Title:

Preventing perioperative bleeding in patients with inherited bleeding disorders

Question:

What is the effectiveness of adjuvant antifibrinolytic agents in the prevention of bleeding for patients with Haemophilia or Von Willibrand disease (VWD) undergoing oral or dental procedures?

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Antifibrinolytic therapy for preventing oral bleeding in patients with haemophilia or Von Willebrand disease undergoing min or oral surgery or dental extractions

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Abstract:

Data Sources:

Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register, a regularly updated database informed by trials identified within electronic databases including MEDLINE. Further defined searches were undertaken in PubMed, Embase, The Cochrane Library, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform. Additional hand searching of relevant journals and books of conference proceedings was undertaken.

Study selection:

Randomised and quasi-randomised controlled trials in people of all ages with haemophilia or VWD undergoing oral or dental procedures using antifibrinolytic agents (tranexamic acid (TXA) or epsilon aminocaproic acid (EACA)) to prevent perioperative bleeding compared to no intervention with or without placebo.

Data extraction and synthesis:

Two authors independently assessed identified publications for inclusion based on defined selection criteria. The two authors performed data extraction and risk of bias assessments using standardised forms and the Cochrane risk of bias tools. A third author, deemed to have particular subject expertise, verified eligibility of inclusion.

Results:

One randomised, double-blinded placebo controlled trial and one quasi randomised trial were included. A total of 59 participants with haemophilia undergoing dental extraction were involved. Both trials evidenced a notable reduction in post-operative

bleeding following dental extraction when either TXA or EACA were used, in addition to routine preoperative factor replacement, when compared to placebo. The number of post-operative bleeds, amount of blood loss and the need for additional clotting factors were reduced in the groups receiving antifibrinolytic therapy. No eligible trials in people with VWD were identified.

Conclusions:

Low quality evidence exists to support the use of adjuvant antifibrinolytic therapy to reduce perioperative bleeding in patients with haemophilia undergoing dental extraction. The limited number of trials identified (N=2), minimal sample size (N=28, N=31),) and historic nature of the studies, originating from the 1970's, in addition to study heterogeneity and subsequent selection bias results in a low quality evidence grade for recommended adjuvant antifibrinolytic therapy. There is no clear indication to alter current practice utilising antifibrinolytic therapy to manage patients with haemophilia undergoing dental surgery in accordance with internationally accepted guidelines. However, further research with standardised study deigns would be welcomed in order enhance the evidence base in the management in people with haemophilia and VWD.

Commentary:

Haemophilia A (deficiency in factor VIII), B (deficiency in factor IX) and Von Willibrand Disease (VWD) are all inherited bleeding disorders. Congenital disorders of the coagulation system increase the risk of significant bleeding complications during or after dental extraction or minor oral surgery (1). Affected individuals typically bleed for longer periods of time and may experience prolonged bleeding due to clot instability but do not bleed more profusely than people with normal coagulation. Historically, the oral health management of people with Haemophilia was exclusively provided within the secondary care environment. A gradual shift towards the sharing of care between primary and secondary services now exists (1,2).

Safe and successful patient centred management for people with inherited bleeding disorders requires collaborative multi-disciplinary working between haematology and dental teams. The severity of the bleeding disorder will influence the level of medical intervention necessary to ensure the safe delivery of dental care. Defective coagulation may require the utilisation of factor concentrate or desmopressin in addition to local haemostatic techniques and the appropriate use of antifibrinolytic agents to prevent catastrophic bleeds following haemostatic challenge including dental intervention.

The use of factor replacement therapy is associated with risks including the transmission of blood borne viruses and the development of inhibitors or antibodies (3). The latter risk negates further use of factor replacement as a consequence of immune mediated response. It is desirable to minimise the use of replacement factor from both a risk and cost perspective. Thus strategies to prevent dental

disease and reduce the risk of operative intervention in those with inherited bleeding disorders is essential.

The authors were specific in the setting of their review selection criteria, including only studies which were both randomised and controlled. Thus very few trials were included (N=2) limiting the authors in their ability to perform planned sensitivity analysis and draw high powered conclusions. A methodological approach to the literature search resulted in a wide range of databases being explored. However, only studies written in English, Dutch, French or German were included. This has limited the authors in the expanse of their literature search. The authors adopted review methodology resulted in no studies involving people with WVD being eligible for inclusion. Thus a key part of the study question posed remains unanswered.

The Haemophilia studies included in the review (5, 6) display significant heterogeneity across sample size and intervention methodologies. In both studies all participants received factor replacement prior to dental extraction, therefore it can be assumed that antifibrinolytic therapy is not a replacement for appropriate levels of factor to facilitate haemostasis. Due to small sample sizes, participants with mild, moderate and severe disease were combined into a single group for analysis in both studies. The lack of discrimination between severity of disease and outcome with intervention hinders the clinical implications of the research presented.

Furthermore, the studies varied in the antifibrinolytic agent used, the dosing and frequency of agent used, whilst in one study dental extractions where performed under general anaesthetic and in the other with the use of local anaesthetic. Furthermore, the additional use of an acrylic plate to protect the formed clot may

have masked the true effect of the EACA. Additionally, the authors of the review highlighted the potential risk of bias in this study.

Such discord between study design inhibits the ability to truly compare data and subsequently inform evidence based practice.

The quality of evidence which currently exists to inform the recommended use of adjuvant antifibrinolytic therapy in the management of patients with inherited bleeding disorders undergoing dental extraction is poor. However, despite the limitations there does appear to be benefit in the use of adjuvant therapy to reduce perioperative bleeding with no significant side effects of the therapy encountered. At present, clinicians should conform to existing guidelines which recommend the use of adjuvant antifibrinolytic therapy (6). However, the research and clinical community involved in the care of people with inherited bleeding disorders are encouraged to seek higher quality evidence from which to inform management strategies.

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