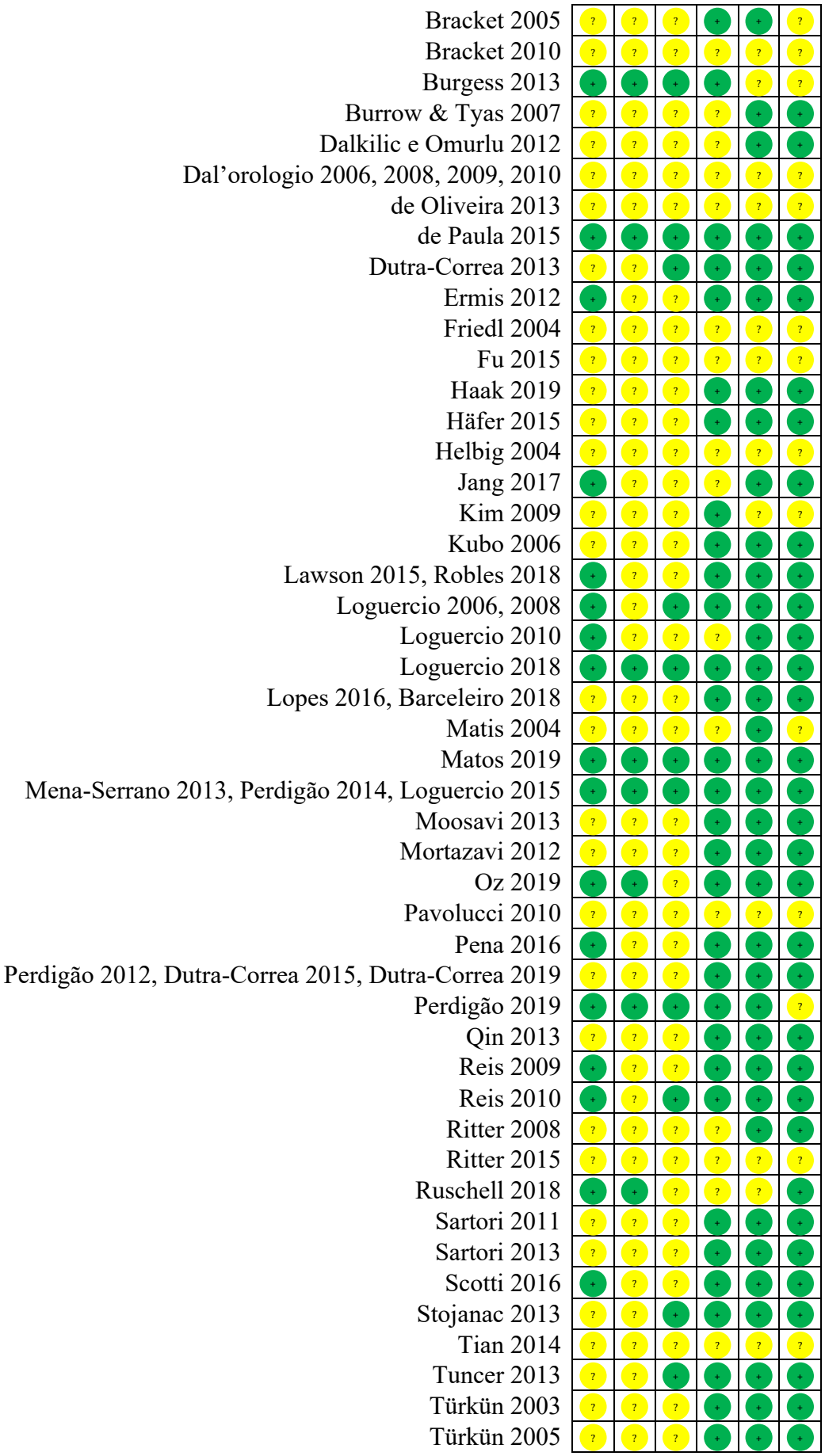
Based on the results herein reported, we concluded that no strategy is better than any other. The authors of this study discourage clinicians, researchers, and teachers from labeling the efficacy of the adhesives based on their bonding strategy.

A)


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

B)


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personal (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Abdalla & Garcia-Godoy 2006
Abdalla & Garcia-Godoy 2007
Araújo 2013
Armstrong 2012
Atalay 2019
Aw 2004, 2005
Batalha-Silva 2009
Bittencourt 2005, Loguercio 2007
Blunck 2013
Boushell 2016


Bracket 2005
Bracket 2010
Burgess 2013
Burrow & Tyas 2007
Dalkilic e Omurlu 2012
Dal'orologio 2006, 2008, 2009, 2010
de Oliveira 2013
de Paula 2015
Dutra-Correa 2013
Ermis 2012
Friedl 2004
Fu 2015
Haak 2019
Häfer 2015
Helbig 2004
Jang 2017
Kim 2009
Kubo 2006
Lawson 2015, Robles 2018
Loguercio 2006, 2008
Loguercio 2010
Loguercio 2018
Lopes 2016, Barceleiro 2018
Matis 2004
Matos 2019
Mena-Serrano 2013, Perdigão 2014, Loguercio 2015
Moosavi 2013
Mortazavi 2012
Oz 2019
Pavolucci 2010
Pena 2016
Perdigão 2012, Dutra-Correa 2015, Dutra-Correa 2019
Perdigão 2019
Qin 2013
Reis 2009
Reis 2010
Ritter 2008
Ritter 2015
Ruschell 2018
Sartori 2011
Sartori 2013
Scotti 2016
Stojanac 2013
Tian 2014
Tuncer 2013
Türkün 2003
Türkün 2005

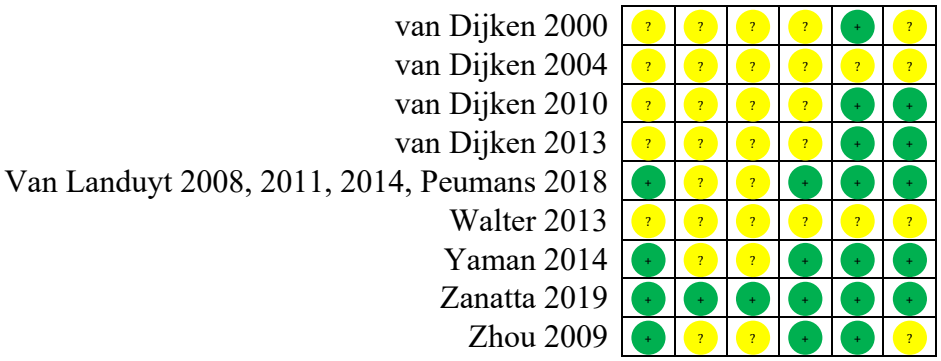


Figure 4.2.1 – A) Risk of bias graph according to the Cochrane Collaboration Tool and B) Risk of bias summary.

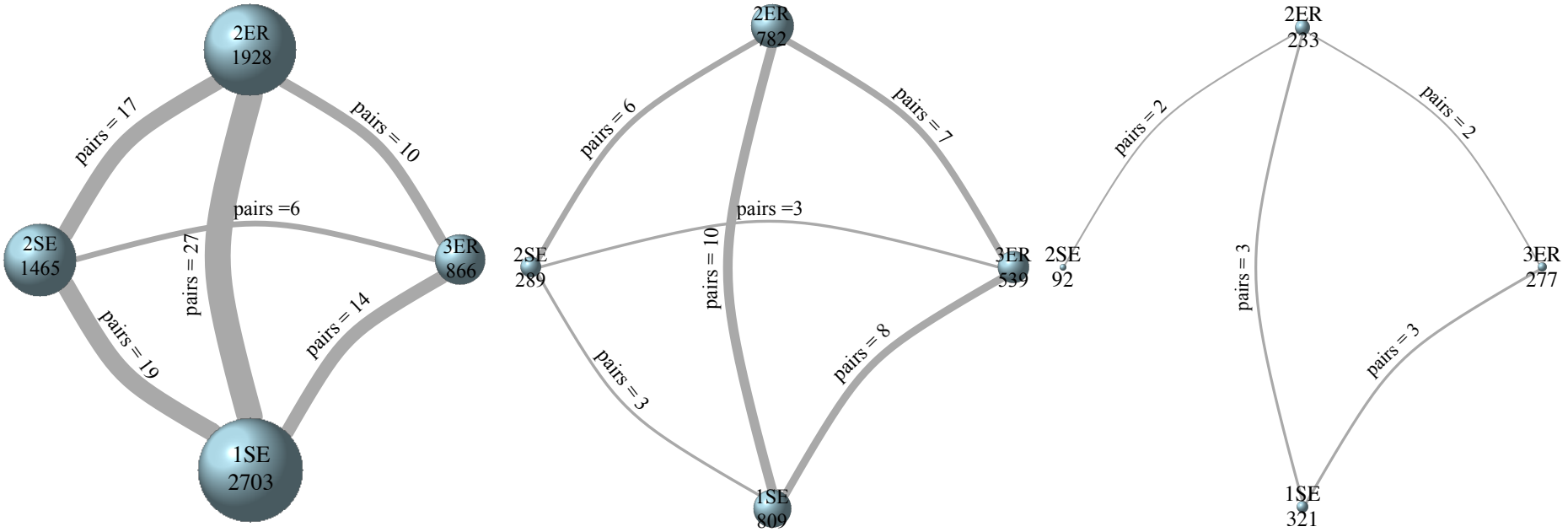


Figure 4.2.2 – Networks of the comparisons of the adhesive strategies at 12 to 24-month (A) at 36 to 48-month (B) and > 48 month (C).

The size of the node reflects the number of evaluated restorations and the thickness of the connecting lines the number of pairs being compared.

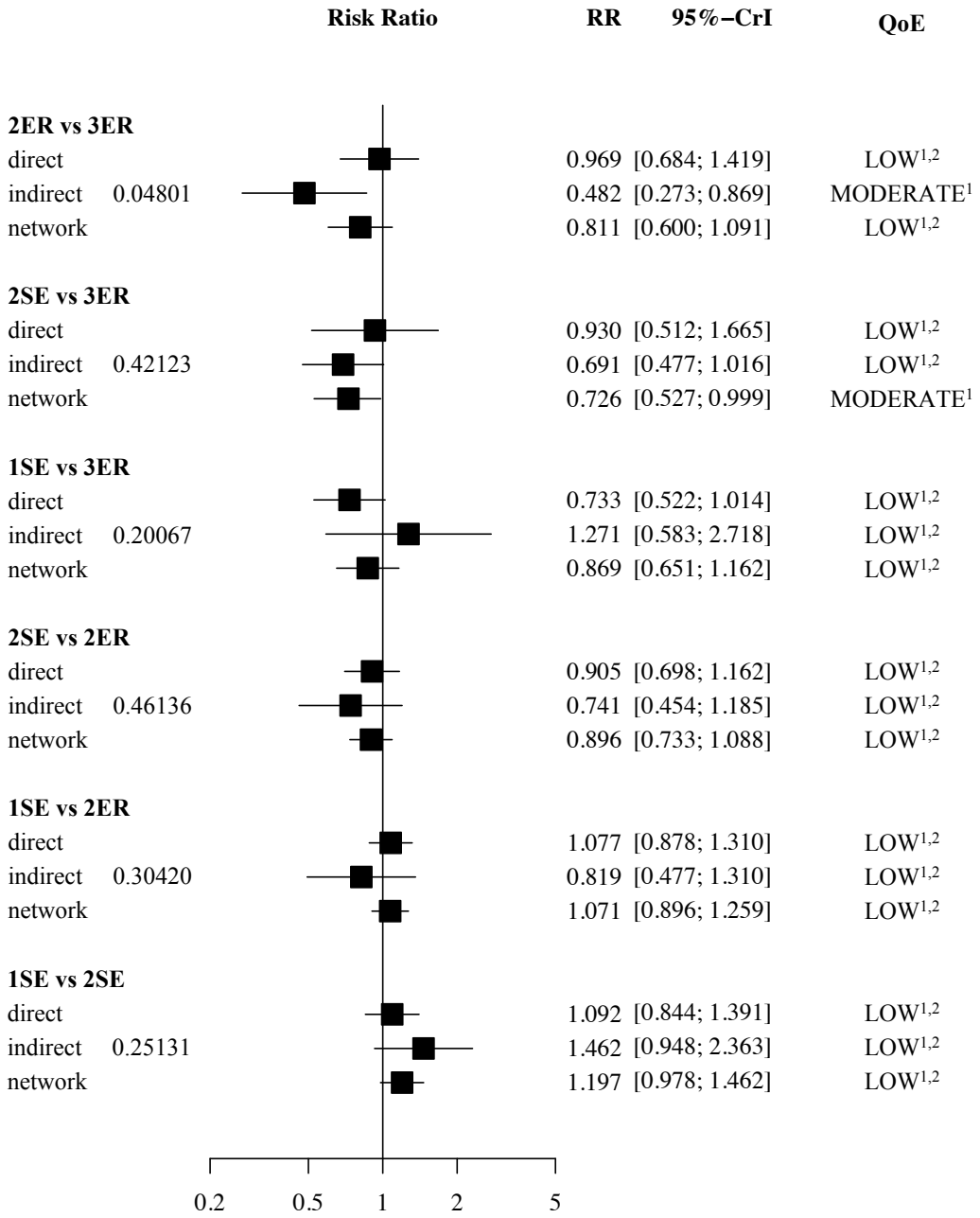


Figure 4.2.3 – Forest plot of direct, indirect and network evidence for retention rates at 12 to 24-month produced by the split node method. QoE – quality of evidence. [1]Most studies are at unclear risk of bias. [2]Imprecise estimatives.

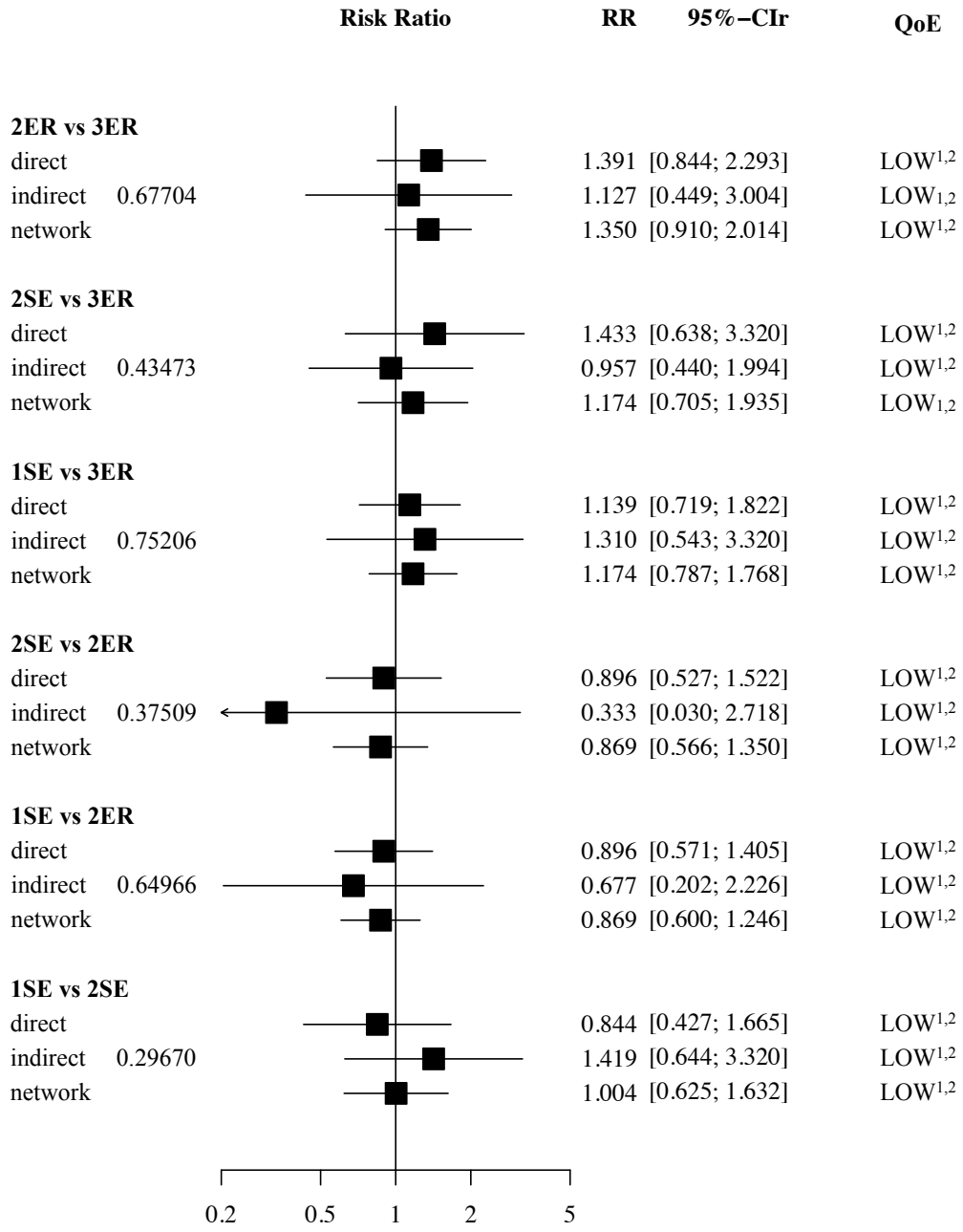


Figure 4.2.4 – Forest plot of direct, indirect and network evidence for retention rates at 36 to 48-month produced by the split node method. QoE – quality of evidence. [1]Most studies are at unclear risk of bias. [2]Imprecise estimatives.

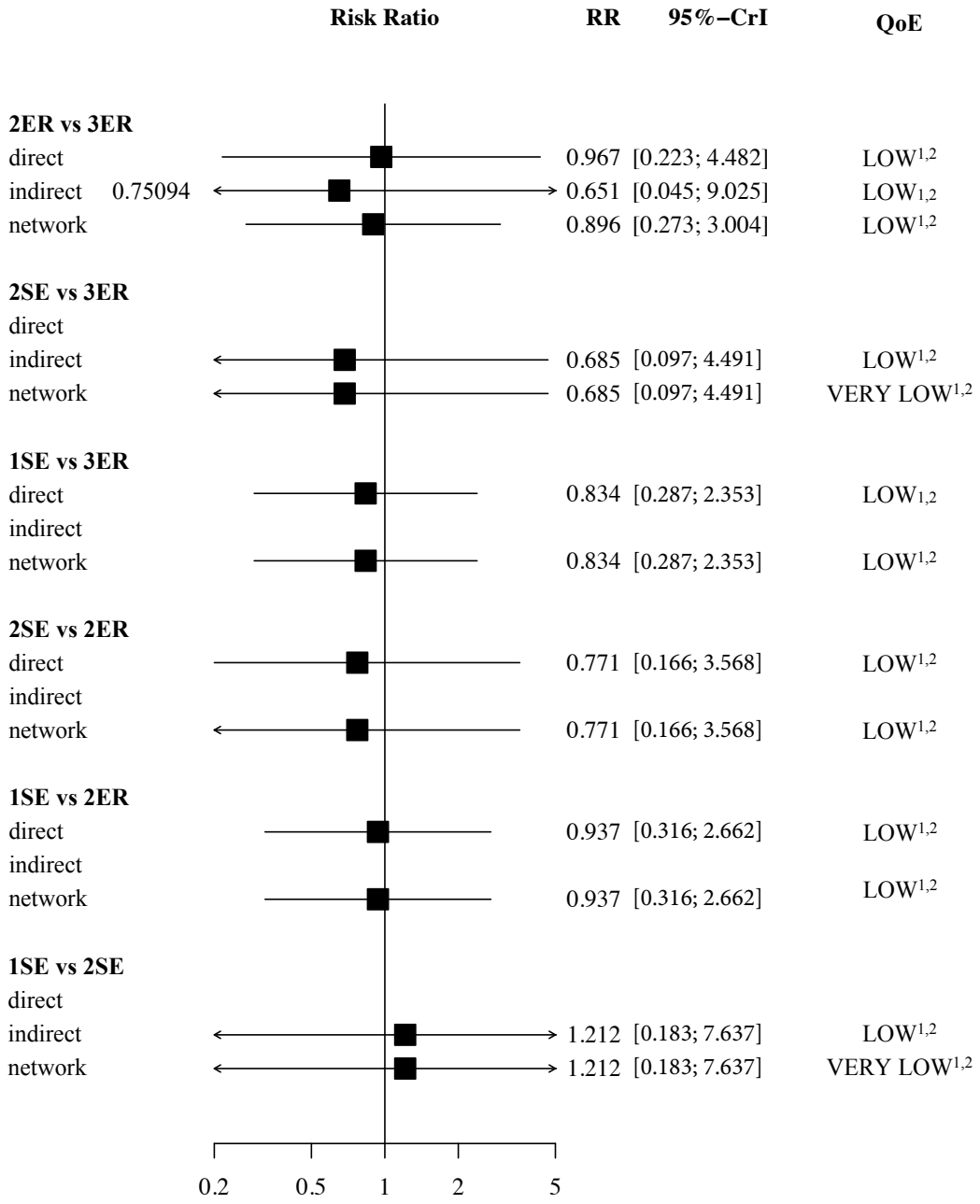
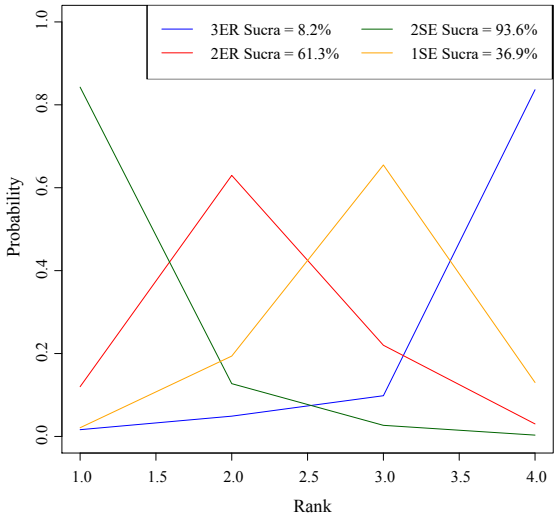
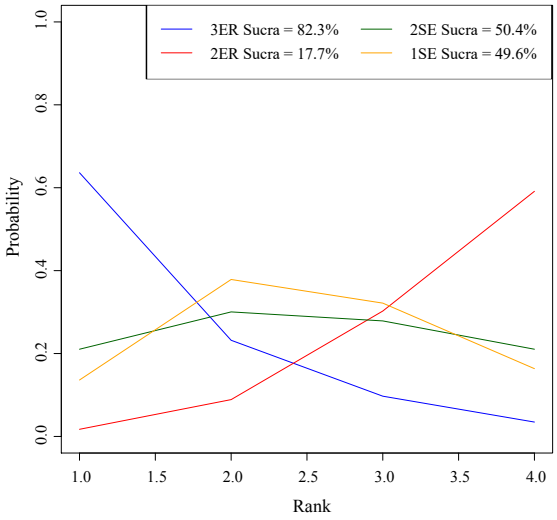


Figure 4.2.5 – Forest plot of direct, indirect and network evidence for retention rates at > 48-month produced by the split node method. QoE – quality of evidence. [1]Most studies are at unclear risk of bias. [2]Imprecise estimatives.

A) At 12 to 24-month



B) At 36 to 48-month



C) At > 48-month

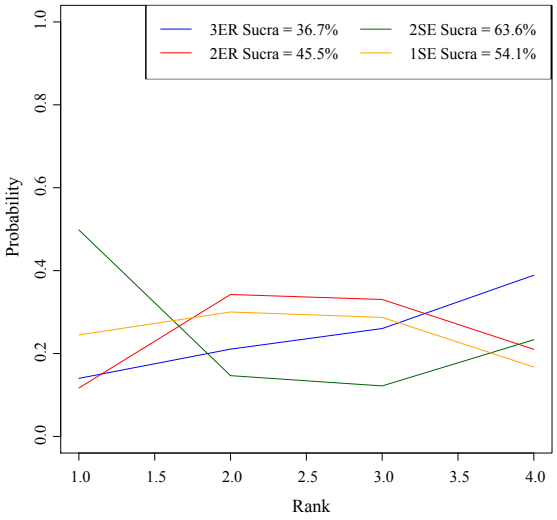
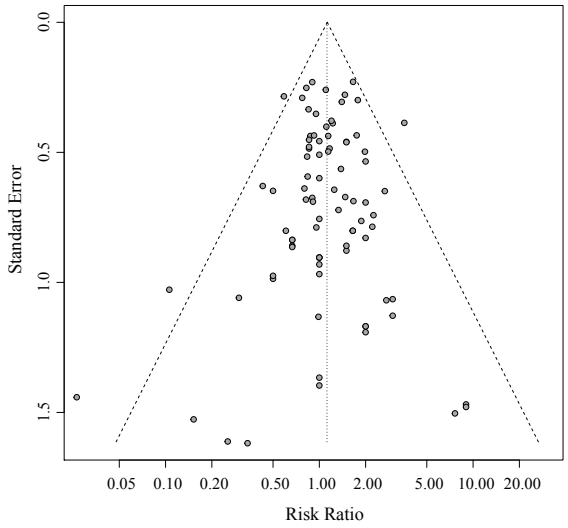
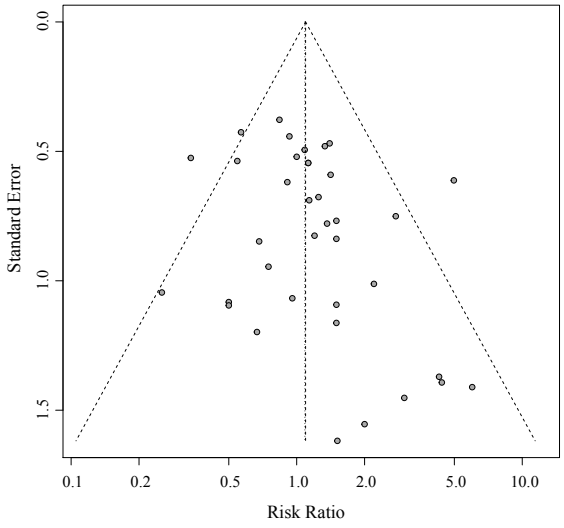


Figure 4.2.6 – Rankogram and SUCRA for loss of the retention showing the cumulative rank order for each adhesive strategy at 12 to 24-month (A), at 36 to 48-month (B) and > 48-month (C).

A) At 12 to 24-month



B) At 36 to 48-month



C) At > 48-month

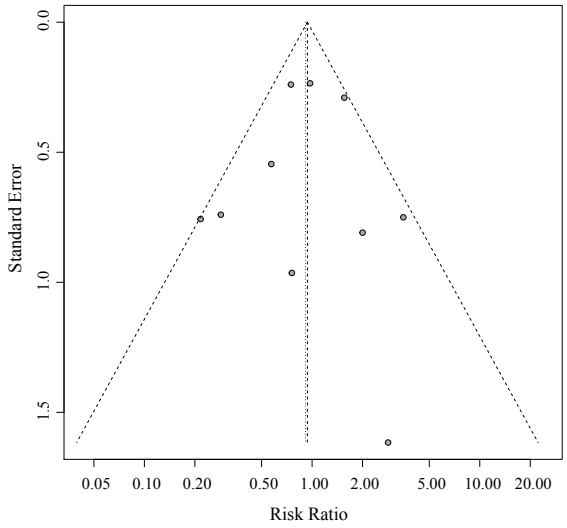


Figure 4.2.7 – Funnel plot of included studies at 12 to24-month (A), at 36 to 48-month (B) and at > 48-month (C).

SUPPLEMENTARY MATERIAL

ARTIGO 2 – Adhesive strategies in cervical lesions: systematic review and a network meta-analysis of randomized controlled trials

Table 4.2.1 Supplementary – Database search strategy.

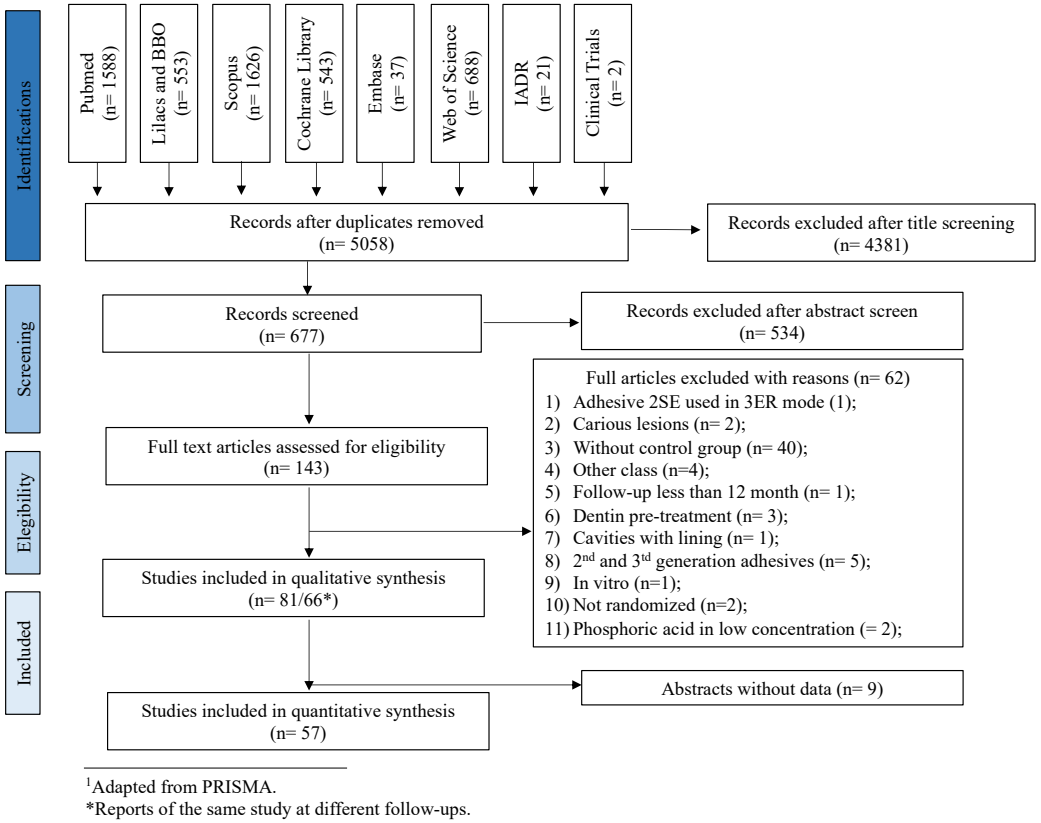
Database (Number of Papers: (5035)	**Search** (February 9, 2019 update on November 20, 2019).
PubMed (1588)	dental restoration, permanent[MeSH Terms] OR dentition, permanent[MeSH Terms] OR tooth erosion[MeSH Terms] OR tooth erosion*[Title/Abstract] OR tooth abrasion[MeSH Terms] OR tooth abrasion*[Title/Abstract] OR dental abrasion*[Title/Abstract] OR tooth cervix[MeSH Terms] OR tooth cervix[Title/Abstract] OR abfraction*[Title/Abstract] OR cervical lesion*[Title/Abstract] OR NCCL*[Title/Abstract] OR class V[Title/Abstract] OR class 5[Title/Abstract] AND dentin-bonding agents[Mesh Term] OR adhesive system*[Title/Abstract] OR bonding agent*[Title/Abstract] OR dental adhesive*[Title/Abstract] OR adhesive material*[Title/Abstract] OR "etch-and-rinse adhesive"[Title/Abstract] OR "etch-and-rinse adhesives"[Title/Abstract] OR "total-etch adhesive"[Title/Abstract] OR "total-etch adhesives"[Title/Abstract] OR "self-etch adhesive"[Title/Abstract] OR "self-etching adhesive"[Title/Abstract] OR "self-etch adhesives"[Title/Abstract] OR "self-etching adhesives"[Title/Abstract] OR "all-in-one adhesive"[Title/Abstract] OR "all-in-one adhesives"[Title/Abstract] OR "one-bottle adhesive"[Title/Abstract] OR "one-bottle adhesives"[Title/Abstract] OR "single-bottle adhesive"[Title/Abstract] OR "single-bottle adhesives"[Title/Abstract] OR universal adhesive*[Title/Abstract] OR "multi-mode adhesive"[Title/Abstract] AND randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial"[tw] OR singl*[tw] OR doubl*[tw] OR trebl*[tw] AND mask*[tw] OR blind*[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic
Scopus (1626)	"t??th erosion" OR "t??th abrasion" OR "dental abrasion" OR "t??th cervix" OR "abfraction*" OR "cervical lesion*" OR "NCCL*" OR "class V" OR "class 5" AND "dentin bonding agent" OR "adhesive system" OR "bonding agent" OR "dental adhesive" OR "adhesive material" OR "etch-and-rinse adhesive" OR "self-etch adhesive" OR "self-etching adhesive" OR "all-in-one adhesive" OR "one-bottle adhesive" OR "single-bottle adhesive" OR "universal adhesive" OR "multi-mode adhesive"
Cochrane Library (543)	#1 MeSH descriptor: [Dental Restoration, Permanent] explode all trees 1288 #2 MeSH descriptor: [Dentition, Permanent] explode all trees 65 #3 MeSH descriptor: [Tooth Erosion] explode all trees 222 #4 (tooth next erosion):ti,ab,kw (Word variations have been searched) 233 #5 MeSH descriptor: [Tooth Abrasion] explode all trees 124 #6 tooth next abrasion (Word variations have been searched) 132 #7 dental next abrasion (Word variations have been searched) 1 #8 MeSH descriptor: [Tooth Cervix] explode all trees 292 #9 tooth next cervix (Word variations have been searched) 306 #10 abfraction (Word variations have been searched) 18 #11 cervical next lesion (Word variations have been searched) 394 #12 NCCL? (Word variations have been searched) 84 #13 class next V (Word variations have been searched) 344 #14 class next 5 (Word variations have been searched) 47 #15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 1995

	#16 MeSH descriptor: [Dentin-Bonding Agents] explode all trees 937 #17 adhesive next system (Word variations have been searched) 505 #18 bonding next agent (Word variations have been searched) 1061 #19 dental next adhesive (Word variations have been searched) 297 #20 adhesive next material (Word variations have been searched) 160 #21 “etch-and-rinse adhesive” (Word variations have been searched) 117 #22 “total-etch adhesive” (Word variations have been searched) 53 #23 “self-etch adhesive” (Word variations have been searched) 356 #24 “all-in-one adhesive” (Word variations have been searched) 25 #25 “one-bottle adhesive” (Word variations have been searched) 36 #26 “single-bottle adhesive” (Word variations have been searched) 13 #27 “universal next adhesive” (Word variations have been searched) 38 #28 “multi-mode adhesive” (Word variations have been searched)3 #29 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 1314 #30 #15 AND #29 Total: 545 (-2 reviews) = 543
Web of Science (688)	TS= ("t*th erosion" OR "t*th abrasion" OR "dental abrasion*" OR "tooth cervix" OR "abfraction*" OR "cervical lesion*" OR "NCCL" OR "class V" OR "class 5") AND TS= ("dentin bonding agent*") OR TS= ("adhesive system*") OR TS= ("bonding agent*") OR TS= ("dental adhesive*") OR TS= ("adhesive material*") OR TS= ("etch-and-rinse adhesive") OR TS= ("etch-and-rinse adhesives") OR TS= ("total-etch adhesive") OR TS= ("total-etch adhesives") OR TS= ("self-etch adhesive") OR TS= ("self-etch adhesives") OR TS= ("self-etching adhesive") OR TS= ("self-etching adhesives") OR TS= ("all-in-one adhesive") OR TS= ("all-in-one adhesives") OR TS= ("one-bottle adhesive") OR TS= ("one-bottle adhesives") OR TS= ("single-bottle adhesive") OR TS= ("single-bottle adhesives") OR TS= ("universal adhsesive") OR TS= ("universal adhesives") OR TS= ("multi-mode adhesive")
LILACS (553)	mh:"dental restoration, permanent" OR "restauração dentária permanente" OR "restauración dental permanente" OR mh:"dentition, permanent" OR tw:"dentição permanente" OR "dentición permanente" OR mh:"tooth erosion" OR tw:"erosão dentária" OR tw:"erosión de los dientes" OR mh:"tooth abrasion" OR tw:"abrasão dentária" OR tw:"abrasión de los dientes" OR mh:"tooth cervix" OR tw:"colo do dente" OR tw:"cuello del diente" OR tw:abfrac* OR tw:"cervical lesions" OR tw:"lesões cervicais" OR tw:"lesiones cervicales" OR tw:nccls OR tw:lcncs OR tw:"class V" OR tw:"class 5" OR tw:"classe V" OR tw:"classe 5" AND mh:"dentin bonding agents" OR tw:"adesivos dentinários" OR tw:"recubrimientos dentinarios" OR tw:"adhesive systems" OR tw:"sistemas adesivos" OR tw:"sistemas adhesivos" OR tw:"bonding agents" OR tw:"agentes de união" OR tw:"agentes de unión" OR tw:"dental adhesives" OR tw:"adesivos dentais" OR tw:"adhesivos dentales" OR tw:"adhesives materials" OR tw:"materiais adesivos" OR tw:"materiales adhesivos" OR tw:"etch and rinse adhesives" OR tw:"adesivos convencionais" OR tw:"adhesivos convencionales" OR tw:"total etch adhesives" OR tw:"condicionamento ácido total" OR tw:"adhesivos de grabado total" OR tw:"self etch adhesives" OR tw:"adesivos autocondicionantes" OR tw:"adhesivos autocondicionantes" OR tw:"self etching adhesives" OR tw:"all in one adhesives" OR tw:"adesivos de passo único" OR tw:"one bottle adhesives" OR tw:"adesivos de frasco único" OR tw:"single bottle adhesives" OR tw:"universal adhesives" OR tw:"adesivos universais" OR tw:"multi mode adhesives"
Embase (37)	“tooth erosion” OR “tooth abrasion” OR “dental abrasion” OR “tooth cervix” OR abfraction OR “cervical lesion” OR NCCL OR “class V” OR “class 5” AND “dentin bonding agent” OR “adhesive system” OR “bonding agent” OR “dental adhesive” OR “adhesive material” OR “etch-and-rinse adhesive” OR “self-etch adhesive” OR “self-etching adhesive” OR “all-in-one adhesive” OR “one-bottle adhesive” OR “single-bottle adhesive” OR “universal adhesive” OR “multi-mode adhesive”

Table 4.2.2 Supplementary – Articles excluded and the reasons for exclusion (n=62).

Author year	Reasons for exclusion
1. Abdalla 2008(27)	Adhesive 2SE used in 3ER mode
2. Alhadainy 1996(28)	Carious lesions
3. Araújo 2015(29)	Without control group
4. Barcellos 2013(30)	Evaluated other class (III and IV)
5. Belluz 2005(31)	Without control group
6. Blunck 2007(32)	Follow-up less than 12 months
7. Burke 2017(33)	Evaluated other class (I and II)
8. Burrow 2008(34), Burrow 2012(35)	Without control group
9. Carvalho 2015(36)	Without control group
10. Çelik 2007(37)	Without control group
11. Çelik 2018(38)	Without control group
12. da Costa 2014(39)	Without control group
13. Duke 1991(40)	Without control group
14. Duke 1994(41)	Dentin pre-treatment
15. Estafan 1999(42)	Without control group
16. Fagundes 2015(43)	Without control group
17. Faye 2015(44)	Without control group
18. Folwaczny 2001(45)	Without control group
19. Fron 2011(44)	Without control group
20. Gallo 2005(46)	Without control group
21. Ghavamnasiri 2012(47)	Carious lesions
22. Hansen 1992(48)	Dentin pre-treatment
23. Heymann 1998(49)	Cavities with lining
24. Horsted-Bindslev 1988(50)	2nd and 3rd generation adhesive
25. Juloski 2015(51)	Without control group
26. Krejci 1990(52)	In vitro
27. Kina 2013(53)	Without control group
28. Kubo 2009(54)	Without control group
29. Kubo 2010(55)	Without control group
30. Kurokawa 2007(56)	Without control group
31. Loguércio 2011(57)	Without control group
32. Mccoy 1998(58)	Phosphoric acid etching at low concentrations
33. Merte 2000(59)	Without control group
34. Moretto 2013(60)	Without control group
35. Neo 1996(61)	Without control group
36. Oz 2018(62)	Without control group
37. Ozel 2010(63), Can Say 2014(64), Can Say 2014(65)	Without control group
38. Özkubat 2018(66)	Follow-up less than 12 months
39. Perdigão 2001(67), Perdigão 2005(68)	Without control group
40. Perdigão 2009(69)	Evaluated other class (I and II)
41. Platt 2014(70)	Without control group
42. Reis 2009(71)	Without control group

43. Ritter 2009(72)	Without control group
44. Sartori 2012(73)	Without control group
45. Schatemberg 2008(74)	Without control group
46. Smales1992(75)	Evaluated other class (IV)
47. Söderholm 2013(76)	Not randomized
48. Swift Jr 2001(77), Souza 2019(78), Souza 2019(79)	Without control group
49. Türkün 2008(80)	Without control group
50. Tyas 1988(81)	2nd and 3rd generation adhesive
51. Tyas 1994(82), Tyas 1996(83)	Phosphoric acid etching at low concentrations
52. van Dijken 2007(84)	2nd and 3rd generation adhesive
53. van Dijken 2008(85)	Not randomized
54. Van Meerbeek 1993(86)	Dentin pre-treatment
55. Van Meerbeek 1996(87)	2nd and 3rd generation adhesive
56. Van Meerbeek 2004(88), Peumans 2007(89)	Without control group
57. Van Meerbeek 2005(88), Peumans 2005(90), 2010(91), 2015(92)	Without control group
58. Vanherle 1991(93)	Without control group
59. Wilder 2009(8)	Without control group
60. Wilson 1995(94)	Without control group
61. Zander-Grande 2011(95)	Without control group
62. Zander-Grande 2014(96)	Without control group



[1]Adapted from PRISMA.
*Reports of the same study at different follow-ups.

Figure 4.2.8 Supplementary – Flowchart of studies included in the network meta-analysis.

Table 4.2.3 Supplementary – Summary of the descriptive characteristics of the primary studies included (n=66).

Study ID	Study design [setting]	Follow-ups (mth)	Subject's age mean ± SD [range] (yrs)	Groups: Type of adhesive -Adhesive brand [number of restorations per group]	Resin composite per group	Rubber dam	Enamel bevel/ Dentin prep	# of operators/ examinators	Evaluation criteria
Abdalla & Garcia-Godoy 2006(97)	Paired [n.r.]	12, 24	n.r. ± n.r. [35-52]	**2ER**- Admira Bond [65] **2SE**- Clearfil SE Bond [65] **1SE**- Hybrid Bond [65]	Clearfil AP-X	Yes	No/Yes	01/02	USPHS
Abdalla & Garcia-Godoy 2007(98)	Multiple restorations [n.r.]	Baseline, 12, 24	n.r. ± n.r. [18-44]	**2ER**- Futurabond NR [64] **1SE**- Futurabond NR [118]	Grandio	Yes	Yes/Yes	01/02	USPHS
Araújo 2013(99)	Paired [university]	6, 12	n.r. ± n.r. [23-54]	**3ER**- Scotchbond Multi-Purpose [31] **1SE**- Adper Easy One [31]	Filtek Z-350 XT	No	No/Yes	01/02	USPHS
Armstrong 2012(100)	Paired [university]	6, 12	n.r. ± n.r. [n.r.]	**3ER**- OptiBond FL [30] **1SE**- Tokuyama Bond Force [30]	Premise Estelite sigma Quick	No/Yes*	n.r./n.r.	n.r./n/r	USPHS
Atalay 2019(101)	Paired [university]	Baseline, 6, 12, 18, 24, 36	n.r. ± n.r. [27-81]	**2ER**- Single Bond Universal [55] **1SE**- Single Bond Universal [110]	Filtek Ultimate	No	Yes/n.r.	01/02	Modified USPHS
Aw 2004,(102) 2005(103)	Paired [university]	Baseline, 6, 12, 24, 36	51 ± n.r. [29-75]	**3ER**- Scotchbond Multi-Purpose [57] **2ER**- Single Bond [57] **2ER**- One Coat [57]	Silux Plus Synergy	No	Yes/No	02/02	Modified USPHS
Batalha-Silva 2009(104)	Paired [university]	Baseline, 6, 12	n.r. ± n.r. [n.r.]	**2ER**- Single Bond 2 [35] **2SE**- Clearfil Protect Bond [35]	Filtek Supreme	n.r.	n.r./n.r.	n.r./n.r.	n.r.
Bittencourt 2005,(105)Loguercio 2007(106)	Paired [university]	Baseline, 6, 12, 18, 36	35 ± n.r. [22-54]	**2ER**- Single Bond [39] **1SE**- Experimental EXM-618 [39]	Filtek A-110	Yes	No/No	02/02	Modified USPHS
Blunck 2013(107)	Paired [n.r.]	12, 24	n.r. ± n.r. [n.r.]	**1SE**- iBond [58] **1SE**- G-Bond [58] **1SE**- Clearfil S3 Bond [58] **3ER**- OptiBond FL [58]	CeramX-Duo	n.r.	No/No	02/n.r.	USPHS
Boushell 2016(108)	Multiple restorations [university]	6, 18, 36, 72	55.4 ± 9.5 [30-75]	**1SE**- Xeno IV [40] **1SE**- Xeno III [39] **2ER**- XP Bond [41]	TPH	No	No/Yes	06/02	Modified USPHS
Brackett 2005(109)	Paired [university]	Baseline, 6, 12, 18	52 ± n.r. [28-69]	**2SE**- Tyrian + One Step [38] **2ER**- One Step [38]	Renew	No	No/No	02/02	Modified Ryge/USPHS
Brackett 2010(110)	Paired [university]	Baseline, 6, 12, 24	n.r. ± n.r. [31-58]	**2SE**- Clearfil SE Bond [40] **1SE**- Clearfil S3 Bond [40]	AP-X	No	No/No	02/02	Modified Ryge/USPHS
Burgess 2013(111)	Paired [university]	Baseline, 6, 12, 24	n.r. ± n.r. [n.r.]	**1SE**- Adper Easy Bond [52] **2SE**- Scotchbond SE [52] **2ER**- Single Bond [52]	Filtek Supreme Plus	Yes	Yes/No	02/02	Modified USPHS
Burrow & Tyas 2007(112)	Multiple restorations [university]	6, 12, 24, 36	61 ± n.r. [n.r.]	**2ER**- Single Bond [30] **2SE**- Clearfil SE Bond [31]	Filtek A-110 Clearfil ST	n.r.	No/No	02/01	n.r.
Dalkilic e Omurlu 2012(113)	Multiple restorations [university]	Baseline, 3, 12, 24	n.r. ± n.r. [30-70]	**2ER**- Single Bond [60] **2SE**- Clearfil SE [72] **1SE**- Xeno III [60]	Filtek Supreme	No	No/Yes	01/01	Modified USPHS

Dall'orologio 2006,(114) 2008,(115) 2009,(116) 2010(117)	n.r. [n.r.]	Baseline, 6, 12, 18, 24, 36, 60, 78, 84	n.r. ± n.r. [n.r.]	**1SE-** iBond [n.r.] **1SE**- AQ Bond [n.r.] **3ER**- Optibond FL [n.r.]	Filtek Z-250	n.r.	n.r./n.r.	03/01	Modified USPHS
de Oliveira 2017(118)	Paired [university]	Baseline, 12, 24	n.r. ± n.r. [20-54]	**2ER**- Peak LC Bond [30] **2SE**- Clearfil SE Protect Bond [60]	Amelogen Plus	No	Yes/No	01/02	Modified USPHS
de Paula 2015(119)	Multiple restorations [university]	Baseline, 6, 12	n.r. ± n.r. [20->49]	**3ER**- OptiBond FL [46] **2ER**- OptiBond Solo Plus [44] **2SE**- OptiBond XTR [44] **1SE**- OptiBond All-in-one [46]	Filtek Supreme Ultra	Yes	No/No	04/02	FDI/Modified USPHS
Dutra-Correa 2013(120)	Paired [university]	Baseline, 6, 18	48.7 ± n.r. [27-79]	**2ER**- XP Bond [30] **1SE**- Xeno V [30]	Esthet X	No	No/No	04/02	FDI/Modified USPHS
Ermis 2012(121)	Multiple restorations [university]	Baseline, 6, 12, 24	50 ± 8.3 [39-79]	**1SE**- Clearfil S3 Bond [81] **3ER**- OptiBond FL [80]	Clearfil AP-X	No	Yes/Yes	01/02	Vanherle
Friedl 2004(122)	Paired [university]	24	n.r. ± n.r. [n.r.]	**1SE-** Prompt L-Pop [61] **3ER**- EBS [61]	Pertac 2	n.r.	n.r./n.r.	n.r./n.r.	Modified USPHS
Fu 2015(123)	Paired [university]	Baseline, 6, 12, 24, 36	n.r. ± n.r. [n.r.]	**2SE**- Adper Scotchbond SE [54] **1SE-** Easy Bond [54] **2ER**- Single Bond [54]	Filtek Supreme Plus	Yes	Yes/No	n.r./n.r.	Modified USPHS
Haak 2019(124)	Paired [university]	Baseline, 6, 12	65 ± 20.5 [43-84]	**1SE-** Scotchbond Universal [110] **3ER-** OptiBond FL [55]	Filtek Supreme XTE	No	Yes/Yes	01/01	FDI
Häfer 2015(125)	Multiple restorations [university]	Baseline, 6, 12, 24, 36	46.7 ± 14.1 [18-66]	**1SE**- Futurabond M [40] **2ER**- Solobond M [40] **3ER**- Syntac Classic [30]	Amaris Tetric EvoCeram	Yes	Yes/Yes	01/01	FDI
Helbig 2004(126)	Multiple restorations [n.r.]	Baseline, 6, 12, 24, 36	n.r. ± n.r. [n.r.]	**2ER**- Solobond M [46] **1SE**- Futurabond [43]	Arabesk Top	n.r.	n.r./n.r.	n.r./n.r.	Modified Ryge
Jang 2017(127)	Multiple restorations [university]	Baseline, 6, 12, 18, 24	55 ± n.r. [30-73]	**2SE**- Clearfil SE Bond [83] **1SE**- Xeno V [81]	Filtek Z-250	No	No/No	n.r./02	Modified FDI
Kim 2009(128)	Paired [university]	Baseline, 6, 12, 24	50 ± n.r. [34-65]	**3ER**- Scotchbond Multi-Purpose [50] **2ER**- EX [50] **1SE**- Adper Prompt [50]	DenFil	No	Yes/Yes	01/02	Modified USPHS
Kubo 2006(129)	Multiple restorations [university]	Baseline, 2, 6, 12, 24, 36, 48, 60	61.3 ± n.r. [45-78]	**2SE**- Clearfil Liner Bond II [37] **2ER**- Single Bond [35]	Clearfil AP-X	No	Yes/Yes	01/03	Modified USPHS
Lawson 2015,(130) Robles 2018(131)	Paired [university]	Baseline, 6, 12, 24, 36, 60	60.1 ± n.r. [n.r.]	**3ER**- Scotchbond Multi-Purpose [42] **2ER**- Scotchbond Universal [42] **1SE**- Scotchbond Universal [42]	Filtek Supreme Ultra	Yes	Yes/No	05/02	USPHS
Loguercio 2006,(132) 2008(133)	Paired [university]	Baseline, 6, 12, 18	38 ± n.r. [20-62]	**2ER**- One Step Plus [58] **2SE**- Tyrian + One Step Plus [58]	Micronew	Yes	No/No	02/02	Modified USPHS
Loguercio 2010(134)	Paired [university]	Baseline, 6, 12, 24	n.r. ± n.r. [20->49]	**1SE-** All Bond SE [33] **2SE-** All Bond SE [33]	Aelite	Yes	No/No	03/02	USPHS

Loguercio 2018(135)	Paired [university]	Baseline, 6, 18	38 ± n.r. [20-62]	**1SE-** Tetric N-Bond Universal [96] **2ER**- Tetric N-Bond Universal [96]	IPS Empress Direct	Yes	Yes/No	02/02	FDI/ USPHS
Lopes 2016, (136) Barceleiro 2018(137)	Paired [university]	Baseline, 6, 18	n.r. ± n.r. [n.r.]	**2ER**- Xeno Select [62] **1SE**- Xeno Select [62]	Evolux	n.r.	n.r./n.r.	n.r./n.r.	FDI
Matis 2004(138)	Paired [university]	Baseline, 6, 18, 36	45 ± n.r. [30-75]	**2SE-** FL Bond [20] **3ER**- Scotchbond Multi-Purpose [20]	Beautifil Silux Plus	Yes	Yes/No	n.r./n.r.	Modified USPHS
Matos 2019(139)	Paired [university]	Baseline, 6, 12, 18	49 ± 9 [20-60]	**2ER**- Ambar Universal [54] **1SE**- Ambar Universal [54]	Opallis	Yes	No/No	02/02	FDI/ Modified USPHS
Mena-Serrano 2013,(140) Perdigão 2014,(141) Loguercio 2015(142)	Paird [university]	Baseline, 6, 18, 36	n.r. ± n.r. [20->49]	**2ER**- Scotchbond Universal [100] **1SE**- Scotchbond Universal [100]	Filtek Supreme Ultra	Yes	No/No	04/02	FDI/ USPHS
Moosavi 2013(143)	Paired [university]	Baseline, 6, 12, 18	n.r. ± n.r. [20-50]	**3ER**- OptiBond FL [30] **2ER**- OptiBond Solo [30] **1SE**- OptiBond All-in-One [30]	Herculite XRV	No	No/No	01/02	USPHS
Mortazavi 2012(144)	Paired [university]	Baseline, 6, 9, 12	n.r. ± n.r. [30-60]	**2SE**- Clearfil SE Bond [12] **3ER**- OptiBond FL [12]	Grandio	Yes	Yes/No	n.r./02	USPHS
Oz 2019(145)	Multiple restorations [university]	Baseline, 6, 12, 24	49 ± n.r. [36-63]	**1SE**- Gluma Universal [41] **2ER**- Gluma Universal [22] **1SE**- All-Bond Universal [41] **2ER**- All-Bond Universal [22] **2ER**- Single Bond 2 [29]	Tetric N-Ceram	No	No/No	01/02	USPHS
Pavolucci 2010(146)	Paired [n.r.]	Baseline, 12	n.r. ± n.r. [n.r.]	**2ER**- Gluma Confort Bond [26] **1SE**- iBond [26]	n.r.	n.r.	n.r./n.r.	n.r./n.r.	Modified USPHS
Pena 2016(147)	Paired [university]	Baseline, 3, 6, 12, 18, 24	n.r. ± n.r. [n.r.]	**2SE**- Clearfil SE Bond [56] **1SE-** Xeno V [56]	Esthet X	No	Yes/No	01/02	Modified USPHS
Perdigão 2012,(148) Dutra-Correa 2015,(149) Dutra-Correa 2019(11)	Multiple restorations [university]	Baseline, 6, 18	47.6 ± n.r. [22-78]	**1SE**- Adper Easy Bond [34] **2SE**- Scotchbond SE [30] **2ER**- Single Bond Plus [32] **3ER**- Scotchbond Multi-Purpose [29]	Filtek Supreme Plus	No	No/No	n.r./02	Modified USPHS
Perdigão 2019(150)	Multiple [university]	Baseline, 18, 36	n.r. ± n.r. [27-77]	**3ER**- Scotchbond Universal + SBMP [34] **2ER**- Scotchbond Universal [34] **2SE**- Scotchbond Universal + SBMP [31] **1SE**- Scotchbond Universal [35]	Filtek Supreme XTE	No	n.r./n.r.	03/02	Modified USPHS
Qin 2013(151)	Multiple restorations [university]	Baseline, 6, 12, 24	44.1 ± n.r. [27-66]	**2SE**- Clearfil SE Bond [58] **1SE**- Adper Prompt [58]	Clearfil X Filtek Z-350	No	Yes/Yes	02/02	Modified USPHS
Reis 2009(152)	Paired [university]	Baseline, 6, 18	n.r. ± n.r. [20->49]	**1SE**- Clearfil S3 Bond [30] **2SE**-Clearfil S3 Bond + Bond SBMP [30] **1SE**- iBond [30] **2SE**- iBond + Bond SBMP [30]	Filtek Supreme Plus Universal	Yes	No/No	02/02	USPHS
Reis 2010(153)	Paired [university]	Baseline, 6, 12, 24	n.r. ± n.r. [20->49]	**2ER**- All Bond 3 [33] **3ER**- All Bond 3 [33]	Aelite	Yes	No/No	03/02	USPHS

Ritter 2008(154)	Multiple restorations [university]	Baseline, 6, 18, 36	55 ± n.r. [36-77]	**3ER**- Gluma Solid Bond [26] **1SE**- iBond [79]	Durafill VS	No/Yes*	Yes/Yes	06/02	USPHS
Ritter 2015(155)	Multiple restorations [university]	Baseline, 6, 18	n.r. ± n.r. [n.r.]	**2SE**- OptiBond XTR [41] **3ER**- OptiBond FL [42]	Herculite Ultra	Yes/No*	No/Yes	04/02	Modified USPHS
Ruschel 2018(156)	Multiple restorations [university]	Baseline, 18	42.6 ± 12.7 [21-67]	**2ER**- Scotchbond Universal [52] **1SE**- Scotchbond Universal [50] **2ER**- Prime & Bond Elect [50] **1SE**- Prime & Bond Elect [51]	Kalore	No	No/Yes	01/02	Modified USPHS
Sartori 2011(157)	Multiple restorations [university]	Baseline, 6, 18, 30	n.r. ± n.r. [n.r.]	**1SE**- Futurabond NR [30] **2ER**- Solobond M [33]	Polofil M	No	No/No	01/02	USPHS
Sartori 2013(158)	Paired [university]	6, 18	42 ± n.r. [22-68]	**1SE**- Adper Easy Bond [32] **2SE**- Adper Easy Bond + Bond SBMP [32]	Filtek Z-250	No	No/No	01/02	Modified USPHS
Scotti 2016(159)	Multiple restorations [university]	12, 24, 36	52.4 ± n.r. [32-63]	**1SE**- G-Bond [46] **3ER**- OptiBond FL [44]	Venus Diamond	Yes	Yes/Yes	02/02	Modified USPHS
Stojanac 2013(160)	Paired [university]	Baseline, 12, 24	n.r. ± n.r. [18-50]	**2ER**- Prime & Bond NT [30] **2SE**- AdheSE [30] **1SE**- Xeno III [30]	Esthet X TetricEvoCeram Dyract eXtra	No	No/No	01/n.r.	Modified USPHS
Tian 2014(161)	Paired [university]	Baseline, 6, 18	n.r. ± n.r. [n.r.]	**2ER**- Tetric N-Bond [50] **1SE**- Tetric N-Bond Self-etch [50]	Tetric N-Ceram	No	No/Yes	01/n.r.	Modified USPHS
Tuncer 2013(162)	Multiple restorations [university]	Baseline, 6, 12, 24	58 ± n.r. [38-73]	**2ER**- Solobond M [62] **1SE**- Futurabond NR [61]	Grandio	No	No/No	01/02	Modified USPHS
Türkün 2003(163)	Paired [university]	Baseline, 6, 12, 24	46 ± n.r. [26-60]	**2SE**- Clearfil SE Bond [49] **2ER**- Prime & Bond NT [49]	Clearfil AP-X TPH Spectrum	No	No/Yes	01/02	USPHS
Türkün 2005(164)	Multiple restorations [university]	Baseline, 3 6, 9, 12	44 ± n.r. [26-59]	**2SE**- Clearfil Protect Bond [85] **1SE**- Xeno III [78]	Esthet-X	No	No/No	01/01	USPHS
van Dijken 2000(165)	Multiple restorations [university]	Baseline, 6, 12, 18, 24, 30, 36	57 ± n.r. [29-88]	**3ER**- EBS [52] **2ER**- One Step [46]	Pertac Hybrid Prisma TPH	No	No/Yes	02/03	Modified USPHS
van Dijken 2004(166)	Multiple restorations [university]	Baseline, 6, 12, 18, 24	58 ± n.r. [46-72]	**2SE**- Clearfil Liner Bond 2 [46] **2ER**- One Coat [46] **1SE**- Prompt L-Pop [52]	Clearfil AP-X Synergy Pertac Hybrid	No	No/Yes	01/03	Modified USPHS
van Dijken 2010(10)	Multiple restorations [university]	Baseline, 6, 12, 18, 24, 36, 48, 60, 72, 84, 96	60.1 ± n.r. [42-84]	**2SE**- Clearfil SE Bond [55] **2ER**- PQ1 [64]	Tetric Ceram Point 4	No	No/Yes	01/03	Modified USPHS
van Dijken 2013(167)	Multiple restorations [university]	Baseline, 6, 12, 18, 24, 36, 48, 60	64.7 ± n.r. [39-84]	**1SE**- G-Bond [67] **3ER**- CFM [51] **2ER**- XP Bond [51]	Gradia Direct	No	No/Yes	01/02	Modified USPHS

Van Landuyt 2008,(168) 2011,(169) 2014,(170) Peumans 2018(171)	Multiple restorations [university]	Baseline, 6, 12, 24, 36, 60, 108	n.r. ± n.r. [20->80]	**1SE**- G-Bond [133] **3ER**- OptiBond FL [134]	Gradia Direct	No	Yes/Yes	02/02	Vanherle
Walter 2013(172)	Multiple restorations [university]	6, 18, 36	n.r. ± n.r. [n.r.]	**1SE**- Xeno III [n.r.] **1SE**- Xeno IV [n.r.] **2ER**- XP Bond [n.r.]	TPH	No	n.r./No	n.r./ 02	Modified USPHS
Yaman 2014(173)	Paired [university]	Baseline, 6, 12, 24, 36	45.12 ± n.r. [32-58]	**2SE**- Clearfil SE Bond [48] **2ER**- XP Bond [48]	Ceram X mono	No	Yes/Yes	02/02	Modified USPHS
Zanatta 2019(174)	Paired [university]	Baseline, 6, 12, 24	n.r. ± n.r. [<20->60]	**2ER**- Scotchbond Universal [38] **1SE**- Scotchbond Universal [38] **2ER**- Single Bond [38] **2SE**- Clearfil SE Bond [38]	Filtek Supreme	No	No/No	04/02	FDI
Zhou 2009(175)	Multiple restorations [university]	Baseline, 3, 6, 12	n.r. ± n.r. [n.r.]	**1SE-** Clearfil 3S Bond [124] **2SE**- Clearfil SE Bond [124] **1SE**- G-Bond [94]	Clearfil AP-X	Yes	Yes/Yes	n.r./02	Modified USPHS

Abbreviations: ID – Identification; mth – months; SD – standard deviation; yrs – years; # – number; n.r. – not reported; 3ER – three-step etch-and-rinse; 2ER – two-step self-etch; 2SE – two-step self-etch; 1SE – one-step self-etch; SBMP – Scotchbond Multi-Purpose; *Depending of access and location of the lesion; USPHS – United States Public Health Service.

Table 4.2.4 Supplementary – Influential analysis to 2ER vs. 3ER comparison.

Influential analysis (Random effects model)				
	RR 95%-CI	p-value	tau^2	I^2
Omitting Aw 2004	1.4741 [0.7422; 2.9276]	0.2677	0.3719	35.9%
Omitting de Paula 2015	1.5648 [0.8777; 2.7898]	0.1291	0.2368	28.8%
Omitting Hafer 2015	1.4808 [0.7711; 2.8435]	0.2383	0.3307	35.7%
Omitting Kim 2009	1.8169 [0.9746; 3.3872]	0.0603	0.1924	21.7%
Omitting Lawson 2015	1.6996 [0.9212; 3.1356]	0.0896	0.2517	30.4%
Omitting Moosavi 2013	1.5868 [0.8542; 2.9478]	0.1439	0.3059	36.1%
Omitting Perdigao 2012	1.7539 [1.0079; 3.0519]	0.0468	0.1428	20.4%
Omitting Perdigao 2019	1.6197 [0.8592; 3.0533]	0.1360	0.3082	35.1%
Omitting Reis 2010	1.4920 [0.8013; 2.7779]	0.2071	0.2981	35.1%
Omitting van Dijken 2000	1.2151 [0.7345; 2.0100]	0.4481	0.0000	0.0%
Omitting van Dijken 2013	1.5306 [0.8174; 2.8661]	0.1836	0.3165	36.6%
Pooled estimate	1.5648 [0.8777; 2.7898]	0.1291	0.2368	28.8%

Details on meta-analytical method:
- Mantel-Haenszel method
- DerSimonian-Laird estimator for tau^2

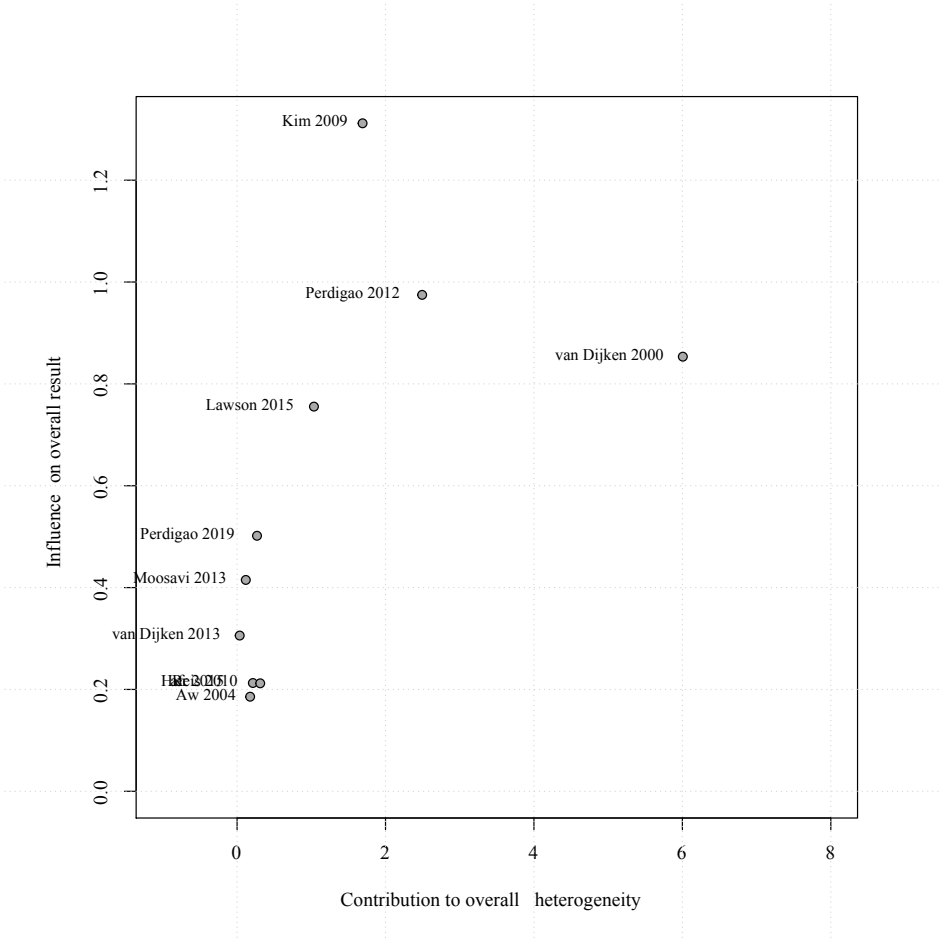


Figure 4.2.9 Supplementary – Baujat plot that evaluated heterogeneity.

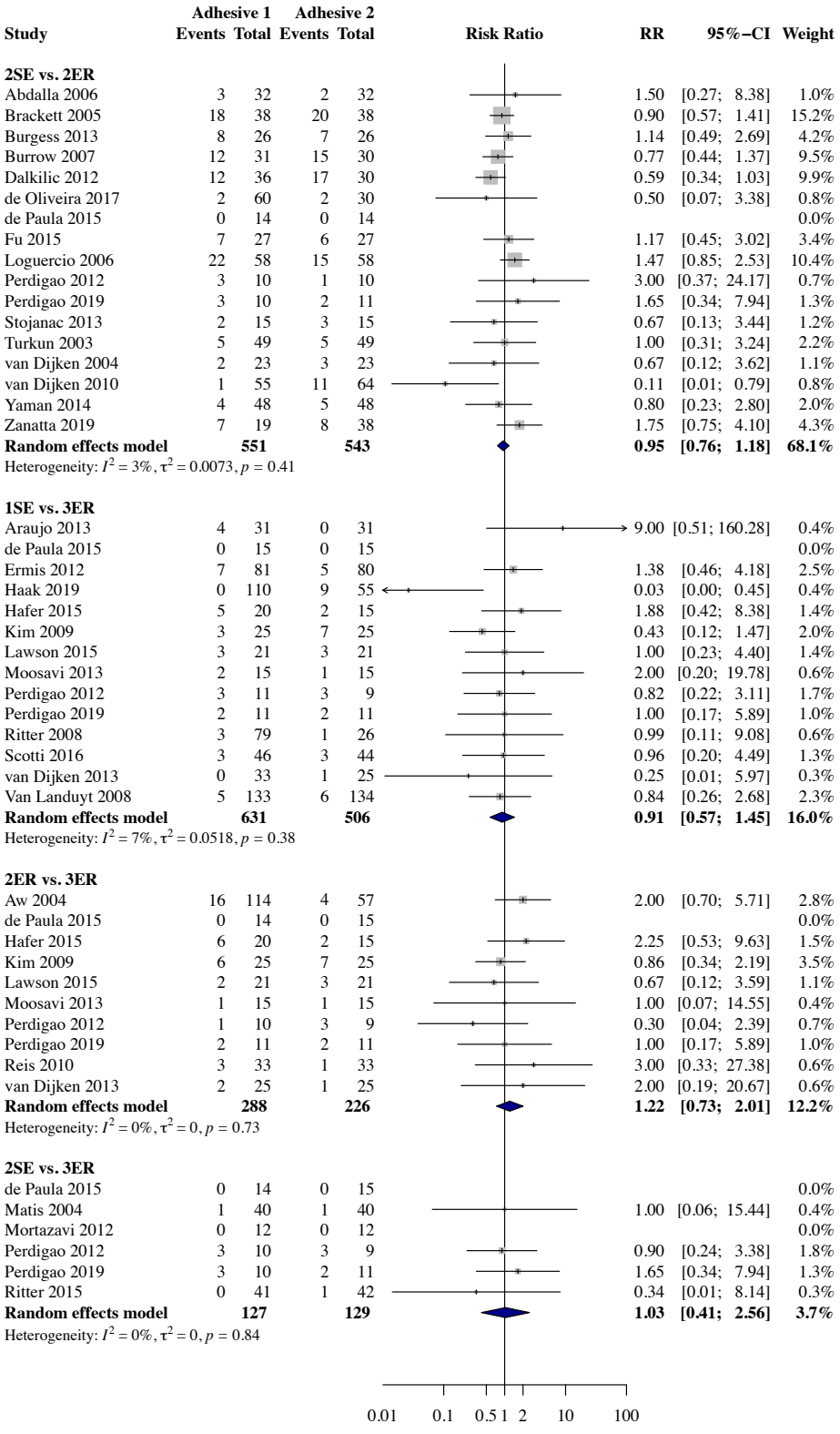


Figure 4.2.10 Supplementary – Forest plots of pairwise comparisons of loss of retention at 12 to 24-month.

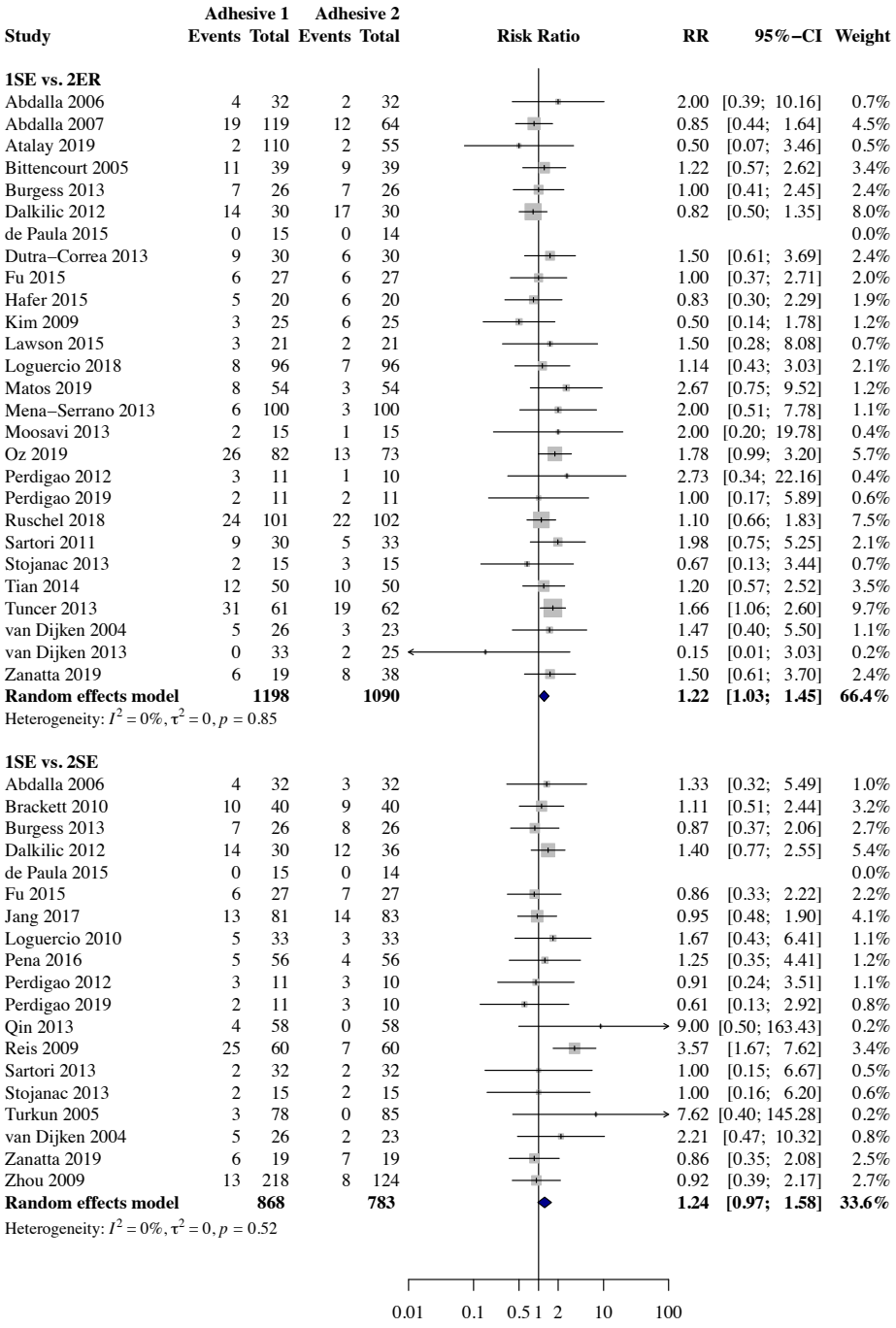


Figure 4.2.10 Supplementary – Continued.

Table 4.2.5 Supplementary – Heterogeneity between pair of comparisons from studies at 12 to 24-month.

	RR	tau^2	I^2
2ER X 3ER	1.2151	0.0000	0.0000
2SE X 3ER	1.0301	0.0000	0.0000
1SE X 3ER	0.9113	0.0000	0.0001
2SE X 2ER	0.9490	0.0228	9.5489
1SE X 2ER	1.2191	0.0019	0.8875
1SE X 2SE	1.2397	0.0289	8.8669

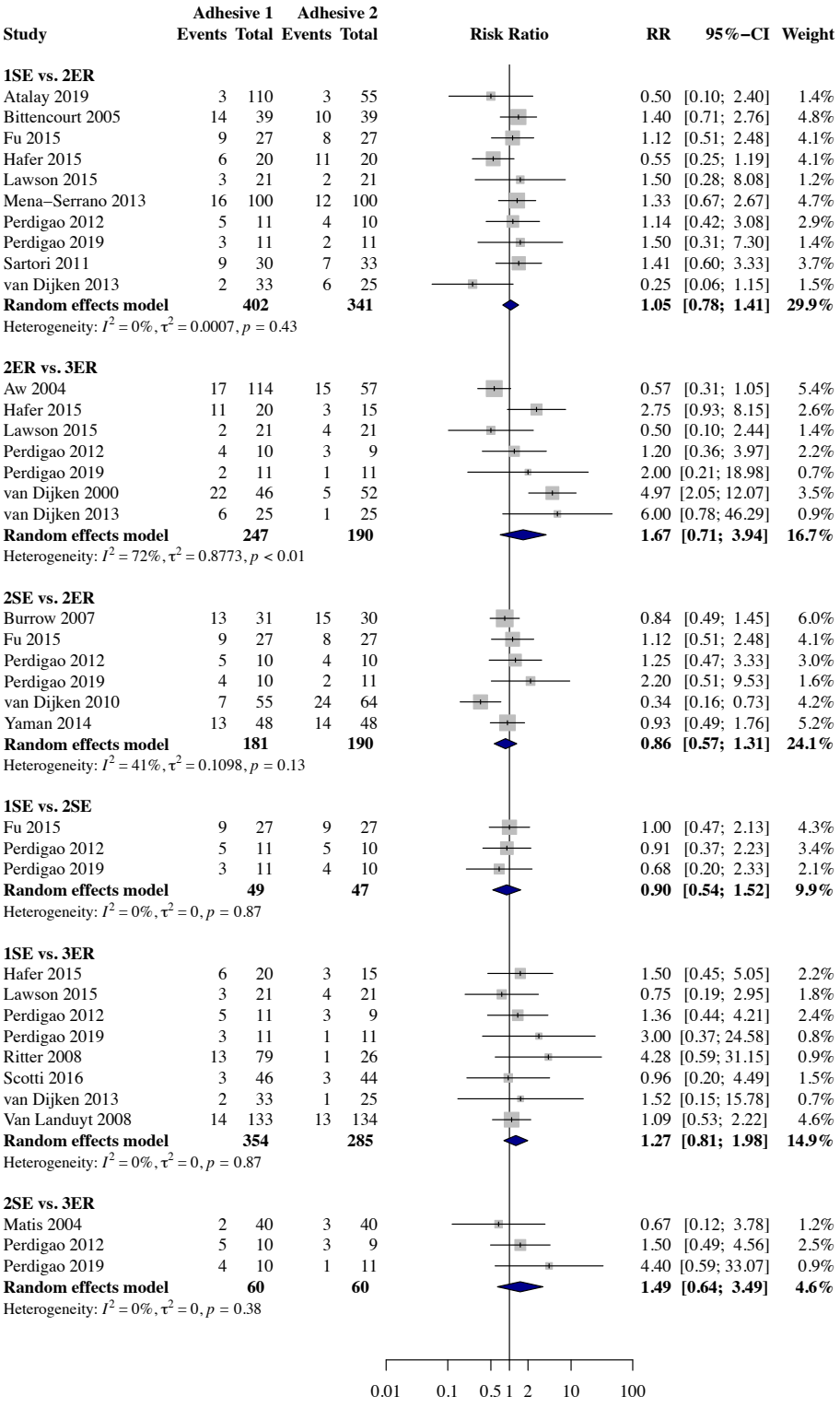


Figure 4.2.11 Supplementary – Forest plots of pairwise comparisons of loss of retention at 36 to 48-month.

Table 4.2.6 Supplementary – Heterogeneity between pair of comparisons from studies at 36 to 48-month.

	RR	tau^2	I^2
2ER X 3ER	1.6715	0.6664	66.6779
2SE X 3ER	1.4946	0.0000	0.0007
1SE X 3ER	1.2692	0.0000	0.0000
2SE X 2ER	0.8633	0.0956	38.0548
1SE X 2ER	1.0477	0.0000	0.0037
1SE X 2SE	0.9033	0.0000	0.0000

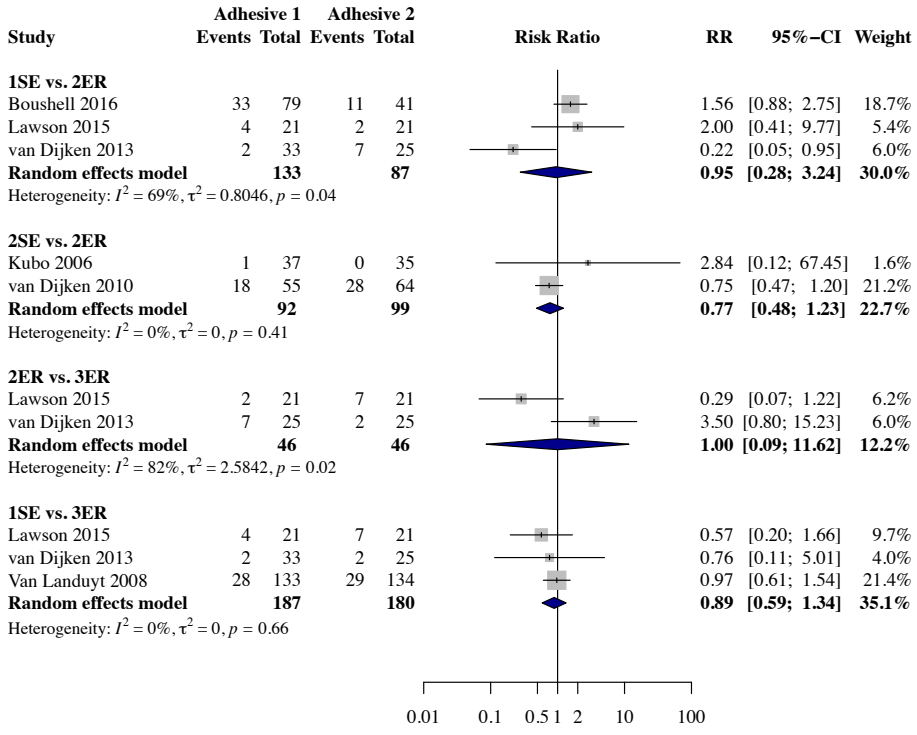


Figure 4.2.12 Supplementary – Forest plots of pairwise comparisons of loss of retention at > 48-month.

Table 4.2.7 Supplementary – Heterogeneity between pair of comparisons from studies at > 48-month.

	RR	tau^2	I^2
2ER X 3ER	0.9970	2.5836	82.3107
1SE X 3ER	0.8880	0.0000	0.0000
2SE X 2ER	0.7698	0.0000	0.0000
1SE X 2ER	0.9470	0.8713	70.4980

Table 4.2.8 Supplementary – Estimates of effects and quality ratings for comparison of bonding strategies for loss of retention in NCCLs.

Follow-up	Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
		RR (95% CrI)	QoE	RR (95% CrI)	QoE	RR (95% CrI)	QoE
12 to 24 months	**2ER vs 3ER**	0.969 (0.684; 1.419)	LOW[1,2]	0.482 (0.273; 0.869)	MODERATE[1]	0.811 (0.600; 1.091)	LOW[1,2]
	2SE vs 3ER	0.930 (0.512; 1.665)	LOW[1,2]	0.691 (0.477; 1.016)	LOW[1,2]	0.726 (0.527; 0.999)	MODERATE[1]
	1SE vs 3ER	0.733 (0.522; 1.014)	LOW[1,2]	1.271 (0.583; 2.718)	LOW[1,2]	0.869 (0.651; 1.162)	LOW[1,2]
	2SE vs 2ER	0.905 (0.698; 1.162)	LOW[1,2]	0.741 (0.454; 1.185)	LOW[1,2]	0.896 (0.733; 1.088)	LOW[1,2]
	1SE vs 2ER	1.077 (0.878; 1.310)	LOW[1,2]	0.819 (0.477; 1.310)	LOW[1,2]	1.071 (0.896; 1.259)	LOW[1,2]
	1SE vs 2SE	1.092 (0.844; 1.391)	LOW[1,2]	1.462 (0.948; 2.363)	LOW[1,2]	1.197 (0.978; 1.462)	LOW[1,2]
36 to 48 months	**2ER vs 3ER**	1.391 (0.844; 2.293)	LOW[1,2]	1.127 (0.449; 3.004)	LOW[1,2]	1.350 (0.910; 2.014)	LOW[1,2]
	2SE vs 3ER	1.433 (0.638; 3.320)	LOW[1,2]	0.957 (0.440; 1.994)	LOW[1,2]	1.174 (0.705; 1.935)	LOW[1,2]
	1SE vs 3ER	1.139 (0.719; 1.822)	LOW[1,2]	1.310 (0.543; 3.320)	LOW[1,2]	1.174 (0.787; 1.768)	LOW[1,2]
	2SE vs 2ER	0.896 (0.527; 1.522)	LOW[1,2]	0.333 (0.030; 2.718)	LOW[1,2]	0.869 (0.566; 1.350)	LOW[1,2]
	1SE vs 2ER	0.896 (0.571; 1.405)	LOW[1,2]	0.677 (0.202; 2.226)	LOW[1,2]	0.869 (0.600; 1.246)	LOW[1,2]
	1SE vs 2SE	0.844 (0.427; 1.665)	LOW[1,2]	1.419 (0.644; 3.320)	LOW[1,2]	1.004 (0.625; 1.632)	LOW[1,2]
> 48 months	**2ER vs 3ER**	0.967 (0.223; 4.482)	LOW[1,2]	0.651 (0.045; 9.025)	LOW[1,2]	0.896 (0.273; 3.004)	LOW[1,2]
	2SE vs 3ER	--	--	0.685 (0.097; 4.491)	LOW[1,2]	0.685 (0.097; 4.491)	VERY LOW[1,2,3]
	1SE vs 3ER	0.834 (0.287; 2.353)	LOW[1,2]	--	--	0.834 (0.287; 2.353)	LOW[1,2]
	2SE vs 2ER	0.771 (0.166; 3.568)	LOW[1,2]	--	--	0.771 (0.166; 3.358)	LOW[1,2]
	1SE vs 2ER	0.937 (0.316; 2.662)	LOW[1,2]	--	--	0.937 (0.316; 2.662)	LOW[1,2]
	1SE vs 2SE	--	--	1.212 (0.183; 7.637)	LOW[1,2]	1.212 (0.183; 7.637)	VERY LOW[1,2,3]

CI: Confidence interval; **RR:** Risk ratio;
QoE: Quality of Evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4.2.1.1 Explanations: 1. Risk of bias: most eligible studies are at unclear risk of bias; 2. Imprecision: Wide confidence interval that includes the null effect; 3. Indirectness: Information provided only by indirect evidence

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4.3 ARTIGO 3: CHALLENGING THE CONCEPT THAT OPTIBOND FL AND CLEARFIL SE BOND ARE GOLD STANDARD ADHESIVES: A SYSTEMATIC REVIEW AND META-ANALYSIS

STATUS: ACEITO.

REVISTA: OPERATIVE DENTISTRY.

ARTIGO 3 – Challenging the concept that OptiBond FL and Clearfil SE Bond are gold standard adhesives: A systematic review and meta-analysis

Short Title: “Gold standard” adhesives: meta-analysis

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PROSPERO acknowledgement of receipt: (158813)

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Conflict of interest: The authors declare no conflict of interest of any kind related to this study.

Source of funding: This study was partially supported by the National Council for Scientific and Technological Development of the Brazilian Government under grants 304105/2013-9 and 305588/2014-1.

ABSTRACT

Purpose: The following PICO question was proposed: “Are retention rates of composite resin restorations in NCCLs when using adhesives considered “gold-standard” (OptiBond FL and Clearfil SE Bond) are higher than those obtained with other adhesives brands”?

Materials and methods: A search were performed in February 2019 (updated in November 2019) in the PubMed/MEDLINE, EMBASE, LILACS, BBO, Web of Science, Cochrane Library, Grey Literature and IADR abstracts (1990-2018); unpublished and ongoing trial registries, dissertations and theses were also searched. Only randomized clinical trials (RCTs) that compared either OptiBond FL or Clearfil SE Bond adhesive with other commercially available adhesives were considered. The risk of bias (RoB) was applied by using the Cochrane Collaboration tool. A meta-analysis was performed for retention rates at different follow-up times using a random effects model for both adhesives. Heterogeneity was assessed with the Cochran Q test and I2 statistics. GRADE assessed the quality of evidence.

Results: After removal of duplicates and non-eligible articles, 25 studies remained for qualitative synthesis as one study was common to the two adhesives, of which 9 studies were used for the OptiBond FL meta-analysis and 14 for the Clearfil SE Bond meta-analysis. No significant differences were observed for retention rates in follow-up periods of 12 to 24 months ($p = 0.97$), 36 to 48 months ($p = 0.72$) or 108 to 156 months ($p = 0.73$) for OptiBond FL; and for 12 to 24 months ($p = 0.10$) and 36 to 48 months ($p = 0.17$) for Clearfil SE Bond. A significant difference was only found for OptiBond FL at 60 to 96 months ($p = 0.02$), but only 3 studies were included in this meta-analysis.

Conclusions: There is no evidence that OptiBond FL and Clearfil SE Bond have higher retention rates than competitive adhesives brands with which they have been compared in RCTs conducted in NCCLs.

Clinical significance: The concept of gold standard dental materials should be reevaluated. There is no evidence in the literature to support the fact that OptiBond FL and Clearfil SE Bond are better than other materials.

Keywords: Dentin-bonding agents. Clinical effectiveness. Non-carious cervical lesions. OptiBond FL. Clearfil SE Bond. Systematic review

INTRODUCTION

Two different bonding strategies can be used in adhesive procedures: the etch-and-rinse technique (ER) and the self-etch (SE) approach. ER adhesives require the previous demineralization of the dental substrates with a 32% to 40% phosphoric acid etchant, followed by a primer and a bonding resin. If the primer and the bonding resin are separate steps, the adhesive is called a 3-step ER system. If the priming and bonding are combined, the adhesive is called a 2-step ER system.

The SE approach does not require a separate conditioning step, as the adhesive is theoretically capable of demineralizing and infiltrating the dental substrates simultaneously.[1] In the 2-step SE approach, an acidic primer is applied before the application of a bonding resin, whereas, in the 1-step SE approach, the contents of the acidic primer and bonding resin are combined in a single-application solution.

From a clinical perspective, it is important to know which type of adhesive can provide the best performance. Systematic reviews have been published attempting to categorize the efficacy of the adhesive systems based on their bonding strategy and number of steps.[2-7] However, all material brands for each bonding strategy were grouped together, ignoring the fact that the efficacy of any adhesive depends on the material's composition, with some of them performing better than others in each bonding strategy.

Among the 3-step ER systems, the adhesive from Kerr Corp, named OptiBond FL (Kerr Corp; Orange, USA), has been considered the gold standard material by many researchers[8-11] because of its good performance in immediate and long-term bond strength tests.[12] Some authors claim that the presence of glycerol phosphate dimethacrylate,[13] which can interact chemically with the hydroxyapatite and the highly filled bonding resin layer (48 wt%) over the primed dental surfaces are responsible for this good performance.

As for as the self-etch strategy, the adhesive Clearfil SE Bond from Kuraray (Tokyo, Japan) is the one considered to be the gold standard material.[10, 14] This recognition was achieved because of the high bond strength values obtained in immediate and aged bonded interfaces.[7, 15, 16] The presence of the 10-MDP monomer, which produces a strong and stable chemical bond and which is less susceptible to degradation, is held to be the main factor in the good performance of this adhesive brand.[17-19]

If these materials are the gold standard, they should be better than other adhesive brands. Therefore, the aim of this systematic review and meta-analysis was to evaluate whether evidence from randomized clinical trials (RCTs) supports the designation of these products as gold standard materials. The following focused research question was posed based on the PICO acronym (P - participant, I - intervention, C - comparator and O - outcome): "Are the retention rates of composite resin restorations in non-carious cervical lesions better when "gold-standard" (OptiBond FL or Clearfil SE Bond) adhesives are used compared with other brands?"

MATERIAL AND METHODS

Protocol and registration

This study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO acknowledgement of receipt: 158813) and followed the

recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[20, 21]

Information Sources and Search Strategy

A search strategy for MEDLINE via PubMed based on the concepts of participant and intervention of the focused PICO question (described at the end of the introduction section) was elaborated. The strategy was adapted to other electronic databases (EMBASE, Cochrane Library, LILACS) and citation databases (Scopus and Web of Science). We did not restrict studies based on publication date and/or language.

Additionally, grey literature was investigated by searching the abstracts of the annual conference of the International Association for Dental Research (IADR) and its regional divisions (1990-2018), the database System for Information on Grey Literature in Europe and dissertations and theses using the ProQuest Dissertations and Theses full-text database as well as the Periódicos Capes Theses database.

Ongoing studies were searched in the following clinical trial registries: Current Controlled Trials (www.controlled-trials.com), International Clinical trials registry platform (http://apps.who.int/trialsearch/), Clinical Trials Register (http://www.clinicaltrials.gov), ReBEC (www.rebec.gov.br) and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). Additionally, we hand-searched the reference lists of all primary and eligible studies of this systematic review for additional relevant publications. The first two pages of the related articles link of each primary study in the PubMed database were also examined.

Eligibility Criteria

We included only randomized clinical trials (RCTs) that compared the retention rates of the 2 so-called gold standard adhesives OptiBond FL or Clearfil SE Bond with other adhesives brands. Studies were excluded if 1) adhesives did not follow the manufacturer's specifications and 2) a comparative adhesive was not included.

Study Selection and Data Collection Process

The articles retrieved by the literature search were evaluated in 3 phases. All studies were initially scanned for relevance by title, and the abstracts of those that were not excluded at this stage were appraised. The next step included the abstract reading, and those articles not excluded had their full text retrieved for further evaluation. The full texts were then read by 2 reviewers (F.D.S.D. and A.B.) to definitively check whether they met the inclusion criteria. Finally, the eligible articles received a study identification (ID) by combining first author and year of publication.

The data were extracted using a standardized form in Excel 2016 (Microsoft; Redmond, WA, USA). Two reviewers independently abstracted information about the intervention from the included articles, including study design, participants, adhesives and composite resin types, mode of isolation of the operative field, cavity preparation (enamel beveling and dentin roughening) and number of examiners/operators and evaluation criteria. In case of disagreement, a decision was reached by consulting a third reviewer. Another worksheet containing the study identification and the outcomes per adhesive group at different follow-up periods was also prepared. If there were multiple reports of the same study (i.e., reports with different follow-up times), data from all reports were extracted directly into a single data-collection form to avoid overlapping data.

Risk of Bias in Individual Studies

The risk of bias of the eligible studies was evaluated by 2 independent reviewers by using the Cochrane Collaboration tool for assessing the risk of bias in RCTs (RoB version 1.0).[22] Disagreements were resolved by discussion.

We evaluated whether the randomization sequence and allocation concealment were adequate. Additionally, we evaluated whether blinding was implemented for participants, personnel and outcomes assessment. Evidence of incomplete outcome data and selective reporting of outcomes was also checked. At the study level, they were judged to be at low risk of bias if all domains were judged to be at low risk of bias.

Summary Measures and Synthesis of the Results

The main outcome evaluated was retention rate, and the meta-analysis was performed using the Meta package of the software R. Analyses were carried out by using the random-

effect model, and pooled-effect estimates were obtained by comparing the retention ratios of OptiBond FL and Clearfil SE Bond with those from other commercial brands of adhesives. We estimated the overall risk ratio (RR) for this binary outcome, presenting their 95% confidence intervals (CI) at different follow-up periods for each adhesive. Data from OptiBond FL and Clearfil SE Bond were summarized into the following follow-ups: 12 to 24 months and 36 to 48 months. For the OptiBond FL, additional follow-ups (60 to 96 months and 108 to 156 months) were evaluated as these data were available. In case a study reported data twice within the range described above, data from the longest follow-up period were used.

Data were extracted using intention-to-treat analysis by using the total number of failures to each treatment arm each follow-up as the nominator and the total number of participants randomized at baseline as the denominator, wherever trial reporting allowed. When trials had more than one adhesive brand being compared with the gold standards, they were included in the meta-analysis separately to provide more than one effect size; however, as in these situations, data from the control group were used more than once, the number of events and the total number of participants were divided among the comparisons to avoid a misleading overpowering of the estimates.[23]

Trials have used several outcome measures: in those applying Vanherle, U.S. Public Health Service or FDI World Dental Federation criteria, we dichotomized Alfa vs. Bravo/Charlie, and these last two were counted as failures.

Only studies classified at low or unclear risk of bias were meta-analyzed. Heterogeneity was evaluated using the Cochran Q test and I2 statistics. The 95% prediction interval was calculated in all meta-analyses with at least 5 studies. Sensitivity analyses were also conducted to investigate the reasons for high heterogeneity whenever detected.

Assessment of the Quality of Evidence using GRADE

The quality of the evidence was graded for each outcome across studies (body of evidence) using the Grading of Recommendations: Assessment, Development and Evaluation (GRADE) (http://www.gradeworkinggroup.org/). This technique allowed determination of the overall strength of evidence for each meta-analysis.[24] The GRADE grades the evidence into 4 levels: very low, low, moderate and high. The “high quality” level suggests high confidence that the true effect lies close to the estimate of the effect. At the other extreme, “very low

quality" suggests very low confidence in the effect estimate, and the estimate reported can be substantially different from what was measured.

For RCTs, the GRADE approach addresses 5 reasons (risk of bias, imprecision, inconsistency, indirectness of evidence and publication bias) for possibly rating down the quality of the evidence by 1 or 2 levels. Each of these aspects was assessed as having "no limitation" (0); "serious limitations" (1 level downgraded) and "very serious limitations" (2 levels downgraded). The GRADEpro Guideline Development Tool, available online (www.gradepro.org), was used to create a summary-of-findings table as suggested in the Cochrane Handbook for Systematic Reviews of Interventions.

RESULTS

Study Selection

The search strategy was conducted initially on February 9, 2019 and was updated on November 20, 2019. A total of 5058 publications were retrieved in all databases. After database screening and duplicate removal, 689 studies were identified, 155 of which were retrieved for further assessment because they appeared to be relevant. A flowchart outlining the study selection process according to the PRISMA Statement[25] can be seen in Figure 1. Of these, 122 were not included for various reasons (Supplementary Table 2), leaving 33 eligible RCTs. From these 33 articles, 8 studies[9, 26-32] reported the same study sample at different follow-ups and therefore received the same study ID. Therefore, 25 studies were eligible for inclusion, with one study being common for both adhesives.[33]

Characteristics of the Included Studies

The characteristics of the 25 eligible studies are listed in Table 4.3.1. Most studies performed multiple restorations per participant and only one did not report this information.[33] OptiBond FL was compared with 8 different commercial brands of adhesives in the eligible studies as follows:

- Clearfil S3 Bond (Kuraray; Tokyo, Japan);[34]
- Clearfil SE Bond (Kuraray; Tokyo, Japan);[35]
- G-Bond (GC; Tokyo, Japan);[36, 37]

- OptiBond All-in-One (Kerr; Orange, USA);[38, 39]
- OptiBond Solo Plus (Kerr; Orange, USA);[38, 39]
- OptiBond XTR (Kerr; Orange, USA);[38, 40]
- PermaQuick (Ultradent; UT, USA);[41]
- Scotchbond Universal (3M ESPE; MN, USA).[42]

The adhesive Clearfil SE Bond was compared with 14 different commercial brands as described below:

- AdheSE (Ivoclar Vivadent; Schaan, Liechtenstein);[43]
- Admira Bond (Voco; Cuxhaven, Germany);[44]
- Adper Prompt (3M ESPE; MN, USA);[45]
- Clearfil S3 Bond (Kuraray; Tokyo, Japan);[46]
- G-Bond (GC; Tokyo, Japan);[47]
- Hybrid Bond (Sun Medical; Shiga, Japan);[44]
- OptiBond FL (Kerr; Orange, USA);[35]
- PQ1 (Ultradent; UT, USA);[48]
- Prime & Bond NT (Dentsply/De Trey; Konstanz, Germany);[49]
- Scotchbond Universal (3M ESPE; MN, USA);[50]
- Single Bond (3M ESPE; MN, USA);[50-52]
- Xeno III (Dentsply/DeTrey, Konstanz, Germany);[52]
- Xeno V (Dentsply/ DeTrey, Konstanz, Germany)[53, 54] and
- XP-Bond (Dentsply/ DeTrey, Konstanz, Germany).[55]

Most of the composite resins used were microhybrids, nanohybrids or nanofilled composite resins. The following commercial brands were used: Premise (Kerr; Orange, USA),[56] Estelite Sigma Quick (Tokuyama; Tokyo, Japan),[56] CeramX-Duo (Dentsply/ DeTrey; Konstanz, Germany),[57] Filtek Z-250 (3M ESPE; MN, USA),[33, 43, 53] Filtek Supreme Ultra (3M ESPE; MN, USA),[38] Clearfil AP-X (Kuraray; Tokyo, Japan),[34, 44-47, 49] Filtek Supreme XTE (3M ESPE; MN, USA),[42] Herculite XRV (Kerr; Orange, USA),[39] Grandio (Voco; Cuxhaven, Germany),[35] Herculite Ultra (Kerr; Orange, USA),[40] Venus Diamond (Kulzer; Hanau, Germany),[36] Gradia Direct (GC; Tokyo, Japan),[37] Amelogen Hybrid (Ultradent; UT, USA),[41] Amelogen Microfill (Ultradent; UT, USA),[41] Prodigy (Kerr; Orange, USA),[41] Filtek A-110 (3M ESPE; MN. USA),[51] Clearfil ST (Kuraray; Tokyo, Japan),[51] Filtek Supreme (3M ESPE, MN, USA),[50, 52] Esthet-X (Dentspl/ DeTrey, Konstanz, Germany),[54] Filtek Z-350 (3M ESPE; MN, USA),[45] TPH Espectrum (Dentsply/De Trey; Konstanz, Germany),[49] Tetric Ceram

(Ivoclar Vivadent; Schaan, Liechtestein),[48] Point 4 (Kerr; Orange, USA)[48] and Ceram X Mono (Dentsply/ DeTrey, Konstanz, Germany).[55]

Most of the studies reported that no rubber dam had been applied,[34, 37, 39, 42, 43, 45, 46, 48-50, 52-55] 6 studies reported the use of rubber dam,[35, 36, 38, 41, 44, 47] another 3 did not report this information,[33, 51, 57] and 2 studies stated that rubber dam was used depending on the location and access to the lesion.[40, 56]

Ten studies[34-37, 41, 42, 45, 47, 54, 55] prepared a small enamel bevel at the incisal/occlusal margin of the lesion, 11 studies[34, 36, 37, 40, 42, 44, 45, 47-49, 52] superficially roughened the exposed dentin with a coarse diamond rotatory instrument, 8 studies[38, 39, 43, 46, 50, 51, 53, 57] did not prepare either the enamel or dentin and 2 studies[33, 56] did not report this information.

Risk of Bias in the Included Studies

The quality assessment of the RoB of included studies both for OptiBond FL and Clearfil SE Bond is presented in Figures 4.3.2 and Figure 4.3.3. From the 12 eligible studies that evaluated OptiBond FL, only one[38] was considered at low risk of bias, while the other 11 were considered at unclear risk of bias. From the 14 studies that evaluated the Clearfil SE Bond studies, 2 studies[43, 50] were considered low risk of bias and the remaining were at unclear risk.

Meta-Analysis

OptiBond FL

Nine studies were included in the meta-analysis, as 3 studies were excluded because of lack of data (they were abstracts).[33, 56, 57] One study provided 3 effect sizes as OptiBond was compared with 3 different adhesives[38] and another provided 2 effect sizes.[39] The results are presented in Figure 4.3.4. No significant differences in the retention rates between groups (OptiBond FL vs. other adhesive brands) were observed at the follow-ups of 12 to 24 months, 36 to 48 months and 108 to 156 months ($p > 0.72$). The risk ratio (RR) and the 95% confidence interval at 12 to 24 months was 0.99 (0.56 to 1.75; $p = 0.97$), at 36 to 48 months was 1.12 (0.61 to 2.03; $p = 0.72$), and at 108 to 156 months 0.94 (0.67 to 1.32; $p = 0.73$). A significant difference was found between the groups at 60 to 96 months, with an average RR of 1.65 (1.07

to 2.53; p = 0.02) in favor of the OptiBond FL. Heterogeneity was not observed in any of the follow-up periods (I2 = 0; p > 0.50).

Clearfil SE Bond

All the 14 studies were included in the meta-analysis, and the results are presented in Figure 4.3.5. Four studies provided 2 effect sizes.[44, 47, 50, 52] No significant differences in the retention rates between groups (Clearfil SE Bond vs. other adhesives) were observed in any of the different follow-up periods (p > 0.10). The risk ratio (RR) and the 95% confidence interval at 12 to 24 months was 1.21 (0.97 to 1.53; p = 0.10) and at 36 to 48 months 1.49 (0.84 to 2.67; p = 0.17). Heterogeneity was observed at the follow-up periods to 36 to 48 months (p = 0.09; I2 = 59%).

Assessment of the Quality of Evidence (GRADE)

The quality of evidence assessed for both OptiBond FL and Clearfil SE Bond in all study follow-ups was low due to limitations in the risk of bias of the eligible studies (most were at unclear risk) and due to imprecision Table 4.3.2. Although the short-term meta-analysis included more than 10 comparisons, the number of events in the short-term follow-ups was quite low, leading to imprecision. In the medium- to long-term follow-ups, imprecision was mainly attributed to the low number of studies and the consequent wide confidence interval around the point estimate.

DISCUSSION

Well-done systematic reviews, with or without meta-analysis, are generally considered to provide the best evidence for the type of study design summarized, as they are based on the findings of multiple studies identified in comprehensive and systematic literature searches. As stated in the introduction section, pairwise meta-analysis involving adhesive systems in NCCLs commonly compare adhesive strategies[4, 5, 7, 58] rather than specific material brands. In these reviews, the so-called ‘gold standard’ adhesives were grouped with other adhesive brands within their classification group, and therefore their individual performance cannot be assessed.

The authors are unaware of a previous systematic review that compared retention rates of specific brands of adhesive systems with other competitive adhesive materials.

The present results challenge the widespread concept that the 3-step ER OptiBond FL (Kerr; Orange, USA) and the 2-step SE Clearfil SE (Kuraray; Tokyo, Japan) are "gold standard" materials. Their overall retention rates were not better than the overall retention rates of other competitive adhesive brands with which they were compared, except at 60 to 96 months for OptiBond FL data. In this follow-up, only 2 studies were included, therefore providing an imprecise estimate.

Although this belief has been in the literature for more than 20 years, it became a stronger evidence the publication of a meta-analytical review of parameters on bond strength values.[10] In their review of laboratory studies,[10] the authors concluded that the best-performing adhesive both in short- and long-term studies was the 3-step ER OptiBond FL (Kerr; Orange, USA) while the second-best performance adhesive was the 2-step SE Clearfil SE Bond (Kuraray; Tokyo, Japan).

The lack of agreement between the meta-analytical review[10] and the present meta-analysis of RCT suggests laboratory and clinical findings are not consistent. While an earlier study reported correlation between laboratory and clinical data, one cannot exclude the fact that this reported correlation was spurious, as it was only found between 'aged' bond-strength data with medium-term retention rates of adhesives.[14]

Nevertheless, this conclusion does not mean that the adhesives OptiBond FL and Clearfil SE Bond are not good adhesives. Indeed, they have good clinical performance with clinical data of up to 13 years of follow-up.[59, 60] Very few adhesive systems have been followed up for such a long time. However, the merged data of OptiBond FL and Clearfil SE Bond from eligible RCTs in short- to long-term studies have not shown superiority of these materials over other brands, suggesting that there are as good adhesives as these two. We do agree with some authors[17, 61] that the clinical performance of the adhesive system is not related to the bonding strategy, but to the product chemical composition. Therefore, any attempt to categorize the efficacy of adhesives based on their classification may be misleading. This may explain why systematic reviews grouping brands of adhesive systems from the same category failed to reach a consensus.[5, 7, 58]

Some considerations about the RCTs included in this systematic review are required. Authors of RCTs of bonding studies have not reported the study findings in a standardized way, and this may lead to misleading conclusions. In some clinical trials, events at the shortest

follow-ups are not carried forward to the longest follow-ups, which may lead to the reporting of misleading results. This misleading report probably occured because the recall rate drops drastically in long-term follow-ups. In these situations, the review authors calculated the retention rates based on the number of recalled restorations and not based on the total number of restorations placed at baseline.

When we collected data for this meta-analysis, we used the total number of restorations at baseline as a reference for all studies. This approach assumes that none of those missed at the follow-up suffered the target outcome, i.e., debonding. Making this assumption, we presented the study results as the best estimate, as we do not know (like the authors of the eligible studies) what happened to the unseen restorations. This approach, although may overestimate the retention rates of the adhesives does not break the random assignment to the treatment groups in the studies.

The other alternative would be to use the number of restorations recalled at each follow-up as a denominator of the retention rate; however, this number is not always provided. Some authors report an overall recall rate and not the recall rate per group,[54] which does not help in data extraction; others do not report the recall rate at all.[35, 39] To make the scenario harder, some study authors report the percentage of events instead of the raw numbers, without specifying whether the denominator of such percentages is the total number of placed restorations at baseline or the total number of evaluated restorations at any follow-up.

All these concerns regarding data extraction indicate an urgent need for standardization of the report of studies conducted on NCCLs. Instead of providing retention rates per follow-up, the use of survival analysis could provide better estimates of what occurs to the adhesives over time.

Another important issue to be addressed is that the great majority of the studies were at unclear risk of bias. To prevent selection bias, the randomization process should be adequately performed, and the random sequence should be protected from foreknowledge until the implementation of the intervention. The latter procedure is called allocation concealment. Only 30% to 40% of eligible studies from this review reported the randomization process used in their study, and only 10% to 15% of the studies adequately reported the allocation concealment.

The poor reporting of the random sequence generation and the allocation concealment in studies conducted in NCCLs has been highlighted in a previous review (Reis et al. 2018) that assessed the compliance of bonding studies in NCCLs to the CONSORT statement,[62] which is

a set of recommendations for reporting clinical trials in biomedical literature. This fact led us to downgrade the quality of evidence in one level for the risk of bias.

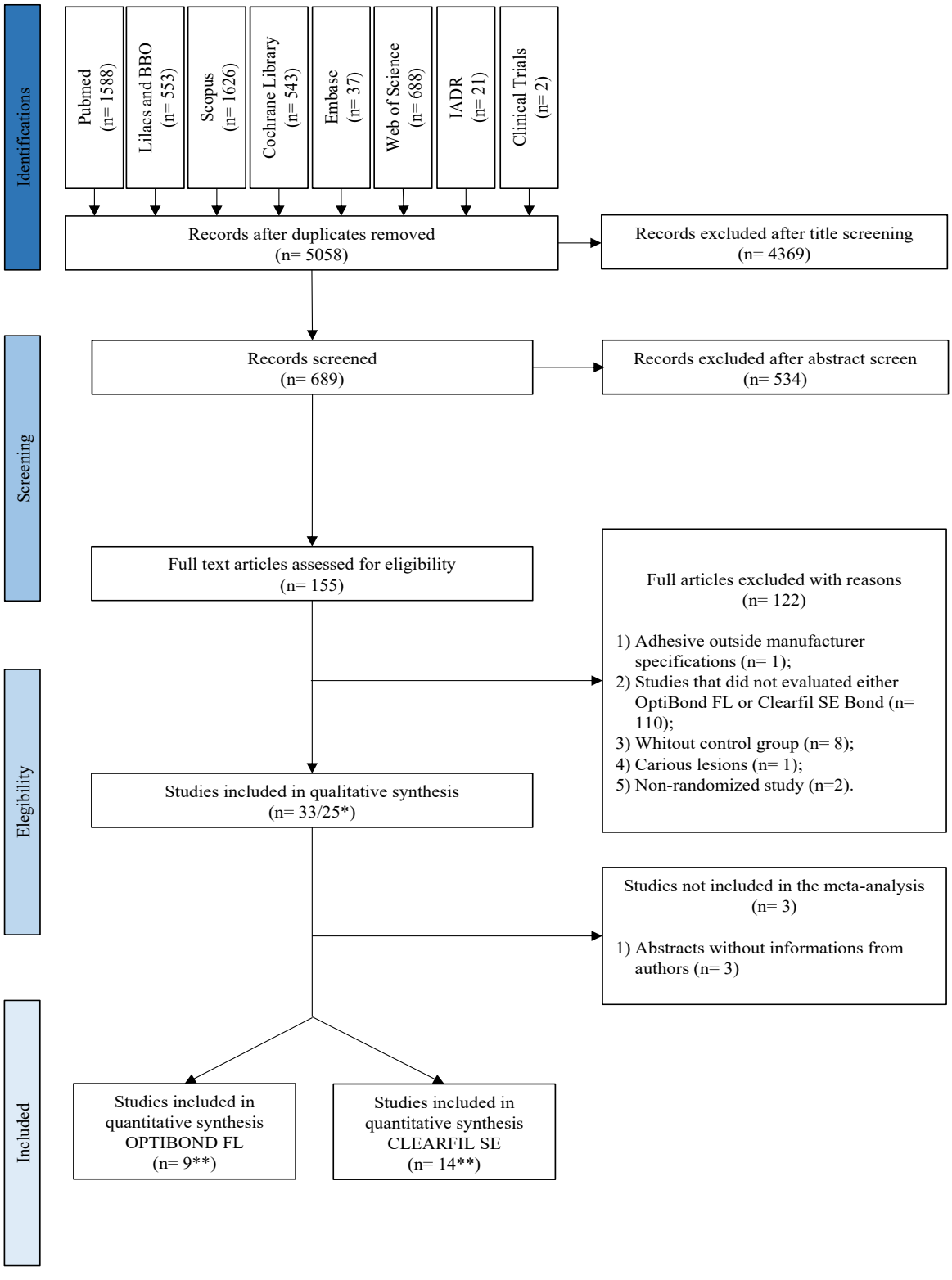
Another important consideration is that most of the RCTs focused on short- and medium-term follow-ups, i.e. 12 to 48 months for both adhesives. In these short-term follow-ups, the number of events, i.e., debonded restorations was low for both groups, leading to imprecise estimates. The body of evidence produced at these follow-ups were also downgraded for imprecision due to the low number of events. Similarly, the long-term follows up were downgraded for imprecision, but due to the low number of studies and wide 95% confidence interval.

Only 3 medium- to long-term studies (5 years or more) for OptiBond FL were found. Clearfil SE Bond was not compared with other adhesive brands in follow-ups equal to or longer than 5 years. The studies of Van Meerbeek 2005[63] and Peumans 2005,[8] 2007,[64] 2010,[65] 2015[60] evaluated the long-term performance of this 2-step SE adhesive, but the authors did not compare it with other adhesive brands, which prevented a meta-analysis of these data.

Based on the available RCTs meta-analyzed in this systematic review, there are adhesives whose performance is similar to that of those currently considered “gold standard” adhesives in the dental market. However, the quality of the body of evidence was considered low, and further randomized clinical trials, mainly with a long-term record of performance, are required.

CONCLUSION

We have no evidence from the available RCTs that compared OptiBond FL or Clearfil SE Bond to support the widespread concept that these adhesives are better than other competitive brands available in the dental market.



[1] Adapted from PRISMA.
*Reports of the same study at different follow-up.
** The adhesives have one study in common.

Figure 4.3.1 – Flow diagram of the study identification.

Table 4.3.1 – Summary of the descriptive characteristics of the primary studies included for each adhesive system (n=26).

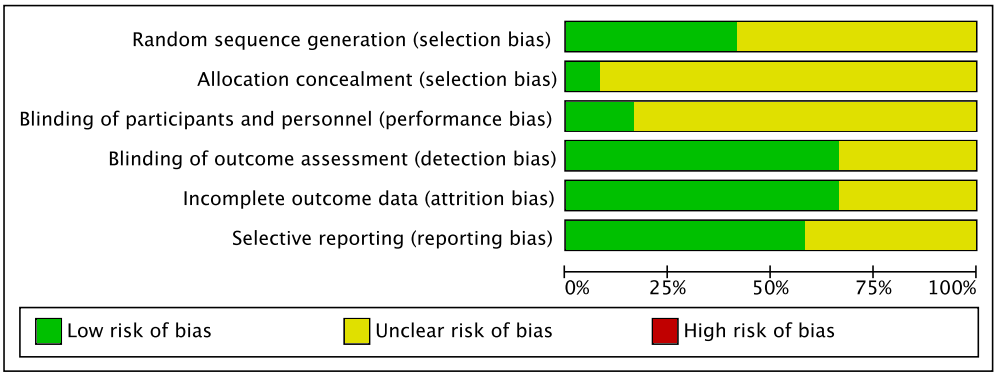
Study ID	Study design [setting]	Follow-ups (mth)	Subject's age mean ± SD [range] (yrs)	Groups: Type of adhesive -Adhesive brand [number of restorations per group]	Resin composite per group	Rubber dam	Enamel bevel/ Dentin prep	# of operators/ examinators	Evaluation criteria
OPTIBOND FL									
Armstrong 2012(100)	Paired [university]	6, 12	n.r. ± n.r. [n.r.]	**3ER**- Optibond FL[a] [30] **1SE-** Tokuyama Bond Force[b] [30]	Premise[a] Estelite Sigma Quick[b]	No/Yes*	n.r./n.r.	n.r./n/r	USPHS
Blunck 2013(107)	Paired [n.r.]	12, 24	n.r. ± n.r. [n.r.]	**1SE**- iBond[c] [58] **1SE**- G-Bond[d] [58] **1SE**- Clearfil S3 Bond[e] [58] **3ER**- Optibond FL[a] [58]	CeramX-Duo[j]	n.r.	No/No	2/n.r.	USPHS
Dall'orologio 2006,(114) 2008,(115) 2009,(116) 2010(117)	n.r. [n.r.]	Baseline, 6, 12, 18, 24, 36, 60, 78, 84	n.r. ± n.r. [n.r.]	**1SE-** iBond[c] [n.r.] **1SE**- AQ Bond[f] [n.r.] **3ER**- Optibond FL[a] [n.r.]	Filtek Z-250[g]	n.r.	n.r./n.r.	3/1	Modified USPHS
de Paula 2015(119)	Multiple restorations [university]	Baseline, 6, 12	n.r. ± n.r. [20->49]	**3ER**- Optibond FL[a] [46] **2ER**- Optibond Solo Plus[a] [44] **2SE**- Optibond XTR[a] [44] **1SE**- Optibond All-in-One[a] [46]	Filtek Supreme Ultra[g]	Yes	No/No	04/02	FDI/Modified USPHS
Ermis 2012(121)	Multiple restorations [university]	Baseline, 6, 12, 24	50 ± 8.3 [39-79]	**1SE**- Clearfil S3 Bond[e] [81] **3ER**- Optibond FL[a] [80]	Clearfil AP-X[e]	No	Yes/Yes	01/02	Vanherle
Haak 2019(124)	Paired [university]	Baseline, 6, 12	65 ± 20.5 [43-84]	**1SE-** Scotchbond Universal[g] [110] **3ER-** Optibond FL[a] [55]	Filtek Supreme XTE[g]	No	Yes/Yes	01/01	FDI
Moosavi 2013(143)	Paired [university]	Baseline, 6, 12, 18	n.r. ± n.r. [20-50]	**3ER**- Optibond FL[a] [30] **2ER**- Optibond Solo Plus[a] [30] **1SE**- Optibond All-in-One[a] [30]	Herculite XRV[a]	No	No/No	01/02	USPHS
Mortazavi 2012(144)	Paired [university]	Baseline, 6, 9, 12	n.r. ± n.r. [30-60]	**2SE**- Clearfil SE Bond[e] [12] **3ER**- Optibond FL[a] [12]	Grandio[k]	Yes	Yes/No	n.r./02	USPHS
Ritter 2015(155)	Multiple restorations [university]	Baseline, 6, 18	n.r. ± n.r. [n.r.]	**2SE**- Optibond XTR[a] [41] **3ER**- Optibond FL[a] [42]	Herculite Ultra[a]	Yes/No*	No/Yes	4/2	Modified USPHS
Scotti 2016(159)	Multiple restorations [university]	12, 24, 36	52.4 ± n.r. [32-63]	**1SE**- G-Bond[d] [46] **3ER**- Optibond FL[a] [44]	Venus Diamond[c]	Yes	Yes/Yes	02/02	Modified USPHS
Van Landuyt 2008,(168) 2011,(169) 2014,(170) Peumans 2018(171)	Multiple restorations [university]	Baseline, 6, 12, 24, 36, 60, 108	n.r. ± n.r. [20->80]	**1SE**- G-Bond[d] [133] **3ER**- Optibond FL[a] [134]	Gradia Direct[d]	No	Yes/Yes	02/02	Vanherle

Van Meerbeek 2004,(176) Peumans 2007,(89) 2012(9)	Paired [university]	6, 12, 24, 36, 60, 84, 156	n.r. ± n.r. [<18->70]	**3ER**- PermaQuick[i] [100] **3ER**- Optibond FL[a] [50]	Amelogen Hybrid[i] Amelogen Microfill[i] Prodigy[a]	Yes	Yes/No	02/02	Vanherle
CLEARFIL SE BOND									
Abdalla & Garcia-Godoy 2006(97)	Paired [n.r.]	12, 24	n.r. ± n.r. [35-52]	**2ER**- Admira Bond[k] [65] **2SE**- Clearfil SE Bond[e] [65] **1SE**- Hybrid Bond[f] [65]	Clearfil AP-X[e]	Yes	No/Yes	01/02	USPHS
Araújo 2015(177)	Multiple restorations [university]	Baseline, 24	45 ± 8 [n.r.]	**2SE**- Clearfil SE Bond[e] [32] **2SE**- AdheSE[h] [32]	Filtek Z-250[g]	No	No/No	01/02	Modified USPHS
Brackett 2010(110)	Paired [university]	Baseline, 6, 12, 24	n.r. ± n.r. [31-58]	**2SE**- Clearfil SE Bond[e] [40] **1SE**- Clearfil S3 Bond[e] [40]	Clearfil AP-X[e]	No	No/No	02/02	Modified Ryge/USPHS
Burrow & Tyas 2007(112)	Multiple restorations [university]	6, 12, 24, 36	61 ± n.r. [n.r.]	**2ER**- Single Bond[g] [30] **2SE**- Clearfil SE Bond[e] [30]	Filtek A-110[g] Clearfil ST[e]	n.r.	No/No	02/01	n.r.
Dalkilic e Omurlu 2012(113)	Multiple restorations [university]	Baseline, 3, 12, 24	n.r. ± n.r. [30-70]	**2ER**- Single Bond[g] [60] **2SE**- Clearfil SE Bond[e] [71] **1SE**- Xeno III[l] [60]	Filtek Supreme[g]	No	No/Yes	01/01	Modified USPHS
Jang 2017(127)	Multiple restorations [university]	Baseline, 6, 12, 18, 24	55 ± n.r. [30-73]	**2SE**- Clearfil SE Bond [83] **1SE**- Xeno V[l] [81]	Filtek Z-250[g]	No	No/No	n.r./02	Modified FDI
Mortazavi 2012(144)	Paired [university]	Baseline, 6, 9, 12	n.r. ± n.r. [30-60]	**2SE**- Clearfil SE Bond[e] [12] **3ER**- Optibond FL[a] [12]	Grandio[k]	Yes	Yes/No	n.r./02	USPHS
Pena 2016(147)	Paired [university]	Baseline, 3, 6, 12, 18, 24	n.r. ± n.r. [n.r.]	**2SE**- Clearfil SE Bond[e] [56] **1SE-** Xeno V[l] [56]	Esthet-X[l]	No	Yes/No	01/02	Modified USPHS
Qin 2013(151)	Multiple restorations [university]	Baseline, 6, 12, 24	44.1 ± n.r. [27-66]	**2SE**- Clearfil SE Bond[e] [58] **1SE**- Adper Prompt[g] [56]	Clearfil AP-X[e] Filtek Z-350[g]	No	Yes/Yes	02/02	Modified USPHS
Türkün 2003(163)	Paired [university]	Baseline, 6, 12, 24	46 ± n.r. [26-60]	**2SE**- Clearfil SE Bond[e] [49] **2ER**- Prime & Bond NT[l] [49]	Clearfil AP-X[e] TPH Spectrum[l]	No	No/Yes	01/02	USPHS
van Dijken 2010(10)	Multiple restorations [university]	Baseline, 6, 12, 18, 24, 36, 48, 60, 72, 84, 96	60.1 ± n.r. [42-84]	**2SE**- Clearfil SE Bond[e] [55] **2ER**- PQ1[i] [64]	Tetric Ceram[i] Point 4[a]	No	No/Yes	01/03	Modified USPHS
Yaman 2014(173)	Paired [university]	Baseline, 6, 12, 24, 36	45.12 ± n.r. [32-58]	**2SE**- Clearfil SE Bond[e] [48] **2ER**- XP Bond[l] [48]	Ceram X mono[l]	No	Yes/Yes	02/02	Modified USPHS
Zanatta 2019(174)	Paired [university]	Baseline, 6, 12, 24	n.r. ± n.r. [<20->60]	**2ER**- Scotchbond Universal[g] [38] **1SE**- Scotchbond Universal[g] [38] **2ER**- Single Bond[g] [38] **2SE**- Clearfil SE Bond[e] [38]	Filtek Supreme[g]	No	No/No	04/02	FDI
Zhou 2009(175)	Multiple restorations [university]	Baseline, 3, 6, 12	n.r. ± n.r. [n.r.]	**1SE-** Clearfil 3S Bond[e] [124] **2SE**- Clearfil SE Bond[e] [124] **1SE**- G-Bond[d] [94]	Clearfil AP-X[e]	Yes	Yes/Yes	n.r./02	Modified USPHS

ID – identification; mth – month; # – number; SD – standard deviation; n.r. – not report; USPHS – United State Public Health Service; FDI – World Dental Federation; *Depending of access and location of the lesion.

[a]Kerr Corporation, Orange, USA.
[b]Tokuyama Dental, Tokyo, Japão.
[c]Kulzer, GmbH, Hanau, Germany.
[d]GC Corporation, Tokyo, Japan.
[e]Kuraray, Tokyo, Japan.
[f]Sun Medical, Shiga, Japan.
[g]3M ESPE, St.Paul, MN, USA.
[h]IvoclarVivadent, Schaan, Liechtenstein.
[i]Ultradent, South Jordan, UT, USA.
[j]DeTrey/Dentsply, Konstanz, Germany.
[k]Voco, Cuxhaven, Germany.
[l]Dentsply Caulk, Mildford, DE.

A)



B)

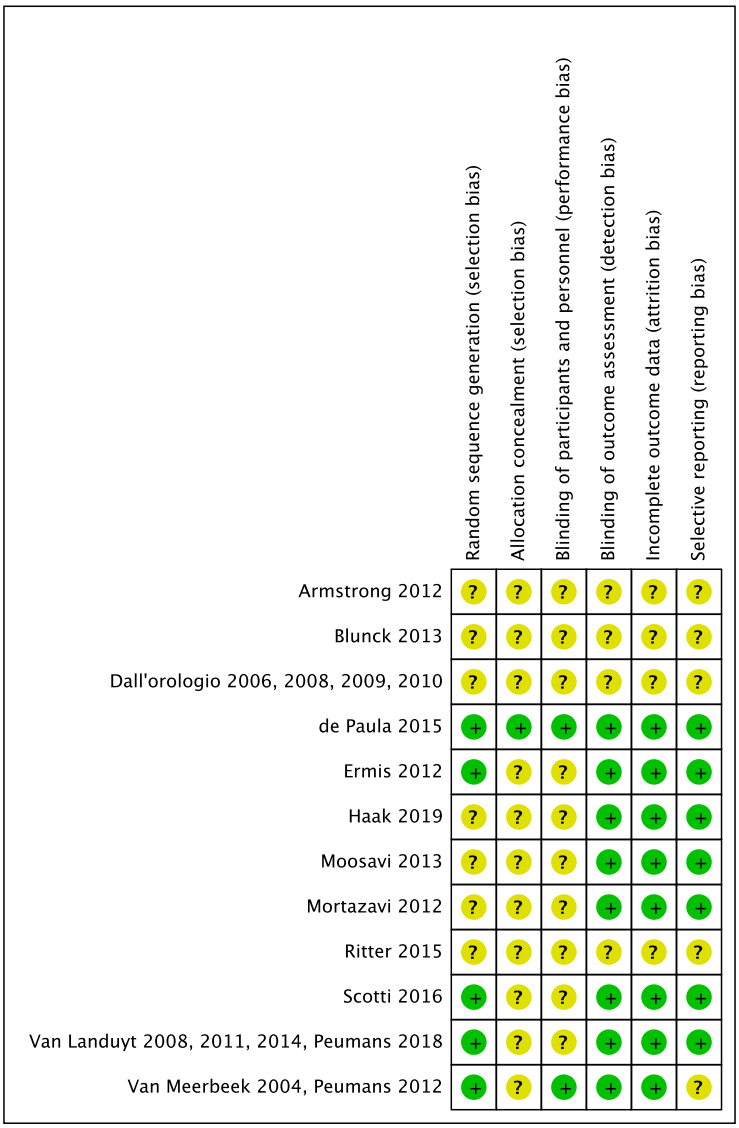
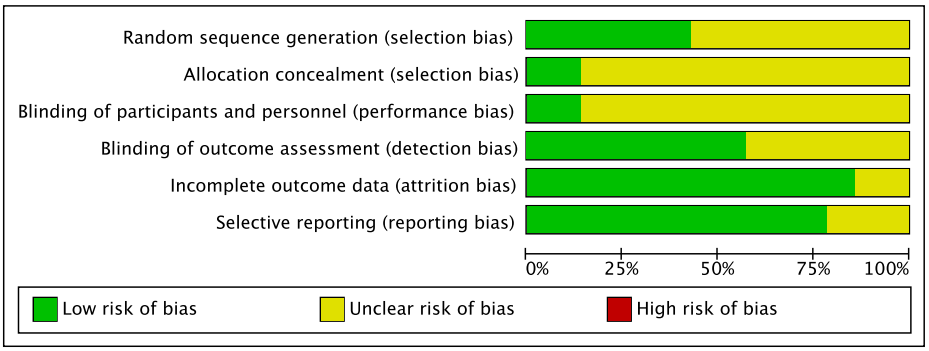


Figure 4.3.2 – A) Risk of bias graph for OptiBond FL according to the Cochrane Collaboration Tool and B) Risk of bias summary for OptiBond FL.

A)



B)

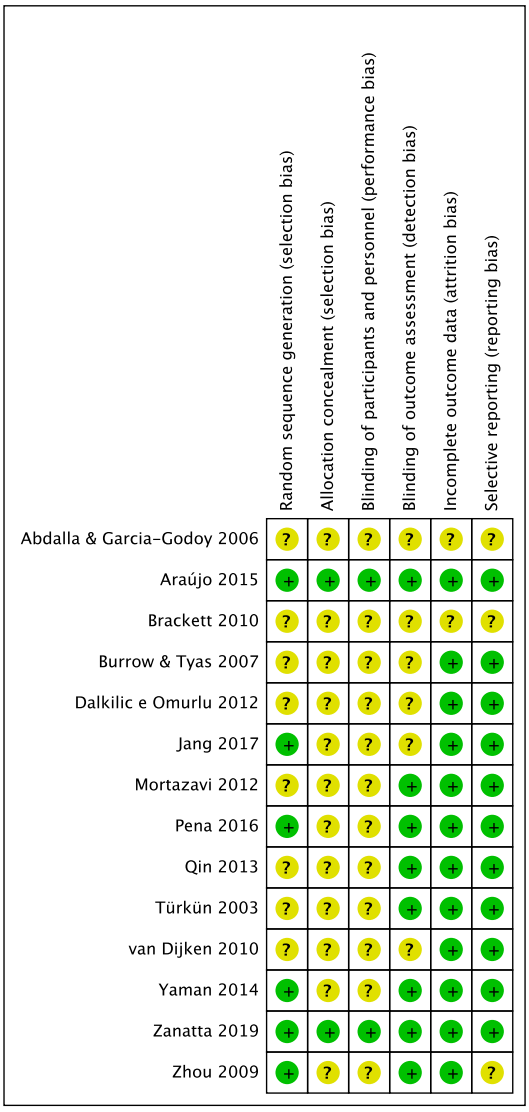


Figure 4.3.3 – A) Risk of bias graph for Clearfil SE Bond according to the Cochrane Collaboration Tool and B) Risk of bias summary for Clearfil SE Bond.

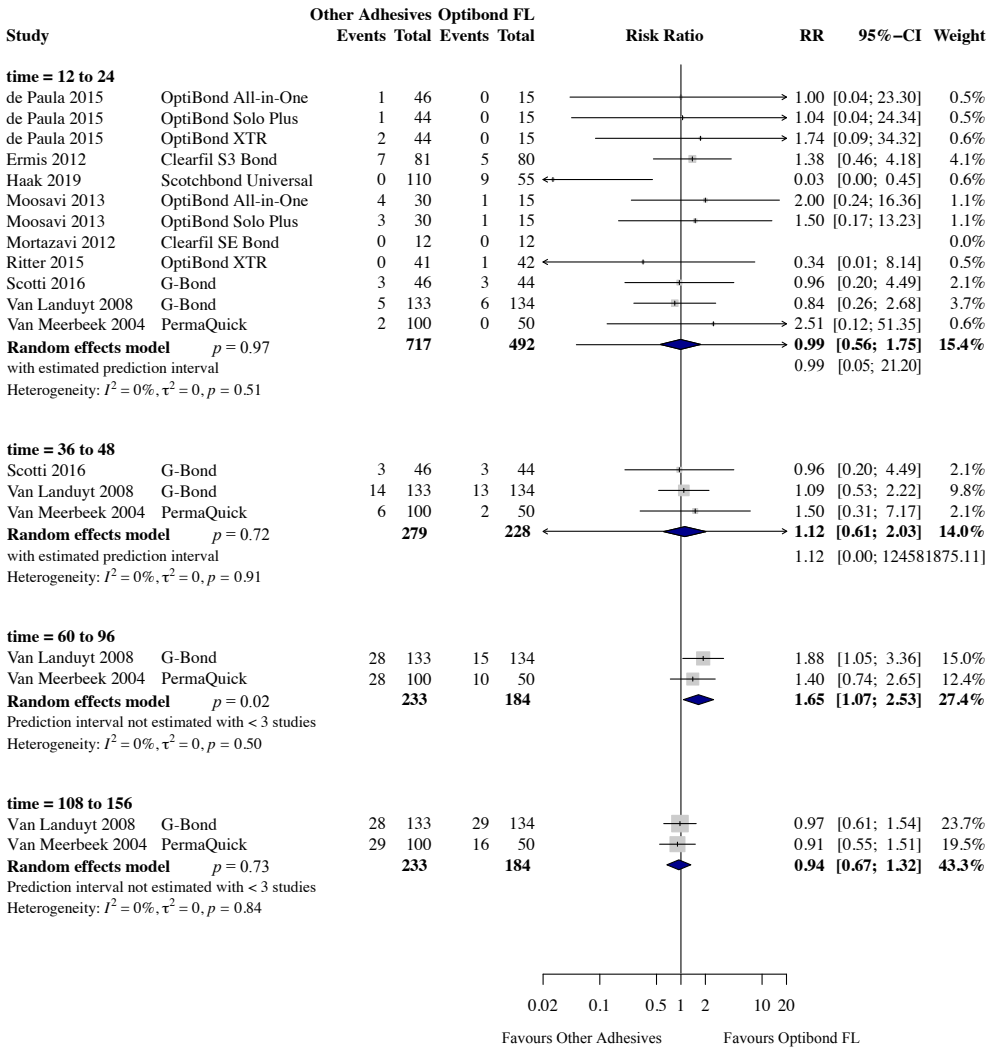


Figure 4.3.4 – Forest plots of the retention rates for OptiBond FL at 12 to 24-month, 36 to 48-month, 60 to 96-month and 108 to 156-month.

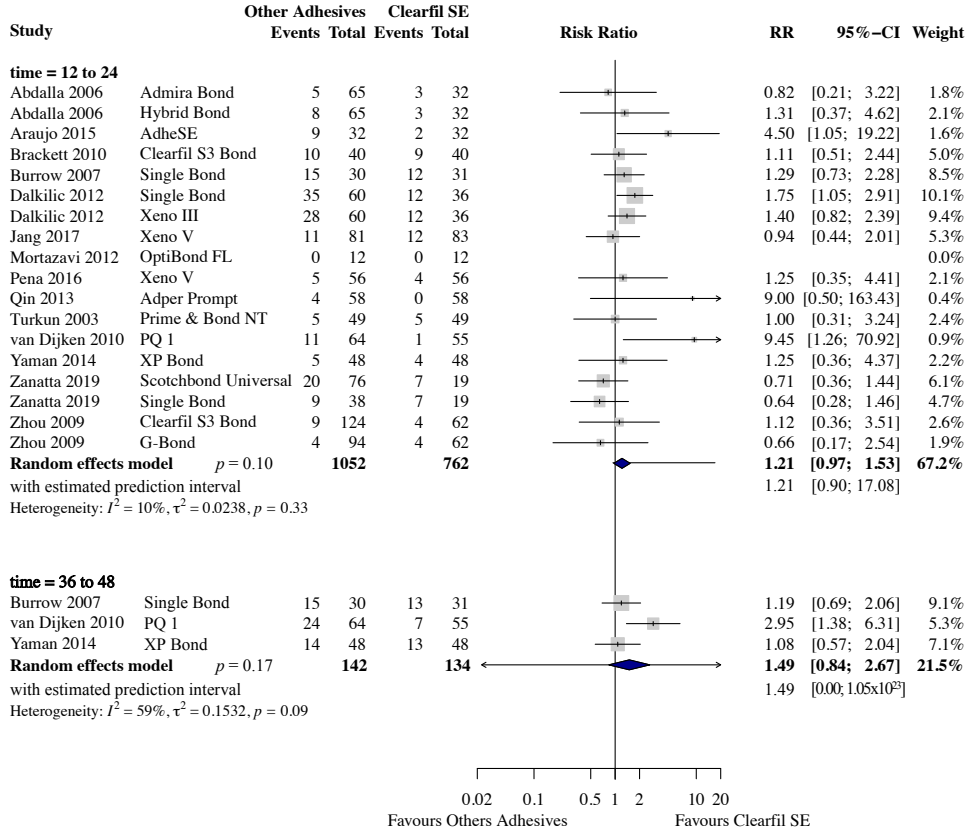


Figure 4.3.5 – Forest plots of the retention rates for Clearfil SE Bond at 12 to 24-month and 36 to 48-month.

Table 4.3.2 – Summary of findings table for OptiBond FL and Clearfil SE Bond.

Retention rates		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Risk with other competitive brands	**Risk with Optibond FL**			
OptiBond FL	Follow up range 12 month to 24 month	39 per 1,000	**39 per 1,000** (22 to 68)	**RR 0.99** (0.56 to 1.75)	1209 (12 RCTs)	⨁⨁◯◯ LOW [a,b]
	Follow up range 36 month to 48 month	82 per 1,000	**92 per 1,000** (50 to 167)	**RR 1.12** (0.61 to 2.03)	507 (3 RCTs)	⨁⨁◯◯ LOW [a,c]
	Follow up range 60 month to 96 month	240 per 1,000	**397 per 1,000** (257 to 608)	**RR 1.65** (1.07 to 2.53)	417 (2 RCTs)	⨁⨁◯◯ LOW [a,d]
	Follow up range 108 month to 156 month	245 per 1,000	**230 per 1,000** (164 to 323)	**RR 0.94** (0.67 to 1.32)	417 (2 RCTs)	⨁⨁◯◯ LOW [a,e]
Clearfil SE Bond	Follow up range 12 month to 24 month	183 per 1,000	**222 per 1,000** (178 to 281)	**RR 1.21** (0.97 to 1.53)	1814 (18 RCTs)	⨁⨁◯◯ LOW [a,e]
	Follow up range 36 months to 48 month	373 per 1,000	**556 per 1,000** (314 to 997)	**RR 1.49** (0.84 to 2.67)	276 (3 RCTs)	⨁⨁◯◯ LOW [a,e]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

SUPPLEMENTARY MATERIAL

ARTIGO 3 – Challenging the concept that OptiBond FL and Clearfil SE Bond are gold standard adhesives: A systematic review and meta-analysis

Table 4.3.3 Supplementary – Database search strategy.

Database (Number of Papers: (5035)	**Search** (November 20, 2019)
PubMed (1588)	dental restoration, permanent[MeSH Terms] OR dentition, permanent[MeSH Terms] OR tooth erosion[MeSH Terms] OR tooth erosion*[Title/Abstract] OR tooth abrasion[MeSH Terms] OR tooth abrasion*[Title/Abstract] OR dental abrasion*[Title/Abstract] OR tooth cervix[MeSH Terms] OR tooth cervix[Title/Abstract] OR abfraction*[Title/Abstract] OR cervical lesion*[Title/Abstract] OR NCCL*[Title/Abstract] OR class V[Title/Abstract] OR class 5[Title/Abstract] AND dentin-bonding agents[Mesh Term] OR adhesive system*[Title/Abstract] OR bonding agent*[Title/Abstract] OR dental adhesive*[Title/Abstract] OR adhesive material*[Title/Abstract] OR "etch-and-rinse adhesive"[Title/Abstract] OR "etch-and-rinse adhesives"[Title/Abstract] OR "total-etch adhesive"[Title/Abstract] OR "total-etch adhesives"[Title/Abstract] OR "self-etch adhesive"[Title/Abstract] OR "self-etching adhesive"[Title/Abstract] OR "self-etch adhesives"[Title/Abstract] OR "self-etching adhesives"[Title/Abstract] OR "all-in-one adhesive"[Title/Abstract] OR "all-in-one adhesives"[Title/Abstract] OR "one-bottle adhesive"[Title/Abstract] OR "one-bottle adhesives"[Title/Abstract] OR "single-bottle adhesive"[Title/Abstract] OR "single-bottle adhesives"[Title/Abstract] OR universal adhesive*[Title/Abstract] OR "multi-mode adhesive"[Title/Abstract] AND randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial"[tw] OR singl*[tw] OR doubl*[tw] OR trebl*[tw] AND mask*[tw] OR blind*[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic
Scopus (1626)	"t??th erosion" OR "t??th abrasion" OR "dental abrasion" OR "t??th cervix" OR "abfraction*" OR "cervical lesion*" OR "NCCL*" OR "class V" OR "class 5" AND "dentin bonding agent" OR "adhesive system" OR "bonding agent" OR "dental adhesive" OR "adhesive material" OR "etch-and-rinse adhesive" OR "self-etch adhesive" OR "self-etching adhesive" OR "all-in-one adhesive" OR "one-bottle adhesive" OR "single-bottle adhesive" OR "universal adhesive" OR "multi-mode adhesive"
Cochrane Library (543)	#1 MeSH descriptor: [Dental Restoration, Permanent] explode all trees 1288 #2 MeSH descriptor: [Dentition, Permanent] explode all trees 65 #3 MeSH descriptor: [Tooth Erosion] explode all trees 222 #4 (tooth next erosion):ti,ab,kw (Word variations have been searched) 233 #5 MeSH descriptor: [Tooth Abrasion] explode all trees 124 #6 tooth next abrasion (Word variations have been searched) 132 #7 dental next abrasion (Word variations have been searched) 1 #8 MeSH descriptor: [Tooth Cervix] explode all trees 292 #9 tooth next cervix (Word variations have been searched) 306 #10 abfraction (Word variations have been searched) 18 #11 cervical next lesion (Word variations have been searched) 394 #12 NCCL? (Word variations have been searched) 84 #13 class next V (Word variations have been searched) 344 #14 class next 5 (Word variations have been searched) 47 #15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 1995 #16 MeSH descriptor: [Dentin-Bonding Agents] explode all trees 937 #17 adhesive next system (Word variations have been searched) 505 #18 bonding next agent (Word variations have been searched) 1061

	#19 dental next adhesive (Word variations have been searched) 297 #20 adhesive next material (Word variations have been searched) 160 #21 “etch-and-rinse adhesive” (Word variations have been searched) 117 #22 “total-etch adhesive” (Word variations have been searched) 53 #23 “self-etch adhesive” (Word variations have been searched) 356 #24 “all-in-one adhesive” (Word variations have been searched) 25 #25 “one-bottle adhesive” (Word variations have been searched) 36 #26 “single-bottle adhesive” (Word variations have been searched) 13 #27 “universal next adhesive” (Word variations have been searched) 38 #28 “multi-mode adhesive” (Word variations have been searched)3 #29 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 1314 #30 #15 AND #29 Total: 545 (-2 reviews) = 543
Web of Science (688)	TS= ("t*th erosion" OR "t*th abrasion" OR "dental abrasion*" OR "tooth cervix" OR "abfraction*" OR "cervical lesion*" OR "NCCL" OR "class V" OR "class 5") AND TS= ("dentin bonding agent*") OR TS= ("adhesive system*") OR TS= ("bonding agent*") OR TS= ("dental adhesive*") OR TS= ("adhesive material*") OR TS= ("etch-and-rinse adhesive") OR TS= ("etch-and-rinse adhesives") OR TS= ("total-etch adhesive") OR TS= ("total-etch adhesives") OR TS= ("self-etch adhesive") OR TS= ("self-etch adhesives") OR TS= ("self-etching adhesive") OR TS= ("self-etching adhesives") OR TS= ("all-in-one adhesive") OR TS= ("all-in-one adhesives") OR TS= ("one-bottle adhesive") OR TS= ("one-bottle adhesives") OR TS= ("single-bottle adhesive") OR TS= ("single-bottle adhesives") OR TS= ("universal adhsesive") OR TS= ("universal adhesives") OR TS= ("multi-mode adhesive")
LILACS (553)	mh:"dental restoration, permanent" OR "restauração dentária permanente" OR "restauración dental permanente" OR mh:"dentition, permanent" OR tw:"dentição permanente" OR "dentición permanente" OR mh:"tooth erosion" OR tw:"erosão dentária" OR tw:"erosión de los dientes" OR mh:"tooth abrasion" OR tw:"abrasão dentária" OR tw:"abrasión de los dientes" OR mh:"tooth cervix" OR tw:"colo do dente" OR tw:"cuello del diente" OR tw:abfrac* OR tw:"cervical lesions" OR tw:"lesões cervicais" OR tw:"lesiones cervicales" OR tw:nccls OR tw:lcncs OR tw:"class V" OR tw:"class 5" OR tw:"classe V" OR tw:"classe 5" AND mh:"dentin bonding agents" OR tw:"adesivos dentinários" OR tw:"recubrimientos dentinarios" OR tw:"adhesive systems" OR tw:"sistemas adesivos" OR tw:"sistemas adhesivos" OR tw:"bonding agents" OR tw:"agentes de união" OR tw:"agentes de unión" OR tw:"dental adhesives" OR tw:"adesivos dentais" OR tw:"adhesivos dentales" OR tw:"adhesives materials" OR tw:"materiais adesivos" OR tw:"materiales adhesivos" OR tw:"etch and rinse adhesives" OR tw:"adesivos convencionais" OR tw:"adhesivos convencionales" OR tw:"total etch adhesives" OR tw:"condicionamento ácido total" OR tw:"adhesivos de grabado total" OR tw:"self etch adhesives" OR tw:"adesivos autocondicionantes" OR tw:"adhesivos autocondicionantes" OR tw:"self etching adhesives" OR tw:"all in one adhesives" OR tw:"adesivos de passo único" OR tw:"one bottle adhesives" OR tw:"adesivos de frasco único" OR tw:"single bottle adhesives" OR tw:"universal adhesives" OR tw:"adesivos universais" OR tw:"multi mode adhesives"
Embase (37)	“tooth erosion” OR “tooth abrasion” OR “dental abrasion” OR “tooth cervix” OR abfraction OR “cervical lesion” OR NCCL OR “class V” OR “class 5” AND “dentin bonding agent” OR “adhesive system” OR “bonding agent” OR “dental adhesive” OR “adhesive material” OR “etch-and-rinse adhesive” OR “self-etch adhesive” OR “self-etching adhesive” OR “all-in-one adhesive” OR “one-bottle adhesive” OR “single-bottle adhesive” OR “universal adhesive” OR “multi-mode adhesive”

Table 4.3.4 Supplementary – Articles excluded and the reasons for exclusion (n=121).

Author year	Reasons for exclusion*
63. Abdalla 2008(27)	Clearfil outside manufacturer specifications
64. Abdalla & Garcia-Godoy 2007(98)	Not evaluated Optibond FL or Clearfil SE
65. Alhadainy 1996(28)	Not evaluated Optibond FL or Clearfil SE
66. Araújo 2013(99)	Not evaluated Optibond FL or Clearfil SE
67. Atalay 2019(101)	Not evaluated Optibond FL or Clearfil SE
68. Aw 2004(102)	Not evaluated Optibond FL or Clearfil SE
69. Aw 2005(103)	Not evaluated Optibond FL or Clearfil SE
70. Barceleiro 2018(137)	Not evaluated Optibond FL or Clearfil SE
71. Barcellos 2013(30)	Not evaluated Optibond FL or Clearfil SE
72. Batalha-Silva 2009(104)	Not evaluated Optibond FL or Clearfil SE
73. Belluz 2005(31)	Not evaluated Optibond FL or Clearfil SE
74. Bittencourt 2005(105)	Not evaluated Optibond FL or Clearfil SE
75. Blunck 2007(32)	Not evaluated Optibond FL or Clearfil SE
76. Boushell 2016(108)	Not evaluated Optibond FL or Clearfil SE
77. Brackett 2005(109)	Not evaluated Optibond FL or Clearfil SE
78. Burgess 2013(111)	Not evaluated Optibond FL or Clearfil SE
79. Burke 2017(33)	Not evaluated Optibond FL or Clearfil SE
80. Burrow 2008(34)	Not evaluated Optibond FL or Clearfil SE
81. Burrow 2012(35)	Not evaluated Optibond FL or Clearfil SE
82. Can Say 2014(65)	Not evaluated Optibond FL or Clearfil SE
83. Can Say 2014(64)	Not evaluated Optibond FL or Clearfil SE
84. Çelik 2007(37)	Not evaluated Optibond FL or Clearfil SE
85. Çelik 2018(38)	Not evaluated Optibond FL or Clearfil SE
86. da Costa 2014(39)	Not evaluated Optibond FL or Clearfil SE
87. de Oliveira 2013(178)	Not evaluated Optibond FL or Clearfil SE
88. Dutra-Correa 2013(120)	Not evaluated Optibond FL or Clearfil SE
89. Dutra-Correa 2015(149)	Not evaluated Optibond FL or Clearfil SE
90. Dutra-Correa 2019(11)	Not evaluated Optibond FL or Clearfil SE
91. Duke 1991(40)	Not evaluated Optibond FL or Clearfil SE
92. Duke 1994(41)	Not evaluated Optibond FL or Clearfil SE
93. Estafan 1999(42)	Not evaluated Optibond FL or Clearfil SE
94. Fagundes 2015(43)	Not evaluated Optibond FL or Clearfil SE
95. Faye 2015(44)	Not evaluated Optibond FL or Clearfil SE
96. Folwaczny 2001(45)	Not evaluated Optibond FL or Clearfil SE
97. Friedl 2004(122)	Not evaluated Optibond FL or Clearfil SE
98. Fron 2011(179)	Not evaluated Optibond FL or Clearfil SE
99. Fu 2015(123)	Not evaluated Optibond FL or Clearfil SE
100. Gallo 2005(46)	Not evaluated Optibond FL or Clearfil SE
101. Ghavamnasiri 2012(47)	Carious lesions
102. Häfer 2015(125)	Not evaluated Optibond FL or Clearfil SE
103. Hansen 1992(48)	Not evaluated Optibond FL or Clearfil SE
104. Helbig 2004(126)	Not evaluated Optibond FL or Clearfil SE
105. Heymann 1998(49)	Not evaluated Optibond FL or Clearfil SE
106. Horsted-Bindslev 1988(50)	Not evaluated Optibond FL or Clearfil SE
107. Juloski 2015(51)	Not evaluated Optibond FL or Clearfil SE

108. Kim 2009(128)	Not evaluated Optibond FL or Clearfil SE
109. Kina 2013(53)	Not evaluated Optibond FL or Clearfil SE
110. Kubo 2006(129)	Not evaluated Optibond FL or Clearfil SE
111. Kubo 2009(54)	Not evaluated Optibond FL or Clearfil SE
112. Kubo 2010(55)	Without control group
113. Kurokawa 2007(56)	Not evaluated Optibond FL or Clearfil SE
114. Lawson 2015(130)	Not evaluated Optibond FL or Clearfil SE
115. Loguercio 2006(132)	Not evaluated Optibond FL or Clearfil SE
116. Loguercio 2007(106)	Not evaluated Optibond FL or Clearfil SE
117. Loguercio 2008(133)	Not evaluated Optibond FL or Clearfil SE
118. Loguércio 2011(57)	Without control group
119. Loguercio 2015(142)	Not evaluated Optibond FL or Clearfil SE
120. Loguercio 2018(135)	Not evaluated Optibond FL or Clearfil SE
121. Lopes 2016(136)	Not evaluated Optibond FL or Clearfil SE
122. Matis 2004(138)	Not evaluated Optibond FL or Clearfil SE
123. Matos 2019(139)	Not evaluated Optibond FL or Clearfil SE
124. Mena-Serrano 2013(140)	Not evaluated Optibond FL or Clearfil SE
125. Mccoy 1998(58)	Not evaluated Optibond FL or Clearfil SE
126. Merte 2000(59)	Not evaluated Optibond FL or Clearfil SE
127. Moretto 2013(60)	Not evaluated Optibond FL or Clearfil SE
128. Neo 1996(61)	Not evaluated Optibond FL or Clearfil SE
129. Oz 2018(62)	Not evaluated Optibond FL or Clearfil SE
130. Oz 2019(145)	Not evaluated Optibond FL or Clearfil SE
131. Ozel 2010(63)	Not evaluated Optibond FL or Clearfil SE
132. Özkubat 2018(66)	Not evaluated Optibond FL or Clearfil SE
133. Pavolucci 2010(146)	Not evaluated Optibond FL or Clearfil SE
134. Platt 2014(70)	Not evaluated Optibond FL or Clearfil SE
135. Perdigão 2001(67)	Not evaluated Optibond FL or Clearfil SE
136. Perdigão 2005(68)	Not evaluated Optibond FL or Clearfil SE
137. Perdigão 2009(69)	Not evaluated Optibond FL or Clearfil SE
138. Perdigão 2012(148)	Not evaluated Optibond FL or Clearfil SE
139. Perdigão 2014(141)	Not evaluated Optibond FL or Clearfil SE
140. Perdigão 2019(150)	Not evaluated Optibond FL or Clearfil SE
141. Peumans 2005(90)	Without control group
142. Peumans 2007(180)	Without control group
143. Peumans 2010(91)	Without control group
144. Peumans 2015(92)	Without control group
145. Reis 2009(71)	Not evaluated Optibond FL or Clearfil SE
146. Reis 2010(153)	Not evaluated Optibond FL or Clearfil SE
147. Ritter 2008(154)	Not evaluated Optibond FL or Clearfil SE
148. Ritter 2009(72)	Not evaluated Optibond FL or Clearfil SE
149. Robles 2018(131)	Not evaluated Optibond FL or Clearfil SE
150. Rouse 2016(181)	Not evaluated Optibond FL or Clearfil SE
151. Rouse 2018(182)	Not evaluated Optibond FL or Clearfil SE
152. Ruschel 2018(156)	Not evaluated Optibond FL or Clearfil SE
153. Sartori 2011(157)	Not evaluated Optibond FL or Clearfil SE
154. Sartori 2012(73)	Not evaluated Optibond FL or Clearfil SE
155. Sartori 2013(158)	Not evaluated Optibond FL or Clearfil SE

156. Schatemberg 2008(74)	Not evaluated Optibond FL or Clearfil SE
157. Söderholm 2013(183)	Non-randomized study
158. Souza 2019(78)	Not evaluated Optibond FL or Clearfil SE
159. Souza 2019(79)	Not evaluated Optibond FL or Clearfil SE
160. Stojanac 2013(160)	Not evaluated Optibond FL or Clearfil SE
161. Swift Jr 2001(77)	Not evaluated Optibond FL or Clearfil SE
162. Swift Jr 2001(184)	Not evaluated Optibond FL or Clearfil SE
163. Tian 2014(161)	Not evaluated Optibond FL or Clearfil SE
164. Tuncer 2013(162)	Not evaluated Optibond FL or Clearfil SE
165. Türkün 2005(164)	Not evaluated Optibond FL or Clearfil SE
166. Türkün 2008(80)	Not evaluated Optibond FL or Clearfil SE
167. Tyas 1988(81)	Not evaluated Optibond FL or Clearfil SE
168. Tyas 1994(82)	Not evaluated Optibond FL or Clearfil SE
169. Tyas 1996(83)	Not evaluated Optibond FL or Clearfil SE
170. van Dijken 2000(165)	Not evaluated Optibond FL or Clearfil SE
171. van Dijken 2008(185)	Non-randomized study
172. van Dijken 2004(166)	Not evaluated Optibond FL or Clearfil SE
173. van Dijken 2007(84)	Not evaluated Optibond FL or Clearfil SE
174. van Dijken 2013(167)	Not evaluated Optibond FL or Clearfil SE
175. Van Meerbeek 1993(86)	Not evaluated Optibond FL or Clearfil SE
176. Van Meerbeek 1996(87)	Not evaluated Optibond FL or Clearfil SE
177. Van Meerbeek 2005(88)	Without control group
178. Vanherle 1991(93)	Not evaluated Optibond FL or Clearfil SE
179. Walter 2013(172)	Not evaluated Optibond FL or Clearfil SE
180. Wilder 2009(8)	Not evaluated Optibond FL or Clearfil SE
181. Wilson 1995(94)	Without control group
182. Zander-Grande 2011(95)	Not evaluated Optibond FL or Clearfil SE
183. Zander-Grande 2014(96)	Not evaluated Optibond FL or Clearfil SE

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5 DISCUSSÃO

5.1 PRINCIPAIS ACHADOS ENTRE AS ESTRATÉGIAS ADESIVAS

Não existem evidências que os sistemas adesivos de 3-passos ER apresentem melhores taxas de retenção que os adesivos de 1-passo SE, no entanto, mostraram reduzida descoloração marginal e melhor integridade marginal (Artigo 1), estando de acordo com outros estudos (19, 21, 186). Entre as estratégias adesivas (3ER, 2ER, 2SE e 1SE) nenhuma se apresentou superior a outra tanto a curto, a médio e longo prazo de acordo com a meta-análise em rede (Artigo 2). Outras meta-análises comparando as estratégias aos pares obtiveram resultados semelhantes (21, 187). Não há evidências de que os adesivos considerados "padrão ouro" OptiBond FL e Clearfil SE Bond apresentem maiores taxas de retenção que outros adesivos com os quais foram comparados em ensaios clínicos randomizados (Artigo 3). Isto vai contra outros estudos em que a performance destes adesivos foi superior tanto em estudos *in vitro* (188-190) quanto *in vivo* (90, 191).

Sendo assim, baseado nas três RSs não houve diferença estatística nas taxas de retenção entre as estratégias adesivas. Salienta-se que a semelhança dos resultados pode ser atribuída ao fato dos ensaios clínicos terem sido realizados com operadores bem calibrados em ambientes universitários otimizando qualquer estratégia adesiva, permitindo a melhor performance de cada material.

Entretanto, alguns autores relatam que o desempenho clínico dos sistemas adesivos não está relacionado à sua abordagem de aplicação, o que se confirmou nos artigos 1 e 2 deste trabalho, mas à alta dependência ou composição química do produto (192, 193). Porém esta informação não foi confirmada no artigo 3, onde diferentes marcas comerciais de adesivos foram comparadas aos adesivos "padrão ouro".

Essas informações devem ser interpretadas com cautela pois, a meta-análise mostrou que existem poucos estudos e a maioria deles se concentra em períodos curtos de acompanhamento para ambos os adesivos. Ou seja, foram incluídos apenas três estudos de médio a longo prazo (quatro anos ou mais) para OptiBond FL e nenhum a longo prazo para o Clearfil SE Bond, pois os estudos de Van Meerbeek et al. (88) e Peumans et al. (90-92, 180) não preencheram os critérios de elegibilidade (grupo comparador).

Potenciais vieses no processo de revisão e implicações para pesquisa

Um dos itens de checagem na condução de ensaios clínicos contido na recomendação CONSORT é o processo de randomização. O que se observou na maioria dos estudos primários incluídos nas três RSs, que a unidade de randomização foi o dente e não o indivíduo, sendo assim, não pudemos resumir os dados de maneira diferente da relatada nos estudos. Outro item pouco reportado entre os estudos foi o sigilo da alocação que juntamente com a geração da sequência no processo de randomização podem minimizar o viés de seleção. Isto corrobora com outra revisão sistemática recente na literatura realizada por nosso grupo de pesquisa (194), que avaliou a aderência ao CONSORT de 138 ensaios clínicos randomizados em LCNCs e o risco de viés destes estudos. Demonstrou que 80% deles obtiveram score 0, ou seja, não relataram pelo menos um dos itens (protocolo, diagrama de fluxo, sigilo da alocação, tamanho da amostra) e apenas 4,3% foram classificados como sendo baixo risco de viés nos seis domínios na ferramenta da Cochrane. Segundo Kunz et al. 2007 (195) estudos não-aleatórios e aleatórios com sigilo de alocação inadequado tendem a superestimar os resultados. Sendo assim, ressalta-se a importância de estudos clínicos randomizados seguirem um protocolo rigoroso de randomização, ocultação da sequência aleatória e cegamento.

Quanto ao processo de extração de dados das RSs, pode ter ocorrido indução ao viés devido a falta de padronização entre os estudos, embora a ADA (5) recomende a coleta de dados de forma cumulativa.

As perdas de retenção das restaurações em cada período de acompanhamento (*recall*) foram relatadas de três maneiras diferentes nos estudos primários:

1. Número absoluto ou percentual de eventos sem especificação quanto a forma de relato cumulativa ou não;

2. Número absoluto ou percentual de eventos sem referência a linha de base (*baseline*) ou ao *recall* do período e

3. Número cumulativo de eventos sucessivamente nos diferentes períodos, não deixando claro a taxa de retorno em cada grupo, fornecendo apenas a taxa de *recall* generalizada no período.

Além disso, os resultados deveriam ser relatados usando o protocolo *intention to treat*, pois leva em consideração todas as restaurações randomizadas no *baseline,* o que não ocorreu na maioria dos estudos. Portanto, não há consenso entre autores na forma de extração e descrição dos resultados. Sendo assim, esse achado exige a necessidade urgente de melhorar o

planejamento e delineamento dos estudos, padronização quanto ao relato de abandono de pacientes e descrição dos resultados nos ECRs em LCNCs. Ou seja, mais estudos clínicos randomizados de acompanhamento a longo prazo, focando em técnica e marcar comerciais específicas, ao invés de estratégias adesivas são necessários.

5.2 IMPLICAÇÕES PARA A PRÁTICA

As estimativas imprecisas para as taxas de retenção estão em conformidade com outros dois estudos (18, 21) que não encontraram diferenças entre as estratégias adesivas. No entanto, além das limitações deste estudo, a qualidade do conjunto de evidências nas três RSs foi considerada baixa devido ao risco “incerto” de viés. Sendo assim, os sistemas adesivos não devem ser rotulados pela sua estratégia adesiva pois sabemos que sua performance está mais relacionada a sua composição química. Tanto na abordagem ER quanto na SE, existem adesivos eficientes e ineficientes, porém quando combinados pelo rótulo de sua estratégia de união, apresentam resultados semelhantes.

6 CONCLUSÃO

Com base nos resultados observados nos estudos pudemos concluir:

- (1) e (2) nenhuma estratégia adesiva é superior a outra em LCNCS e
- (3) os adesivos considerados “padrão ouro” não apresentaram melhores taxas de retenção que os demais adesivos a eles comparados.

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ANEXO A: PROSPERO REGISTRATION NUMBER: CRD42016037743

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Back

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Dear Ms Simas
Thank you for submitting details of your systematic review *Clinical effectiveness of self-etch adhesives of a step in restoration of non-carious cervical lesions: a systematic review* to the PROSPERO register. We are pleased to confirm that the record has been published on the database.
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You are free to update the record at any time, all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility. You can log in to PROSPERO and access your records at
http://www.crd.york.ac.uk/PROSPERO
An email reminder will be sent to you on the anticipated completion date, prompting you to update the record.
Comments and feedback on your experience of registering with PROSPERO are welcome at: crd-register@york.ac.uk
Best wishes for the successful completion of your review.

Yours sincerely
Jimmy Christie
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PROSPERO is funded by the National Institute for Health Research and produced by CRD, an academic department of the University of York.

ANEXO B: PROSPERO REGISTRATION NUMBER: CDR42018112672

National Institute for Research

Back

PROSPERO
International prospective register of systematic reviews

Dear Ms Dreweck,

Thank you for submitting details of your systematic review "Which adhesive strategy is most clinically effective in non-carious cervical lesions (NCCL): a systematic review and a mixed treatment comparison meta-analysis" to the PROSPERO register. We are pleased to confirm that the record will be published on our website within the next hour.

Your registration number is: CRD42018112672

You are free to update the record at any time, all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility. You can log in to PROSPERO and access your records at https://www.crd.york.ac.uk/PROSPERO

Comments and feedback on your experience of registering with PROSPERO are welcome at: crd-register@york.ac.uk

Best wishes for the successful completion of your review.

Yours sincerely,

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