UNIVERSIDADE FEDERAL DO RIO DE JANEIRO

Centro de Ciências da Saúde

Faculdade de Odontologia

ALINE BORBUREMA NEVES

ANÁLISE LABORATORIAL E AVALIAÇÃO ECONÔMICA DO CIMENTO DE IONÔMERO DE VIDRO

Rio de Janeiro

2019

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Tese de doutorado submetida ao Programa de Pós-graduação em Odontologia (Área de Concentração: Odontopediatria) da Faculdade de Odontologia da Universidade Federal do Rio de Janeiro como parte dos requisitos para obtenção do título de Doutor em Odontologia (Área de Concentração: Odontopediatria).

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Rio de Janeiro
2019

FICHA CATALOGRÁFICA

Neves, Aline Borburema.

Análise laboratorial e avaliação econômica do cimento de ionômero de vidro. – Rio de Janeiro: UFRJ / Centro de Ciências da Saúde, Faculdade de Medicina, 2019.

106 f.: il.; 30 cm.

Orientadora: Aline de Almeida Neves.

Tese (doutorado) – UFRJ, Faculdade de Medicina, Programa de Pós-Graduação em Odontologia (Odontopediatria), 2019.

Referências: f. 99-106.

1. Materiais Dentários. 2. Cimentos de Ionômeros de Vidro. 3. Avaliação de Custo-Efetividade. 4. Microtomografia por Raio-X. 5. Revisão Sistemática. - Tese. I. Neves, Aline de Almeida. II. Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Faculdade de Medicina, Programa de Pós-Graduação em Odontologia (Odontopediatria). III. Título.

DEDICATÓRIA

Dedico este trabalho a Deus e
à minha amada família.

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AGRADECIMENTOS

Agradeço a Deus por tantas bênçãos concedidas e também por tudo que ainda viverei. Tudo é dEle, por Ele e para Ele. E, como diz minha citação favorita: “Ao recapitular a nossa história passada, havendo revisado cada passo de progresso até ao nosso nível atual, posso dizer: Louvado seja Deus! Ao ver o que Deus tem realizado, encho-me de admiração e de confiança na liderança de Cristo. Nada temos que recear quanto ao futuro, a menos que esqueçamos a maneira em que o Senhor nos tem guiado, e os ensinos que nos ministrou no passado.” (Ellen G. White - Testimonies, Life Sketches, pag. 196, 1915).

Aos meus pais, Paulo Cesar e Maria do Carmo, e ao meu irmão André Lucas por todo amor sempre. Todas as minhas conquistas também são de vocês! Obrigada por lutarem comigo e não medirem esforços para a concretização de todos esses sonhos. Amo vocês de todo o meu coração.

Ao meu amado noivo Clevison por tanto carinho, cuidado e amor. Obrigada por estar comigo e me apoiar em todo e qualquer momento. Amo você e este é simplesmente o início das nossas conquistas por toda a vida.

À minha querida orientadora professora Aline de Almeida Neves. É uma honra imensa ter trabalhado e convivido (e ainda compartilhar o mesmo nome) com uma pessoa tão incrível. Muito obrigada por todo apoio e pela orientação maravilhosa. Você merece todo sucesso do mundo.

À todos os queridos professores que fizeram parte da minha trajetória até aqui. Vocês mudaram a minha vida e sempre serei grata por tudo.

À todos os colegas, professores e funcionários da Faculdade de Odontologia UFRJ e do departamento de Odontopediatria. Vocês são um time de excelência.

À minha banca. Obrigada por aceitarem o convite com tanto carinho.

À minha amada equipe da São Leopoldo Mandic Rio de Janeiro, aos meus queridos alunos e pacientes. Vocês me fizeram crescer como profissional e sempre serei grata por todos os bons momentos compartilhados.

“Porque o Senhor dá a sabedoria
e da sua boca vem o conhecimento e o
entendimento.” (Provérbios 2:6)

RESUMO

NEVES, Aline Borburema. **Análise laboratorial e avaliação econômica do cimento de ionômero de vidro**. Rio de Janeiro, 2019. Tese (Doutorado em Odontologia – Área de concentração: Odontopediatria) – Faculdade de Odontologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2019.

Resumo: O objetivo desta tese foi analisar o cimento ionômero de vidro (CIV) quanto às suas características laboratoriais e seu custo-efetividade (CE). O estudo 1 avaliou a recuperação da densidade mineral da dentina cariada de dentes bovinos após a aplicação de materiais à base de silicato de cálcio e CIV comparado ao cimento de óxido de zinco e eugenol (OZE) por meio de micro-CT. Como resultado, todos os cimentos testados aumentaram a densidade mineral em relação ao OZE, porém, enquanto o Biodentine™ apresentou resultados inferiores, o CIV, o MTA e Portland apresentaram um potencial remineralizador semelhante e melhor. O estudo 2 objetivou caracterizar e comparar o grau de porosidade e a distribuição do tamanho dos poros de quatro CIVs. Os espécimes foram preparados de acordo com as normas ISO 9917-1 e escaneados em micro-CT. Observou-se que o grau de porosidade e a distribuição do tamanho de poros dos CIVs testados não foram semelhantes. Dentre grupos de CIVs restauradores de alta e baixa viscosidade, o Ketac Molar™ Easymix apresentou menor porosidade. O estudo 3 foi delineado como uma revisão sistemática onde avaliou-se a efetividade clínica e o custo-efetividade do CIV comparado a outros materiais/intervenções. Com base no PICO, ensaios clínicos randomizados (ECR) contendo análises de CE em pacientes que receberam qualquer tipo de tratamento dentário com CIV comparado a outros tratamentos e materiais foram incluídos. A análise qualitativa foi realizada para cada ensaio clínico randomizado e para a análise econômica. A qualidade da evidência e força de recomendação foram determinadas com o GRADE. Os dados de CE apresentaram alto risco de viés em alguns domínios. A maioria dos ECR apresentaram baixo risco de viés. Na análise econômica, o CIV apresentou-se como o material com melhor CE. Na meta-análise, o CIV e outros materiais/técnicas apresentaram risco semelhante de falhas, apesar do tempo de acompanhamento. De acordo com o GRADE, para 36 meses de acompanhamento, a certeza da evidência foi alta. Assim, o CIV é eficaz em comparação com outros materiais ou técnicas e apresenta o melhor CE. Conclui-se, então, que o CIV pode ser considerado um material de excelência em Odontologia, tanto em análises laboratoriais quanto na avaliação econômica, quando comparado a outros materiais e técnicas.

Palavras-chave: Materiais dentários; Cimento de ionômero de vidro; Bioatividade; Micro CT; Avaliação econômica; Custo efetividade; Revisão sistemática.

ABSTRACT

NEVES, Aline Borburema. **Laboratory analysis and economic evaluation of glass ionomer cements**. Rio de Janeiro, 2019. Tese (Doutorado em Odontologia – Área de concentração: Odontopediatria) – Faculdade de Odontologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2019.

Abstract: The aim of this thesis was to analyze the glass ionomer cement (GIC) regarding its laboratorial characteristics and its cost-effectiveness (CE). Study 1 evaluated carious dentin recovery of mineral density in bovine teeth after application of calcium silicate-based materials and GIC compared to zinc oxide eugenol cement (ZOE) using the micro-CT. As a result, all the tested cements increased mineral density in relation to ZOE. Biodentine™ presented lower mineral density changes, however GIC, MTA and Portland showed a similar and higher remineralization potential. Study 2 aimed to characterize and compare the degree of porosity and the pore size distribution of four GICs. The specimens were prepared according to ISO 9917-1 standards and scanned in a micro-CT. The degree of porosity and the pore size distribution of the tested GICs were not similar. Among groups of high and low viscosity restorative GICs, Ketac Molar™ Easymix presented lower porosity. Study 3 was designed as a systematic review to evaluate the clinical efficacy and cost-effectivity of GIC compared to other materials / interventions. Based on PICO, randomized controlled trials (RCTs) containing EC analyzes including patients receiving any type of dental treatment with GIC compared to other treatments and materials were included. Qualitative analysis was performed for each randomized clinical trial and for economic analysis. The quality of evidence and strength of recommendation were determined with GRADE. EC data presented a high risk of bias in some domains. Most RCTs were at low risk of bias. Regarding the economic analysis, GIC was the material with the best CE. In the meta-analysis, the GIC and other materials/techniques presented a similar risk of failure, despite the follow-up time. According to GRADE, for 36 months of follow-up, the certainty of the evidence was high, showing that GIC may be considered effective compared to other materials or techniques and presents the best CE. It is concluded that GICs represents a material of excellence in dentistry, both in laboratory analysis and in economic evaluation, when compared to other materials and techniques.

Keywords: Dental materials; Glass ionomer cements; Bioactive; Micro CT; Economic evaluation; Cost-effectiveness; Systematic review.

RESUMEN

NEVES, Aline Borburema. **Análisis de laboratorio y evaluación económica del cemento de ionómero de vidrio.** Rio de Janeiro, 2019. Tese (Doutorado em Odontologia – Área de concentração: Odontopediatria) – Faculdade de Odontologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 2019.

Resumen: El objetivo de esta tesis fue analizar el cemento de ionómero de vidrio (CIV) en lo que se refiere a sus características de laboratorio y costo-efectividad (CE). El estudio 1 evaluó la recuperación de la densidad mineral de la dentina cariada de dientes bovinos después de la aplicación de materiales a base de silicato de calcio y CIV comparado al cemento de óxido de zinc y eugenol (OZE), por medio del Micro-CT. Como resultado, todos los cementos probados han incrementado la densidad mineral en comparación al OZE. El Biodentine presentó resultados inferiores, ya el CIV, el MTA y Portland presentaron semejante potencial remineralizante. El estudio 2 objetivó caracterizar y comparar el grado de porosidad y la distribución del tamaño de los poros de 4 CIV. Los especímenes fueron preparados de acuerdo con las normas ISO 9917-1 y escaneados en Micro-CT. Se observó que el grado de porosidad y la distribución del tamaño de los poros de los CIV probados no fueron similares. Entre los grupos de CIVs restauradores de alta y baja viscosidad, el Ketac Molar^{TM}Easymix presentó menor porosidad. El estudio 3 fue delineado como una revisión sistemática donde se evaluó si el CIV es el material odontológico con más costo-efectivo y su eficacia clínica comparado a otros materiales / intervenciones. Con base en el PICO, los ensayos clínicos aleatorizados (ECR) que contenían análisis de CE incluyendo pacientes que han recibido cualquier tipo de tratamiento dental con CIV comparado a otros tratamientos y materiales se incluyeron. El análisis cualitativo se realizó en cada ensayo clínico aleatorizado y para el análisis económico. La calidad de la evidencia y la fuerza de recomendación se determinó con GRADE. Los datos de CE presentaron un alto riesgo de parcialidad en algunos ámbitos. La mayoría de los ECR presentaron un bajo riesgo de parcialidad. En el análisis económico, el CIV se presentó como el material con mejor CE. En el meta-análisis, el CIV y otros materiales / técnicas presentaron un riesgo similar de fallas, a pesar del tiempo de seguimiento. De acuerdo con GRADE, para 36 meses de seguimiento, la certeza de la evidencia fue alta. Así, el GIC es eficaz en comparación con otros materiales o técnicas y presenta el mejor CE. Se concluye que el CIV representa un material de excelencia en Odontología, tanto en análisis de laboratorio y en la económica, en comparación con otros materiales y técnicas.

Palabras-clave: Materiales dentales; Cemento de ionómero de vidrio; bioactividad; Micro CT; Evaluación económica; Costo de efectividad; Revisión sistemática.

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ESTUDO 1

ESTUDO 2

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LISTA DE SIGLAS

ATCC	*American Type Culture Collection*
BMP	*Bitmap*
CHEERS	*Consolidated Health Economic Evaluation Reporting Standards*
GRADE	*Grading of Recommendations Assessment, Development and Evaluation*
ICER	*Incremental cost-effectiveness ratio*
IPC	Índice de preços ao consumidor
ISO	*International Organization for Standardization*
KCl	Cloreto de potássio
KH_2PO_4	Fosfato monopotássico
LILACS	Literatura Latino-americana e do Caribe em Ciências da Saúde
Medline	*Medical Literature Analysis and Retrieval System Online*
MeSH	*Medical Subject Headings*
NaCl	Cloreto de sódio
NaH_2PO_4	Fosfato monossódico
pH	Potencial Hidrogeniônico
PICO	*Population, Intervention, Comparison e outcome*
PRISMA-P	*Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols*
PROSPERO	*Internacional Prospective Register of Systematic Review*

LISTA DE ABREVIATURAS

CIV	Cimento de ionômero de vidro
HMI	Hipomineralização molar-incisivo
Micro-CT	Microtomografia de raios X
MTA	Agregado trióxido mineral
OZE	Óxido de zinco e eugenol
TRA	Tratamento restaurador atraumático
UFC	Unidade formadora de colônia
VOI	Volume de interesse

LISTA DE SÍMBOLOS

%	Porcentagem
±	Mais ou menos
°	Graus
μL	Microlitro
μm	Micrometro
C	Celsius
mL	Mililitro
mm	Milímetro
mmol	Milimol

Sumário

1 INTRODUÇÃO

O tratamento odontológico ainda é uma necessidade real em todo o mundo, principalmente devido ao fato de que a cárie dentária não tratada em dentes permanentes e decíduos está entre as dez condições mais prevalentes do mundo (MARCENES *et al.*, 2013; ATCHISON e WEINTRAUB, 2017). Não somente a doença cárie está associada à necessidade de tratamento operatório, mas também os defeitos dentários, como a hipomineralização molar-incisivo (HMI) e outras alterações. A HMI afeta mais de 800 milhões de pessoas em todo o mundo (SCHWENDICKE *et al.*, 2018) e é descrita como um defeito qualitativo do esmalte (WEERHEIJM *et al.*, 2001; WEERHEIJM *et al.*, 2003) podendo resultar em fratura pós-eruptiva do esmalte/esmalte e dentina (NEVES, AMERICANO*, et al.*, 2019) e está frequentemente associada à lesão cariosa. De fato, crianças com HMI apresentam maior necessidade de tratamento odontológico comparado aos pacientes sem esta condição (JALEVIK e KLINGBERG, 2002). Portanto, essas doenças estão associadas à uma elevada carga econômica global e, considerando a escassez de recursos financeiros na maioria dos países, o conhecimento sobre as características laboratoriais, a eficácia e os custos dos tratamentos e materiais odontológicos utilizados são importantes para a alocação de recursos e diminuição dos custos de forma a maximizar o benefício à toda população (MORGAN *et al.*, 2012; LISTL *et al.*, 2015).

Muitos dos recursos técnicos destinados aos cuidados de saúde ainda são direcionados ao tratamento das lesões cariosas e, neste caso, a abordagem minimamente invasiva para o tratamento da doença cárie visa preservar maior quantidade de tecido dentário através da utilização do potencial de remineralização de novos materiais restauradores (DAI *et al.*, 2011). Em se tratando de economia em saúde, os custos diretos relacionados ao atendimento odontológico são estimados em mais de 290 bilhões de dólares por ano e melhorias na higiene bucal podem estar relacionadas com uma diminuição nos gastos e redução em outros custos indiretos (LISTL *et al.*, 2015). O tratamento odontológico convencional pode ser oneroso para a maioria da população e uma abordagem de acordo com os conceitos de mínima intervenção podem ser uma alternativa em saúde pública, uma vez que existe uma alta prevalência de doenças orais não tratadas (KASSEBAUM *et al.*, 2017). O tratamento restaurador atraumático (TRA) em segmentos preventivo, como selante dentário com cimento de ionômero de vidro (CIV) e em sua forma restauradora (restauração de TRA) são exemplos de odontologia minimamente invasiva e o CIV é o material odontológico de escolha para tal técnica operatória (FRENCKEN, 2017).

Dentre as técnicas atuais em odontologia minimamente invasiva, pode-se citar também a utilização de materiais bioativos como forma a induzir a remineralização da dentina cariada. A indução de uma resposta biológica específica na interface entre o material e os tecidos dentários, formando uma união, é definida como bioatividade (WATSON *et al.*, 2014). A remineralização da dentina parcialmente desmineralizada visa a renucleação de cristais minerais na estrutura da hidroxiapatita (BESINIS *et al.*, 2014). O processo de remineralização convencional, também conhecido como “*top to bottom approach*” utiliza, na presença de fluoreto, soluções contendo íons cálcio e fosfato (DAI *et al.*, 2011). Entretanto, outras estratégias têm sido atualmente estudadas, em presença de análogos biomiméticos (conhecidas como “*bottom up approach*”), onde a utilização de materiais à base de silicato de cálcio, como o Agregado Trióxido Mineral (MTA) e o Biodentine^{TM} (Septodont, Saint Maur des Fosses, France) tem sido sugeridas (KIM, J. *et al.*, 2010).

Dos materiais à base de silicato de cálcio, o agregado trióxido mineral (MTA) foi primeiramente indicado para reparos radiculares e, por sua biocompatibilidade e bioatividade, demonstrou-se um crescente interesse na sua aplicação em dentina coronária. O Biodentine^{TM}, pode ser considerado uma evolução do MTA com relação à redução do tempo de presa (ATMEH *et al.*, 2012), o que favorece sua utilização na clínica odontológica. Este material toma presa por meio de uma reação de hidratação, com a dissolução de grânulos de silicato de cálcio, de modo a produzir hidróxido de cálcio e hidratos de silicato de cálcio. Sua matriz detém grânulos não hidratados e contém pequenos espaços preenchidos por água onde o hidróxido de cálcio se distribui, o que proporciona elevada alcalinidade (ATMEH *et al.*, 2012). Dentre estes dois materiais à base de silicato de cálcio, o Biodentine^{TM} apresenta melhores propriedades bioativas, por induzir a formação de apatita após imersão em solução de fosfato (HAN e OKIJI, 2011).

O cimento de policarboxilato de zinco foi o precursor do CIV, tendo sido desenvolvido a partir do cimento fosfato de zinco, e já se encontrava disponível no final dos anos 1960. Em comparação com o cimento fosfato de zinco, o cimento de policarboxilato de zinco apresenta maior resistência à tração, menor solubilidade aos fluidos orais e alguma adesão ao esmalte dentário (Foley *et al.*, 2002). Além disso, o cimento policarboxilato zinco adicionado de fluoreto ("*tannin-fluoride*") pode reduzir o aporte de bactérias cariogênicas em remoção parcial de tecido cariado e promover a remineralização (Bjorndal, 2011; Hayashi *et al.*, 2011).

Dentre os materiais odontológicos utilizados para remineralização dentinária está o CIV. Este cimento foi introduzido em 1975 e sua utilização é amplamente difundida na odontologia restauradora. O potencial de remineralização dos CIVs é proporcionado pela liberação de íons de flúor e cálcio/estrôncio, que atua na re-formação de apatita, repondo os íons dos tecidos desmineralizados (Watson *et al.*, 2014). Fatores como aplicabilidade clínica, liberação de fluoreto, indução de hipermineralização, associada à deposição mineral nos poros da dentina e sua adesão química aos tecidos dentários (Ten Cate e Van Duinen, 1995; Kim, Y. K. *et al.*, 2010) fazem do CIV um material de referência em Odontologia. Sendo assim, os cimentos à base de silicato de cálcio e os CIVs são utilizados em odontologia minimamente invasiva visando a biomineralização dentinária. Estas duas classes de cimentos odontológicos restauradores à base de água são bons "substitutos da dentina", imitando suas propriedades físicas e mecânicas (Watson *et al.*, 2014).

As propriedades físicas, químicas ou mecânicas dos CIVs podem ser influenciadas por vários fatores e, dentre eles, a presença de porosidades e/ou bolhas após a mistura do material pode diminuir sua resistência mecânica (Nomoto e Mccabe, 2001). No entanto, um equívoco comum diz respeito ao conceito de porosidade versus defeitos do material durante a sua manipulação, incluindo bolhas de ar (Mitchell e Douglas, 1997). Foi demonstrado que alguns dos poros em CIVs podem estar relacionados com a reação de maturação lenta do material (Nicholson, 2018). De fato, a análise de porosidade realizada por meio de dados volumétricos em microtomografia computadorizada de raios X (micro-CT) confirmou que a distribuição de volume de poros nos CIVs é complexa e altamente variável, mas diminui com o tempo (BENETTI *et al.*, 2015).

Em se tratando da avaliação da mineralização da dentina cariada por meio da utilização de materiais bioativos, é importante conhecer as peculiaridades deste tecido dentário e as melhores técnicas para sua análise. A dentina apresenta-se como um tecido colagenoso mineralizado complexo (GOLDBERG *et al.*, 2011; LIU, LI*, et al.*, 2011), com sua fase mineral dividida em intrafibrilar e extrafibrilar. A fase extrafibrilar está localizada no interior dos espaços intersticiais que separam as fibrilas de colágeno. Já, as apatitas intrafibrilares, são depositadas no interior ou adjacente às zonas de gap das moléculas de colágeno, e se estendem ao longo dos espaços microfibrilares dentro da fibrila (LIU, MAI*, et al.*, 2011). Como a remineralização intrafibrilar é fundamental para restauração das propriedades mecânicas da dentina (KIM, Y. K. *et al.*, 2010), avaliações utilizando técnicas não destrutivas são fundamentais para se determinar o potencial bioativo dos materiais em reconstruir tanto a dimensão quanto a hierarquia estrutural dos tecidos mineralizados.

Nesse contexto, a utilização da técnica de micro-CT permite a comparação antes e após um procedimento experimental e a visualização da estrutura interna de um objeto, por uma reconstrução tridimensional do objeto estudado (ZOU *et al.*, 2009; NEVES ADE *et al.*, 2010). Assim, o uso desta técnica apresenta-se em crescente expansão em pesquisas odontológicas (OLEJNICZAK *et al.*, 2007). Com base nisto, o micro-CT tem sido amplamente utilizado para avaliações da desmineralização do esmalte e dentina, com a determinação dos perfis de densidade mineral baseados nas diferenças entre os coeficientes de atenuações dos raios X nos tecidos (ZOU *et al.*, 2009).

Com relação aos materiais bioativos e sua utilização na clínica odontológica, apesar de apresentarem aplicabilidade e potencial de remineralização, ainda há poucos estudos sobre o uso clínico do Biodentine™ como biomaterial substituto da dentina (KOUBI *et al.*, 2013; HASHEM *et al.*, 2015), e somente um artigo comparando este material ao CIV (HASHEM *et al.*, 2015). Em uma busca no *Clinical Trials*, não há estudos em andamento que avaliem a efetividade dos cimentos Biodentine™ e policarboxilato de zinco, comparados ao CIV, para capeamento pulpar indireto em odontopediatria. Ao contrário, diversos ensaios clínicos randomizados e revisões sistemáticas sobre o ionômero tem sido realizados, porém há poucos dados sobre avaliações de custo-efetividade. As avaliações econômicas em saúde são importantes para determinar se os benefícios de determinado investimento em assistência médica são mais valorosos que o custo de oportunidade (Lomas et al., 2018). É necessário identificar a carga econômica das doenças e seu tratamento para avaliar a alocação de recursos e possíveis economias monetárias (Listl et al., 2015).

Apesar de as propriedades do CIV não serem similares a outros materiais, revisões sistemáticas concluíram que não há diferença entre as taxas de sobrevivência do CIV comparado a resina composta ou amálgama para restaurações e selantes (FRENCKEN *et al.*, 2012; MICKENAUTSCH e YENGOPAL, 2012; RAGGIO *et al.*, 2013; SCHWENDICKE *et al.*, 2016). Em termos de custos diretos, o TRA e o uso de CIV no atendimento odontológico operatório parece ser uma alternativa viável e econômica na clínica odontológica (SMALES e HAWTHORNE, 1996; MICKENAUTSCH *et al.*, 2002). Mas não somente os custos diretos são importantes para a avaliação da economia em saúde, mas também a eficácia do material avaliado. A análise da economia em saúde é importante para determinar prioridades na atenção à saúde e nas políticas públicas e entre os diferentes tipos de avaliação econômica, a análise de custo-efetividade é um tipo de avaliação econômica que considera custos e suas conseqüências em algum curso de ação (MICKENAUTSCH *et al.*, 2002; OSCARSON *et al.*, 2003).

Assim, o conhecimento sobre as características laboratoriais e valores monetários relacionados ao custo-efetividade com cada material utilizado e sua efetividade clínica são de extrema importância para uma prática clínica eficaz ao longo do tempo e econômica para toda população.

2 PROPOSIÇÃO

2.1 Objetivo geral

Analisar o cimento ionômero de vidro quanto às suas características laboratoriais de bioatividade e porosidade, e realizar uma revisão sistemática de avaliação econômica sobre o custo-efetividade da utilização deste material na clínica odontológica.

2.2 Objetivos específicos

- Estudo 1

Em uma avaliação *in vitro*, avaliar o potencial remineralizador dos cimentos Biodentine^{TM}, agregado trióxido mineral (MTA), Portland e cimento de ionômero de vidro convencional, comparando com o cimento de óxido de zinco e eugenol, na alteração da densidade mineral da dentina artificialmente cariada.

- Estudo 2

Caracterizar e comparar o grau de porosidade e a distribuição do tamanho dos poros dos cimentos de ionômero de vidro restauradores de alta e baixa viscosidade Ketac Molar^{TM} Easymix (3M ESPE, Seefeld, Germany), Maxxion R (FGM, Joinville, Brazil), Riva self-cure (SDI, Victoria, Australia) e Vitro Molar (DFL, Rio de Janeiro, Brazil) com a técnica não-destrutiva micro-CT.

- Estudo 3

Por meio de uma revisão sistemática, avaliar a efetividade clínica e observar se o CIV é o material odontológico com melhor custo-efetividade comparado à resina composta, selantes de resina, verniz fluoretado, amálgama, placebo, educação em saúde bucal e outros materiais odontológicos em diferentes procedimentos clínicos em crianças, adolescentes, adultos e idosos.

3 DELINEAMENTO DA PESQUISA

3.1 Considerações iniciais e tipos de estudos

A presente tese de doutorado foi estruturada de forma a responder questionamentos sobre características laboratoriais e econômicas do cimento ionômero de vidro. A mesma foi subdivida em artigos científicos e objetivou a avaliação destes tópicos por meio de dois estudos *in vitro* e uma revisão sistemática sobre o custo de tais materiais odontológicos utilizados para procedimentos restauradores.

No primeiro estudo, o potencial remineralizador de cimentos odontológicos utilizados para recuperação da densidade mineral da dentina cariada de dentes bovinos foi avaliado por meio da técnica não destrutiva de microtomografia de raios-X. Assim, como o CIV é um dos materiais odontológicos restauradores mais utilizados em Odontopediatria e clínica geral, os demais trabalhos visaram analisar importantes fatores sobre este cimento.

O segundo trabalho teve por objetivo caracterizar e comparar o grau de porosidade e a distribuição do tamanho dos poros de quatro cimentos de ionômero de vidro restauradores de alta e baixa viscosidade comumente utilizados pelos cirurgiões-dentistas no Brasil para procedimentos restauradores em Odontopediatria e clínica odontológica, sendo estes os cimentos Ketac Molar^{TM} Easymix (3M ESPE, Seefeld, Germany), Maxxion R (FGM, Joinville, Brazil), Riva self-cure (SDI, Victoria, Australia) e Vitro Molar (DFL, Rio de Janeiro, Brazil). Tal análise foi realizada com a técnica não-destrutiva micro-CT.

Para os estudos laboratoriais, foram realizados cálculos amostrais e uma explicação detalhada sobre a obtenção, preparo e avaliação das amostras. Visando o cegamento e devida aleatorização, as amostras foram alocadas por um terceiro participante do estudo. O mesmo não participou do preparo das amostras ou da avaliação final. Todas as avaliações foram realizadas por meio de programas de computador, sendo que tal avaliador não participou das análises laboratoriais.

O terceiro estudo foi delineado como uma revisão sistemática onde se avaliou se o cimento de ionômero de vidro (CIV) é o material odontológico mais custo-efetivo e sua eficácia clínica comparado a outros materiais/intervenções em dentes decíduos e permanentes.

3.2 Primeiro estudo

O objetivo do primeiro estudo laboratorial foi avaliar as alterações na densidade mineral da dentina cariada após a aplicação de materiais à base de silicato de cálcio (Biodentine^{TM}, MTA e cimento Portland) e um ionômero de vidro convencional comparado a um material controle (cimento de óxido de zinco e eugenol).

Seleção dos espécimes

No presente estudo *in vitro*, o cálculo amostral foi realizado e o nível de significância foi estabelecido em 1% e poder de 0,95, o que resultou em oito amostras por grupo. Foram adicionados 20% de cada amostra, resultando em 10 espécimes por grupo.

De um *pool* de incisivos bovinos extraídos, armazenados em formalina tamponada a 2% por um período máximo de 6 meses, 10 elementos sadios, sem manchas, linhas de fratura ou outros defeitos macroscopicamente visíveis foram selecionados. Cinco discos de dentina foram obtidos de cada espécime seccionando a dentina radicular transversalmente usando um disco de diamante (300 µm) montado em uma máquina de corte (Isomet, Buehler, Lake Bluff, IL, EUA) sob refrigeração constante. Cada disco de dentina obtido da parte radicular foi distribuído aleatoriamente em um dos cinco grupos experimentais, a fim de evitar viéses em relação às diferenças na densidade mineral entre os espécimes e permitir uma análise de medidas repetidas.

Modelo de formação do biofilme bacteriano para indução de lesões de cárie artificiais

Um modelo microbiano de múltiplas espécies para a preparação de lesões de cárie artificiais foi utilizado no presente estudo. As cepas de *Streptococcus mutans* (ATCC 25175), *Streptococcus sobrinus* (ATCC 33478) e *Lactobacillus casei* (ATCC 393) foram reativadas de suas culturas originais em meio de cultura *Brain Heart Infusion Agar* (BHI Agar) por 48 h a 37° C, com 5 % de CO_2 para verificar o grau de pureza de cada linhagem. Em seguida, uma série de colônias bacterianas foram coletadas e suspendidas individualmente em 25 mL de meio caldo BHI (Difco, Sparks, EUA). A concentração de células foi determinada após incubação a 37 ° C por 24 horas, em espectrofotômetro no comprimento de onda de 625 nm, obtendo densidade celular equivalente a 1,5 x 10^8 unidades formadoras de colônia (UFC) por mililitro (UFC/mL) com absorbância entre 0,08 a 0,13.

Os espécimes dentários foram fixados com cera pegajosa derretida em placas de cultura de poliestireno com 24 poços (TPP, ZellkulturTestplatte 24 F), deixando a superfície dentinária exposta. Após a esterilização da placa com óxido de etileno gasoso, o inoculo microbiano (15µL/poço) e meio de cultura (BHI suplementado com sacarose a 10%, 1,485µL/poço) foram adicionados a cada poço, representando assim um inóculo com uma concentração final de aproximadamente 5 X 10^6 UFC/mL. O conjunto foi incubado em microaerofilia por quatro dias a 37 ° C para formar um biofilme cariogênico maduro. A cada 24h, o meio de cultura suplementado com sacarose foi renovado em cada poço (1400 dos 1500µL / poço) por aspiração com uma pipeta. O pH do sistema foi em torno de 4. Todos os procedimentos foram realizados dentro de uma câmara de fluxo de ar laminar, sob ambiente asséptico.

Ao final do ensaio de biofilme, os fragmentos de dente foram removidos dos poços e limpos com uma escova de dentes macia e água e, em seguida, imersos em água Milli-Q dentro de um ultra-som por 15 minutos.

Experimento com os cimentos

Após o período de produção de lesões de cárie artificiais, a amostra (50 blocos de dentina) foi dividida em cinco grupos de cimento (n = 10 por grupo), sendo: 1) óxido de zinco e eugenol (OZE); 2) Biodentine™ (Septodont, Saint-Maur-des-Fossés, France); 3) MTA (Angelus, Londrina, PR, Brasil); 4) Cimento Portland (Hidracal, Canoas, RS, Brasil) e 5) CIV (Ketac Molar™, 3M ESPE, Seefeld, Germany). Nenhum pré-tratamento foi realizado sobre a dentina cariada.

Metade de cada espécime recebeu o cimento testado e a outra metade foi coberta com cera (controle negativo) (Figura 1). Cada material foi manipulado e aplicado aos blocos de dentina de acordo com as instruções do fabricante.

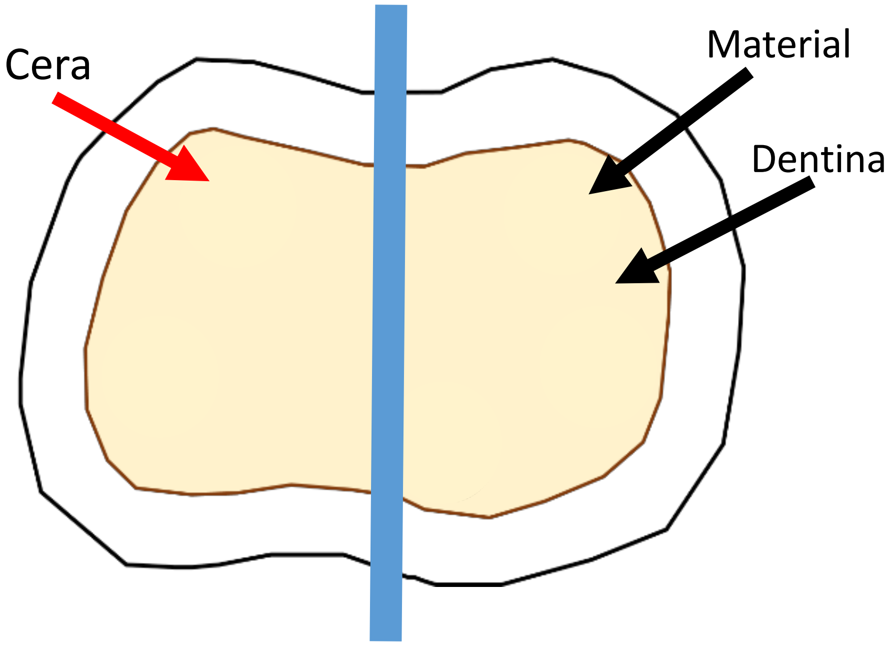

Figura 1: Esquema da inserção do material na superfície lisa em dentina hígida e metade do espécime coberto com cera.

As amostras foram colocadas em frascos fechados contendo gaze estéril embebida em solução salina tamponada com fosfato (PBS) por 30 dias. A solução de PBS (136.4 mmolL^{-1} NaCl, 2.7 mmol L^{-1} KCl, 8.2 mmol L^{-1} NaH_2PO_4 e 1.25 mmol L^{-1} KH_2PO_4 em 1000 mL de água destilada: pH 7.4) foi utilizada para desencadear bioatividade nos grupos experimentais, conforme proposto anteriormente (HAN e OKIJI, 2011).

Avaliação em Micro-CT

Após o período experimental com os cimentos testados, os espécimes foram escaneados em um micro-CT de alta energia (Skyscan 1173, Bruker micro-CT, Kontich, Belgium). Os espécimes foram envolvidos em parafilme durante os procedimentos de escaneamento para evitar ressecamento. O escaneamento durou aproximadamente 85 minutos para cada amostra.

Após a aquisição das imagens, as seções transversais de cada espécime foram reconstruídas usando um software dedicado (NRecon, Bruker) utilizando-se parâmetros padronizados. A reconstrução foi importada para um software de visualização 3D (Dataviewer, Bruker) e um volume de interesse (VOI) com 2,5 mm de espessura foi selecionado. O VOI selecionado foi importado para o programa ImageJ (implementação do Fiji) e uma projeção de intensidade média foi obtida de cada espécime para avaliação dos perfis de densidade. Os perfis foram retirados em cada pixel a partir da superfície até 250 μm de profundidade na dentina.

Os perfis das superfícies cobertas e expostas foram plotados e o parâmetro de perda mineral ∆Z foi calculado para cada perfil em cada amostra. Os valores de ∆Z dos perfis da superfície coberta foram subtraídos dos valores obtidos das superfícies expostas para calcular a mudança mineral final em cada amostra. Valores positivos de ∆Z indicam perda mineral, enquanto valores negativos indicam aumento da densidade mineral.

3.3 Segundo estudo

Dois CIVs convencionais para restauração, comercialmente disponíveis no Brasil (MaxxionR, FGM, Joinville, Brasil e Riva *selfcure,* SDI, Victoria, Austrália) e dois CIVs de alta viscosidade (Ketac Molar™ Easymix, 3M ESPE, Seefeld, Alemanha e Vitro Molar, DFL, Rio de Janeiro, Brasil) foram utilizados no presente estudo. Todos os cimentos eram autopolimerizáveis e de mistura manual. Os espécimes foram preparados de acordo com as normas ISO 9917-1 para cimentos à base de água.

Cálculo amostral

O cálculo amostral baseou-se em um estudo anterior (Bonifacio *et al.*, 2009) e utilizou valores de propriedades mecânicas correspondentes aos mesmos CIVs utilizados no presente estudo por meio de um teste T (BioEstat, v.5.3, Instituto Mamiruá, AM, Brasil). O nível de significância foi estabelecido em 1% e o poder do teste em 0,95. Como resultado, obteve-se um tamanho amostral de 8 amostras por grupo. Ao adicionar 20% desse valor, o número final alcançado foi de 10 amostras por grupo, com um total de 40 espécimes.

Confecção dos espécimes

Amostras padronizadas foram fabricadas em moldes cilíndricos com 4,0 ± 0,1 mm de diâmetro e 6,0 ± 0,1 mm de altura (100,5 mm^3) (Figura 2). Todas as amostras foram preparadas por um único operador seguindo as instruções do fabricante quanto à proporção, preparação, técnica de mistura e manuseio. A manipulação do cimento foi realizada em temperatura ambiente (25 ± 1 °C) e umidade relativa não controlada completamente, mas em torno de 50 ± 5%.

Os moldes foram lubrificados com vaselina sólida e os CIVs foram misturados com uma espátula de plástico em blocos de papel até se obter um cimento brilhante e homogêneo. O material foi imediatamente colocado nos moldes com o auxílio de uma seringa de inserção (Centrix, DFL, Rio de Janeiro, Brasil) e o excesso de cimento foi removido. Em seguida, uma leve pressão digital foi aplicada no molde para adaptação final do material. Dez minutos depois, após o endurecimento inicial da amostra, os espécimes foram removidos dos moldes e uma fina camada de vaselina foi aplicada ao redor dos espécimes para evitar a sinérese. As amostras foram então armazenadas em água destilada por 24 horas a 37 °C.

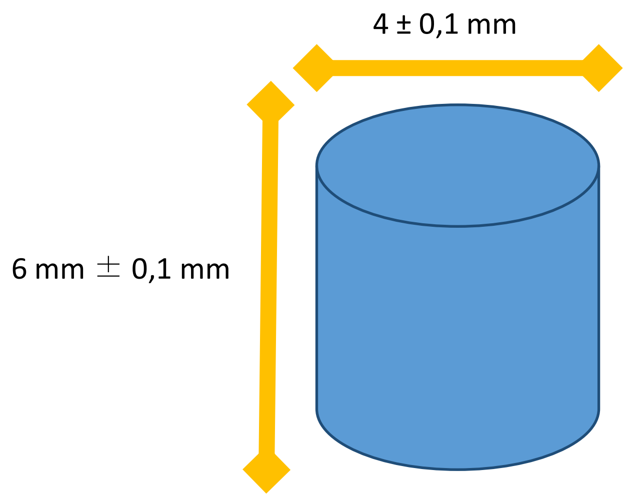

Figura 2: Esquema dos corpos de prova dos quatro tipos de cimento de ionômero de vidro.

Escaneamento no micro-CT e reconstrução

As amostras foram escaneadas em um micro-CT de alta energia (Skyscan 1173, Bruker, Kontich, Bélgica) com parâmetros de aquisição definidos. O tempo de escaneamento foi de aproximadamente 70 minutos para cada amostra. As projeções foram salvas como imagens em formato tiff de escala de cinza de 16 bits. Após a aquisição da imagem, a reconstrução foi realizada utilizando um software (NRecon, v.1.6.9, Bruker) com parâmetros padronizados para minimização de artefatos, incluindo correção de artefatos em anel de 1, correção de endurecimento do feixe de 25% e limites de contraste (0 - 0,15) . As imagens foram reconstruídas no formato de 8 bit*.BMP.

Análise da porosidade

Os volumes transversais de cada espécime foram recortados digitalmente com um raio de 150 pixels (1,82 mm) e 5 mm de altura (77,8 mm^3), a fim de excluir áreas superficiais externas e possivelmente não homogêneas dos cimentos e padronizar as leituras . Um filtro mediana 3D com raio de 1 pixel foi aplicado a cada volume cortado para reduzir o ruído e, após isso, os histogramas de todas as imagens foram normalizados de acordo com os valores médios de cinza para cada grupo de cimento. O limiar para poros foi fixado no valor de cinza 40 após análise da representatividade de espécimes em cada grupo. A porosidade total, assim como a distribuição dos tamanhos dos poros foram obtidas para cada amostra experimental do grupo cimento. Os poros foram considerados pequenos se o volume fosse menor que 0,01 mm^3 e grande se o volume fosse maior que 0,01 mm^3.

3.4 Terceiro estudo

A análise da economia em saúde é importante para determinar prioridades na atenção à saúde e nas políticas públicas. Dentre os diferentes tipos de avaliação econômica, a análise de custo-efetividade é um tipo de avaliação econômica que considera custos e suas consequências em algum curso de ação (MICKENAUTSCH *et al.*, 2002; OSCARSON *et al.*, 2003). Desta forma, o objetivo deste terceiro estudo foi realizar uma revisão sistemática sobre o custo-efetividade do CIV comparado à resina composta, selantes de resina, verniz fluoretado, amálgama, placebo, educação em saúde bucal e outros materiais dentários em diferentes procedimentos clínicos em crianças, adolescentes, adultos e idosos.

Com base nos critérios PICO (População - P, Intervenção - I, Comparação - C e Desfechos - O), ensaios clínicos randomizados contendo análises de custo-efetividade com pelo menos 1 ano de acompanhamento incluindo crianças, adolescentes, adultos ou pacientes idosos (P) que receberam qualquer tipo de tratamento dentário operatório com cimento de ionômero de vidro (I) comparado com aqueles que receberam outros tipos de tratamento como resina composta, selantes de resina, verniz fluoretado, amálgama, placebo , educação em saúde bucal e outros materiais odontológicos e / ou outros tipos de CIV (C) e sua relação custo-efetividade (O) foram incluídos.

O protocolo desta revisão sistemática foi registrado no banco de dados PROSPERO (*Internacional Prospective Register of Systematic Review*) sob o número de registro CRD42017061052, e foi relatado de acordo com o PRISMA-P (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols*) e três outras diretrizes sobre a preparação de revisões sistemáticas de avaliações econômicas.

Com base nos elementos da pergunta PICO, o vocabulário controlado termos MeSH, termos livres e palavras-chave foram definidos e utilizados para executar a estratégia de busca usando uma combinação dessas palavras. Esta estratégia foi utilizada para não impor restrições e maximizar a busca por artigos. A busca manual também foi realizada e a lista de referências de cada artigo relevante foi pesquisada manualmente. Não houve nenhuma restrição de idioma e ano de publicação.

Cinco bases de dados foram consultadas e atualizadas até abril de 2019: MEDLINE via PubMed, Scopus, Web of Science, Cochrane *Library* e Lilacs / BBO. A literatura cinzenta (*OpenGrey*) também foi pesquisada. Alertas foram criados em cada banco de dados para informar sobre possíveis novos artigos.

Dois revisores (ABN e MBM) realizaram, de forma independente, a estratégia de busca, a fim de identificar os estudos elegíveis e avaliar títulos e resumos dos estudos identificados em todas as bases de dados eletrônicas. Os estudos incluídos nesta revisão sistemática foram estudos de intervenção do tipo ensaio clínico randomizado que continham a análise de custo-efetividade de cimentos de ionômero de vidro e outros materiais odontológicos ou estratégias em vários tratamentos dentários em avaliações econômicas completas. Estudos com menos de 1 ano de acompanhamento, estudos observacionais, revisões de literatura, cartas ao editor, resumos, relatos ou séries de casos, ensaios não controlados, estudos de avaliação econômica parciais, avaliações econômicas baseadas em modelos e estudos com relação de custo-efetividade incremental não relatada (ICER) foram excluídos.

Dados referentes às características dos participantes e dados dos estudos incluídos como autor(es), ano de publicação, país, perspectiva da avaliação econômica, desenho do estudo, idade, número total de participantes, tipo de dentes, intervenção e comparador, desfechos, assim como dados que dizem respeito à avaliação econômica, tais como taxa de desconto e horizonte temporal foram extraídos em formulários de extração e analisados por dois autores (ABN e MBM).

Em relação aos dados econômicos, os valores foram extraídos para cada estudo e os custos totais e ICER foram inflacionados até fevereiro de 2019 por dois autores (ABN e CLV). Para os valores em outras moedas que não estavam descritos em dolar americano, a conversão para US$ foi feita utilizando os valores descritos nos estudos e o ano base do estudo original e, posteriormente, foi necessário corrigir os valores até fevereiro de 2019, tendo como referência o Índice de Preços ao Consumidor (IPC). Para valores originalmente descritos em dólares norte-americanos, somente foi necessário corrigir os valores atualizando o ano base de análise até fevereiro de 2019 utilizando IPC.

A análise qualitativa foi realizada para cada ensaio clínico randomizado e para a análise econômica. A avaliação do risco de viés foi analisada para cada estudo incluído. Para avaliação do estudo primário (ensaio clínico) o handbook da Cochrane foi utilizado - "*Bias Risk Assessment of Randomized Controlled Studies" tool* (Cochrane Handbook 5.0.1). Entre os sete domínios Cochrane, dois não foram considerados como domínios-chave devido a diferenças entre as técnicas operatórias e o aspecto clínico dos materiais, a saber, os domínios: cegamento dos operadores e participantes e cegamento dos examinadores. Para o domínio de cegamento, se o avaliador final foi cegado, mas o operador e o paciente não foram cegados para a intervenção, o estudo foi classificado como baixo risco de viés. Nesta revisão, os domínios-chave foram geração de sequência aleatória, ocultação de alocação e relato seletivo do desfecho. Os estudos foram classificados como baixo risco de viés se esses domínios-chave fossem adequados. Para avaliar o risco de viés de ensaios clínicos randomizados com avaliação econômica realizada paralelamente, todos os ensaios clínicos primários e sem a análise de custos foram avaliados objetivando esclarecer importantes fatores em cada domínio.

Para a avaliação de qualidade das análises econômicas, a ferramenta CHEERS (*Consolidated Health Economic Evaluation Reporting Standards*) (HUSEREAU *et al.*, 2013) foi utilizada. O CHEERS é composto por 24 itens baseados na seguinte subdivisão: 1) Título e resumo; 2) Introdução; 3) Métodos; 4) Resultados; 5) Discussão e 6) Outros (Fonte de financiamento e conflitos de interesse). A qualidade da evidência (certeza nas estimativas de efeito) foi determinada para o desfecho utilizando o GRADE (*Grading of Recommendations Assessment, Development and Evaluation*). A qualidade da evidência pode variar de muito baixa a alta.

Para análise quantitativa do desfecho dos estudos incluídos, comparando o desempenho clínico (falhas) entre o CIV e outros materiais, a meta-análise foi realizada usando o Software RevMan 5.3 (Review Manager v. 5.3, The Cochrane Collaboration; Copenhague, Dinamarca). A falha foi sub-agrupada para o horizonte temporal, considerando as taxas de falhas e o total de cada material ou estratégia. A incidência de falhas (eventos) e o número total de dentes ou pacientes (com restaurações de CIV ou selantes) e grupo controle (outros materiais / técnicas) foram incluídos para calcular a Razão de Risco com intervalo de confiança de 95%. Uma análise de subgrupo foi realizada de acordo com o seguimento.

Modelos de efeitos aleatórios foram empregados porque os estudos não eram funcionalmente equivalentes com objetivo de generalizar os resultados da metanálise (BORENSTEIN M, 2009). A heterogeneidade foi testada usando o índice I^2. A meta-análise não foi executada para dados de custo.

4 DESENVOLVIMENTO DA PESQUISA

4.1 Artigo 1 – Mineral density changes in bovine carious dentin after treatment with bioactive dental cements: A comparative micro-CT study.

Publicado na revista *Clinical Oral Investigations* – Qualis A1.

4.2 Artigo 2 – Porosity and pore size distribution in high viscosity and conventional glass ionomer cements: A micro-CT study

Submetido para publicação na revista *Dental Materials Journal* – Qualis A2.

4.3 Artigo 3: Is glass ionomer cement the most cost-effective dental material? A cost-effectiveness systematic review and meta-analysis of clinical effectiveness of randomized clinical trials with economic evaluation performed alongside.

Submetido para publicação na revista *Journal of Dentistry* – Qualis A1.

4.1 Artigo 1 – Mineral density changes in bovine carious dentin after treatment with bioactive dental cements: A comparative micro-CT study.

Publicado na revista *Clinical Oral Investigations* – Qualis A1.

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Clinical Oral Investigations
https://doi.org/10.1007/s00784-018-2644-2

ORIGINAL ARTICLE

Mineral density changes in bovine carious dentin after treatment with bioactive dental cements: a comparative micro-CT study

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Received: 30 May 2018 / Accepted: 11 September 2018

Abstract

Objectives To evaluate the potential of conventional glass ionomer cement (GIC), Biodentine™, MTA, and Portland cement to induce mineral density changes in carious dentin compared to zinc oxide eugenol control cement (ZOE).

Materials and methods Fifty blocks of bovine root dentin were prepared and a biofilm model using ATCC strains of *S.mutans*, *S.sobrinus*, and *L.casei* was used to promote artificial dentin lesions. After demineralization, the blocks were randomly divided into the five cement groups. Half of the surface of each specimen received the tested material and the other half was covered with wax (control). Samples were stored in phosphate buffered saline solution for 30 days and after that were scanned in a micro-CT with standardized parameters. Dentin mineral density changes were calculated using differences in plot profiles of the exposed and control carious dentin. Friedman's test, followed by Wilcoxon signed-rank test was used with 5% significance.

Results Mean ΔZ values for the cements were 48.63 ± 19.09 for the control (ZOE), 63.31 ± 32.59 for Biodentine™, 114.63 ± 72.92 for GIC, 109.56 ± 66.28 for MTA, and 106.88 ± 66.02 for Portland cement. All cements showed a statistically significant increase in ΔZ values compared to the control, but Biodentine™ values were statistically significantly lower compared to GIC and the other calcium silicate cements.

Conclusions Tested materials present potential to induce mineral density changes in carious bovine dentin. MTA, Portland, and GIC showed higher bioactivity potential than Biodentine™.

Clinical relevance Based on minimally invasive concept, materials with remineralization potential can be used to preserve diseased but still repairable dental tissue.

Keywords Dentin caries · Bioactive cements · Micro-CT · MTA · Glass ionomer

Introduction

Although technical resources destined to oral health care are still mostly directed to the treatment of cavitated dental caries lesions, a contemporary and more conservative approach, based on minimally invasive treatments, has been proposed to preserve diseased, but repairable dental tissue, supported by the remineralization potential of new restorative materials [1–3].

Among current techniques in minimally invasive dentistry, the use of bioactive materials as a way to induce remineralization of carious dentin precludes induction of a specific biological response at the interface between the material and the dental tissue [4]. Remineralization of partially demineralized dentin aims to promote re-nucleation of mineral crystals into the structure of hydroxyapatite [5]. Examples of bioactive materials include calcium silicate-based and glass ionomer cements.

Dentin is a complex collagenous mineralized tissue [6, 7] and during clinical procedures, dental materials are applied at the surface of diseased tissue in an attempt to restore mineral density and keep the tooth vitality [8]. For this reason, analysis of mineral changes in dentin using non-destructive

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Published online: 15 September 2018

laboratorial techniques is important to establish the bioactive potential of dental materials in reestablishing the structural hierarchy of mineralized tissues. In this regard, micro-computed tomography (micro-CT) has been used to evaluate enamel and dentin mineralization dynamics by obtaining mineral density profiles of the tissues based on X-ray attenuations [9, 10].

Thus, the aim of the present study was to evaluate mineral density changes in demineralized carious dentin induced by contemporary calcium silicate-based materials (Biodentine™, MTA, and Portland cement) and a conventional glass ionomer compared to a control material (zinc oxide-eugenol cement).

Materials and methods

Specimen selection

For this in vitro study, sample size calculation was performed with a 1% significance level and power of 0.95, resulting in eight samples per group. Adding 20% of the sample, each evaluated group was composed of ten specimens.

From a pool of extracted bovine incisors, obtained from fresh slaughter and stored in 2% buffered formalin for a maximum of 6 months, ten sound teeth, without stains, fracture lines, or other macroscopically visible defects were selected.

Five dentin disks were obtained from each specimen by sectioning the root dentin transversally using a diamond disk (300 μm) mounted on a cutting machine (Isomet, Buehler, Lake Bluff, IL, USA) under water cooling. From each root, one dentin disk was randomly assigned to one of the five experimental groups in order to avoid bias regarding differences in mineral density among the specimens and allowing a repeated measure analysis.

Artificial caries formation using a microbial model

A multi-species microbial model for preparing artificial caries lesions was used in the present study. The reference strains of *Streptococcus mutans* (ATCC 25175), *Streptococcus sobrinus* (ATCC 33478), and *Lactobacillus casei* (ATCC 393) were reactivated from its original cultures in Brain Heart Infusion Agar (BHI Agar) medium for 48 h at 37 °C, with 5% CO_2 to verify the degree of purity of each strain. After that, a loopfull of bacterial colonies were collected and suspended individually, in 25 mL of BHI Broth medium (Difco, Sparks, USA). The concentration of cells was determined after incubation at 37 °C for 24 h, in a spectrophotometer at wavelength 625 nm, obtaining cell density equivalent to 1.5×10^8 colony forming units (CFU) per milliliter (CFU/mL) at absorbance between 0.08 to 0.13.

Each dentin disk was fixed with hard wax inside a 24-well culture plate, leaving the dentin surface exposed. After sterilization of the plate with ethylene oxide gas, microbial inoculum (15 μl/well) and culture medium (BHI supplemented with 10% sucrose, 1.485 μl/well) were added to each well, representing thus an inoculum with a final concentration of approximately 5×10^6 CFU/mL. The set was incubated in microaerophilic conditions for 4 days at 37 °C to form a mature cariogenic biofilm. Every 24 h, sucrose-supplemented culture medium was renewed in each well (1400 of the 1500 μL/well) by aspiration with a pipette. The pH of the system was around 4. All procedures were performed inside a laminar air-flow chamber, under aseptic environment.

At the end of the biofilm assay, the tooth fragments were removed from the wells and cleaned with a soft toothbrush and water and after that, by immersion in Milli-Q water inside an ultrasound bath for 15 min.

Experimental period with bioactive cements

After the experimental period of artificial caries lesions production, the sample (50 dentin blocks) was assigned to five cement groups ($n = 10$ per group; one slab from each incisor) as follows: (1) zinc-oxide eugenol (ZOE), (2) Biodentine™ (Septodont, Saint-Maur-des-Fossés, France), (3) MTA (Angelus, Londrina, PR, Brazil), (4) Portland cement (Hidracal, Canoas, RS, Brazil), and (5) a conventional glass ionomer cement (Ketac Molar™, 3M ESPE, Seefeld, Germany - GIC). No pre-treatment was performed at the dentin surface. Half part of each specimen received the tested cement and the other half was covered with soft wax (negative control). Each material was manipulated and applied to the dentin blocks according to manufacturer's instructions.

Samples were placed in closed vials containing sterile gauze soaked in phosphate buffered saline solution (PBS) for 30 days. The PBS solution (136.4 $mmolL^{-1}$ NaCl, 2.7 mmol L^{-1} KCl, 8.2 mmol L^{-1} NaH_2PO_4, and 1.25 mmol L^{-1} KH_2PO_4 in 1000 mL of distilled water: pH 7.4) was used to trigger bioactivity in the experimental groups, as previously proposed [11].

Micro-CT examination

After the experimental period with the tested cements, the specimens were scanned in a high-energy micro-CT (Skyscan 1173, Bruker micro-CT, Kontich, Belgium). They were wrapped in parafilm™ during the scanning procedures to avoid desiccation. Acquisition parameters included: 70 kV, 114 μA, detector size 2240 × 2240 pixels, 8.19-μm pixel size, 1-mm thick Al filter, 1-s exposure time, 0.5° rotation step over 360°, frame averaging of 5, and random movements of 40. Scanning time was approximately 85 min for each specimen.

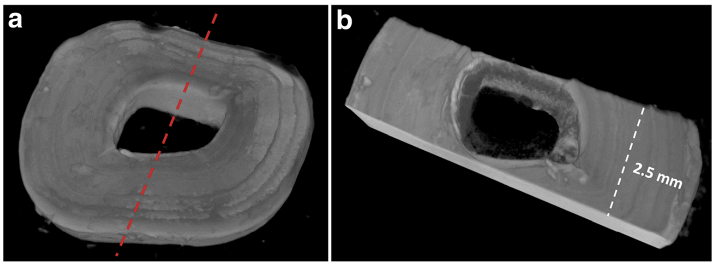

Fig. 1 **a** Reconstruction of one bovine root slab. Red dotted line denote specimen halves used for control (soft wax) and cement application after dentin demineralization. **b** Volume of interest used to produce the average intensity gray value projection

After acquisition, cross-sections of each specimen were reconstructed using a proprietary software (NRecon, Bruker) using standardized parameters: ring artifact correction of 10, beam hardening correction of 75%, no noise reducing filters, and input of minimum (0) and maximum (0.15) contrast limits. The reconstructed stack (Fig. 1a) was imported into a 3D visualization software interface (Dataviewer, Bruker) and a volume of interest (VOI), at the middle of the root part (2.5 mm thickness) was selected (Fig. 1b). The selected VOI was imported in ImageJ (Fiji implementation) and an average intensity projection (AIP) was obtained from each specimen for evaluation of density profiles. Figure 2a shows one of the average intensity projections. In each projection, two profiles of density values along a line were obtained (one at the exposed—red dotted line and one at the covered—blue dotted line dentin region). The profiles were taken at each pixel starting from the dentin surface up to 250 µm deep into the dentin layer.

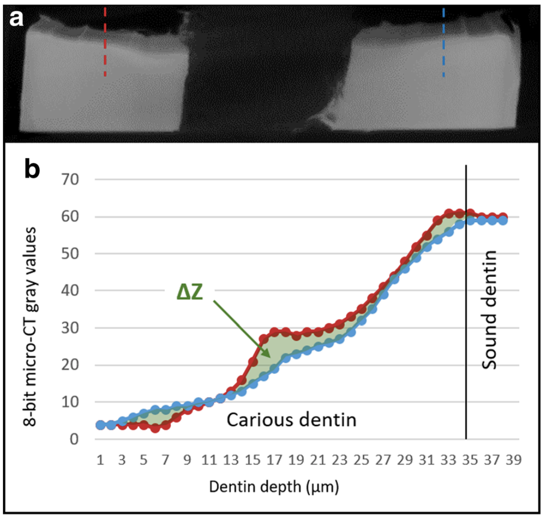

Fig. 2 **a** Average gray value intensity projection where mineral density paths (dotted lines) were taken. Red path denote dentin area exposed to the bioactive cements while blue path shows control path covered with soft wax during the experimental period. **b** Graph illustrating calculation of ΔZ values from the difference between mineral density paths of experimental (red) and control (blue) sides of root slabs

Profiles from covered and exposed surfaces were plotted and the mineral loss parameter ΔZ was calculated for each profile in each specimen (Fig. 2b). ΔZ values from the covered surface profiles were subtracted from values obtained from exposed surfaces to calculate the final mineral change in each specimen. Positive ΔZ values indicate mineral loss while negative values indicate mineral density increase.

Statistical analysis

Normality was checked by Shapiro-Wilk test. Null hypothesis of normality was rejected and thus following a repeated sample approach, Friedman's test followed by Wilcoxon signed rank test were employed for analyses of significant differences among experimental groups. The magnitude of the effect was calculated for statistically significant differences following the formula proposed for non-parametric evaluations [12]. The effect size was further classified as small (< 0.20), medium (between 0.21 and 0.79), and large (> 0.80) as previously defined [13].

Results

Mean ΔZ values in each experimental group are represented in Table 1 and Fig. 3. Conventional glass ionomer, MTA, and Portland cements showed higher increase in mineral density values compared to Biodentine™ and control (OZE). The magnitude of the significance was indeed large for the comparison of these cements to the control but somewhat lower (medium) for the comparison with Biodentine (Table 1). Differences between Biodentine™ and the control were statistically significant, but only with a small effect size.

Discussion

For many years, replacement of tooth tissues by dental materials was considered as passive [4]. However, by analyzing the interaction of biologically active materials and tooth tissues, concepts as bioactivity have been defined as

Table 1 Mean ± standard deviation ΔZ values in each experimental group. Different superscript letters denote statistical difference (Wilcoxon signed-rank test, $p < 0.05$). Statistically significant differences are followed by effect size values and threshold classification

Material	Mean ΔZ ± sd	Significant differences	Effect size	Threshold
ZOE	− 48.63 ± 19.09[a]	ZOE × GIC	1.00	Large
		ZOE × BIO	0.19	Small
		ZOE × MTA	0.97	Large
		ZOE × PORT	0.96	Large
GIC	− 114.63 ± 72.92[b]	GIC × BIO	0.78	Medium
BIO	− 63.31 ± 32.59[c]	BIO × MTA	0.75	Medium
		BIO × PORT	0.74	Medium
MTA	− 109.56 ± 66.28[b]	–	–	–
PORT	− 106.88 ± 66.02[b]	–	–	–

ZOE zinc oxide and eugenol cement, *GIC* glass ionomer cement, *BIO* Biodentine, *MTA* mineral trioxide aggregate, *PORT* Portland cement

materials which promote a specific biological response, as a result of the interaction with the tooth tissues [5, 14]. With this concept in mind, the main purpose of the present study was to evaluate the potential of calcium silicate-based cements and a conventional GIC to increase mineral density in carious dentin compared with a conventionally used temporary restorative material (ZOE).

In the present study, all tested cements were able to increase mineral density in carious bovine dentin compared to the control (ZOE), corroborating other laboratorial reports [15–18]. Biodentine™, however, resulted in less increase in mineral density, compared to the other calcium silicate-based cements (MTA, Portland) and GIC. This is not in fully agreement with a recent evaluation of mineral density changes in carious human dentin, which found similar bioactive potential for Biodentine™ and GIC [19]. Differences in the experimental design and analysis may explain this fact. In the literature, however, there have been attempts to increase the bioactivity of Biodentine™ by the addition of bioactive glasses for instance [18, 20].

Indeed, fluoride releasing glass ionomer and calcium silicate-based cements are both known to promote remineralization of carious dentin [14, 21]. Since first developments in glass ionomer cements and its introduction in restorative dentistry [22], clinical indications for this material have progressively increased. Factors as clinical applicability, biocompatibility, fluoride release, and chemical adhesion [23–25] turn this material into an excellent alternative in restorative dentistry. It must be clear, however, that remineralization of carious dentin with GIC happens at the expense of fluoride and strontium ions released by the material and accumulated at the interface [4, 21, 26].

Another type of water-based materials is the calcium-silicate cements. They have been initially indicated for root dentin perforation repair [27] and by its biocompatibility and bioactivity there has been a growing interest in its application over carious dentine. Biodentine™ was developed as an alternative to conventional MTA cements with shorter setting time, to serve as a dentin replacement [28]. The bioactivity mechanism of the calcium silicate-based cements if based on the

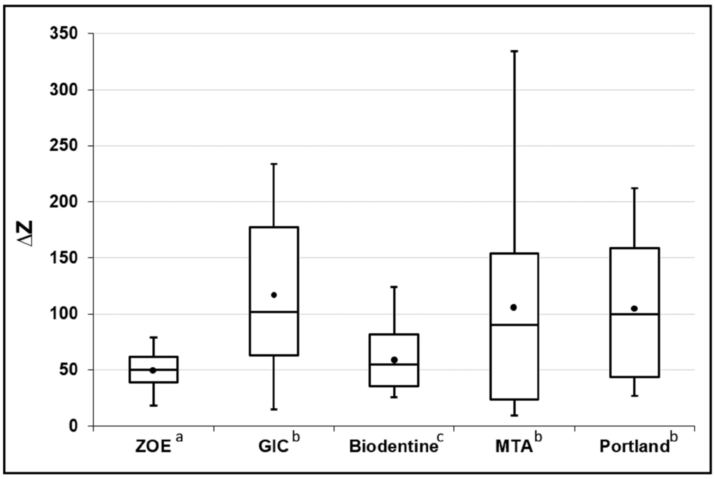

Fig. 3 Box plot of ΔZ distribution among the experimental groups. Different superscript letters denote statistical significant differences (Wilcoxon signed rank test, $p < 0.05$)

formation of hydroxyapatite compounds at the cement surface after immersion in phosphate solutions [11, 15, 16].

In the present study, artificial caries were produced using a microbial model to form cariogenic biofilm. Compared to chemically induced artificial caries models, microbial models have the advantage of producing dentin carious lesions with both mineral loss and the destruction of the organic component, which resembles more the clinical situation [29]. The microstructure of the resulting demineralized dentin produced with microbial biofilm models is however, not fully investigated [29], and this may be viewed as a limitation of the present study since mechanisms of hard tissue interaction between the dental cements and the carious dentin are not fully understood.

As an analytical tool to evaluate mineral changes in dentin, micro-CT represents an excellent option due to its tridimensional nature, which allows analyzing the whole bulk of the specimen, obtains volumetric results, and visualizes the internal structure of an object based on a three-dimensional reconstruction [30]. Moreover, being a nondestructive technique, it allows longitudinal follow-up of samples after specific experimental treatments [31, 32].

Although the use of non-human teeth could be considered a limitation of this study, bovine teeth are considered as possible substitutes for human teeth [33] due to the similar chemical composition between these two substrates [34].

Based on the results of the present study, conventional glass ionomer, MTA, and Portland cement presented a similar and higher potential of increasing mineral density of carious bovine dentin compared to Biodentine™. As a clinical relevance, based on minimally invasive concept, these dental materials with remineralization potential can be used to preserve diseased but still repairable dental tissue.

Acknowledgments The authors are grateful to the Department of Pediatric Dentistry and Orthodontics in Federal University of Rio de Janeiro (UFRJ) and Laboratory for Nuclear Instrumentation (UFRJ).

Funding The work was supported by the Department of Pediatric Dentistry and Orthodontics and Laboratory for Nuclear Instrumentation of Federal University of Rio de Janeiro. This study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Pesquisa Científica (CNPq), and Fundação Carlos Chagas de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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4.2 Artigo 2 – Porosity and pore size distribution in high viscosity and conventional glass ionomer cements: A micro-CT study

Submetido na revista *Dental Materials Journal* – Qualis A2.

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Abstract

Glass-ionomer cements (GICs) have been frequently used as restorative materials due to its simple clinical handling, physical and mechanical properties, biocompatibility and bioactivity. However, these characteristics may be influenced by the porosity of the material after setting and/or presence of defects. High-viscosity GICs (HVGICs) are considered to perform clinically better than conventional GICs due to improved mechanical properties. Thus, the aim of the present study was to compare the degree of porosity and pore size distribution of conventional GICs and HVGICs using a non-destructive micro-CT technique. For this *in vitro* study, a total of 40 specimens were produced (n=10 per group) using two conventional (Riva self-cure and MaxxionR) and two HVGICs (Ketac™Molar Easymix and Vitro Molar). The specimens were prepared according to ISO 9917-1 standards for water-based cements, were scanned in a high energy micro-CT device and reconstructed with standardized parameters. Total porosity and distribution of pore size were obtained for each sample in each group. After checking normality of data with Shapiro-Wilks test, a Kruskal-Wallis followed by Student-Neuman-Keuls proof was used to detect differences in porosity among the experimental groups with a 5% significance level. Ketac™Molar Easymix showed statistically significant lower total porosity (0.15%) than MaxxionR (0.62%), Riva (0.42%) and Vitro Molar (0.57%). Pore size in all experimental cements were within the small-size range (<0.01 mm^3), but Vitro Molar showed statistically significant higher numbers of larger pores (>0.01mm^3). It is possible to conclude that major differences regarding porosity and pore size may exist among high viscosity and conventional GICs.

Keywords: Glass ionomer cements, porosity, micro-CT

Introduction

Over the last years, glass-ionomer cements (GICs) have gained a prominent role in restorative dentistry due to its broad clinical indications. In fact, GICs can be successfully used as restorative materials and fissure sealants[1], as well as bonding agents for orthodontic appliances, luting agents for indirect restorations, cavity liners and bases[2]. This material became appealing in operative dentistry due to properties as: easy handling, chemical bonding to enamel and dentine, coefficient of thermal expansion similar to the tooth structure and alleged bioactive properties, such as release of biologically active ions, including fluoride[3,4]. Among polyalkenoate based cements, many brands of GICs are presently available on the market indicated as temporary or long-term restorative materials[5, 6].

Results from a recent systematic review indicated that GICs present better survival rates than composites when used to restore cervical carious lesions both in permanent and primary teeth, but was however, not indicated for load-bearing areas, also in both dentitions[7]. These relatively disappointing results were associated with physical and mechanical properties of conventional GICs, which reduce its clinical use as long-term restoratives compared with composite resins for load-bearing areas[8]. However, mechanical properties of GICs have improved and the relative newly classified high-viscosity glass-ionomer cements (HVGIC) are currently showing better success and/or survival rates, especially for single-surfaces ART restorations[9-11].

Indeed, physical, chemical or mechanical properties of GICs may be influenced by several factors and among them, the presence of voids after mixing procedures and setting may decrease the mechanical strength of the material[12]. However, a common misconception relates to the concept of material porosity versus material defects, including bubbles or air-voids[13]. It has been recently demonstrated that some of the pores in GICs could be related to the material slow maturation reaction[14]. In fact, pore analysis performed on micro-CT tomography volumetric data confirmed that pore volume distribution in the GICs is complex and highly variable, but decreases with time after setting[15].

Different techniques have been used for evaluation of porosity in GICs, such as transmitted light with a stereomicroscope[13], scanning electron microscope (SEM) evaluation[16,17] and microcomputed tomography (micro-CT)[15,18]. Among them, micro-CT evaluation has a clear advantage because it allows a non-destructive 3D visualization and quantification of internal structure, both qualitatively and quantitatively[19]. However, to the best of our knowledge, there is no study evaluating and comparing the porosity of different conventional and high-viscosity glass-ionomer cements (HVGIC) used in dental clinical practice.

Therefore, the purpose of the present study was to compare the degree of porosity and pore size distribution of two commercially available conventional GICs with two HVGICs using a non-destructive micro-CT technique. The null hypotheses were that all tested GICs have similar porosity degree and there is no difference in pore size distribution among the tested materials.

Methodology

Two commercially available, conventional restorative GICs, namely MaxxionR (FGM, Joinville, Brazil) and Riva self-cure (SDI, Victoria, Australia) and two HVGICs, Ketac Molar™ Easymix (3M ESPE, Seefeld, Germany), and Vitro Molar (DFL, Rio de Janeiro, Brazil) were used in the present study (Table 1). All cements were of the hand-mixed, self- cured type. Test specimens were prepared according to ISO 9917-1 standards for water-based cements.

Sample size calculation

The sample size calculation was based on a previous study[20], and used mechanical properties values corresponding to the same GICs used in the present study by means of a T-Test (BioEstat, v.5.3, Instituto Mamiruá, AM, Brazil). The significance level was established in 1% and the power of the test in 0.95. As a result, a sample size of 8 samples per group was obtained. By adding 20% of this value, the final number reached was 10 samples per group, with a total of 40 specimens.

Test specimens

Standardized cylindrical specimens were fabricated in molds with 4.0±0.1 mm diameter and 6.0±0.1 mm height (100.5 mm^3). All specimens were prepared by a single operator following the manufacturer's instructions regarding proportion, preparation, mixing technique and handling. Cement manipulation was carried out at room temperature (25±1°C) and relative humidity not completely controlled, but around 50±5%.

The molds were lubricated with solid petroleum jelly, and the GICs were mixed with a plastic spatula on paper blocks until a glossy and homogeneous cement was obtained. The material was immediately placed in the molds with the aid of insertion syringes (Centrix, DFL, Rio de Janeiro, Brazil) and excess cement was removed. Then, a slight digital pressure was applied on the mold for final material adaptation. Ten minutes later, after initial sample hardening, the specimens were removed from the molds and a thin layer of petroleum jelly was painted around the specimens to prevent syneresis. The samples were then stored in distilled water for 24 hours at 37°C 21.

Micro-CT scanning and reconstruction procedures

The samples were scanned in a high energy micro-CT device (Skyscan 1173, Bruker, Kontich, Belgium) with the following acquisition parameters: 70kV, 114μA, 2240 x 2240 pixel matrix, 12.11μm pixel size, 1 mm thick Al filter, 800ms exposure time, 0.5° rotation step over 360°, frame averaging of 5 and random movements of 30. Scanning time was approximately 70 minutes for each specimen. Projections were saved as 16-bit grayscale tiff format images. After image acquisition, reconstruction was accomplished using a proprietary software (NRecon, v.1.6.9, Bruker) with standardized parameters for artifact minimization including ring artifact correction of 1, beam hardening correction 25% and input of contrast limits (0 – 0.15). Images were reconstructed in 8-bit *.BMP format.

Porosity analysis

The cross-sectional volumes of each specimen were digitally cropped to fit a 150 pixel (1.82 mm) radius and 5 mm height cylinder (77.8 mm3), in order to exclude outer, and possibly non-homogeneous surface areas of the cements and standardize readings. A 3D median filter with 1-pixel radius was applied to each cropped volume to reduce noise and after that, the histograms of all images were normalized according to mean gray values for each cement group. Threshold for pores was fixed at gray value 40 after iterative user-based analysis of representative specimens in each group. Total porosity, as well as the distribution of pore sizes were obtained for each experimental cement group samples. Pores were considered small if volume was equal or less than 0.01 mm^3 and large if volume was higher than 0.01mm^3 (Figure 1).

Statistical analysis

Normality of data was checked with Shapiro-Wilks test. As the null hypothesis of normality was rejected, Kruskal-Wallis followed by Student-Neuman-Keuls proof was used to detect differences in porosity among the experimental groups using BioEstat 5.3 statistical package (Instituto Mamirauá, Tefé, AM, Brazil).

Results

Table 2 shows total porosity values for the tested cements. It is possible to note that Ketac™ Molar Easymix showed statistically significant lower values (0.15%) than MaxxionR (0.62%), Riva self-cure (0.42%) and Vitro Molar (0.57%). Table 3 shows that the majority of pores, in all tested cements were within the small size range (< 0.01 mm^3), but Vitro Molar showed statistically significant higher percentages of larger pores (> 0.01 mm^3). Figure 2 shows 3D volume renderings obtained from after image acquisition and reconstruction of one representative specimens of each group.

Discussion

GICs are composed by a polyalkenoic acid aqueous solution which reacts with a basic powdered glass component[2]. After setting, these cements may, however, present voids or defects which can reduce its clinical performance[12, 15]. In view of the improved HVGICs, the aim of the present study was to analyze the porosity of commercially available hand-mixed conventional and HVGICs usually used in restorative dentistry using a non-destructive 3D technique. The materials used in the present study have been previously evaluated in randomized clinical trials, showing good results[10, 22-24], and for this reason, they were chosen for the present evaluation.

Pore volume determination within a material is highly dependent on the type and resolution of the experimental technique used in the evaluation. For this reason, comparison of results should be done with caution. In fact, higher porosity values have been recently found for self-cured GICs (2.7-3.5%) after 24h of setting using gas adsorption measurements[15], which can be understandable if the resolution used by the authors (2nm) is compared to the resolution used in the present study (12μm). The type of analysis often also results in different porosity values and in fact, bidimensional SEM analysis have often reported higher total porosity values for HVGICs, ranging around 2 to 3% for Ketac™ Molar Easymix[17, 25] and 8% for Fuji IX[16]. Specifically regarding 3D porosity analysis in micro-CT, the threshold method used to define voids has plays also an important role in the total measurements. Previous studies did not disclose how the threshold for pores was established[26]. In the present study, an iterative method based on histogram distribution was chosen for all specimens.

The null hypothesis of the present study was rejected as the degree of porosity and pore size distribution of the tested GICs were not similar, with Ketac™ Molar Easymix presenting the lowest porosity. This cement is classified as HVGIC and we attribute the favorable results obtained in the present study to the high wettability of the powder by the liquid presented by this material[27]. Nonetheless, in the present study, only hand-mixed cements were used and, the total porosity was low for all cements (< 1%). This may be due to a general improvement in the formulation of hand-mixed GICs.

Threshold for voids in GICs has been set as higher than 0.01 mm^2 (Mitchell & Douglas, 1997), but measurements reported by these authors were bidimensional, measured in surface area. Others have reported void measurements in diameters[26, 28], but some do not report pore size distribution[17, 25]. In the present study, the threshold of 0.01 mm^3 was chosen to allow classification between pores and defects (large pores).

Nomoto et al. (2004) found a mean of 0.10% porosity in hand-mixed Ketac™ Molar samples, corroborating results of the present study (0.15%). He found however, much less “voids” than in the samples examined in the present study (mean 32 voids per sample compared to mean 700 voids found in the present study). This has probably occurred due to detection of only larger voids (with more than

0.01mm³). The present study has detected pores within small size range, corroborating results obtained by others[15].

Additionally, it has been also previously demonstrated that the hand-mixed method was favored for low-viscosity and for HVGICs as it resulted in only minor effects on compressive strength and porosity[18]. Aiming to minimize the incorporation of larger pores or bubbles and the “operator effect”, a syringe was used in the present study to insert the cement into the molds. Previous studies have failed to disclose differences in mechanical properties[29] and porosity[25] caused by variation in the method of insertion, some studies have shown that this method favors particle agglutination, reduces the air bubble incorporation, and improves mechanical properties[12, 17].

Despite the fact that many studies evaluated the porosity of different types, mixing methods and brands of GICs[13, 16, 17, 25, 28], very few have used the nondestructive micro-CT technique[15, 18]. Micro-CT allows the evaluation of the whole bulk of the specimen and the visualization of its internal structure[30].

With the increasing management of caries lesion based on the concept of minimally invasive dentistry, the use of GIC for remineralization of carious dentin by the release of fluoride and strondium ions aims to preserve diseased but still repairable dental tissue[30, 31]. HVGICs have been widely used in atraumatic restorative treatments mainly because of its higher survival percentages[9] and its low failure rate for posterior restorations, which may be comparable to amalgam in primary[10] and permanent[32] molars. In order to expand the survival lifetime of GIC restorations, reduce costs, knowing that porosity is related with changes in mechanical properties and it is also associated with the clinical results, the used of the HVGIC Ketac™ Molar Easymix may result in increased success / survival of the restorative treatment as this GIC showed the lowest value of porosity, within a small size range.

Conclusions

Among the groups, Ketac™ Molar Easymix presents the lowest porosity and, for the present evaluation, can be considered the best restorative conventional GIC for clinical practice.

Acknowledgments

The authors are grateful to the Department of Pediatric Dentistry and Orthodontics in Federal University of Rio de Janeiro (UFRJ) and Laboratory for Nuclear Instrumentation (UFRJ). This study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Pesquisa Científica (CNPq) and Fundação Carlos Chagas de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

Tables

Table 1: Details of glass ionomer cements used in the present study.

Material	Manufacturer	Batch number
Ketac™ Molar Easy Mix	3M ESPE (Seefeld, Germany)	56633
MaxxionR	FGM (Joinville, SC, Brazil)	150915
Riva Self Cure	SDI (Melbourne, Australia)	621141V
Vitro Molar	DFL (Rio de Janeiro, Brazil)	15111766

Table 2: Mean percentage of total porosity for each experimental glass ionomers.

Glass Ionomer Cement	Total porosity (%)*
Ketac™ Molar Easy Mix	0.15^a
MaxxionR	0.62^b
Riva Self Cure	0.42^b
Vitro Molar	0.57^b

*Different lowercase superscript letters indicate statistical difference (Kruskal-Wallis followed by Student-Neuman-Keuls proof, $p<0.05$).

Table 3: Percentage (%) distribution of pore size among the experimental groups.

Pore size	Ketac™ Molar Easy Mix	MaxxionR	Riva Self Cure	Vitro Molar
Small pores (< 0.01 mm^3)	99.89 ± 0.23^a	99.81 ± 0.09^a	99.95 ± 0.07^a	99.50 ± 0.22^b
Large pores (> 0.01 mm^3)	0.11 ± 0.23^a	0.08 ± 0.09^a	0.05 ± 0.07^a	0.50 ± 0.22^b

*Different lowercase superscript letters in each row indicate statistical difference (Kruskal-Wallis followed by Student-Neuman-Keuls proof, $p<0.05$).

Legend for the figure

Figure 1: Glass ionomer specimens and porosity. 1) Original specimen. 2) After volume of interest application. 3) Cross-section after normalization and filter. 4) Iterative threshold applied. 5) Pores.

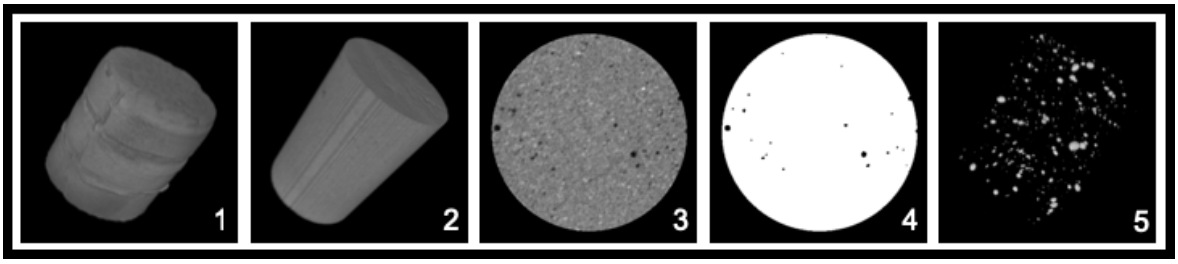
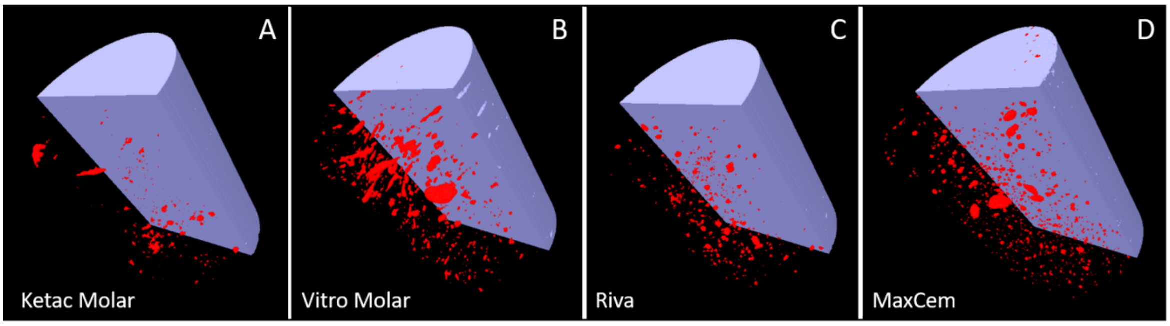


Figure 2: 3D volume rendering obtained after image acquisition and reconstruction of one representative specimen of each studied group.



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4.3 Artigo 3: Is glass ionomer cement the most cost-effective dental material? A cost-effectiveness systematic review and meta-analysis of clinical effectiveness of randomized clinical trials with economic evaluation performed alongside.

Submetido na revista *Journal of Dentistry* – Qualis A1.

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Abstract

Objectives: to evaluate the clinical and cost-effectiveness of glass ionomer cement (GIC) compared with other dental materials/interventions in deciduous and permanent teeth.

Sources: Six electronic databases were searched and results updated until March 2019.

Study selection: According to PICO criteria, randomized clinical trials (RCT) containing cost-effectiveness (CE) analysis in patients (Participants) receiving any type of operative treatment with GIC (Intervention) compared with those receiving other types of treatment/dental materials or types of GIC (Comparison) to establish the most cost-effective (Outcome) over time. The risk of bias in RCT was evaluated using the Cochrane guidelines and for the economic analysis (EA) the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was used. The quality of evidence was analysed using GRADE system. Meta-analysis was conducted comparing failures between GIC and other materials over time. Economic data were inflated to February 2019.

Data: From 2031 studies, six RCTs were included in qualitative and quantitative analysis. The follow-up was between 1 to 4 years. Three studies performed 3% discount rate. Quality of CE data was at high risk of bias for some points. The majority of the included RCT studies were at low risk of bias. For EA, almost all of the studies described GIC as the most cost-effective material. In meta-analysis, GIC and other materials/techniques presented similar risk of failures despite of the follow-up evaluation.

Conclusions: GIC is clinical effective compared with other materials/techniques and presented the best CE among dental materials for direct restorations and sealant.

Clinical significance:

As Glass-ionomer cements are widely used in dental practice, dentists should be aware that this material is clinical effective and have the best cost-effectiveness to

be used as dental sealant and in restorative treatment, as ART, compared to other materials and techniques.

Key-words: Economic evaluation, Glass ionomer cements, Systematic review, Clinical trials, Meta-analysis.

1 Introduction

Operative dental treatment is still a real need worldwide, due to the fact that untreated dental caries in permanent and primary teeth are one of the most prevalent conditions of the world (MARCENES *et al.*, 2013; ATCHISON e WEINTRAUB, 2017). Moreover, dental defects such as molar incisor hypomineralization (MIH), described as a qualitative enamel defect (WEERHEIJM *et al.*, 2001; WEERHEIJM *et al.*, 2003) with post-eruptive enamel breakdown over time (NEVES, AMERICANO*, et al.*, 2019) affects more than 800 million people across the globe (SCHWENDICKE *et al.*, 2018), and are also associated with increased operative care needs (JALEVIK e KLINGBERG, 2002). Thus, such prevalent diseases are associated with a global economic burden and considering that resources in health are always scarce, knowledge of operative treatment costs and its effectiveness are important to allocate resources and to save costs to the benefit of the population (MORGAN *et al.*, 2012; LISTL *et al.*, 2015).

Direct costs related to dental care are estimated globally to be more than U$290 billion per year and thus, improvements in oral care which could decrease expenditure and reduce other important indirect costs, as productivity loss, are very welcome (LISTL *et al.*, 2015). Conventional dental treatment is certainly still expensive for most of the world population and minimal intervention approaches may be an alternative in public health in face of the high prevalence of untreated oral diseases (KASSEBAUM *et al.*, 2017). The atraumatic restorative treatment (ART), with its application in preventive and restorative interventions, can be mentioned as an example of minimally invasive dentistry approaches, being glass ionomer cement (GIC) the material of choice (FRENCKEN, 2017).

In fact, glass ionomer cements have a wide application in operative dentistry, due to clinical factors as remineralization, biocompatibility and chemical adhesion, preserving affected but repairable dental tissue (BEIRUTI *et al.*, 2006; NEVES, BERGSTROM, *et al.*, 2019). Other indications include liners, sealants, coatings and luting cements (LADHA e VERMA, 2010; NGO e OPSAHL-VITAL, 2014). Recent systematic reviews have described no differences in survival rates of GIC compared to composites or amalgam for restorations and sealant in primary teeth or occlusal surfaces of permanent teeth (FRENCKEN *et al.*, 2012; MICKENAUTSCH e YENGOPAL, 2012; RAGGIO *et al.*, 2013; SCHWENDICKE *et al.*, 2016). In terms of direct costs, ART using GIC in operative dental care seems to be a viable and economic alternative (SMALES e HAWTHORNE, 1996; MICKENAUTSCH *et al.*, 2002). However, not only are the treatment costs important in health economics, but also the effectiveness of the selected material.

Health economics analyses are important for public policy-makers to determine priorities in health care. Among different types of economic evaluation, cost-effectiveness analysis considers costs and its consequences in some course of action (MICKENAUTSCH *et al.*, 2002; OSCARSON *et al.*, 2003). So, the aim of this systematic review was to evaluate if GIC is the most clinical effective and cost-effective dental material compared with any other dental material, oral health or placebo intervention in children, adults or elderly patients.

2 Materials and methods

Protocol registration and reporting

The protocol of this systematic review has been registered at PROSPERO database under registration number CRD42017061052, and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (SHAMSEER *et al.*, 2015) and three other guidelines on preparation of systematic reviews of economic evaluations (THIELEN *et al.*, 2016; VAN MASTRIGT *et al.*, 2016; WIJNEN *et al.*, 2016).

Eligibility criteria

Based on PICO criteria (Population - P, Intervention - I, Comparison - C, and Outcomes - O), randomized clinical trials (RCT) containing cost-effectiveness (CE) analysis (piggyback) (Piggy-Back AnalysisPiggy-back analysis, 2008) with at least 1-year follow-up including children, adolescents, adults or elderly patients (P) who received any type of operative dental treatment with glass ionomer cement (I) compared with those receiving other types of treatments as composite restorations or sealants, fluoride varnish, amalgam, placebo, oral health education and other dental materials and/or other types of GIC (C) to establish the most effective and cost-effective (O) were included.

Search strategy

Based on the PICO question elements, the controlled vocabulary Medical Subject Headings (MeSH terms) and free terms keywords were defined and used to perform the search strategy using a combination of these words. A systematic search strategy was developed for MEDLINE, via PubMed, by one evaluator (ABN) and, after that, adapted for the other databases. An expert librarian (DM) guided the search and the adaptation for each database. Controlled vocabulary as MeSH terms and synonyms were used in order to not impose any restrictions and to maximise the search for articles (Table 1). A hand search was also performed and the references of each relevant article were manually searched. There were no language restrictions.

Five databases were consulted and updated up to April 2019 as follow: MEDLINE via PubMed, Scopus, Web of Science, The Cochrane Central Register of Controlled Trials (CENTRAL/CCTR) and Lilacs/BBO. The grey literature (OpenGrey) was also searched (Table1). Alerts were created in every database to inform about possible new articles.

Inclusion criteria, Data selection and analysis

Two reviewers (ABN and MBM) performed, independently, the search strategy, in order to identify the eligible studies and evaluate titles and abstracts of all identified studies from all electronic databases. The studies included in this systematic review were piggyback RCTs that evaluated the cost-effectiveness of glass ionomer cements and others dental materials or strategies in several dental treatments in full economic evaluations. Studies with less than 1 year follow-up, observational studies, literature reviews, letters to editor, abstracts, case or series reports, uncontrolled trials, partial economic evaluation trials, model-based economic evaluations and studies with not reported incremental cost-effectiveness ratio (ICER) were excluded.

Articles in duplicate, searched and available in more than one database were considered just one time. For articles that had insufficient data in title and abstract, the full text version were independently evaluated to check if they met the inclusion criteria. Any disagreement was solved through discussion with a third reviewer (LCM).

Data extraction

Data regarding characteristics of the participants and data from the included studies as author(s), year of publication, country, perspective, study design, age, total number of participants, type of teeth, intervention and comparator, outcomes, as well as data regarding the economic evaluation, such as discount rate and time horizon were extracted in extraction forms and analysed by two authors (ABN and MBM). Regarding economic data, values were extracted for each study and total costs and ICER were inflated to February 2019 US$ by two authors (ABN and CLV). For values in other currencies than United States dollars, the conversion to US$ was done using the currencies of the original study base year, and it was subsequently necessary to correct the values by updating them from the analysis base year until February 2019. This correction took as reference the Consumer Price Index (CPI), which is an economic indicator. For values originally described in US dollars it was just necessary to correct the values by updating them from the analysis base year until February 2019 using CPI. Original currencies and values are depicted in brackets.

For other information not described in the article, the author was contacted by e-mail or other social networks up to three times. If, after the contact attempts, no response from the author was achieved, the study was not included in the evaluation.

Risk of bias and quality assessment

Qualitative analysis was performed for each RCT and for the economic analysis. Risk of bias assessment were extracted and analysed for each included study.

To analyse the primary clinical trial, the "Bias Risk Assessment of Randomized Controlled Studies" tool (Cochrane Handbook 5.0.1) (HIGGINS JPT, 2011) was used. The following items were considered at the study level: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and professionals; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting and 7) other possible sources of bias. Disagreements between evaluators were solved through discussion. If necessary, a third reviewer was consulted (AAN). The score was determined according to the Cochrane Handbook for Systematic Reviews (HIGGINS JPT, 2011). For low risk of bias in each domain, the study received the green colour, in high risk, red. When the response was not clear or not described in the study, they were classified as uncertain bias, with yellow colour.

Among the seven Cochrane domains, two were not considered as key domains due to clear differences between operative techniques and clinical aspect of the dental materials, namely the domains: blinding of the operators and participants and blinding of the examiners. If the final evaluator was blinded, but the operator and patient were not blinded for the intervention, the study was classified as low risk of bias. Key domains considered in the present study were random sequence generation, allocation concealment and incomplete outcome data. Studies were classified as low risk of bias if these key domains were adequate. To evaluate the risk of bias of randomized clinical trials with economic evaluation performed alongside, the primary publication with all the information about the RCT and without the cost analysis were also consulted, aiming to clarify important keys in each domain.

For the economic analysis, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (HUSEREAU *et al.*, 2013) was used to evaluate the quality of the included CE studies report. CHEERS is composed by 24 items based on the following subdivision: 1) Title and abstract; 2) Introduction; 3) Methods; 4) Results; 5) Discussion and 6) Other (Source of funding and conflicts of interest).

The quality of the evidence (certainty in the estimates of effect) was determined for the outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, whereby randomized clinical trials starts as high evidence, and the quality of, or certainty in, the body of evidence decreases to moderate, low or very low quality, if serious or very serious issues, related to risk of bias, inconsistency, indirectness, imprecision and publication bias, are present. In addition, the quality of the evidence can be upgraded if the magnitude of effect is large or very large, or if the effect of all plausible confounding factors would be to reduce the effect, or suggest a spurious effect. In this way, the quality of the evidence may vary from very low to high.

Quantitative assessment

To evaluate the effectiveness outcome of the included studies comparing the clinical performance (failures) of GIC and other materials, a meta-analysis was performed using RevMan Software 5.3 (Review Manager v. 5.3, The Cochrane Collaboration; Copenhagen, Denmark). Failure was sub grouped for the time horizon considering failures rates and the total for each material or strategy. Situations as caries incidence, retention over time, number of dental treatments and children referred for specialist care, mechanical failures, secondary caries and extractions were considered as failures, according to each study. The incidence of restorations / sealants failures or caries (events) and the total number of teeth or patients (with GIC restorations or sealants) and control (other materials / techniques) group were included to calculate the Risk Ratio (RR) with a 95%

confidence interval (CI). A sub-group analysis was performed according to the follow-up.

Random-effects models were employed because the studies were not functionally equivalent and the objective was to generalize the results from the meta-analysis (BORENSTEIN M, 2009). Heterogeneity was tested using the I^2 index. Meta-analysis was not performed for cost data.

3 Results

Study selection

According to the selection process (Figure 1), a total of 2031 studies were screened in six databases. After removing duplicates, 1078 articles remained and were assessed for title and abstract contents. Among these, 20 full-text articles were considered eligible and read in full text. Four studies were found by hand search of the references and were also read in full text. Eighteen studies were excluded, by not fulfilling the inclusion criteria such as: research protocols, study overlaps, studies that only performed cost analysis, studies with incomplete economic evaluations, full text not available and study design which were not RCT. Thus, six studies met the inclusion criteria and were included in qualitative synthesis and five in the quantitative analysis (TAGLIAFERRO *et al.*, 2013; DA MATA *et al.*, 2014; GOLDMAN *et al.*, 2016; GOLDMAN *et al.*, 2017; TONMUKAYAKUL e ARROW, 2017; GOLDMAN *et al.*, 2018).

Characteristics of included studies

Characteristics of the included cost-effectiveness studies are depicted in table 2. The studies were performed in four different countries: Ireland (DA MATA *et al.*, 2014), China (GOLDMAN *et al.*, 2016), Australia (TONMUKAYAKUL e ARROW, 2017) and three of them were conducted in Brazil (TAGLIAFERRO *et al.*, 2013; GOLDMAN *et al.*, 2017; GOLDMAN *et al.*, 2018). Five studies informed the perspective of the economic analysis (TAGLIAFERRO *et al.*, 2013; GOLDMAN *et al.*, 2016; GOLDMAN *et al.*, 2017; TONMUKAYAKUL e ARROW, 2017; GOLDMAN *et al.*, 2018) and most of them were based on a government program perspective. The study designs comprised a controlled clinical trial (TAGLIAFERRO *et al.*, 2013), a randomized controlled trial (DA MATA *et al.*, 2014), a randomized community trial (GOLDMAN *et al.*, 2016), a pragmatic randomized controlled trial (TONMUKAYAKUL e ARROW, 2017), a cluster-randomized controlled clinical trial (GOLDMAN *et al.*, 2017) and randomized clinical trial (GOLDMAN *et al.*, 2018).

The follow-up for economic outcomes comprised from one year to 4 years' time horizon. Just one study was conducted in elderly adults participants (DA MATA *et al.*, 2014), while the other five studies were conducted in infant patients. Only one study was performed in primary teeth (TONMUKAYAKUL e ARROW, 2017) and three papers described comparisons with GIC used as a dental sealant (TAGLIAFERRO *et al.*, 2013; GOLDMAN *et al.*, 2016; GOLDMAN *et al.*, 2017).

Only three studies described the discount rate (set in 3% per year) (GOLDMAN *et al.*, 2016; GOLDMAN *et al.*, 2017; GOLDMAN *et al.*, 2018). However, two studies did not perform the discount rate because of the short time horizon (just one year) (DA MATA *et al.*, 2014; TONMUKAYAKUL e ARROW, 2017). All the included studies performed sensitivity analysis (analysis of uncertainty) (TAGLIAFERRO *et al.*, 2013; DA MATA *et al.*, 2014; GOLDMAN *et al.*, 2016; GOLDMAN *et al.*, 2017; TONMUKAYAKUL e ARROW, 2017; GOLDMAN *et al.*, 2018).

Quality evaluation of economic assessment

Regarding the methodological quality of the cost-effectiveness studies, overall data was at low risk but for specific topics the studies were at high risk of bias (Figure 2). Regarding the first topic of CHEERS statement, the title did not describe interventions in two studies (DA MATA *et al.*, 2014; TONMUKAYAKUL e ARROW, 2017). Only one study (DA MATA *et al.*, 2014) did not depicted the study perspective – 16.7% of the included studies. Although three papers did not performed the discount rate (TAGLIAFERRO *et al.*, 2013; DA MATA *et al.*, 2014; TONMUKAYAKUL e ARROW, 2017), two of them presented only one year time horizon, so they were not classified as high risk of bias (DA MATA *et al.*, 2014; TONMUKAYAKUL e ARROW, 2017). Three papers did not perform the exchange rate and conversion (DA MATA *et al.*, 2014; TONMUKAYAKUL e ARROW, 2017). Finally, half of the included trials did not report potential conflicts of interest (DA MATA *et al.*, 2014; TONMUKAYAKUL e ARROW, 2017; GOLDMAN *et al.*, 2018).

Risk of bias of the randomized clinical trials

The risk of bias for the six included studies is described in Figure 3. In qualitative analysis, seven domains were evaluated according to the Cochrane collaboration tool. To evaluate the risk of bias of each RCT, the primary study was also analysed and main findings about the RCT conduction were also considered (TAGLIAFERRO *et al.*, 2011; CHEN *et al.*, 2012; DE AMORIM *et al.*, 2014; HILGERT *et al.*, 2014; ARROW e KLOBAS, 2015; HILGERT *et al.*, 2015). The majority of the included studies were at low risk of bias (DA MATA *et al.*, 2014; GOLDMAN *et al.*, 2016; GOLDMAN *et al.*, 2017; TONMUKAYAKUL e ARROW, 2017).

For the evaluation of key domains in each study, random sequence generation and allocation concealment were at low risk of bias in less than 75% RCT, and incomplete outcome data were 100% at low risk of bias. Concerning blinding of personnel, final evaluator and participants was not full possible in two studies (TAGLIAFERRO *et al.*, 2013; GOLDMAN *et al.*, 2018). The majority of the included studies were classified as low risk of bias for selective reporting and other bias.

Meta-analysis and Certainty of evidence

Five studies were included in quantitative synthesis (DA MATA *et al.*, 2014; GOLDMAN *et al.*, 2016; GOLDMAN *et al.*, 2017; TONMUKAYAKUL e ARROW, 2017; GOLDMAN *et al.*, 2018). It can be observed that GIC and other materials/techniques presented similar risk of failures despite of the follow-up evaluation. At 12 months, 47.4% (n=119) of 251 GIC restorations or sealants (n=187) failed while 73.3% (n=255) of other materials/techniques (n=193) failed RR 0.30 [0.00, 43.54] p=0.64, I^2=99%. At 36 months, 30.4% (n=133) of 437 GIC restorations or sealants failed while 21.7% (n=116) of other materials/techniques (n=534) failed RR 1.19 [0.97, 1.48] p=0.1, I^2=0%. At 48 months, 2.6% (n=9) of 345 GIC restorations or sealants failed while 3.5% (n=40) of other materials/techniques (n=1142) failed RR 0.74 [0.37, 1.52] p=0.42 (Figure 4). Overall results agree with these results and similarity between comparisons were detected RR 0.70 [0.43, 1.14] p=0.16, I2= 92%. This evidence was assessed and qualified as very low, low, high and moderate, respectively (Table 3).

Glass ionomer utilization and cost-effectiveness

Dental sealant

Half of the included studies compared the cost-effectiveness of GIC as dental sealant and other materials or strategies (TAGLIAFERRO *et al.*, 2013; GOLDMAN *et al.*, 2016; GOLDMAN *et al.*, 2017). Tagliaferro et al (2013) evaluated children with high and low risk for caries development and subdivided in three groups 1) dental sealant: oral health education + a single application of modified glass ionomer resin (Vitremer) sealant 2) varnish: oral health education every three months + varnish biannualy; and 3) control: oral health education every three months. The best cost-effectiveness (CE) ratio was to GIC sealant with US$134.63 [US$ 119.80] in high caries risk group per saved occlusal surface (SOS). Evaluating the incremental cost-effectiveness ratio (ICER), sealing high-caries risk children permanent first molars showed a value of US$121.77 [US$108.36] per additional SOS (TAGLIAFERRO *et al.*, 2013). In other study, high-viscosity glass-ionomer cement (HVGIC) sealant and other three strategies (LED thermocured HVGIC sealant; glass-carbomer sealant and composite resin sealant) were evaluated and comparing HVGIC with composite resin (DOMINATED) the cost was US$121.72 [US$105] when preventing one or more dentine caries, while LED thermocured HVGIC cost US$133,31 [US$115] compared to resin sealant (DOMINATED). Comparing LED thermocured HVGIC and HVGIC the ratio results in US$155.34 [US$134] cost per lesion prevented. When performed an ICER with a projection to 1000, LED thermocured HVGIC was the most cost-effective among the groups (GOLDMAN *et al.*, 2016). Finally, Goldman et al (2017) evaluated the prevention of cavitated dentine caries lesions comparing ART HVGIC sealant, supervised toothbrushing and composite resin sealant, and comparing ART and composite sealant (DOMINATED) ICER, the saving was US$40.74 [US$ 37], comparing supervised toothbrush with ART the cost was US$290.66 [US$ 264]. In an ICER projected to 1000 scenarios, composite sealant presented the cost save of US$18.72 [US$ 17], compared to toothbrush and ART was dominated (GOLDMAN *et al.*, 2017).

Atraumatic Restorative Treatment – ART

Comparing ART with HVGIC and conventional treatment with modified GIC in survival percentage of restorations, Da Mata et al (2014) observed that for cost-effectiveness ratio, ART was 0.18 when performed by a dentist and 0.14 for a hygienist, and for conventional restoration was 0.29. In that evaluation, ART was the most cost-effective treatment (DA MATA *et al.*, 2014). Tonmukayakul et al (2017) compared ART with standard care (metallic or adhesive restoration) and the ICER in ART was US$628.91 [AU$ 719 - US$589] for saved per referred avoided and additional US$34.10 [AU$ 39 - US$31.94] per another additional treatment (TONMUKAYAKUL e ARROW, 2017). Goldman et al (2018), comparing ART with HVGIC, ultra-conservative treatment and conventional restorative treatment with amalgam, considering failed restorations and restored teeth with new carious lesion or extracted, found that, in the ICER for all restorations comparing ART to amalgam US$ 1.59 [US$ 1.44] was saved. For single-surface restorations, comparing ART to amalgam resulted in a cost of US$56.15 [US$51], and for multiple surfaces, ART resulted in a save of US$12.11 [US$11]. In a projection to 1000 and for single-surface restorations, comparing ART to amalgam resulted in a reduction of the cost to US$31.93 [US$29] (GOLDMAN *et al.*, 2018).

4 Discussion

Health economic evaluations are important to determine if the benefits of investments in health care are value and higher than the opportunity cost (LOMAS *et al.*, 2018). Moreover, it is really necessary to identify the economic burden of the diseases and its treatment to evaluate the resources allocation and possible monetary saves (LISTL *et al.*, 2015). Direct and indirect costs associated with global economic burden of dental diseases exceed US$ 400 billion yearly (DA MATA *et al.*, 2014) and it is known that untreated dental caries are among the ten most prevalent conditions of the world (MARCENES *et al.*, 2013; ATCHISON e WEINTRAUB, 2017) while dental defects, as molar incisor hypomineralization (MIH) are also extremely prevalent (SCHWENDICKE *et al.*, 2018), being these conditions which are associated with a higher amount of treatment needs. Nevertheless, economic evaluations on the prevention or treatment of dental conditions are still scarse (LADEWIG *et al.*, 2018). Based on this economic burden, minimal interventions, such as ART approach could be an excellent alternative in public health (KASSEBAUM *et al.*, 2017) and for that, GIC is the dental material of choice (FRENCKEN, 2017).

With this in mind, the main purpose of the present systematic review was to evaluate if GIC is the most cost-effective restorative dental intervention in different clinical procedures. In fact, this proved to be true, as among other materials/techniques GICs presented the best CE among dental materials for direct restorations and sealants. Although a Piggyback study (economic data collected within a clinical trial) present some issues inherent of the conduction of such evaluation, it is still an appropriate way to analyse health economics data and in fact, it is one of the most common method of conducting economic analysis (O'SULLIVAN *et al.*, 2005). For that reason, only randomized clinical trials containing CE analysis, as piggyback studies, with at least 1-year follow-up were included.

The included studies were performed in four different countries but the majority were conducted in Brazil. There is a need to conduct full economic evaluations in many different countries as this informative data is important to resource allocation and to save costs within specific health care systems (MORGAN *et al.*, 2012; LISTL *et al.*, 2015).

Determination of the economic analysis perspective is an useful tool as it determine the relevant measures in the study (O'SULLIVAN *et al.*, 2005) and although a recommendation to increase the generalization of economic analysis by adopting the societal perspective has been given (DRUMMOND *et al.*, 2005), in the present review most of included studies were based on a government program perspective which describes the payer, as the Nation Health System (SUS) in Brazil, for example. From the included studies, 16.7% did not describe this perspective and were classified as high risk of bias according to the CHEERS statement.

Despite the fact that RCT time horizon are often just long enough to observe the differences between the treatments and short trials can be a challenge for economic evaluations (O'SULLIVAN *et al.*, 2005), only RCT longer than 1-year follow up were included in the present analysis. Regarding discount rate, that reflects the individual time preferences (HJELMGREN *et al.*, 2001), half of the included studies described the discount rate set as 3% per year but other studies did not mention the discount rate, probably because of the short time horizon. Despite the fact that standard discount rate is set in 5%, recommendations are still imprecise and normally a discount between 2.5-10% is acceptable (HJELMGREN *et al.*, 2001). It is recommended that the discount rate should be performed in studies with time horizon longer than one year (DRUMMOND e JEFFERSON, 1996), and for that reason, in CHEERS quality analysis, studies with 1-year follow up that did not perform discount were not classified as high risk of bias. As economic data can vary over time, currency conversions should be performed (DRUMMOND e JEFFERSON, 1996) and in the present evaluation, costs were corrected and inflated until February 2019 to US dollar.

In this systematic review, the CHEERS statement was used to evaluate the quality of the included CE studies as this tool provides a checklist recommendation aiming to improve health economics reporting (HUSEREAU *et al.*, 2013). CHEERS represent an easy tool and as there is a huge need to standardization in health economic studies, its use could improve the generalization of the report (LADEWIG *et al.*, 2018), as there is no gold standard tool for economic evaluation (GRIFFIN e JONES, 2013). As the present analysis were based on piggyback evaluations, each primary RCT was also consulted as they contain informative data about clinical parameters and study design and useful information to evaluate the risk of bias according to Cochrane tool. For the evaluation of key domains in each study, random sequence generation and allocation concealment were at low risk of bias in less than 75% RCT. Besides the qualitative analysis, the quantitative evaluation was performed in order to evaluate which material had the best clinical performance over time in association with results of the economic analysis and in meta-analysis. In this regard, GIC and other materials/techniques presented similar risk of failures despite of the follow-up evaluation. The meta-analysis was performed using only data classified as failures in each RCT. Regarding studies with 36 months follow up, the quality of evidence was assessed as high, which comprises two RCTs. Finally, as it is not recommended (HIGGINS JPT, 2011), the meta-analysis was not performed for cost data.

Based on present data, it can be observed that in economic analysis of GIC used as dental sealant, this material was more cost-effective than oral health education, application of dental varnish, composite sealant and supervised toothbrush. Strategies for the prevention of dental caries such as dental sealants are necessary and effective (AHOVUO-SALORANTA *et al.*, 2013; AHOVUO-SALORANTA *et al.*, 2017; LADEWIG *et al.*, 2018), but still very little information is available regarding the cost-effectiveness of each strategy. A systematic review of economic evaluations of dental sealants describe that cost-effectiveness vary due to many differences in methodology among the studies, but despite of the type of material, sealing permanent teeth is more cost-effective in risk-based patients (AKINLOTAN *et al.*, 2018).

Regarding the use of GIC as ART restorative material, this approach was more cost-effective than conventional treatment, standard care with metallic or adhesive restorations, ultra conservative treatment and the use of amalgam. Additionally, the effectiveness of GIC can be similar to other treatments as observed in the present meta-analysis and in other systematic reviews where no difference between the survival rates of GIC and other operative treatments were found (FRENCKEN *et al.*, 2012; MICKENAUTSCH e YENGOPAL, 2012; RAGGIO *et al.*, 2013; SCHWENDICKE *et al.*, 2016).

The present systematic review is the first to demonstrate that GIC is not only clinically effective compared with other dental materials or techniques but is also the most cost-effective approach among materials for direct restorations and sealants. However, there is a need of standardization in conducting and reporting economic evaluations in dentistry and in fact, the major limitation of the present data is associated with the variability of economic data reported. Other factors such as long term follow-up, discount rate, perspective and the decision of comparative alternatives are require in future cost-effectiveness studies. We highlight the need of further well designed studies evaluating the cost-effectiveness of dental materials in many operative approaches.

Conclusions

GICs are clinically effective and have the best cost-effectiveness to be used as dental sealants and in ART restorations compared to other materials and techniques. The present economic data can be used for decision makers to the best allocation of resources in public and private health and this data can help planners to choose the most advantage approach in operative dentistry.

Acknowledgements

The authors are grateful to the Department of Pediatric Dentistry and Orthodontics of the Federal University of Rio de Janeiro (UFRJ). This study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Pesquisa Científica (CNPq) and Fundação Carlos Chagas de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

Figures

Figure 1. PRISMA flow diagram of the search results from the databases.

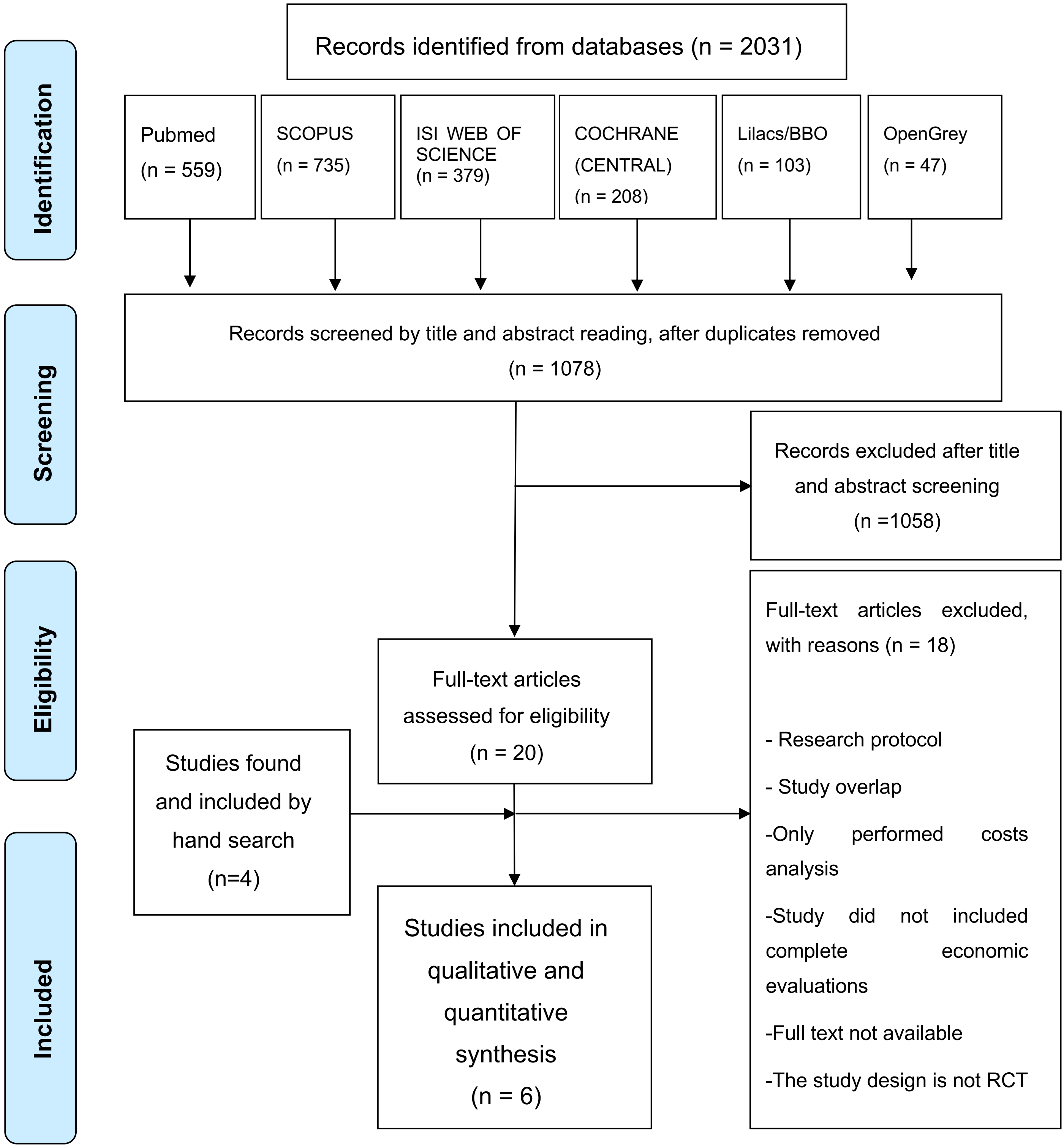


Figure 2. Methodological quality of the cost-effectiveness studies according to CHEERS statement.

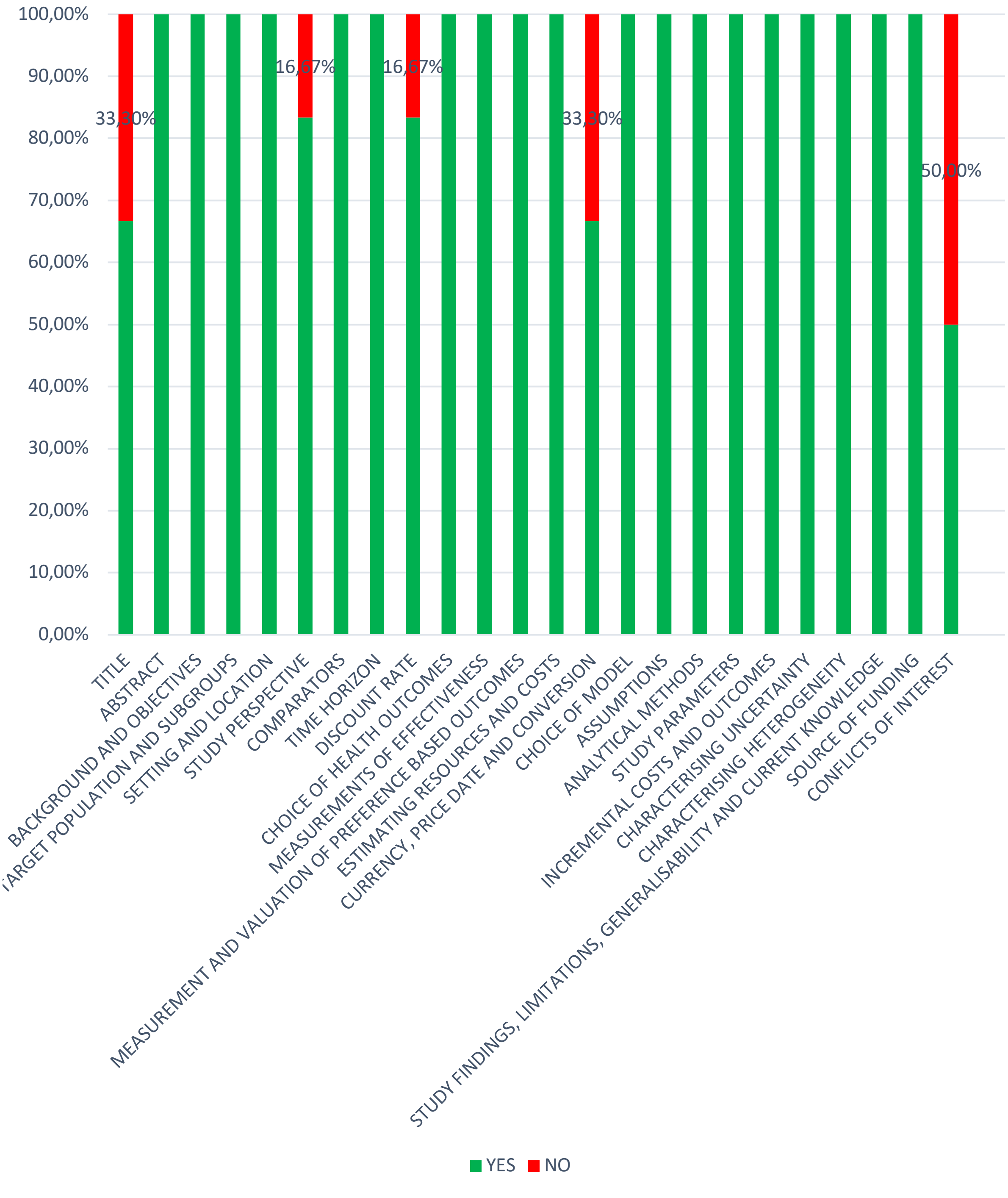


Figure 3. Risk of bias for the six included randomized clinical trials.

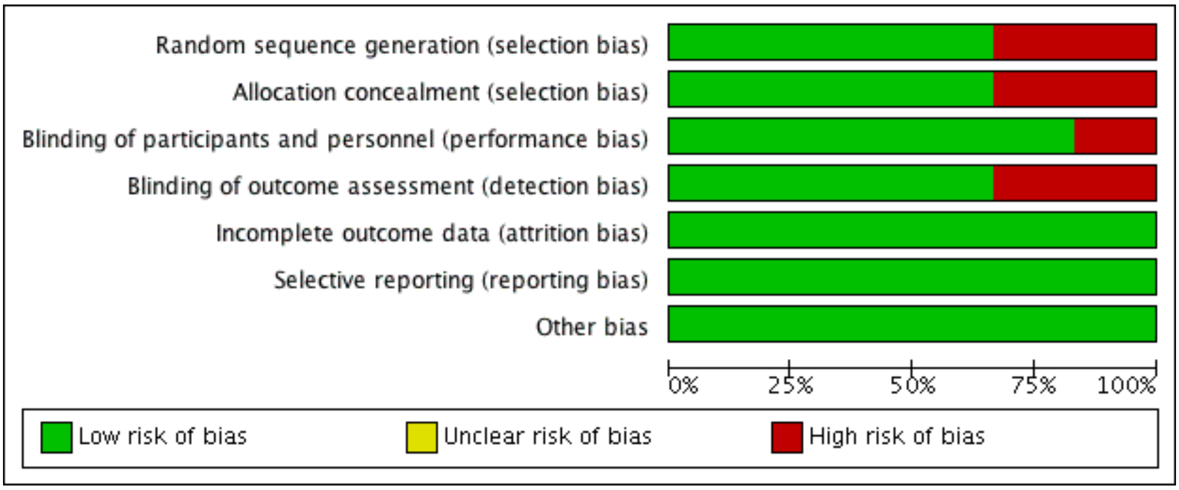
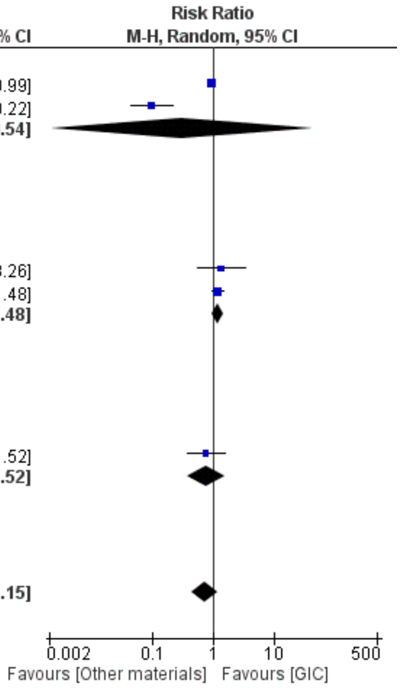


Figure 4. Forest plot of failures incidence of randomized clinical trials with economic evaluation performed alongside.

	GIC		Other materials			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
1.1.1 12 months						
Da Mata et al, 2014	113	124	125	128	26.9%	0.93 [0.88, 0.99]
Tonmukayakul et al, 2016	6	127	62	127	15.8%	0.10 [0.04, 0.22]
Subtotal (95% CI)		**251**		**255**	**42.7%**	**0.30 [0.00, 43.54]**
Total events	119		187			
Heterogeneity: Tau² = 12.77; Chi² = 153.00, df = 1 (P < 0.00001); I² = 99%						
Test for overall effect: Z = 0.47 (P = 0.64)						
1.1.2 36 months						
Goldman et al, 2017	6	51	15	170	14.4%	1.33 [0.55, 3.26]
Goldman et al, 2018	127	386	101	364	25.6%	1.19 [0.95, 1.48]
Subtotal (95% CI)		**437**		**534**	**40.0%**	**1.19 [0.97, 1.48]**
Total events	133		116			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
1.1.3 48 months						
Goldman et al, 2016	9	345	40	1142	17.3%	0.74 [0.37, 1.52]
Subtotal (95% CI)		**345**		**1142**	**17.3%**	**0.74 [0.37, 1.52]**
Total events	9		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
Total (95% CI)		**1033**		**1931**	**100.0%**	**0.70 [0.43, 1.15]**
Total events	261		343			
Heterogeneity: Tau² = 0.24; Chi² = 47.38, df = 4 (P < 0.00001); I² = 92%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Chi² = 1.82, df = 2 (P = 0.40), I² = 0%						



Tables

Table 1. Electronic database and search strategy (April/2019)

Pubmed	(((((((Glass Ionomer Cements[MeSH Terms]) OR Cements Polyalkenoate[Title/Abstract]) OR Glass Ionomer Cement*[Title/Abstract]) OR Glass polyalkenoate cement[Title/Abstract]) OR GIC[Title/Abstract]) OR Glass ionomer[Title/Abstract])) AND (((((((((((Cost-Benefit Analysis[MeSH Terms]) OR Cost Benefit Analys*[Title/Abstract]) OR Cost Effectiveness[Title/Abstract]) OR Cost Utility Analysis[Title/Abstract]) OR Analyses Cost Utility[Title/Abstract]) OR Economic Evaluat*[Title/Abstract]) OR Analysis Marginal[Title/Abstract]) OR Cost Benefit*[Title/Abstract]) OR Cost Effectiveness Analysis[Title/Abstract]) OR Cost*[Title/Abstract]) OR Benefit*)
Scopus	(TITLE-ABS-KEY (glass AND ionomer AND cements) OR TITLE-ABS-KEY (cements AND polyalkenoate) OR TITLE-ABS-KEY (glass AND ionomer AND cement*) OR TITLE-ABS-KEY (glass AND polyalkenoate AND cement) OR TITLE-ABS-KEY (gic) OR TITLE-ABS-KEY (glass AND ionomer)) AND (TITLE-ABS-KEY (cost-benefit AND analysis) OR TITLE-ABS-KEY (cost AND benefit AND analys*) OR TITLE-ABS-KEY (cost AND effectiveness) OR TITLE-ABS-KEY (cost AND utility AND analysis) OR TITLE-ABS-KEY (analyses AND cost AND utility) OR TITLE-ABS-KEY (economic AND evaluat*) OR TITLE-ABS-KEY (analysis AND marginal) OR TITLE-ABS-KEY (cost AND benefit*) OR TITLE-ABS-KEY (cost AND effectiveness AND analysis) OR TITLE-ABS-KEY (cost*) OR TITLE-ABS-KEY (benefit*)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re"))
Web of Science	TS=(Glass Ionomer Cements) OR TS=(Cements Polyalkenoate) OR TS=(Glass Ionomer Cement*) OR TS=(Glass polyalkenoate cement) OR TS=(GIC) OR TS=(Glass ionomer) AND TS=(Cost-Benefit Analysis) OR TS=(Cost Benefit Analys*) OR TS=(Cost Effectiveness) OR TS=(Cost Utility Analysis) OR TS=(Analyses Cost Utility) OR TS=(Economic Evaluat*) OR TS=(Analysis Marginal) OR TS=(Cost Benefit*) OR TS=(Cost Effectiveness Analysis) OR TS=(Cost*) OR TS=(Benefit*)
Cochrane CENTRAL	#1 MeSH descriptor: [Glass Ionomer Cements] explode all trees 714 #2 Glass Ionomer Cement* or Glass ionomer 1125 #3 GIC 213 #4 Cements Polyalkenoate or "Glass polyalkenoate cement" 20 #5 #1 or #2 or #3 or #4 1205 #6 MeSH descriptor: [Cost-Benefit Analysis] explode all trees 6250 #7 Cost Benefit Analys* or Cost Benefit* 16072 #8 Cost Effectiveness or Cost Effectiveness Analysis 21341 #9 Cost Utility Analysis or Analyses Cost Utility 2290 #10 Cost* 57784 #11 Benefit* 90864 #12 #6 or #7 or #8 or #9 or #10 or #11 129964

	#13	Economic Evaluat*	8317
	#14	Analysis Marginal	2215
	#15	#13 or #14	10313
	#16	#12 or #15	132814
	#17	#5 and #16	208
Lilacs BBO	tw:((mh:"Glass Ionomer Cements" OR cements polyalkenoate OR glass ionomer cement$ OR glass polyalkenoate cement OR gic OR glass ionomer OR cimento ionômero vidro OR CIV OR ionômero)) AND tw:((mh:"Cost-Benefit Analysis" OR cost benefit analys$ OR cost effectiveness OR cost utility analysis OR analyses cost utility OR economic evaluat$ OR analysis marginal OR cost benefit$ OR cost effectiveness analysis OR cost$ OR custo OR benefício OR custo benefício OR custo efetividade))		
OpenGrey	(ionomer OR glass ionomer cement)		

Table 2: Characteristics and main results of the included cost-effectiveness studies.

Citation/Year	Country/ Perspective	Study design	Age range (mean) years	Number of participants	Intervention(s)	Comparator(s)	Outcome	Type of teeth	Results - Outcome	Results - Economic Analysis [according to the author]*	Discount rate	Time horizon
Tagliaferro et al, 2013	Brazil/ Government service provider (SUS)	Controlled Clinical Trial	6-8 years old	268 children	*High and low risk children (Sealant)*: oral health education + a single application of modified glass ionomer resin (Vitremer) sealant *High and low risk children (varnish)*: oral health education every three months + varnish biannualy.	*High and low risk children (control)*: oral health education every three months.	Saved occlusal surface – caries incidence	First permanent molars	Effectiveness for each group: -High risk control Mean: 0.39 (0.72 SD) -High risk varnish Mean: 0.29 (0.68 SD) -High risk sealant Mean: 0.06 (0.25 SD) -Low risk control Mean: 0.12 (0.40 SD) -Low risk varnish Mean: 0.09 (0.29 SD) - Low risk sealant Mean: 0.02 (0.15 SD) For high risk, only sealant group showed the lowest value for incremental caries	The best cost-effectiveness (CE) ratio was to GIC sealant with US$134.63 [US$ 119.80] in high caries risk group per saved occlusal surface (SOS). *Incremental cost-effectiveness (ICER) ratio* Sealing high-caries risk children permanent first molars showed a value of US$121.77 [US$108.36] per additional SOS. Compared to the groups, sealing permanent molars in high caries risk children with GIC is the most cost-effective alternative	Not performed	24 months

									incidence compared to control and the same to varnish group.			
Da Mata et al, 2014	Ireland/ Not available	Randomized controlled trial	65-88 years old	82 elderly adults	ART with high strength glass ionomer cement	Conventional treatment with modified glass ionomer cement	Survival percentage of restorations	Permanent teeth	*Success rate* *-ART restorations* 91.1% (113/124). *-Conventional restorations* 97.7% (125/128).	*Total cost* For ART US$24.08 [€16.86 - US$21.87], and US$41.00 [€28.71 - US$37.24] for conventional treatment. *Cost-effectiveness ratio* For ART was 0.18 when performed by a dentist and 0.14 for a hygienist. For conventional restoration was 0.29. ART was the most cost-effective treatment.	Not performed	1 year
Goldman et al, 2016	China/ Government oral health services program for implementation in school perspective	Randomized community trial	Average age 8 years-old	Baseline: 405 schoolchildren After 4 years: 365 participants	High-viscosity glass-ionomer cement (HVGIC) sealant; HVGIC with heat application (LED thermocured HVGIC) sealant; Glass-carbomer sealant.	Composite resin sealant.	Development of new dentine caries lesions – caries prevention effectiveness.	Permanent molars.	*Cumulative survival* -HVGIC: 97.3% (9 new dentine carious lesion) -LED thermocured HVGIC: 98% (7 new dentine carious lesion) -Glass carbomer 94.5% (19 new dentine carious lesion)	*Costs* Glass carbomer group was the most expensive group - US$4.333 [US$ 3.738], followed by LED thermocured HVGIC - US$2.739 [US$ 2.363], HVGIC - US$2.429 [US$ 2.095] and composite resin sealant - US$1.942 [US$ 1.675]. *ICER* Comparing HVGIC with composite	3% per year	4 years

									-Composite sealant: 96.4% (14 new dentine carious lesion)	resin (DOMINATED) the cost was US$121.72 [US$105] when preventing one or more dentine caries, while LED thermocured HVGIC cost US$133,31 [US$115] compared to resin sealant (DOMINATED). Comparing LED thermocured HVGIC and HVGIC the ratio results in US$155.34 [US$134] cost per lesion prevented. *ICER (from 1000 projections)* ICER of HVGIC compared to composite resin sealant was US$68.39 [US$ 59] for each new occurrence of cavitated dentine caries lesion that was treated. The comparison between LED HVGIC and HVIC resulted in US$46.37 [US$ 40] for additional carious lesion. Comparing LED thermocured HVGIC and resin sealant (DOMINATED), the ICER was		

										US$60.28 [US$ 52]. LED thermocured HVGIC was the most cost-effective among the groups.		
Tonmukayakul et al, 2017	Australia/ Service provider perspective	Pragmatic randomized controlled trial	Mean 3.8 years old Age range Test: 1.0–5.5 years; Control: 1.1– 5.2 years	254 children	ART	Standard care (metallic or adhesive restoration)	Number of dental treatment and children with early childhood caries referred for specialist care.	Deciduous teeth	ART group received more dental treatment than standard care group (p< 0.01) and only 6 children were referred to specialist care from 127 children (95% CI 6.14 – 6.27). In Standard care group, 62 of 127 children were referred to the pediatric dentist (95% CI 61-63).	***Costs*** In ART group, the total cost was US$120.58 [AU$ 137.860 - US$112.93] and for standard care group US$155.89 [AU$ 178.217 - US$146.00]. ***ICER*** In ART, US$628.91 [AU$ 719 - US$589] was saved per referred avoided and additional US$34.10 [AU$ 39 - US$31.94] per another additional treatment. ***ICER (from 1000 iterations)*** ART - Cost save per referral case avoided: US$572.10 [AU$ 654.05 - US$ 535.80] (95% CI AU$ 483.91 – 677.70). ART - Cost save per additional dental treatment: US$31.63 [AU$ 36.16 - US$ 29.62] (95%CI AU$31.10 – 41.56).	Not performed	1 year

Goldman et al, 2017	Brazil / Government program perspective	Cluster-randomized controlled clinical trial	6-7 years-old	Baseline: 145 After 3 years: 102 children	ART HVGIC Sealant Supervised toothbrushing	Composite resin sealant	Prevention of cavitated dentine caries lesions	First permanent molars	*Effectiveness* 90.2% (6 dentine carious lesion in 51 sealants) - ART HVGIC 91.4% (12 dentine carious lesion in 120 sealants) - Composite resin sealant 95.6% (3 dentine carious lesion in 50) - supervised toothbrush.	*Costs for the sample* US$4.12 [US$3.74] for composite sealant US$7.95 [US$7.22] for ART HVGIC US$20.43 [US$18.56] for supervised toothbrush. *Costs in projection to 1000:* - Composite sealant: US$5.30 [US$4.81] - ART HVGIC: US$5.35 [US$ 4.86] - Supervised toothbrush: US$9.71 [US$ 8.82] *ICER* Comparing ART and composite sealant (DOMINATED), the saving was US$40.74 [US$ 37]. Comparing supervised toothbrush with ART, the cost was US$290.66 [US$ 264]. *ICER in projection to 1000:* In that scenario, composite sealant	3%	3 years

										presented the cost save of US$18.72 [US$ 17], compared to toothbrush and ART was dominated.		
Goldman et al, 2018	Brazil / Government program perspective	Randomized clinical trial	6-7 years-old	280 children	ART with HVGIC Ultra-conservative treatment	Conventional restorative treatment with amalgam	Failed restorations consequences and restored teeth with new carious lesion or extracted (survival %).	Primary teeth	*Survival %* *-All restorations* Amalgam: 72.6% ART HVGIC: 66.8% *-Single-surface* Amalgam: 93.4% ART HVGIC: 90.1% *-Multiple surfaces* Amalgam: 64.7% ART HVGIC: 56.4%	*Cost per restoration* *-All restorations* Amalgam: US$11.17 [US$ 10.15] ART HVGIC: US$11.26 [US$ 10.23] *-Single-surface* Amalgam: US$8.72 [US$ 7.92] ART HVGIC: US$ 9.82 [US$ 8.92] *-Multiple surfaces* Amalgam: US$13.63 [US$ 12.38] ART HVGIC: US$12.71 [US$ 11.54] *ICER* *For the sample – all failures* *-All restorations* Comparing ART to amalgam, saved US$ 1.59 [US$ 1.44] *-Single-surface* Compare ART to amalgam resulted in a cost of US$56.15 [US$51].	3%	3 years

										-Multiple surfaces ART resulted in a save of US$12.11 [US$11]. *Projection to 1000* *-All restorations* The cost increased to US$6.61 [US$6] comparing ART to amalgam. *-Single-surface* Compare ART to amalgam resulted in a reduction of the cost to US$31.93 [US$29]. *-Multiple surfaces* ART resulted in a save of US$5.50 [US$5] per failure prevented.		

*Values regarding economic data according to the study are depicted in brackets. Inflated values to February 2019 are described in the text.

Table 3. Evidence profile: Risk of failures for GIC and other materials / techniques.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With other treatments	With GIC		Risk with other treatments	Risk difference with GIC
Failures - Overall											
2964 (5 RCTs)	not serious	very serious [a]	not serious	serious [b]	none	⊕◯◯◯ VERY LOW	343/1931 (17.8%)	261/1033 (25.3%)	**RR 0.70** (0.43 to 1.15)	178 per 1.000	**53 fewer per 1.000** (101 fewer to 27 more)
Failures (follow up: 12 months)											
506 (2 RCTs)	not serious	very serious [a,c]	not serious	serious [b]	strong association	⊕⊕◯◯ LOW	187/255 (73.3%)	119/251 (47.4%)	**RR 0.30** (0.00 to 43.54)	733 per 1.000	**513 fewer per 1.000** (733 fewer to 31.196 more)
Failures (follow up: 36 months)											
971 (2 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	116/534 (21.7%)	133/437 (30.4%)	**RR 1.19** (0.97 to 1.48)	217 per 1.000	**41 more per 1.000** (7 fewer to 104 more)
Failures (follow up: 48 months)											
1487 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⊕⊕⊕◯ MODERATE	40/1142 (3.5%)	9/345 (2.6%)	**RR 0.74** (0.37 to 1.52)	35 per 1.000	**9 fewer per 1.000** (22 fewer to 18 more)

CI: Confidence interval; **RR:** Risk ratio
(a). Wide variation in the effect estimates across studies and little or no overlap of confidence intervals associated with the effect estimates (b). Upper or lower confidence limit crosses the effect size is greater than 25% in either direction (c). Considerable heterogeneity.

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5 CONSIDERAÇÕES FINAIS

A presente tese teve por objetivo realizar uma análise laboratorial sobre bioatividade de cimentos odontológicos e sobre a porosidade de cimentos de ionômero de vidro, assim como efetuar uma avaliação econômica sobre o custo-efetividade do CIV em diversos procedimentos operatórios. Durante muitos anos considerou-se os procedimentos odontológicos restauradores como passivos, ou seja, simplesmente substituindo a estrutura dentária perdida (WATSON *et al.*, 2014). Entretanto, observou-se que alguns materiais apresentam interação com os tecidos e podem ser biologicamente ativos (NIU, ZHANG*, et al.*, 2014; VALLITTU *et al.*, 2018). De fato, os resultados da presente pesquisa mostraram que a aplicação do cimento de ionômero de vidro na dentina cariada resultou em um aumento na sua densidade mineral. Sendo o CIV um material com grande relevância clínica em odontologia (NICHOLSON e CROLL, 1997; CROLL e NICHOLSON, 2002; SIDHU e NICHOLSON, 2016), o seu grau de porosidade e seu custo-efetividade também foram analisados de forma individualizada.

Os materiais odontológicos são classificados como bioativos quando apresentam uma resposta biológica específica na interface entre o material e o tecido dentário como ocorre com os cimentos de silicato de cálcio (NIU, JIAO*, et al.*, 2014). Ao comparar os cimentos de silicato de cálcio MTA e Biodentine^{TM} ao CIV convencional, Portland e o controle (OZE), observou-se no estudo 1 que, o CIV, MTA e Portland apresentaram um potencial aumento na densidade mineral dos espécimes tratados com tais materiais.

Um grande diferencial do estudo 1 consistiu no fato de a avaliação das mudanças na densidade mineral da dentina ser conduzida utilizando-se o método não destrutivo e tridimensional. De fato, o micro-CT permite analisar a totalidade da amostra, obter resultados volumétricos e visualizar a estrutura interna de um objeto com base em sua reconstrução tridimensional (SWAIN e XUE, 2009). Apesar da utilização de dentes bovinos poder apresentar-se como uma limitação do estudo, estes são considerados como possíveis substitutos para dentes humanos (YASSEN *et al.*, 2011) devido à composição química similar entre ambos os substratos (TERUEL JDE *et al.*, 2015). Conclui-se então que os materiais avaliados no estudo 1 poderiam ser utilizados visando uma maior preservação da dentina cariada, com base no conceito de odontologia minimamente invasiva.

As indicações clínicas dos cimentos de ionômero de vidro aumentaram progressivamente desde o seu desenvolvimento e introdução na Odontologia restauradora (BAIG *et al.*, 2015). Fatores como aplicabilidade clínica, biocompatibilidade, liberação de flúor e adesão química tornam esse material uma excelente alternativa em procedimentos odontológicos operatórios (TEN CATE e VAN DUINEN, 1995; AMARAL *et al.*, 2006; BEIRUTI *et al.*, 2006). Como demonstrado no primeiro estudo, o CIV apresenta potencial de remineralização da dentina cariada, porém esta alteração da densidade ocorre à custa de íons flúor e estrôncio liberados pelo material e acumulados na interface entre o material e o tecido dentário (NGO *et al.*, 2006; KIM, Y. K. *et al.*, 2010; WATSON *et al.*, 2014).

Um importante fator relacionado ao CIV é que após a manipulação este pode apresentar poros característicos do próprio material e/ou bolhas inerentes à manipulação, diminuindo seu desempenho clínico ao longo do tempo (NOMOTO e MCCABE, 2001; BENETTI *et al.*, 2015). Desta forma, o estudo 2 teve como objetivo avaliar a porosidade de CIVs convencionais e de alta viscosidade comumente utilizados em Odontologia restauradora . Apesar de todos os CIVs testados já terem sido utilizados em ensaios clínicos randomizados, o grau de porosidade e a distribuição do tamanho dos poros dos CIVs testados não foram semelhantes entre os materiais, com o CIV Ketac™ Molar Easymix apresentando a menor porosidade.

No estudo 2, os CIVs avaliados são comumente utilizados no Brasil e foram subdivididos em CIVs convencionais, MaxxionR (FGM, Joinville, Brasil) e Riva self-cure (SDI, Victoria, Austrália), e CIVs de alta viscosidade, sendo o Ketac Molar™ Easymix (3M ESPE, Seefeld, Alemanha) e Vitro Molar (DFL, Rio de Janeiro, Brasil). Todos os cimentos foram espatulados manualmente, já que somente o Riva *self-cure* apresenta uma versão encapsulada no Brasil. Desta forma, para uma comparação mais fidedigna, todos os CIVs utilizados estavam em sua apresentação pó-líquido. Já foi demonstrado anteriormente que a mistura manual é adequada para CIVs, já que este tipo de manipulação resultou em poucos efeitos na resistência à compressão e porosidade (NOMOTO *et al.*, 2004) e com o objetivo de minimizar a incorporação de poros ou bolhas maiores e o "efeito do operador", uma seringa Centrix foi utilizada para inserir o cimento nos moldes no presente estudo.

Para avaliar a porosidade de cimentos ionoméricos, poucos estudos utilizaram técnicas não destrutivas para avaliação da porosidade (NOMOTO *et al.*, 2004; BENETTI *et al.*, 2015). Para o estudo 2 a técnica do Micro-CT foi utilizada para analisar a porosidade e a mesma, por permitir a avaliação de toda a amostra de forma tridimensional (NEVES, BERGSTROM*, et al.*, 2019), apresenta-se como uma excelente opção para avaliação e visualização da estrutura interna de materiais dentários.

Como o CIV é utilizado para remineralização da dentina cariada devido à sua liberação de íons flúor e estrôncio visando preservar o tecido dental cariado, porém ainda reparável (BEZERRA *et al.*, 2012; NEVES, BERGSTROM*, et al.*, 2019), tal material é largamente utilizado com base no conceito da Odontologia minimamente invasiva. Com base no resultados do estudo 2, e a fim de expandir a sobrevida das restaurações de GIC e reduzir custos, sabendo que a porosidade está relacionada à mudanças nas propriedades mecânicas e também está associada aos resultados clínicos, o uso do GIC Ketac™ Molar Easymix pode resultar em aumento no sucesso do tratamento restaurador.

Dentro do conceito de mínima intervenção, a utilização do CIV na técnica do tratamento restaurador atraumático, tanto como restauração quanto como selante, apresenta-se como uma excelente alternativa em saúde pública (KASSEBAUM *et al.*, 2017), principalmente no que diz respeito à economia em saúde. Ainda há poucas avaliações econômicas sobre prevenção e/ou tratamento odontológico (LADEWIG *et al.*, 2018) e análise do custo-efetividade de materiais utilizados em Odontologia. Com base nisto, o objetivo do estudo 3 foi avaliar se o GIC é o material odontológico com melhor custo-efetividade em diferentes procedimentos odontológicos.

A identificação dos custos das doenças e de seus tratamentos para avaliar a alocação de recursos e possíveis economias monetárias é de extrema importância em termos de economia em saúde (LISTL *et al.*, 2015). É importante frisar que dentre os artigos selecionados para a presente revisão sistemática de análise econômica, a maioria dos estudos incluídos eram brasileiros e há uma necessidade real de condução de avaliações econômicas completas em diferentes países. Como a maior parte dos artigos incluídos no estudo 3 eram nacionais, isto explica o fato de que, embora a recomendação para aumentar a generalização da avaliação seja adotar a perspectiva da sociedade (DRUMMOND *et al.*, 2005), na presente revisão a maioria dos estudos foram baseados na perspectiva do programa de governo, como do Sistema Único de Saúde, por exemplo, que é o pagador do tratamento em diversos contextos no Brasil.

Dados econômicos são importantes para a alocação de recursos e economia de custos nos serviços de saúde (MORGAN *et al.*, 2012; LISTL *et al.*, 2015). Avaliações econômicas em saúde são necessárias para determinar se os benefícios de determinado investimento em saúde possuem um valor real e se são maiores do que o custo de oportunidade (LOMAS *et al.*, 2018). Para se permitir uma comparação, porém, há necessidade de padronização tanto na execução dos estudos quanto no relatório da informação. Como ainda não há um padrão-ouro para avaliação da qualidade metodológica de estudos de custo em saúde (GRIFFIN e JONES, 2013), o CHEERS representa uma ferramenta fácil e o uso da mesma poderia melhorar a generalização dos estudos (LADEWIG *et al.*, 2018).

Como um grande diferencial em termos de revisão sistemática de avaliações econômicas, não somente uma análise qualitativa foi realizada no estudo 3, mas também uma meta-análise foi conduzida com o objetivo de avaliar qual material odontológico apresenta o melhor desempenho clínico ao longo do tempo e associou-se este resultado à análise econômica. Como não é recomendado (HIGGINS JPT, 2011), a metanálise não foi realizada para dados de custo. Como resultado da análise quantitativa, o GIC e outros materiais/técnicas apresentaram risco semelhante de falhas, apesar do tempo de acompanhamento.

A revisão sistemática descrita no estudo 3 é a primeira a demonstrar que o GIC é tanto clinicamente eficaz em comparação a outros materiais ou técnicas odontológicas quando usado como selante dentário ou para tratamentos restauradores, quanto apresenta o melhor custo-efetividade entre os materiais para restaurações diretas e selantes.

Os resultados reportados na presente tese permitem concluir que o cimento de ionômero de vidro representa um material de excelência em Odontologia, apresentando potencial de remineralização da dentina cariada e sendo o material com melhor custo-efetividade dentre os materiais e técnicas estudados nesta avaliação. Como há diversas opções de CIVs comercializados no Brasil e exterior, a escolha de um cimento que apresente boas propriedades laboratoriais, como menor porosidade, propriedades clínicas e em termos de avaliação econômica, é de extrema necessidade, visto que este material pode ser utilizado em saúde pública. Espera-se que tais dados sejam relevantes para tomada de decisão em saúde, tanto no nível individual quanto à nível governamental, além de incentivar a execução de estudos utilizando materiais dentários na área laboratorial e em análises econômicas em saúde.

6 CONCLUSÕES

O cimento de ionômero de vidro representa um material de excelência em Odontologia, tanto em análises laboratoriais quanto na avaliação econômica, quando comparado a outros materiais e técnicas.

- O estudo laboratorial avaliando a bioatividade dos materiais à base de silicato de cálcio (Biodentine™, MTA e cimento Portland) e um ionômero de vidro convencional comparado a um material controle (cimento de óxido de zinco e eugenol) na dentina desmineralizada demonstrou que todos os cimentos testados foram capazes de aumentar a densidade mineral na dentina bovina cariada em relação ao controle (OZE).
- O cimento Biodentine™ apresentou resultados inferiores comparado aos demais cimentos à base de silicato de cálcio no que diz respeito ao aumento da densidade mineral na dentina cariada. Já o CIV, o MTA e o cimento Portland apresentaram um potencial semelhante no aumento da densidade mineral da dentina bovina cariada.
- A hipótese nula de que todos os CIV apresentariam características de porosidade similares foi rejeitada, uma vez que o grau de porosidade e a distribuição de tamanho de poros dos CIVs testados não foram semelhantes.
- Dentre grupos de CIVs restauradores de alta (Ketac Molar™ Easymix e Vitro Molar) e baixa viscosidade (Maxxion R e Riva self-cure) e entre cada material especificamente, o Ketac Molar™ Easymix apresentou menor porosidade.
- Na revisão sistemática de custo-efetividade, entre outros materiais / técnicas, os CIVs apresentaram o melhor CE entre os materiais para restaurações diretas e selantes.
- Na análise econômica do CIV utilizado como selante dental, este material foi mais custo-efetivo do que educação em saúde bucal, aplicação de verniz fluoretado, selante resinoso e escovação supervisionada.

- Em relação ao uso de CIV em TRA, essa abordagem foi mais custo-efetiva que o tratamento convencional, uso de restaurações metálicas ou adesivas, o tratamento ultraconservador e restaurações de amálgama.

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