THE EFFECT OF CHITOSAN DEXTRAN GEL AS A HAEMOSTATIC AND ANTI ADHESION AGENT IN THE CENTRAL NERVOUS SYSTEM AND EVALUATION OF HAEMOSTATIC MECHANISM OF SKELETAL MUSCLE TISSUE

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By

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Table of Contents

ABSTRACT

INTRODUCTION

Haemostasis and adhesion prevention in surgery is of paramount importance to prevent complications. It is even more important in neurosurgical procedures where even minor complications can lead to devastating consequences. There is constant work in the direction of development of both haemostatic and anti-adhesion agents with recent research with the use of chitosan dextran gel and autologous muscle tissue showing promise.

Normal wound healing following surgery may lead to adhesion formation with the development of adhesions correlating to the presence and amount of blood clot. This linking of bleeding and adhesion formation is key to adhesion prevention. The amount and site of adhesion formation will often influence the postoperative course of the patient. While there have been many substances developed in an attempt to prevent adhesions, this thesis will examine Chitosan dextran (CD) gel and muscle for their potential role in neurological surgery. CD gel has previously been shown to be effective as a haemostat and as an anti- adhesion agent in endoscopic sinus surgery while autologous muscle has been shown to be effective with major vascular injury.

This thesis will examine Chitosan Dextran gel in central nervous system and also try to explore the potential mechanisms of action of muscle tissue in bleeding control.

METHODS

The haemostatic and anti adhesion potential of Chitosan Dextran gel was studied with the help of sheep models.

A neurosurgical burr hole model was used to assess the safety and efficacy of Chitosan Dextran gel on the dura and brain tissue. Bleeding control was tested at the level of bone, dura and brain separately with both Chitosan Dextran gel and Gelfoam paste on separate burr holes. Baseline bleeding was measured at the time of injury using the Boezaart scale, and then every two minutes after the application of each agent until complete haemostasis or 10 minutes, whichever was earlier. Safety was assessed through MRI scans and histopathological analysis.

To further assess the antiadhesion potential of Chitosan Dextran gel, a sheep model of spinal laminectomy was used. Gelfoam paste was again used as the control agent. Following the laminectomy procedure and exposure of dura, the test agent, i.e, Chitosan Dextran gel or Gelfoam or normal saline wash was applied on the dura and the wound was closed. Healing was allowed for three months. The efficacy of adhesion prevention was assessed by Peel test and MRI scans. Histopathology was performed to assess safety of the agent.

In vitro studies were performed to evaluate the haemostatic action of muscle tissue. Muscle extracts were prepared by dissolving crushed snap-frozen muscle tissue in saline. Plain saline was used as control. Prothrombin time, activated partial thromboplastin time (APTT), thrombin time, and platelet aggregation studies were performed on both muscle extract and saline. Prothrombin time and APTT were repeated using factor VII–deficient plasma, factor X–deficient plasma, lupus plasma, and contact pathway inhibited plasma.

RESULTS

1. The efficacy and safety profiles of Chitosan Dextran gel were comparable to those of Gelfoam in the neurosurgical burr hole study. The logistic regression model suggested that Chitosan Dextran gel was more effective at stopping bleeding after two minutes, the clinical significance may be small and this should be tested in a model with greater volume of bleeding with more intervention numbers.

2. With regards to antiadhesion efficacy of Chitosan Dextran gel in the sheep model of laminectomy there was a significant reduction in adhesions when compared to the untreated (normal saline) group. However when compared to the Gelfoam treated group there was no significant difference. MRI did not show any difference in the overall epidural fibrosis among the three groups.

3. In vitro muscle coagulation studies did not show any significant difference between muscle and saline except in the APTT using factor X-deficient plasma. Higher concentrations of muscle extract showed an increase in platelet aggregation.

CONCLUSION

Chitosan Dextran gel is an effective safe haemostatic and anti-adhesive agent in the central nervous system. Further work is needed to extend its use in neurosurgical procedures in humans.

Platelet aggregation appears to play an important role in the haemostatic action of muscle tissue and further study of this mechanism may improve the development of new topical haemostatic agents.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Sukanya Rajiv

PREFACE

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

1. Rajiv, Sukanya, Marguerite Harding, Ahmed Bassiouni, Camille Jardeleza, Amanda Drilling, Craig James, Thanh Ha, Steve Moratti, Simon Robinson, and Peter-John Wormald. "The efficacy and safety of chitosan dextran gel in a burr hole neurosurgical sheep model." *Acta neurochirurgica* 155, no. 7 (2013): 1361-1366.
2. Rajiv S, Rodgers S, Bassiouni A, Vreugde S, Wormald PJ. "Role of crushed skeletal muscle extract in haemostasis." *Int Forum Allergy Rhinol*, 2015; In Press

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