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Intracranial Foreign Body Granuloma Caused by Oxidized Cellulose Polymer and Etherified Sodium Carboxymethyl Cellulose: An Experimental Study with Orictolagus Cuniculus Rabbits

Fitra
Department of Neurosurgery, Faculty of Medicine of Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Corresponding author email: afalfitra@gmail.com

Djoko Legowo
Veterinary Faculty, Airlangga University, Surabaya, Indonesia
Email: djoko-l-2@fkh.unair.ac.id

Budi Utomo
Faculty of Medicine, Airlangga University, Surabaya, Indonesia
Email: budiutomo@fk.unair.ac.id

Nur Setiawan Suroto
Department of Neurosurgery, Faculty of Medicine of Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Email: setiawan.dr@gmail.com

Muhammad Arifin Parenrengi
Department of Neurosurgery, Faculty of Medicine of Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Email: muhammad.arifin@fk.unair.ac.id

Asra Al-Fauzi
Department of Neurosurgery, Faculty of Medicine of Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Email: asra.al@fk.unair.ac.id

Abstract---*The purpose of this study was to analyze the brain tissue response to several haemostatic agents used during surgery, such as oxidized cellulose polymer and etherified sodium carboxymethyl cellulose on the brain of 30 Oryctolagus cuniculus rabbits. At weeks 1, 2, and 3, the specimens were euthanized. Histological examination showed etherified sodium carboxymethyl cellulose and oxidized cellulose polymer cell response. We established a significant association in foreign body granuloma. It elicited that etherified sodium carboxymethyl cellulose and oxidized cellulose polymer were linked with a substantial foreign body reaction at any point throughout the trial.*
Keywords---*etherified sodium carboxymethyl cellulose, granuloma, oryctolagus cuniculus rabbits, oxidized cellulose polymer, topical hemostatic*

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Introduction

Topical hemostatic plays an important role in safe neurosurgery to control bleeding and reduces the risk for surgical complications. For several purposes, such as control of bleeding or dural closure, topical hemostasis is left in place intentionally during surgery. In the last decade, several different studies have identified the possible adverse effects related to topical hemostasis. Although considered safe, there are several studies identified that several topical hemostatic agents had a connection with foreign body granuloma that may occur months or years (Carvalho & Marchi, 2013; Pereira, 2018).

Oxidized cellulose polymer is the most widely used topical hemostatic agent in neurosurgery. Oxidized cellulose polymer is non-sticky, attaches to surgical substances, can be moulded into various forms and sizes, does not chip when exposed to liquids, and withstands compression without losing its characteristics. This material should not be infused into an aqueous solution before application since dry application increases hemostatic action. However, the acidic nature of oxidized cellulose polymer may exacerbate local inflammation and prolong the usual healing process (Tomizawa, 2005; Arnaud et al., 2009; Chiara et al., 2018).

Recent advancements in the formulation, texture, and active component elements of hemostatic dressings such as etherified sodium carboxymethyl cellulose have resulted in significant advancements. Unlike Oxidized Cellulose Polymer, when it comes into contact with fluids, etherified sodium carboxymethyl cellulose clings to the site, starts blood coagulation, stops bleeding, and forms a protective covering, thus promoting optimum wound healing. Because it is water-soluble, it may be easily removed by washing without disrupting the clotted surface. At the moment, only a few research have been conducted on etherified sodium carboxymethyl cellulose, including its adverse effects (Arnaud et al., 2009; Li et al., 2016).

Case reports and short series have described postoperative intracranial foreign body granulomas. Except for etherified sodium carboxymethyl cellulose, Neurosurgeons seem to underestimate the importance of this clinical problem. The purpose of this research is to examine 30 Oryctolagus cuniculus rabbits with foreign body granulomas after a brief period of Oxidized Cellulose Polymer and etherified sodium carboxymethyl cellulose usage in neurosurgical models. To our knowledge, there is still very limited study that reveals the adverse effects of etherified sodium carboxymethyl cellulose (Shui et al., 2017; Casaburi et al., 2018).

Methods

Study design

The research protocol was authorized by the authorities of Universitas Airlangga's Department of Veterinary (Experimental Animal Studies, study number 2.KE.035.2.2019). The experimental study used 30 adults Oryctolagus cuniculus rabbits that were at least five months old and weighed between four and five kilograms. After one week (ten animals), two weeks (ten animals), and three weeks of healing, hystologic examination was performed (ten animal).

Materials preparation

Etherified sodium carboxymethyl cellulose introduced to the market as BloodSTOP®, a product of LifeScience PLUS (LifeScience PLUS, Inc., Mountain View, CA, USA), and oxidized cellulose polymer introduced to the market as Surgicel®, a product of Ethicon, were utilized in this research. The FDA has approved all products as safe for external temporary bleeding control (Saravana, 2009; Kalnins, 1971).

Medication of animals

All operation was done under general anaesthetic administered intramuscularly. The animals were premedicated with a mixture of 65 mg kg-1 ketamine and 4 mg kg-1 xylazine intramuscularly into the hind leg. Each animal received an intramuscular injection of 100 000 IU benzylpenicillin. Following surgery, the animals received analgesics for three days, once daily, muscularly. Animal were randomly divided into two groups (Group: oxidized cellulose polymer and etherified sodium carboxymethyl cellulose), each containing 15 rabbits. Each group were then divided into three subgroups. The division is based on how many days after the craniotomy in which they will be sacrificed, corresponding to the craniotomy procedure (day 7, day 14, and day 21) (Yadnya et al., 2016; Ermayanti et al., 2016).

Craniotomy protocol

The tops of the heads of the animals were shaved between the eyes and the ears. The skin was sterilized with a solution of iodine. After administering a local anesthetic (1 mL Pehacain) subcutaneously, a midline incision was created, and the skin and periosteum were reflected to reveal the skull vault. Rectangle bone defects (diameter 8 mm, length 15 mm) were bored into the inner cortex using a bone trephine. An attempt has been made to avoid contact with the dura mater. Following bone plate removal, the dura mater was incised with a micro scissor. After opening the dura, the cortical veins were identified and a 5-mm long and 5-mm deep parenchymal lesion was created using a surgical knife number 11 until parenchymal bleeding occurred on the brain surface. Several sheets of the hemostatic agent, either etherified sodium carboxymethyl cellulose or oxidized cellulose polymer for each sample, were applied to the wound. Continuous administration of 0.9 percent NaCl solution to the lesions was performed until hemostasis was achieved. The skin was sutured properly. The animals were humanly killed with pentobarbital after observation period of 1, 2 and 3 weeks.

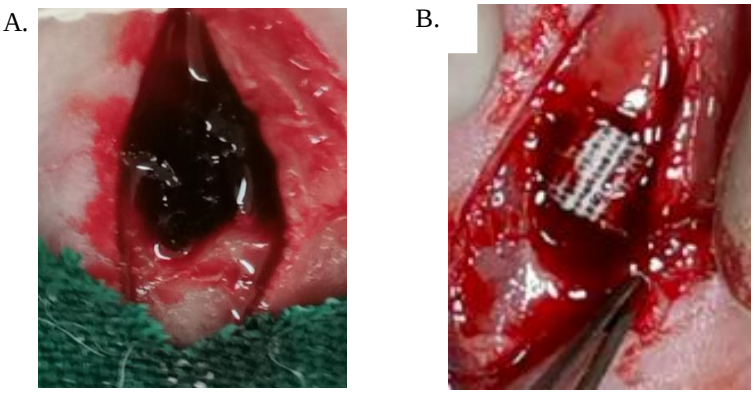

Figure 1. The Parenchymal lesion in the rabbit brain following placement of haemostatic agents.
A: lesion placement with oxidized cellulose polymer
B: lesion placement with etherified sodium carboxymethyl cellulose

Histopathological examination

For four hours, the specimens were preserved in cold 4% formaldehyde. The tissues were frozen in Optimum Cutting temperature compound (Sakura Finetek, Torrance, CA). Sections were cut to a thickness of 5 mm, attached on charged slides, and allowed to air dry for 5 minutes before staining. Staining with hematoxylin and eosin was carried out according to the procedure. The samples were analyzed using a light microscope (Hansen & Berthelsen, 2000; Gage et al., 2006).

Results and Discussion

Thirty animals were utilized in the research. All animals recovered normally and were killed as scheduled. The two groups, oxidized cellulose polymer and etherified sodium carboxymethyl cellulose, were compared from all brain fragments. The final study comprised 30 animals, and figures 2 illustrate the histological foreign body granuloma findings for each intervention. Oxidized cellulose polymer and etherified sodium carboxymethyl cellulose both have a nearly identical pattern of foreign body granuloma development. There is no distinction between the two. Additionally, all samples collected at various periods had a pretty high correlation between the three findings, indicating that foreign body granulomas started to develop in the 1 week and likely lasted until the 3 weeks. Both etherified sodium carboxymethyl cellulose and oxidized cellulose polymer have been found to be associated with the development of foreign body granulomas in animal brains. Not only histologically but also macroscopically, all samples revealed the presence of tissue classified as foreign body granulomas in each lesion evaluated using oxidized cellulose polymer and etherified sodium carboxymethyl cellulose (Figure 2). The foreign body granuloma was large enough to surround the whole lesion, suggesting that it related to the topical hemostasis measure employed (Zhang et al., 2020; Coseri et al., 2013).

Figure 2. The lesion in the parenchymal cortex two weeks after application of the etherified sodium carboxymethyl cellulose. The lesion was cover by foreign body granulomas (arrow)

A. B.

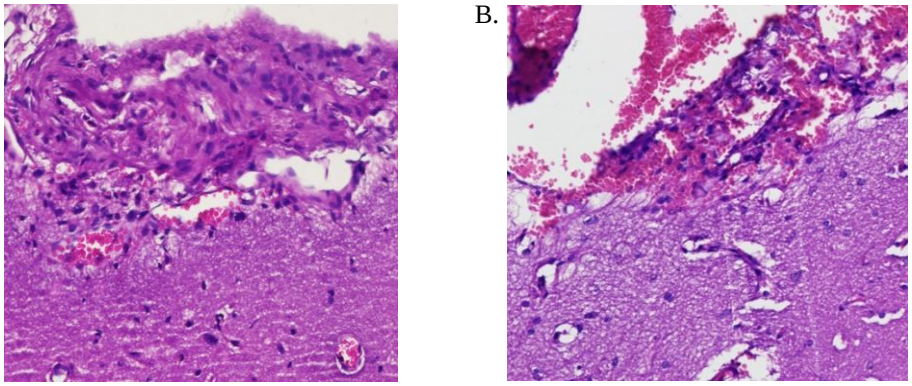

Figure 3. Hematoxylin and eosin stained sections of brain tissue from animal.
A: 20x magnificion of foreign body granuloma (circle) after placement with oxidized cellulose polymer
B: 20x magnificion of foreign body granuloma (circle) after placement with etherified sodium carboxymethyl cellulose

Foreign body granulomas are widely documented in general surgery and consist mostly of non-absorbable material left in the abdomen unintentionally, often resulting in lawsuit. However, in neurosurgery, only a few case reports have been published in which non-absorbable material such as cotton gauze or cotton balls was left behind inadvertently after intracranial surgery? If foreign body granulomas develop during neurosurgery, they are more likely to be produced by material left behind deliberately, such as oxidized cellulose and gelatin sponge, non-absorbable material such as cotton gauze used to wrap aneurysms, or synthetic sutures (Al-afif et al., 2018). Recently, materials used in micro vascular decompression surgery for trigeminal neuralgia, such as polytetrafluoroethene (PTFE), were reported to produce foreign body granuloma, which resulted in recurrence of trigeminal neuralgia (Pressman et al., 2020).

Oxidized cellulose polymer was supposed to have antimicrobial properties. Later studies discovered that the Oxidized Cellulose Polymer induced resistance to infection was due to an acidic pH fatal to bacteria. Oxidized cellulose polymer lowers the pH of the culture medium and reduces the number of fibroblasts, while other topical hemostatic did not affect the pH of the culture medium or cell count. However, a subsequent study discovered that oxidized cellulose polymer promotes infection and susceptibility to infection in several locations, including the intracranial region. The presence of a small amount of foreign body has been observed to increase susceptibility to infection. Oxidized cellulose polymer's acidic local pH affects the surrounding tissue through the acidic tissue fluid, thus retarding healing and should not be used in an infected wound (Tomizawa, 2005).

Foreign body granuloma produced by retained material inside the skull or surrounding soft tissues is exceptionally common in surgical practice, although it has historically been underreported and addressed rarely due to the potential of medicolegal complications for surgeons. It is difficult to quantify the incidence of FBG inside the skull or surrounding soft tissues, although it is believed to be between 0.1 and 1 per 1000 cranial/intracranial

procedures. According to reports, the problem happens about once or twice throughout the career of a normal neurosurgeon. After cranial surgery, FBG situated inside the skull or surrounding soft tissues has been reported considerably less often in the neurosurgical literature than in general surgery, thoracic, orthopedic, gynecologic, and urologic operations (Akhaddar et al., 2018; Estébanez et al., 2021).

In this study, we wanted to compare the usage of etherified sodium carboxymethyl cellulose, a recently marketed topical hemostatic agent. To our knowledge, there is practically no research examining the adverse consequences of etherified sodium carboxymethyl cellulose in neurosurgery or foreign body granuloma formation after using this agent. Ali Akhdar et al Akhaddar et al. (2018), explained in a systematic review study that the existence of granulomas in neurosurgery should still be a serious concern since clinically foreign body granuloma can cause seizures, infection, or recurrence of prior illness that can be acute or delayed. Further research is required to understand the mechanism by which foreign body granulomas occur in certain individuals after surgery and why all topical hemostatic medications generate foreign body granulomas in animal experiments (Barnard & Millner, 2009; Emilia et al., 2011).

Conclusion

Our study demonstrates that oxidized cellulose polymer and etherified sodium carboxymethyl cellulose performed intracranial foreign body granuloma in 30 rabbits after underwent surgery. Topical hemostasis should be taken into consideration in intentionally left in place after brain surgery. Visual examination of post-application photos revealed the presence of foreign body granuloma within brain parenchyma defects after using oxidized cellulose polymer or etherified sodium carboxymethyl cellulose. Histologic examination revealed a distinct foreign body granuloma tissue reaction to oxidized cellulose polymer and etherified sodium carboxymethyl cellulose at the application site.

Declaration of interest

The authors and all other authors have no conflicts of interest to declare. The studies reported here were designed and performed using established scientific methods with impartial data collection and analysis. The authors are responsible for the content of the article.

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