THE EFFECT OF TOPICAL ANTIFIBRINOLYTICS AND A NOVEL CHITOSAN GEL ON HAEMOSTASIS AND WOUND HEALING IN ENDOSCOPIC SINUS SURGERY

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By

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Abstract

Introduction:

Endoscopic sinus surgery (ESS) is at present the gold standard therapeutic modality for chronic rhinosinusitis (CRS) resistant to medical therapy. Whilst results from ESS for CRS are generally good, postoperative bleeding and impaired wound healing with adhesion formation remains a concern. Due to patient discomfort and the detrimental effects on wound healing caused by most packing materials, many surgeons no longer routinely use nasal packing. Surgeons have in the past sought agents which would provide post-operative haemostasis without detrimentally affecting wound healing. Antifibrinolytics have been available for many years, however, their topical application has only been explored in the last few years. Recently different forms of chitosan have separately shown significant promise as powerful haemostatic and anti-adhesion agents. The aim of this thesis was to explore the progressive understanding of the interaction between haemostasis and wound healing with possible development of a novel agent.

Methods:

The first step to scientifically assess bleeding after sinus surgery was to develop a standardised method of video endoscopy and grading the surgical field during ESS. This was done as a multinational collaborative trial.

Once this assessment tool was validated a randomised controlled trial evaluating the effect of two antifibrinolytics (epsilon aminocaproic acid and tranexamic acid) was conducted.

Further evaluation was then conducted on other possible hemostatic and anti-adhesion substances. This included various combinations of a novel chitosan gel. These gels were trialled *in vitro* to determine their effect on human nasal fibroblasts

derived from CRS patients. Fibroblast adhesion and proliferation as well as closure of standardised wounds were studied. The most promising of these gels was then used in an in vivo sheep model.

Once effectiveness of the chitosan-dextran gel was shown in the laboratory, this was evaluated against a number of currently available hemostatic and anti-adhesion substances in a standardised model of wound healing in sheep with CRS. This model had been previously extensively validated in our department. Full thickness mucosal injuries were created on the lateral nasal wall and ethmoids of twenty sheep and recombinant tissue factor (rTF), SprayGel or Chitosan-Dextran derivative gel applied topically in a randomized fashion. Adhesion formation and severity as well as microscopic wound healing and ciliary function were analysed at day 28, 56, 84 and 112 post initial surgery.

A further sheep study was conducted applying chitosan dextran gel to standardised mucosal injuries and comparing its effect on the control of bleeding to control. Bleeding time and grade were recorded and wound healing monitored via serial videoendoscopy over two weeks and objectively measured.

Results:

a) Assessment of the bleeding scales showed that inter and intra observer reliability for both scales tested were significantly improved by employing a standardized video-endoscopy technique. The Wormald scale proved to be more reliable and sensitive to changes in the most common surgical fields encountered in ESS.

b) Tranexamic acid showed a modest but clinically significant improvement in the surgical field at 2, 4 and 6 minutes after application. Epsilon aminocaproic acid did not effectively improve the surgical field.

c) Nasal fibroblast adhesion and proliferation were significantly impaired with dextran and chitosan. The most effective ratio that delayed but did not prevent wound closure were 5 % chitosan: 5 % dextran gel.

d) In a standardised sheep model of mucosal wound healing the chitosan gel significantly decreased lateral nasal wall and ethmoidal adhesions at all time points. The chitosan group had a significantly greater percentage of re-epithelialisation and reciliation than control and rTF. In addition the mean cilial grade in the chitosan group was significantly better than control.

e) The chitosan dextran gel was significantly more haemostatic at 2,4, and 6 minutes after injury with no significant difference noted in wound healing.

Conclusions:

Standardised methods of videoendoscopy and grading the surgical field in ESS are valuable tools for further research. Tranexamic acid significantly improved the surgical field to a moderate degree in ESS compared to control. Chitosan gel is a promising new powerful haemostatic bio-polymer which has a mild inhibitory effect on fibroblast attachment and proliferation. This may partially explain the significant improvement in microscopic wound healing and reduction in adhesion formation seen in a sheep model of chronic sinusitis. Future work evaluating this gel in the setting of a human trial is currently underway.

Declaration

I declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution, and that to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

I further consent to the thesis being made available for photocopying and loan if applicable, if accepted for the award of the degree.

Theodore Athanasiadis

Preface

A portion of the work described within this thesis has been submitted for publication, as listed below:

- Athanasiadis T, Beule A, Embate J, Steinmeier E, Field J, Wormald PJ. Standardized video-endoscopy and surgical field grading scale for endoscopic sinus surgery: a multi-centre study. *Laryngoscope* 2008;118(2):314-319.

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- Valentine R, Athanasiadis T, Moratti S, Robinson S, Wormald PJ. The efficacy of a novel chitosan gel on haemostasis following endoscopic sinus surgery in a sheep model of chronic rhinosinusitis. *Laryngoscope*, 2008; In Press

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