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APLICAÇÃO TÓPICA DE ÁCIDO TRANEXÂMICO EM PACIENTES ANTICOAGULADOS SUBMETIDOS À CIRURGIA ORAL MENOR. REVISÃO SISTEMÁTICA E META-ANÁLISE

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APLICAÇÃO TÓPICA DE ÁCIDO TRANEXÂMICO EM PACIENTES ANTICOAGULADOS SUBMETIDOS À CIRURGIA ORAL MENOR. REVISÃO SISTEMÁTICA E META-ANÁLISE

Dissertação apresentada ao Programa de Pós-Graduação em Odontologia, da Universidade Federal de Sergipe, para obtenção do título de Mestre em Odontologia.

Orientador: Prof. Dr. Paulo Ricardo S. Martins Filho
Co-orientadora: Profª Drª Maria de Fátima Batista de Melo

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RESUMO

A terapia anticoagulante oral é amplamente utilizada para a prevenção primária de eventos tromboembólicos em indivíduos com fibrilação atrial e próteses valvares. O tratamento de pacientes anticoagulados que necessitam de procedimentos odontológicos cirúrgicos é variado e controverso devido à discussão sobre a possibilidade de hemorragia não controlada ou de complicações tromboembólicas. Atualmente, o ácido tranexâmico (ATX) administrado de forma intravenosa tem se mostrado eficaz no controle de sangramento em diversos tipos de cirurgias. Entretanto, até o momento, não há evidências sobre a eficácia e segurança do ATX tópico na redução de sangramento de pacientes anticoagulados submetidos a procedimentos cirúrgicos, incluindo as cirurgias orais de pequeno porte. O objetivo desta revisão sistemática com meta-análise é investigar a eficácia e a segurança do ATX tópico no controle do sangramento pós-operatório em pacientes anticoagulados submetidos à cirurgia oral menor. Uma busca sistemática no PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), OpenThesis e banco de dados internacional para ensaios clínicos (clinicaltrials.gov) até maio de 2015 foi realizada. Uma pesquisa na literatura-cinza foi feita através do Google Scholar. A revisão foi restrita a estudos publicados em versões de texto completo, sem restrição de idioma. Dois revisores de forma independente rastrearam os resultados da busca e identificaram os ensaios clínicos que compararam o uso de ATX tópico *versus* outro agente hemostático tópico, placebo ou a interrupção / redução da terapia anticoagulante antes da cirurgia. Os defechos pré-definidos incluiram o sangramento dentro da primeira semana de pós-operatório com necessidade de intervenção clínica e eventos tromboembólicos. O risco de viés foi avaliado de acordo com as diretrizes da Cochrane para os ensaios clínicos. O risco relativo (RR) foi calculado para avaliar o efeito da aplicação tópica de ATX no controle da hemorragia pós-operatória. Heterogeneidade estatística foi analisado pelo teste Q de Cochran e índice de I^2. Para examinar o potencial viés de publicação, foi criado um *funnel plot* das estimativas individuais, em unidades logarítmicas, contra o erro padrão. Após triagem dos títulos e resumos, 21 artigos foram lidos na íntegra e 7 ensaios clínicos foram incluídos na meta-análise (totalizando 533 pacientes). O RR combinado para o número de pacientes que receberam ATX tópico em comparação com o grupo controle foi de 0,42 (95% IC 0,21 a 0,84; p = 0,01), indicando um efeito protetor do ATX sobre o sangramento após cirurgia oral menor. Uma moderada heterogeneidade entre os estudos foi observada (I^2 = 26%), a qual desapareceu (I^2 = 0%) após análise de subgrupo para as diferentes estratégias utilizadas nos grupos controle. A análise de subgrupos revelou que o ATX tópico foi eficaz na prevenção de sangramento pós-operatório em comparação ao placebo (RR = 0,09; IC de 95%: 0,02 a 0,48; p = 0,004) e ácido épsilon-aminocapróico (RR = 0,12, IC 95% 0,01 a 0,94; p = 0,04). No entanto, nenhuma diferença significativa foi observada nas outras análises. Não houve casos de eventos tromboembólicos em nenhum estudo, tanto no grupo do ATX quanto no controle, durante os primeiros sete dias de acompanhamento. Os dados disponíveis sugerem que a irrigação do sítio cirúrgico seguido por bochechos com ATX reduz o risco de sangramento, na primeira semana de pós-operatório, em cirurgia oral menor de pacientes anticoagulados. No entanto, ensaios clínicos adicionais devem ser realizados para comparar a eficácia do ATX em relação aos agentes hemostáticos absorvíveis.

Palavras-Chaves: Ácido tranexâmico; Cirurgia bucal; Hemorragia; Hemostasia Cirúrgica.

ABSTRACT

Oral anticoagulants are widely used for primary prevention of thromboembolic events in patients with atrial fibrillation and prosthetic heart valves. The treatment of patients under OAT who need oral surgery procedures is varied and controversial due to the discussion on the uncontrolled bleeding and the possibility of thromboembolic complications. Currently, intravenous tranexamic acid (TXA) has been proven to be effective in preventing bleeding in several types of surgery, including orthognathic surgery. To the best of our knowledge, there is no evidence on the efficacy and safety of topical TXA in reducing blood loss in anticoagulated patients undergoing minor oral surgery procedures. The aim of this systematic review with meta-analysis is to investigate the efficacy and safety of topical TXA to prevent postoperative bleeding in anticoagulated patients undergoing minor oral surgery. A systematic search in PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), OpenThesis and international database for clinical trials from inception to May 2015 was done. A grey-literature search was conducted through Google Scholar. Our search was restricted to studies published in full-text versions, without language restriction. Two reviewers independently screened the search results and identified clinical trials that compared the use of topical TXA *versus* other topical hemostatic agent, placebo or interruption/decrease of anticoagulant therapy prior to the surgery. Our predefined outcomes were bleeding within the first postoperative week with need for clinical intervention and thromboembolic events. The risk of bias was assessed according to the Cochrane guidelines for clinical trials. The pooled relative risk (RR) was calculated for the effect of topical application of TXA on postsurgical bleeding. Statistical heterogeneity was assessed using the Cochran Q test and quantified by the I^2 index. To assess potential publication bias we created a funnel plot by plotting the individual estimates in log units against the standard error. After screening titles and abstracts, 21 full-text articles were assessed for eligibility and 7 clinical trials were included in the final analysis (a total of 533 patients). The combined RR for the number of patients receiving TXA in comparison to the control group was 0.42 (95% CI 0.21 to 0.84; p = 0.01), indicating a protective effect of topical TXA on bleeding after minor oral surgeries. A moderate between-study heterogeneity was observed (I^2 = 26%) that disappeared (I^2 = 0%) after subgroup analysis by different strategies used in the control groups. Subgroup analysis revealed that topical TXA was effective to prevent postsurgical bleeding compared to placebo (RR = 0.09; 95% CI 0.02 to 0.48; p = 0.004) and epsilon-aminocaproic acid (RR = 0.12; 95% CI 0.01 to 0.94; p = 0.04). However, no significant difference was observed in other analysis. There were no cases of thromboembolic events in any study, in either the TXA or the control groups, during the one to 7 day follow-up period after surgery. Available data suggest that irrigation of surgical site with TXA followed by mouthwash during the first postoperative week can reduce the risk of bleeding after minor oral surgeries in anticoagulated patients. However, additional trials should be conducted to compare TXA efficacy over absorbable hemostatic materials.

Key words: Tranexamic acid; Oral surgery; Hemorrhage.

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1) INTRODUÇÃO

Os anticoagulantes orais são drogas comumente prescritas para prevenção primária de eventos tromboembólicos na fibrilação atrial e em pacientes com próteses cardíacas, bem como na prevenção secundária após embolismo sistêmico em pacientes com doenças reumáticas da valva mitral, prolapso da valva mitral, calcificação anular mitral, regurgitação mitral não reumática e ateromas aórticos móveis ou placas aórticas maiores do que 4 mm (SCHULMAN, 2003).

A maior desvantagem do uso de anticoagulantes orais é o aumento do risco de hemorragias após injúrias traumáticas e procedimentos cirúrgicos. Na maioria das vezes são administrados em pacientes idosos, onde a demanda para procedimentos de exodontia é mais elevada (BROEKEMA et al., 2014) e o risco de sangramento pós-operatório é significante (KÄMMERER et al., 2014). Desta forma, esses pacientes estão mais susceptivéis a sofrer uma hemorragia indesejável (BATISTA, 2010), bem como trismos ou obstrução de vias aéreas superiores por consequências de grandes hematomas (BUMP, KOLODNY, 1973).

Os agentes anticoagulantes orais mais utilizados são os inibidores da agregação plaquetária (ácido acetilsalisílico e clopidogrel) e antagonistas da vitamina K (varfarina, acenocumarol e feprocumon) (BROEKEMA et al., 2014). A varfarina, por ter indicação em múltiplas situações - como a fibrilação atrial e tromboembolismo venoso, é o fármaco anticoagulante oral mais utilizado (AMERICAN HEART ASSOCIATION, 2001). Habitualmente, esta medicação é administrada para prevenção de manifestações tromboembólicas, e reduz o risco de eventos trombólicos arteriais em 70% e tromboembolismo venoso recorrente em 90% (NEMATULLAH et al., 2009). Todavia, deve-se ter atenção especial quando o paciente necessita de intervenção cirúrgica, já que sua suspensão pode acarretar em aumento do risco de tromboembolismo e sua não remoção pode gerar um quadro de hemorragia pós-operatória de difícil controle e de grande repercussão (SOUTO et al., 1996).

Na literatura ainda não existe um consenso geral sobre a conduta pré- e trans-operatória mais adequada para pacientes anticoagulados, principalmente no caso de uso prolongado de varfarina. No passado, a prática de suspensão do uso de anticoagulante oral era rotineira, sendo proposta por diversos autores, por alguns dias antes do procedimento cirúrgico (BLINDER et al., 1999), o que acarreta um maior risco de tromboembolismo para o

paciente. Garcia et al. (2008) realizaram um estudo prospectivo do efeito da interrupção de varfarina por 5 dias antes de vários procedimentos cirúrgicos de pequeno porte. Os autores concluíram que esta interrupção está associada com um risco 0,7% de tromboembolismo e um risco ainda mais elevado de episódios de sangramento clínicos significativos (1,7%). Desta forma, a interrupção da terapia anticoagulante, em especial a varfarina, pode aumentar o risco de tromboembolismo, como o acidente vascular cerebral, o qual pode estar associado com a mortalidade e morbidade de longo prazo (LONGSTRETH et al., 2001).

Entretanto, nos últimos anos, a continuação da terapia anticoagulante nos casos de cirurgias orais menores tem se destacado, principalmente em associação a um agente hemostático local (CARTER, GOSS, 2003). Assim, o regime de anticoagulante oral permanece inalterado e o paciente deve ser tratado com várias medidas hemostáticas locais incluindo o uso de esponjas de colágeno, celulose oxidada, cola de fibrina, suturas e ácido tranexâmico para reduzir o risco de hemorragia (SINDET-PEDERSEN et al., 1989; BERNADONI SOCORRO et al.,1998; BLINDER et al., 1999; CARTER et al., 2003; BACCI et al., 2010).

O ácido tranexâmico é classificado como um agente anti-fibrinolítico, análogo de lisina, que forma um complexo reversível com o plasminogênio e a plasmina (CARTER et al., 2003; GANDA, 2013). Ao bloquear competitivamente a conversão de plasminogênio em plasmina, esta ligação inibe a ação proteolítica da plasmina no coágulo de fibrina e receptores de plaquetas, de modo a inibir a fibrinólise na ferida cirúrgica (DUNN, GOA, 1999; Mc CORMACK, 2012; SONG et al., 2013).

A vantagem evidente da inibição local da fibrinólise em pacientes anticoagulados é a simplicidade e eficácia do tratamento combinado com a ausência de efeitos secundários graves. Uma vez que a terapia anticoagulante não é descontinuada, o paciente não é exposto a potenciais complicações, tais como tromboembolismo e suas consequências (KEARON, HIRSCH, 1997). A hemostasia pode ser alcançada rapidamente e com segurança sem o risco de complicações maiores (CARTER et al., 2003).

Uma série de revisões sistemáticas com meta-análises foram publicadas demonstrando forte evidência de que a administração do ácido tranexâmico reduz o sangramento e a necessidade de transfusão sanguínea em artroplastias de joelho (YU et al., 2015; GANDHI et al., 2013), cirurgias de quadril (XU et al., 2015; WEI, LIU, 2015; GHADHI et al., 2013) e da coluna vertebral (CHERIYAN et al., 2015; ZHANG et al., 2014), sem aumento do risco de

complicações tromboembólicas incluindo infarto do miocárdio, trombose venosa profunda e embolia pulmonar.

Resultados semelhantes foram observados por Song et al. (2013) e Olsen et al. (2015) após a realização de revisão sistemática com meta-análise para avaliação da eficácia do ácido tranexâmico sobre a redução da perda de sangue em pacientes hígidos submetidos à cirurgia ortognática. Em ambos os estudos, os autores sugeriram a administração intravenosa de ácido tranexâmico para controle de sangramento intraoperatório, mas indicaram a necessidade de estudos a respeito da eficácia do medicamento em sua forma tópica. Até o momento, não existem revisões sistemáticas com meta-análise para avaliação da eficácia e segurança do ácido tranexâmico tópico na redução do sangramento em pacientes sob terapia anticoagulante oral submetidos a procedimentos de cirurgia oral menor, muito comuns na prática odontológica.

2) OBJETIVO

- Avaliar, através de uma revisão sistemática com meta-análise, a eficácia do uso tópico de ácido tranexâmico na redução do risco de sangramento pós-operatório e sua segurança em relação a complicações tromboembólicas em pacientes em uso de terapia anticoagulante e são submetidos a procedimentos de cirurgia oral menor sem alteração do protocolo do fármaco anticoagulante.

3) MATERIAL E MÉTODOS

Esta revisão sistemática e meta-análise foi conduzida de acordo com o modelo PRISMA (Preferred ReportingItems for Systematic Reviewsand Meta-Analyses) (MOHER, 2010) e suplementada pelo Manual da Cochrane Collaboration (HIGGINS et al., 2011). Um protocolo de revisão sistemática foi concebido *a priori* e registrado na base de registro de revisões sistemáticas PROSPERO (número de registro CRD 42014013072).

3.1) Estratégia de busca

Foram utilizadas as bases de dados eletrônicas PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), OpenThesis (www.openthesis.org), além do Google Acadêmico e a base de dados internacional para ensaios clínicos (www.clinicaltrials.gov) até maio de 2015. Nossa busca foi restrita a estudos na íntegra, em sua versão completa, sem restrições de língua. A lista de referências de todos os estudos elegíveis e revisados foi manualmente analisada para identificação de estudos adicionais a serem incluídos.

Os termos de busca incluíram “tranexamic acid”, “oral surgery”, “oral surgical procedures”, “dental extraction”, “toothextraction”, “third molar”, “anticoagulants”, “oral hemorrhage”, “hemorrhage”, “oral hemorrhage”, e “bloodloss”.

A estratégia de busca foi estruturada utilizando os seguintes termos: ((“tranexamic acid”) AND (“oral surgery” OR “oral surgical procedures” OR“dental extraction” OR “tooth extraction” OR“third molar”) AND (“oral hemorrhage” OR “hemorrhage” OR “blood loss”)). Para o banco de dados OpenThesis, os termos de pesquisa foram (“tranexamic acid” AND “oral surgery”). Não foram realizados filtros durante a busca, para ampliar o número de artigos elegíveis.

3.2) Critérios de elegibilidade e seleção dos estudos

Dois autores (PRSM-F e SJAV), de forma independente, analisaram os estudos para possível inclusão seguindo os seguintes critérios de elegibilidade. Divergências entre os autores foram resolvidas em consenso ou por um terceiro revisor (TSS):

População: pacientes anticoagulados submetidos à cirurgia oral menor, independente do tipo de procedimento cirúrgico.

Grupo de Intervenção e Controle: uso tópico de ácido tranexâmico por pelo menos 48 horas após a cirurgia *versus* outro agente local hemostático, placebo (solução inócua) ou interrupção/diminuição da dose da terapia anticoagulante.

Desfecho: sangramento na primeira semana de pós-operatório com necessidade de intervenção e eventos tromboembólicos clínicos (infarto do miocárdio, acidente vascular cerebral, embolia sistêmica, trombose de uma válvula cardíaca mecânica, trombose da câmara cardíaca, trombose venosa profunda ou embolia pulmonar). Os estudos elencados deveriam relatar pelo menos o número de pacientes ou sítios cirúrgicos com sangramento pós-operatório como desfecho.

Desenho do Estudo: ensaios clínicos (ECs) que avaliassem que uso do ácido tranexâmico no sangramento pós-operatórios de cirurgias orais menores.

Estudos com pacientes apresentando RNI (Razão Normalizada Internacional) ou outros parâmetros de coagulação do sangue dentro do padrão de normalidade no período pré-operatório ou com anormalidades de coagulação, incluindo hemofilia, transplantados hepáticos e doença hepática, foram excluídos. Além disso, nós excluimos estudos usando ácido tranexâmico em pacientes saudáveis e estudos utilizando ácido tranexâmico intravenoso na perda sanguínea em procedimentos de cirurgia oral.

3.3) Extração dos dados e avaliação do risco de viés

Usando uma folha padronizada de coleta de dados (apêndice A), foram extraídas as seguintes informações: autores, ano de publicação, tipo do estudo, características demográficas dos participantes do estudo, tipo de cirurgia, tipo patologia e anticoagulante oral, a dose e o tempo de ácido tranexâmico, grupo controle, período de acompanhamento pós-operatório, número de sítios cirúrgicos ou pacientes com sangramento pós-operatório.

O risco de viés foi avaliado de acordo com as diretrizes da Cochrane para ensaios clínicos. Foram avaliados sete domínios de avaliação: geração de sequência aleatória e ocultação de alocação (viés de seleção), cegamento dos participantes e profissionais (viés de performance) ou não, cegamento de avaliação do desfecho (viés de detecção), desfechos incompletos (viés de atrito), relato de desfecho seletivo (viés de relato), e outras fontes potenciais de viés. O risco de viés foi avaliado como sendo baixo, incerto ou alto de acordo com critérios estabelecidos (HIGGINS et al., 2011).

3.4) Medidas de tratamento, síntese de dados e qualidade da evidência

O risco relativo resumido foi calculado para o efeito da aplicação tópica do ácido tranexâmico no sangramento pós-cirúrgico. Um *forest plot* foi usado para apresentar graficamente o tamanho do efeito e o intervalo de confiança (IC) de 95%. Cada estudo foi representado por um quadrado no gráfico, sendo este proporcional ao peso do estudo na meta-análise. Valores de $p<0,05$ para duas caudas foi utilizado para determinar significância estatística.

A variabilidade entre os estudos foi avaliada usando o teste Q (COCHRAN, 1954) e quantificada pelo índice I (HIGGINS e THOMPSON, 2002). Índices menores do que 25% indicaram baixa heterogeneidade entre os estudos, entre 25 e 75% moderada heterogeneidade e acima de 75% alta heterogeneidade (HIGGINS, THOMPSON, 2002). Na presença de moderada ou alta heterogeneidade, as estimativas reunidas e o IC de 95% correspondente foram calculadas com base no modelo de efeitos aleatórios utilizando o método DerSimonian-Laird. Em caso de baixa heterogeneidade, um modelo de efeitos fixos foi utilizado.

No modelo de efeitos aleatórios de meta-análise, o risco para os estudos individuais foi assumido a variar em torno do tamanho do efeito combinado (BORENSTEIN, 2010). Possíveis fontes de heterogeneidade foram analisadas: (1) critérios utilizados para mensuração de sangramento pós-operatório, (2) associação de outro agente local hemostático e (3) o método de aplicação tópica de ácido tranexâmico. A análise dos subgrupos de acordo com as possíveis fontes de heterogeneidade também foi realizada.

Para avaliar a presença de viés de publicação, um gráfico de *funnel plot* foi criado para as estimativas individuais em unidades logaritmicas versus o erro padrão. Para avaliar o viés de publicação, foi analisado visualmente o perfil de simetria do gráfico, com posterior teste de Begg e Mazumbar com continuidade de correção (BEGG e MAZUMDAR, 1994). Os estudos maiores e mais precisos encontram-se na parte superior do gráfico, próximo à medida de efeito combinada, indicada pela linha ortogonal. Já os estudos considerados menores e menos precisos estão espalhados em ambos os lados da linha. No caso de distribuição simétrica dos estudos, não há evidência de viés de publicação. A análise de sensibilidade "leave-one-out" foi realizada omitindo um estudo de cada vez e analisando a influência de cada estudo individual no tamanho efeito combinado (STERNE , EGGER e SMITH, 2001).

Todas as análises foram conduzidas utilizando o programa Review Manager 5.3 (Cochrane IMS, Copenhagen, Denmark).

4) RESULTADOS

Topical Application of Tranexamic Acid in Anticoagulated Patients Undergoing Minor Oral Surgery.

A Systematic Review and Meta-Analysis

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Abstract

Background: The peri-operative management of patients under long-term anticoagulant therapy remains a great challenge for dentists. In recent years, studies have shown evidence to continue oral anticoagulant therapy for minor oral surgeries, emphasizing the role of local hemostasis.

Type of Studies Reviewed: This systematic review included clinical trials that compared the use of topical tranexamic acid (TXA) versus other topical hemostatic agents, placebo or interruption/decrease of anticoagulant therapy for minor oral surgeries. The authors included only studies in which the investigators evaluated bleeding within the first postoperative week with need for clinical intervention. The risk of bias was assessed according to the Cochrane guidelines for clinical trials. The pooled relative risk (RR) was calculated for the effect of topical application of TXA on postsurgical bleeding.

Results: 7 clinical trials were included in the meta-analysis. The combined RR for the number of patients receiving TXA in comparison to the control group was 0.42 (95% CI 0.21 to 0.84; $p = 0.01$), indicating a protective effect of topical TXA on bleeding after minor oral surgeries. Subgroup analysis revealed that topical TXA was effective to prevent postsurgical bleeding compared to placebo and epsilon-aminocaproic acid. No cases of thromboembolic events was reported in any study.

Practical Implications: Irrigation of surgical site with TXA followed by mouthwash during the first postoperative week can reduce the risk of bleeding after minor oral surgeries in anticoagulated patients.

Key words: Decision making; dental care for chronically ill patients; evidence-based dentistry; hemorrhage; oral surgical procedures.

Introduction

Oral anticoagulants are widely used for primary prevention of thromboembolic events in patients with atrial fibrillation and prosthetic heart valves and secondary prevention after systemic embolism in patients with rheumaticmitral-valve disease, mitral-valve prolapse, mitral annular calcification, nonrheumaticmitral regurgitation, and mobile aortic atheromas or aortic plaques larger than 4 mm.[1] However, the major drawback of oral anticoagulant therapy (OAT) is related to increased risk of bleeding after traumatic injuries and surgical procedures.[2] Patients receiving OAT are generally older, present multiple comorbidities, and receive several medications.[3] In addition, elderly patients usually have high demand for oral surgery procedures, which can further increase their risk of bleeding and hinder the treatment.[2,4]

Warfarin is the most used oral anticoagulant to control and prevent thromboembolic events classified as an antagonist of vitamin K, an essential cofactor for the synthesis of clotting factors II, VII, IX and X and protein C and S. Although warfarin has a narrow therapeutic range, the dose required to achieve therapeutic anticoagulation is very close that leads to over-anticoagulation. Therefore, patients receiving warfarin requires frequent monitoring to avoid potentially life-threating complication including the risk of serious bleeding.[5] The median annual rate of major bleeding associated to the warfarin ranges from 0.9 to 2.7 percent, especially in elderly patients, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, and renal insufficiency.[6]

Regard to increased risk of bleeding, determining the clinical protocol at long-term OAT to reduce the risk during surgery or invasive procedures remains controversial; while different recommendations have been proposed including the reduction, discontinuation, or substitution of OAT with heparin prior to surgical procedure. However, there is strong evidence that OAT patients undergoing oral surgeries should not discontinue their medication due to the risk of thromboembolic complication.[2] In the last years, studies have indicated that maintaining OAT associated to topical use of tranexamic acid (TXA) and other local hemostatic agents does not result in an increased risk of bleeding during and after minor oral surgeries.[7–12]

TXA, a synthetic derivative of the amino acid lysine, is an antifibrinolytic agent that blocks lysine-bindings sites on plasminogen reducing the local degradation of fibrin by plasmin. TXA works to stabilize and inhibit the degradation of existing clots, and is widely used to limit bleeding in clinical practice. A series of systematic reviews and meta-analyses were published showing strong evidence that TXA is effective in reducing blood loss and transfusion requirements in knee arthrosplasty[13–15], hip[13,15,16] and spinal surgeries[17,18], without increased thromboembolic complications such as myocardial infarction, deep venous thrombosis, and pulmonary embolism. Similar results were observed in healthy patients during orthognathic surgery receiving intravenous TXA.[19,20] However, to the best of our knowledge, there is no evidence about the efficacy and safety of topical TXA in reducing blood loss in anticoagulated patients undergoing minor oral surgery procedures.

This systematic review meta-analyzed the outcomes of clinical trials investigating the efficacy and safety of topical TXA to prevent postoperative bleeding in anticoagulated patients undergoing minor oral surgery when compared to other hemostatic therapies.

Material and Methods

This systematic review and meta-analysis was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[21] and supplemented by guidance from the Cochrane Collaboration Handbook.[22] A protocol of this systematic review was designed *a priori* and was registered in the PROSPERO database (registration number CRD 42014013072).

Search Strategy

We searched for clinical trials at PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), OpenThesis and website clinicaltrials.gov (international database for clinical trials) from inception to May 2015. A grey-literature search was conducted through Google Scholar. Our search was restricted to studies published in full-text versions, without language restriction. The reference lists of all eligible studies and reviews were also manually scanned to identify additional studies for inclusion.

The structured search strategy used the following terms: ((“tranexamic acid”) AND (“oral surgery” OR “oral surgical procedures” OR “dental extraction” OR “tooth extraction” OR “third molar”) AND (“oral hemorrhage” OR “hemorrhage” OR “blood loss”)). For the OpenThesis database, the search terms were (“tranexamic acid” AND “oral surgery”). No filter was performed to the search, to expand the number of eligible articles.

Study Selection and Eligibility Criteria

Two reviewers (PRSM-F and SJAV) independently screened the search results and identified studies that were potentially relevant based on paper’s title and abstract. Relevant studies were read in full-text and selected according to eligibility criteria. Disagreement between the two reviewers was resolved by consensus or by a third reviewer (TSS).

The following PICOT (population, intervention, controls, outcome, and study type) elements were used to define the eligibility criteria: (1) *population:* anticoagulated patients undergoing to the minor oral surgery; (2) *intervention and controls:* the use of topical TXA for at least 48h after surgery *versus* other topical hemostatic agent, placebo (innocuous solution) or interruption/decrease of anticoagulant therapy prior to the surgery; (3) *predefined outcomes*: bleeding within the first postoperative week with need for clinical intervention and

thromboembolic events (myocardial infarction, stroke, systemic embolism, thrombosis of a mechanical heart valve, thrombosis of the cardiac chamber, deep-vein thrombosis or pulmonary embolism); and (4) *type:* clinical trials. Eligible studies must report at least the number of patients or surgical sites with postoperative bleeding as end point.

Data from patients with INR (International Normalized Ratio) or other blood coagulation parameters within the normal range in the preoperative period or with coagulation abnormalities including hemophilia and liver disease were excluded. In addition, we excluded studies or groups that modified the OAT and used perioperative intravenous or oral TXA on blood loss in minor oral surgery procedures.

Data Extraction and Risk of Bias Assessment

Using a standardized data extraction sheet, the following information was extracted and recorded from studies: demographic characteristics of study participants, pathology and anticoagulant medication, type of oral surgery, dosage and timing of TXA, control group intervention, duration of follow-up, and outcome data.

The risk of bias was assessed according to the Cochrane guidelines for clinical trials. We assessed seven domains for evaluation: sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. We rated the risk of bias as low, unclear, or high according to established criteria.[22]

Data Synthesis

The pooled relative risk was calculated for the effect of topical application of TXA on postsurgical bleeding. A *forest plot* was used to graphically present the effect sizes and the 95% CIs. Each study was represented by a square in the plot that was proportional to the study's weight in the meta-analysis. A 2-tailed $p < 0.05$ was used to determine significance.

Statistical heterogeneity was assessed using the Cochran Q test[23] and quantified by the I^2 index.[24] A random-effects model of DerSimonian-Laird was used to pool estimates and corresponding 95% CI assuming that the risk for individual trials vary around pooled effect size.[25] A possible source of between-study heterogeneity which we noted prior to performing

our study was the different strategies used in the control groups. Therefore, a subgroup analysis was performed according to this potential source of heterogeneity.

To assess potential publication bias we created a *funnel plot* by plotting the individual estimates in log units against the standard error.[26] "Leave-one-out" sensitivity analysis was conducted by omitting one study at a time and examining the influence of each individual study on the pooled effect size.[27] All analyses were conducted using Review Manager 5.3 (Cochrane IMS, Copenhagen, Denmark).

Results

Data Sources

We identified 1630 potentially relevant studies from electronic databases, Google Scholar, and cross-references. After screening titles and abstracts, 21 full-text articles were assessed for eligibility and 7 clinical trials were included in the final analysis. Flow diagram of the selection of studies and specific reasons for exclusion are detailed in Figure 1.

Study Characteristics

The total number of patients included in the trials was 483. Dental extractions were the most common oral procedure, followed by periapical surgery and implants. Most patients aged over 60 years and received warfarin therapy before surgery. All studies used TXA for irrigation of surgical site and mouthwash (2 to 7 days) to prevent postoperative bleeding during the 7-day postoperative period. In three studies[7,8,28], TXA was associated with other hemostatic agent.

The efficacy of TXA was compared with placebo solution in two studies[12,29], with EACA as a mouthwash in one study[30], and with an absorbable hemostatic material in two studies.[7,8] In the study by Sacco et al.[28] and Borea et al.[31], comparator was the reduction or discontinuation of OAT until INR values within therapeutic range (between 1.5 and 2.5). All patients received sutures after surgical procedures. The main characteristics (number of patients, age, anticoagulant therapy, intervention, procedures, and follow-up visits) of clinical trials are presented in Table 1.

Risk of Bias

Figure 2 provides a summary of risk of bias characteristics for all 7 clinical trials. For the domains of random sequence generation and allocation concealment, most studies (71.5%) had a high or unclear risk of bias, while 42.9% and 28.5% of studies had low risk of performance and detection bias, respectively. For all other domains (incomplete outcome data, selective reporting, and other bias), most of trials were rated as low risk of bias.

Data Synthesis

The 7 clinical trials included in this analysis randomized 249 patients to receive TXA and 284 received other treatments assigned as controls. The combined RR for the number of patients receiving TXA in comparison to the control group was 0.42 (95% CI 0.21 to 0.84; p = 0.01), indicating a protective effect of topical TXA on bleeding after minor oral surgeries. A moderate between-study heterogeneity was observed (p = 0.22, I^2 = 26%) (Figure 3). There were no cases of thromboembolic events in any study, in either the TXA or the control groups, during the one to 7 day follow-up period after surgery.

Subgroup analysis and publication bias

Although all included clinical trials examined a similar question (effect of topical TXA for prevention of postsurgical bleeding in anticoagulated patients undergoing minor oral surgery procedures), we assumed the control group as a potential source of between-study heterogeneity once that is used on the relative risk calculation. We stratified the meta-analysis into four subgroups: TXA vs. placebo solution, TXA vs. EACA, association of TXA and absorbable hamostatic material vs. absorbable hamostatic material, and association of TXA and absorbable hamostatic material vs. reduced dosage of OAT. The heterogeneity decreased markedly from 26 to 0% within the subgroups, suggesting that the heterogeneity was attributable to the different strategies used to prevent postsurgical bleeding in the control group.

Subgroup analysis revealed that topical TXA was effective to prevent postsurgical bleeding compared to placebo (RR = 0.09; 95% CI 0.02 to 0.48; p = 0.004) and EACA (RR = 0.12; 95% CI 0.01 to 0.94; p = 0.04). However, no significant difference was observed for the absorbable haemostatic material (RR = 0.77; 95% CI 0.32 to 1.86; p = 0.56) and reduced or

discontinued dosage of OAT (RR = 0.59; 95% CI 0.25 to 1.43; p = 0.24) (Figure 3). Sensitivity analysis indicated the robustness of our findings, and evidence of publication bias was not observed in our meta-analysis (Figure 4).

Discussion

Although life expectancy has improved for decades due to gradual improvement in health-care delivery services, elderly people tends to have a higher prevalence of chronic diseases, physical disabilities, mental illnesses and other comorbidities.[32] Since cardiovascular disease is the most common cause of mortality in elderly people worldwide, oral anticoagulants are widely used for long-term prevention or treatment of cardiovascular events, such as stroke and myocardial infarction. For this reason, the management of patients on OAT requiring surgical procedure remains a challenge due to the risk of increased bleeding if therapy is continued.[33]

TXA is one of the most common antifibrinolytic medication used in controlling blood loss after oral surgeries in anticoagulated patients. Recently, two meta-analyses[19,20] of RCTs confirmed that intravenous TXA reduces intraoperative blood loss in orthognathic surgery, but high-level of evidence is lacking for the use of topical application. Our meta-analysis showed that irrigation of surgical site with TXA followed by mouthwash in anticoagulated patients without therapy modification or withdrawal might reduce the risk of bleeding during the first postoperative week, especially compared to placebo solution (91% decrease in risk) and EACA mouthwash (88% decrease in risk).

These findings are in contrast to those from the other studies which suggested that patients receiving OAT within the therapeutic range can be carried out safely and without complication to the minor oral surgical procedures without any additional hemostatic measures[34–36], as the use of topical haemostatic agents. According to the Wahl[37], however, although there are no well-documented cases of serious postoperative bleeding complications after dental surgery in patients receiving OAT within the therapeutic range, there are good legal reasons to continue OAT for dental surgery in addition to the application of local measures to control post-surgical bleeding. In a recent meta-analysis, it was observed that perioperative continuation of warfarin did not increase the risk of bleeding compared with discontinuing or modifying the warfarin dose for patients undergoing minor dental procedures.[38]

Although our subgroup analysis has shown no difference for the risk of bleeding between the use of topical TXA and anticoagulant dose modification, the risk of thromboembolic events should not be overlooked if OAT is modified before dental procedures.[37] In a systematic review performed by Wahl[37], in 542 documented cases in 493 patients of withdrawing the OAT for dental procedures, 1% of patients had serious embolic complications, including 4 deaths. Therefore, our results also suggest that anticoagulant treatment does not need to be drawn or reduced before oral surgery, as long as local hemostatic measures including suture and irrigation of surgical site with TXA followed by mouthwash with this agent are performed for these patients.

Other hemostatics agents such as autologous fibrin sealant, absorbable gelatin sponges, and oxidized cellulose polymer have also been indicated in surgical practice. Suwannuraks et al.[39] reported the efficacy of a combination of celluloid splint and fibrin glue in controlling bleeding during oral surgeries. Others recommended the use of fibrin sealant in combination with absorbable gelatin sponge[40] or oral swish and swallow rinses of TXA solution[41]for patients with bleeding disorders. Minimal bleeding complications were also observed using oxidized regenerated cellulose[34] or gelatin sponge[42]after minor oral surgical procedures in anticoagulated patients. Interestingly, our results showed that local hemostasis with absorbable hemostatic materials (gelatin sponge, fibrin glue or oxidized regenerated cellulose) was not more effective in preventing bleeding than TXA mouthwash in combination with gelatin sponge or oxidized regenerated cellulose. Unfortunately, we didn´t find any study comparing the efficacy of topical application of TXA alone with absorbable hemostatic materials. Since TXA may be a better cost-effective option to minimize bleeding risks after minor oral surgeries, further studies are still necessary to support the superiority of TXA over absorbable hemostatic materials.

Systemic infusion of antifibrinolytic agents has been used for many years to reduce bleeding and need for transfusion in various surgical procedures, including orthognathic surgeries.[43] However, systemic administration of these agents can increase the tendency to thrombosis and the risk of thromboembolism. To avoid or at least reduce the risk of thromboembolic events such as deep vein thrombosis, myocardial infarction, and pulmonary embolism, topical TXA has been indicated for several surgical procedures.[44–47] Our meta-analysis suggests that topical TXA in minor oral surgeries is safe, since no cases of thromboembolic events was observed during the follow-up period up to 7-day after surgery in studies evaluated. Therefore, in addition to the efficacy in reducing the risk of bleeding in

anticoagulated patients, irrigation of surgical site with TXA followed by mouthwash can minimize its systemic absorption, and, consequently, concerns about possible side-effects.

Although no evidence of publication bias, this systematic review presents some limitations. First, the quality of the evidence is limited to the quality of studies included in this meta-analysis. None of the studies had an overall low risk of bias. In most cases, we found potential bias for selection that may lead to large estimates of effects and problems to controlling for unknown and unmeasured factors.[48] Second, the studies included in this meta-analysis contain relatively small samples sizes, which may lead to an extreme beneficial treatment effect. The aim of the sample size calculations is to assure that statistical power is acceptable while maintaining a small probability of a type I error.[49] In this meta-analysis, only one study[29] reported the power calculation and estimates of sample size for planning the trial. Finally, we are unable to explore differences in TXA efficacy according to surgical type, duration of the surgery, mouthwash regimen, and preoperative and postoperative hematological data, which may lead in confounding and performance bias.

Conclusions

Despite these limitations, available data suggest that irrigation of surgical site with TXA followed by mouthwash during the first postoperative week can reduce the risk of bleeding after minor oral surgeries in anticoagulated patients with no risk of thromboembolism. However, additional trials should be conducted to compare TXA efficacy over absorbable hemostatic materials.

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Legends

Table 1. Characteristics of studies included in the meta-analysis.

Figure 1. Flow chart of the search process.

Figure 2. Risk of bias assessment.

Figure 3. Forest plot for the risk of postosurgical bleeding.

Figure 4. Funnel plot assessing potential publication bias.

Table 1. Characteristics of studies included in the meta-analysis.

Author	Year	n	Age (y)	Anticoagulant therapy		Intervention	Procedures	Follow-up visits
				INR	Agents			
Sindet-Pedersen	1989	39	53 - 66	not reported	Warfarin / dicumarol	T: 4.8% TXA, irrigation of surgical site + mouthwash for 7 days C: Placebo solution	Dental extractions, periapical surgery, excision of gingival hyperplasia	7th day
Borea	1993	30	T: 62.7 C: 61.1	T: 3.0 - 4.5 C: 1.5 - 2.5	not reported	T: 5% TXA, irrigation of surgical site + mouthwash for 7 days C: Discontinuation of OAT until INR values between 1.5 and 2.5 + placebo solution	Dental extractions	1st and 7th days
Ramström	1993	93	T: 70.5 C: 68	not reported	Warfarin / dicumarol / phenprocoumon	T: 4.8% TXA, irrigation of surgical site + mouthwash for 7 days C: Placebo solution	Dental extractions and periapical surgery	7th day
Souto	1996	41	56.3	T: 2.82 C: 3.50	Acenocoumarol	T: 0.5g TXA, irrigation of surgical site + mouthwash for 2 days C: Cold water irrigation + EACA as mouthwash for 2 days	Dental extractions	7th day
Blinder	1999	150	35 - 90	T: 2.19 (1.5 – 3.58) C1: 2.38 (1.5 – 3.6) C2: 2.7 (1.9 – 4.0)	Coumarin anticoagulants	T: 0.5g TXA, irrigation of surgical site + mouthwash for 4 days + resorbable gelatin sponge C1: Resorbable gelatin sponge C2: Fibrin glue + resorbable gelatin sponge	Dental extractions	1st and 7th days
Carter	2003	49	65	T: 3.0 (2.3 – 4.0) C: 3.1 (2.1 – 4.0)	Warfarin	T: 4.8% TXA, irrigation of surgical site + oxidized cellulose sponge + mouthwash for 7 days C: Oxidized cellulose sponge + fibrin glue	Dental extractions	1st, 3rd and 7th days
Sacco	2007	131	T: 61.5 C: 64	T: 2.89 C: 1.77	Warfarin / Acenocoumarol	T: TXA, irrigation of surgical site + gelatin or oxidized cellulose sponge + mouthwash for 2 days C: Reduction of OAT until INR values between 1.5 and 2.0	Dental extractions, removal of cysts, and implants	1st and 7th days

T: TXA group; C: control. INR, International Normalized Ratio. EACA, epsilon-aminocaproic acid.

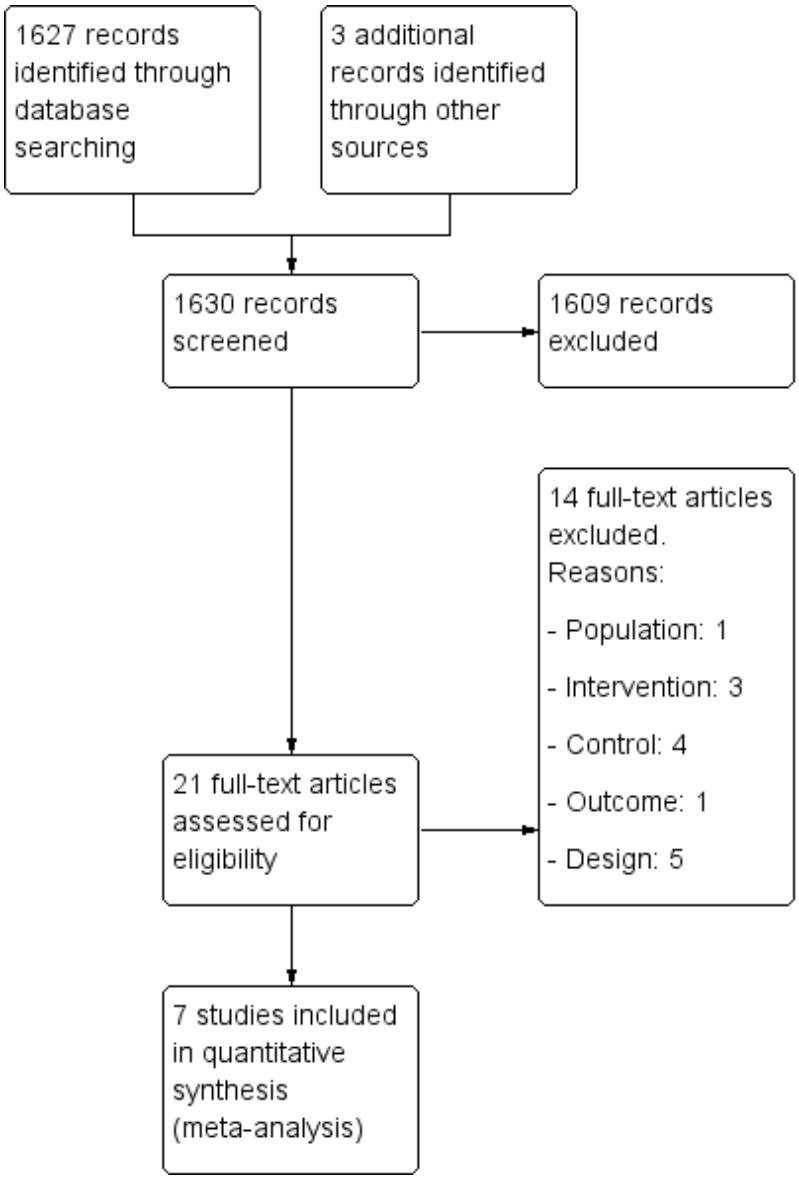

Figure 1. Flow chart of the search process.

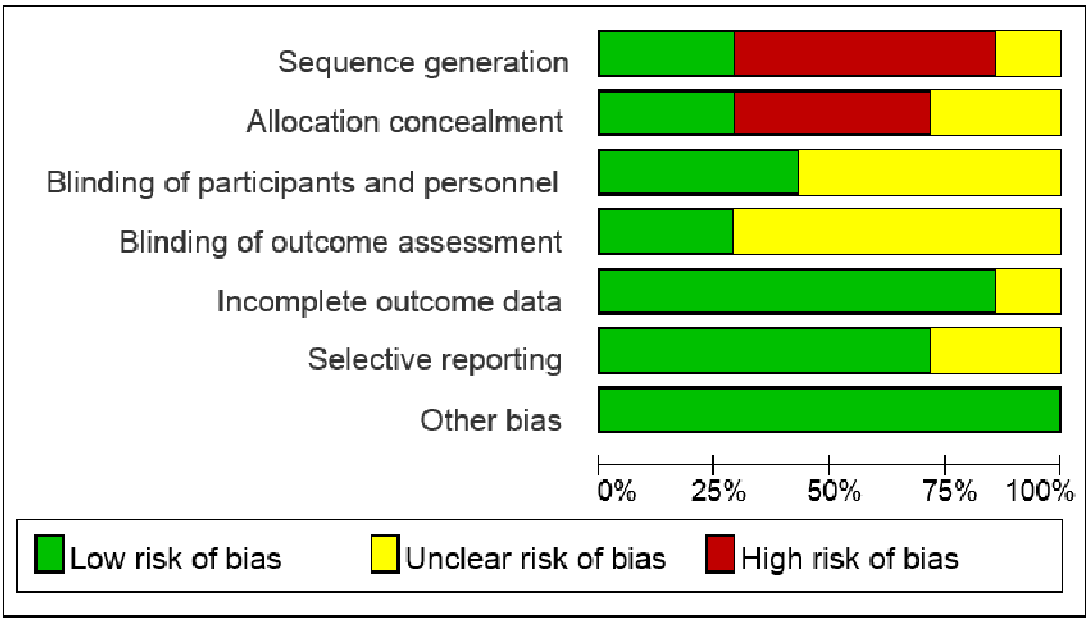

Figure 2. Risk of bias assessment.

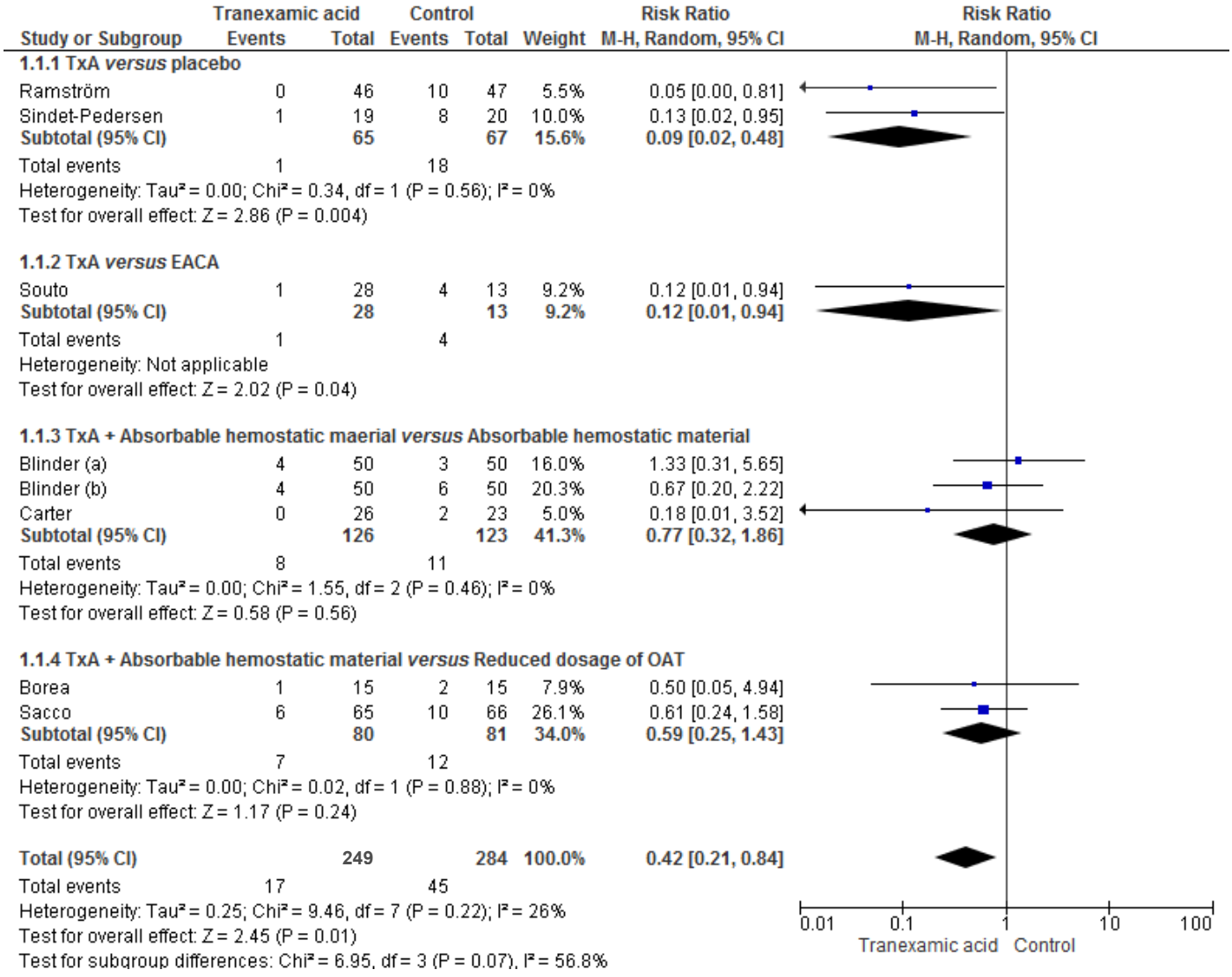

Figure 3. Forest plot for the risk of postosurgical bleeding.

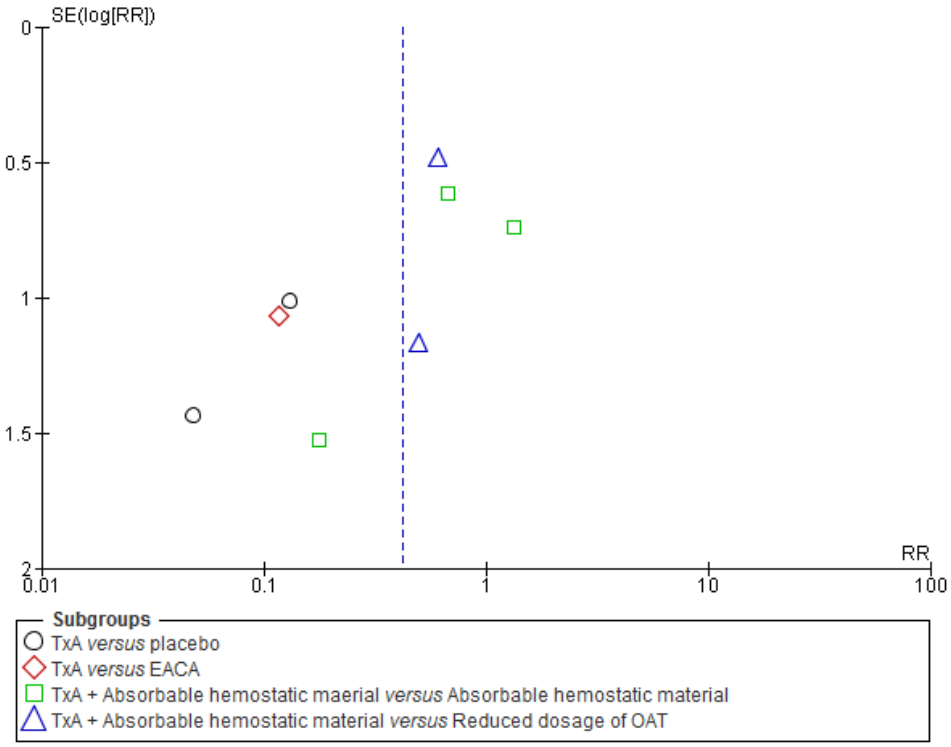

Figure 4. Funnel plot assessing potential publication bias.

5) CONSIDERAÇÕES FINAIS

Os dados avaliados nesta meta-análise sugerem a eficácia do uso do ácido tranexâmico tópico no controle do sangramento de cirurgias orais menores em pacientes sob terapia anticoagulante na primeira semana de pós-operatório, em especial em relação ao grupo placebo, além de segurança em relação ao risco de eventos tromboembólicos. Entretanto, a análise mostra que mais estudos clínicos bem delineados são necessários para avaliar a efetividade do ácido tranexâmico tópico principalmente em comparação a outros agentes hemostáticos locais.

6) COMUNICADO A IMPRENSA (PRESS RELEASE)

A EFICÁCIA DO ÁCIDO TRANEXÂMICO EM CIRURGIAS ODONTOLÓGICAS

Com o crescente acesso e informação na área odontológica, os pacientes estão cada vez mais mantendo sua dentição natural à medida que envelhecem. Neste contexto, as cirurgias orais passaram a ser mais indicadas em pessoas idosas, que apresentam alguma doença geral, dentre elas as alterações cardíacas ou vasculares. Desta maneira muitos pacientes que necessitam de procedimento cirúrgico odontológico fazem uso de anticoagulantes orais, que são drogas comumente prescritas para prevenção e tratamento de eventos tromboembólicos associados a condições clínicas importantes como fibrilação atrial, doença cardíaca isquêmica, acidente vascular cerebral entre outras.

Porém, estes pacientes, quando necessitam de uma cirurgia na boca ou outro procedimento cirúrgico, tem o risco aumentado de sangramento, visto que esta é a maior desvantagem dos anticoagulantes orais. Baseado nisso, foi realizada uma análise, através de uma revisão sistemática, de vários artigos que descreveram o uso do ácido tranexâmico em forma de bochecho no controle do sangramento após cirurgias bucais em pacientes em uso de anticogulantes orais. Os dados da pesquisa revelaram a eficácia deste agente hemostático no controle do sangramento durante a primeira semana de pós-operatório, sendo mais significante quando comparado ao placebo. Entretanto, foi verificada a necessidade de estudos adicionais que comparem a eficácia do ácido tranexâmico em relação a outros agentes hemostáticos locais, como as esponjas de fibrina.

Contatos: Sara Vasconcellos (sarajulianad@yahoo.com.br) e Paulo Saquete (martins-filho@ufs.br). Universidade Federal de Sergipe, Hospital Universitário, Laboratório de Patologia Investigativa. Rua Cláudio Batista, s/n. Bairro Sanatório. Aracaju, Sergipe, Brasil. CEP: 49060-100.

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APÊNDICES

Autor/Ano	
Local do Estudo	
Tipo de estudo	
Cegamento	Descrição:
Objetivos	
Hipótese	
Critérios de Inclusão	
Critérios de Exclusão	
Variáveis estudadas	
Média Idade	
Amostra por sexo	
RNI média	
Tipo Anticoagulante	
Tipo de Patologias	
Grupo 1 (teste)/nº pacientes	
Grupo 2 (controle)/ nº pacientes	
Outras considerações	
Dose/Tempo Ac. Tranexâmico	
Tipo de Cirurgia	
Tipo Controle sangramento	
PO (nº dias)/ Avaliação	
Desfecho (RNI ou sangramento)	
Dia do sangramento	
Quantos episódios de sangramento	
Complicações Pós-Operatórias	
Análise estatística	
Total de Pacientes	
Perdas de pacientes	Descrição:
Limitações	
Conclusões	

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Topical application of tranexamic acid in anticoagulated patients undergoing minor oral surgery procedures: systematic review and meta-analysis

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
18/08/2014

4 Anticipated completion date
Give the date by which the review is expected to be completed.
01/12/2015

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	Yes	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Paulo Martins-Filho

7 Named contact email
Enter the electronic mail address of the named contact.
martins-filho@ufs.br

8 Named contact address
Enter the full postal address for the named contact.
Universidade Federal de Sergipe, Campus da Saúde. Laboratório de Patologia Investigativa, Programa de Pós-Graduação em Odontologia. Rua Cláudio Batista, s/n Bairro Sanatório. Aracaju, Sergipe, Brasil. CEP.: 49060-100.

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
79 9898-0521

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed

as 'None' if the review is not affiliated to any organisation.
None

Website address:

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Professor	Paulo	Martins-Filho	Universidade Federal de Sergipe
Dr	Thiago	Santos	Universidade Federal de Sergipe
Professor	André Luis	Faria-e-Silva	Universidade Federal de Sergipe
Ms	Sara Juliana	Vasconcellos	Universidade Federal de Sergipe
Professor	Maria de Fátima	Melo	Universidade Federal de Sergipe

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
There was no funding source for this study

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
Is topical application of tranexamic acid more effective than placebo in preventing post-operative bleeding in anticoagulated patients undergoing minor oral surgery procedures?

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
We will search MEDLINE, SCOPUS, Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL) and international database for clinical trials www.clinicaltrials.gov from inception to May 2015. Our search will include RCTs published in full-text versions, without language restriction. The search will include a hand search of cross-references from original articles and reviews. Search terms will include “tranexamic acid”, “oral surgery”, “oral surgical procedures”, “dental extraction”, “tooth extraction”, “third molar”, “anticoagulants”, “oral hemorrhage”, “hemorrhage”, and “oral hemorrhage”, “blood loss”.

17 URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Post-operative bleeding in anticoagulated patients undergoing minor oral surgery procedures

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Anticoagulated patients who underwent minor oral surgery

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Local acid tranexamic

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Other local hemostatic agent or placebo (innocuous solution, interruption or decrease of anticoagulant therapy prior to the surgery)

22 Types of study to be included initially
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Randomized controlled trials

23

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AUTHOR INFORMATION PACK

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DESCRIPTION

Introduced in 1913, the monthly *The Journal of the American Dental Association* is the nation's premier dental journal - a reliable, peer-reviewed source of information on dentistry and dental science. Each issue of JADA is available in print, online at JADA Online and via a mobile Web application.

What Does JADA Have to Offer?

Today's JADA offers a wide range of information for ADA-member dentists and its other readers around the world: **peer-reviewed research** on current and developing topics in dentistry; **clinical information** in such areas as biomaterials, pharmacology, and cosmetic and esthetic dentistry as well as general dental practice; **reports** on the increasingly important relationship between dental health and overall health; **news and views** on the issues of the day; **explorations** of practice building and legal topics; **a continuing education** program.

Best-Read Dental Journal

Judging from the feedback received, The Journal is meeting the needs of its readers. Yearly independent readership studies consistently rank JADA as the nation's best-read dental journal. And ADA members rank it among the most important benefits of Association membership.

JADA's 100-Year History

In 1913 the ADA was known as the National Dental Association, and the publication that would become JADA was introduced as the quarterly Official Bulletin, later to be renamed The Journal of the National Dental Association. In 1917, the Journal expanded to a monthly publication, with a lengthy subscription list that placed it at the forefront of dental literature.

The Journal's ascendancy spurred a number of other, long-respected dental periodicals to cease publishing. The once venerable Dental Register stopped the presses for good in 1923. And even the Dental Cosmos, long the bellwether of dental journalism, disappeared in 1938. One year later, the Journal adopted its current title, The Journal of the American Dental Association, or JADA.

Just after World War II, JADA became a twice-monthly publication. The goal was to reduce the bulk of each issue and to boost readership and advertising revenues. But that experiment failed, and The Journal returned to a monthly publication schedule in 1948.Through the decades, JADA has changed with the times and the shifting needs of its readers, improving its appeal to its primary audience: dentists in clinical practice. Each issue includes full-text articles on emerging research and in-depth

reviews of cutting-edge clinical developments. JADA also provides editorials and feature articles on the many ethical and practice issues that dentists encounter each day. The Journal also covers the latest industry news, ADA events and updates on policies affecting dental practice.

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INTRODUCTION

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Originality and exclusivity. The JADA Editor will consider only articles that are original, have not been published elsewhere and have been submitted exclusively to JADA.

BEFORE YOU BEGIN

Clinical trials

CONSORT statement. Authors of articles about clinical trials must adhere to the Consolidated Standards of Reporting Trials statement (http://www.consort-statement.org/consort-statement/overview0). Authors of manuscripts about clinical trials must use intention-to-treat analysis.

Registration of clinical trials. Effective March 1, 2013, as a condition for publication of any report of a clinical trial that began enrollment of participants on or after March 1, 2013, JADA requires that the clinical trial be registered publicly before any participants are enrolled in the study. Trials that began enrollment prior to March 1, 2013 also must be registered, but registration of such trials after enrollment of participants has begun is acceptable. The specific trial registry name and the registry number (for example, "ClinicalTrials.gov identifier NCT00000000" must be submitted with each manuscript that is a report of a clinical trial. Observational studies—those in which the investigator does not assign the intervention—will not require registration. JADA editors will check manuscripts on submission to determine if the study required registration. Clinical trials need not be registered on any specific website; a list of registries acceptable to JADA is available on the International Committee of Medical Journal Editors website (http://www.icmje.org/about-icmje/faqs/clinical-trials-registration). If such a manuscript is accepted for publication, the trial registry name and registration number will be published at the end of the article's abstract.

Systematic reviews and meta-analyses

PRISMA statement. Authors of systematic reviews must adhere to Preferred Reporting Items for Systematic Reviews and Meta-Analyses, available at http://www.prisma-statement.org/statement.htm.

Manuscript designation

When published, manuscripts will be placed in one of the JADA departments listed below. The editor will designate each submission to the appropriate section.

Unless otherwise noted, manuscripts must be no longer than 10 double-spaced pages (roughly 3,000 words), exclusive of title page, abstract, acknowledgments, references and illustrations (tables, figures, text boxes).

Peer-reviewed articles
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Length. Unless otherwise noted above, manuscripts must be no longer than 10 double-spaced pages (roughly 3,000 words), exclusive of title page, abstract, acknowledgments, references and illustrations.

NOTE: The Journal does not accept submissions of serial articles (Part I, Part II, etc.).

Page setup. Pages should have 1-inch margins and must be numbered consecutively throughout the document.

Title page. Each manuscript should have a title page bearing the complete title of the manuscript and complete information on all authors. It should be the first page of the manuscript. Each author's degrees must be listed on the title page. JADA generally does not publish U.S. fellowships and honorary degrees and designations. Degrees below the master's level generally are not listed, unless they are the highest degree attained.The title page should designate the corresponding author and list that author's complete mailing address for the purposes of directing reprint requests after publication.

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Acknowledgments. Acknowledgments should be submitted on a separate page.

Illustrations. A maximum of four figures—charts, graphs or photographs—and four tables may be submitted. (See next paragraph for an exception to this rule.) Each separate chart, graph or photograph will be counted as a separate illustration; illustrations should not be grouped together as a single illustration. Tables and figures should augment, not repeat, the text. Figures and tables should be numbered consecutively according to the order in which they are cited in the text. Regarding clinical figures, JADA will accept only digital files of at least 4 inches (roughly 100 millimeters) in width and at least 300 or more dots per inch and in JPEG, TIFF or EPS format. These may be uploaded on JADA ScholarOne Manuscripts. JADA cannot accept original histologic slides and radiographs. However, The Journal will accept digital files of radiographs, magnetic resonance images and magnetic resonance angiograms. The publisher reserves the right to reject any figure that does not meet the necessary quality standards for publication. (Exception. For only articles on esthetic care, authors are invited to provide sufficient numbers of high-quality photographs to present their material comprehensively, provided that there is an appropriate ratio of text to photographs: the length of the manuscript must be sufficient to support placement of photographs within the text. As a rule of thumb, assume an outside limit of three photographs per manuscript page.) Any patient who is clearly identified in the article (either in text or in photographs) must sign a form indicating his or her consent to be thus depicted in the article. This consent form (PDF) must be submitted with the manuscript.

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No abstract may exceed 250 words. If an abstract goes over that word count, JADA ScholarOne Manuscripts will flag it and direct the author to shorten the abstract. The word counts given in parentheses after each subhead are not requirements, merely suggestions to help keep authors within the 250-word limit. As long as an abstract in total does not exceed 250 words regardless of the length of the individual sections, it will be acceptable.

Original Contributions: full article
Background (30 words). A summary of the general topic and the purpose or hypotheses of the study.

Methods (50 words). A description of the materials (generic names of drugs and equipment should be used, unless the particular brands are crucial to the study); the methods (including the type of study design); the participants (important eligibility criteria, number and selection process).

Results (50 words). A statement of the primary results of the study; the types of analyses used should be indicated, as should levels of statistical significance and confidence intervals.

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Practical Implications (30 words). A description of the practical implications of the findings; in other words, an answer to the question, "What does this mean for a dentist's practice?" Where possible, authors should provide information on further resources regarding the clinical and practical implications of their articles.

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Types of Studies Reviewed (50 words). A description of the types of studies reviewed, including identification of the criteria used to select them and the method by which these criteria were applied.

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Practical Implications (30 words). A description of the practical implications of the findings; in other words, an answer to the question, "What does this mean for a dentist's practice?" Where possible, authors should provide information on further resources regarding the clinical and practical implications of their articles.

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Case Description (75 words). A description of the disorder as manifested in the cases presented in the article, as well as the treatment undertaken and the expected vs. actual outcomes.

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Citations in the reference list should follow this basic style: Periodical

1. Lauterbach M, Martins IP, Castro-Caldas A, et al. Neurological outcomes in children with and without amalgam-related mercury exposure: seven years of longitudinal observations in a randomized trial. JADA 2008;139(2):138-145. Book

2. Cohen S, Burns RC. Pathways of the pulp. 8th ed. St. Louis: Mosby; 2002:196. Book chapter

3. Byrne BE, Tibbetts LS. Conscious sedation and agents for the control of anxiety. In: Ciancio SG, ed. ADA Guide to Dental Therapeutics. 3rd ed. Chicago: American Dental Association; 2003:17-53.<li Government publication

4. Medicine for the public: Women's health research. Bethesda, Md.: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health; 2001. DHHS publication 02-4971. World Wide Website

5. Hoffman ED, Klees BS, Curtis CA. Brief summaries of Medicare & Medicaid: Title XVIII and Title XIX of the Social Security Act as of November 1, 2007. Baltimore, Md.: U.S. Department of Health and Human Services, Center for Medicare & Medicaid Services, Office of the Actuary; 2007. "http://www.cms.hhs.gov/ MedicareProgramRatesStats/downloads/ MedicareMedicaidSummaries2007.pdf" Accessed Aug. 28, 2008. Publication in press

6. McCoy J. Alteration in periodontal status as an indicator of general health. JADA (in press). NOTE: Authors should double-check the status of any in-press work cited in their reference lists before submitting the final manuscript to JADA. Presentation

7. Eichenstadt L, Brenner T. Caries levels among low-income children: report of a three-year study. Paper presented at: 146th Annual Session of the American Dental Association; Oct. 7, 2005; Philadelphia.

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