HISTOLOGICAL EFECTS OF FIBRIN GLUE AND ADHESIVE SEALANTS ON SPINAL CORD

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Disclosure of funding: This work was carried out by funding from the European Research Council.

None of the authors have any personal or institutional financial interests in any of the materials used in this study.

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INTRODUCTION

Fibrin glues have a variety of applications in neurosurgery.[1,2,3] A number of safety studies using fibrin glues were conducted before they became established in clinical practice.[4,5] Tisseel® (Baxter, Illinois, US) has been used successfully in experimental primate models of intradural brachial plexus repair.[6,7] Following brachial plexus reconstruction surgery in humans, we use Tisseel®, to attach reimplanted nerves to the spinal cord because they cannot be sutured.

Recently a number of synthetic dural sealants have become popular in spinal surgery. These products are licensed for extradural use but there are reports of them being used for intradural applications.[8] They may therefore come in to contact with CNS tissue deliberately or inadvertently. However, there remains a paucity of information on the histological effects of these polyethylene glycol (PEG) hydrogel and glutaraldehyde sealants on CNS tissue.

Brachial plexus injury can have a devastating impact on young patients. Brachial plexus reimplantation after trauma aims to improve functional outcomes.[9] It requires the application of fibrin glue to the reimplanted nerves as they cannot be sutured to the spinal cord. Rat models of brachial plexus repair aim to improve our understanding of this injury and allow us to consider new treatments, which may be translated to clinical practise. Although manufacturers of BioGlue® and Adherus® do not recommend intradual spinal application of these products we wanted to assess the histological effects they produce and the potential consequences of their deliberate or inadvertent placement on the spinal cord.

Tisseel® fibrin glue is a two component sealant. The sealer protein solution contains human fibrinogen and aprotinin, which prevents premature fibrinolysis. The thrombin solution contains human thrombin and calcium chloride. On application, these proteins mix to form a clot that mimics the final stages of the normal clotting cascade. The manufacturers state that Tisseel® is absorbed completely by 10-14 days. Tisseel® is licensed for application to the surface of tissues either to control bleeding or to stop or prevent fluid leaks but has been used safely for many intradural applications in spinal surgery.

BioGlue® (CryoLife Inc. Georgia, US) surgical adhesive is also a two component sealant. It has been used in cardiovascular surgery [10,11,12] and more recently has become popular in neurosurgery to achieve a watertight dural closure. [8] It is composed of a bovine serum albumin and glutaraldehyde solution. The two components are dispensed in a predefined ratio and applied through a special applicator tip where cross linkage occurs. The glutaraldehyde covalently bonds the bovine serum albumin molecules together as well as to lysine on cell surface proteins and proteins in the extracellular matrix. The manufacturers advise that BioGlue® should not be used in confined spaces with close proximity to nerve structures and a study has shown that it may cause acute nerve injury. [13]

Adherus® (HyperBranch Medical Technologies Inc., North Carolina, US) dural sealant is another two component sealant. It comprises a synthetic absorbable hydrogel sealant, namely an activated polyethylene glycol (PEG) ester solution and polyethyleneimine. When the solutions are mixed together within the tip of the applicator, the precursors crosslink to form a hydrogel sealant. After application the hydrogel gradually breaks down in to water-soluble molecules and is absorbed in 90 days, according to the manufacturers. Adherus® is recommended for use only on the dura mater. Being a hydrogel there is a theoretical risk of expansion and the manufacturers advise it should not be used in confined spaces.

Although the use of PEG hydrogel and glutaraldehyde dural sealants is gaining popularity in neurosurgery, there is limited information on the effects of these compounds when applied either deliberately or inadvertently to the central nervous system. We compared the histological effects of Tisseel® fibrin glue and two synthetic dural sealants: BioGlue® and Adherus®, on the spinal cord in a rat model of intradural brachial plexus repair.

MATERIALS & METHODS

Forty-one Sprague-Dawley rats weighing 200-250g (Harlan Laboratories, UK) were anaesthetised using 2.5L/min Vetflurane (Abbott Laboratories Ltd, UK) inhaled solution. A posterior midline incision was made in the neck from the mid-cervical spine to T2. The muscles were split until the hemi-laminae of C7 & T1 were exposed. An operating microscope (Carl Zeiss Ltd, Cambridge, UK) was used to perform hemi-laminectomies at C7 and T1 using a bone rongeur (Fine Science Tools, Foster

City, CA, USA). The dura was opened and hitched with a 10.0 vicryl suture (Johnson & Johnson, UK) at the level of the T1 dorsal root. A sharp hook was placed under the T1 dorsal root and the nerve was transected adjacent to the dorsal root entry zone, making sure the spinal cord was not damaged. (Figure 1) The nerve was then re-positioned back on to the spinal cord and two drops of either Tisseel®, Adherus®, BioGlue® or no glue (control) was applied. The dura was left open as it is difficult to oppose but the fascia and muscle layer were closed with continuous absorbable sutures and the skin with interrupted sutures. All animals were placed in a recovery cage and given Novox® (Vedco, MO, USA) analgesia for three days post-operatively.

Four experimental groups were employed. In the control group, Group 1 (n=9), the dorsal root was transected and repositioned on the spinal cord but no fibrin glue or dural sealant was applied. In Group 2 (n=8) Tisseel® was applied to the nerve root and spinal cord to adhere the transected nerve to the cord. In Groups 3 (n=10) and 4 (n=14) Bioglue and Adherus® were applied.

Two to three rats in each group were sacrificed at days 7, 14 and 28. After terminal anaesthesia they were pericardially perfused and fixed with 4% paraformaldehyde (PFA). The cervical spine with its attached vertebrae and muscles was dissected and placed in PFA for 24 hours. This tissue was placed in Decalcifier-II (Surgipath Europe Ltd., Cambridgeshire, Great Britain) solution for 18 hours. Samples were then sequentially placed in 10% and 20% sucrose for cryopreservation and embedded in optimum cutting temperature (OCT) (Bright Cryo-M-Bed; Jencons Scientific Ltd, Leighton Buzzard, UK) embedding media before being rapidly frozen with dry ice, mounted on a specimen holder and cut in coronal sections at 20µm thickness. The sections were stained with Haematoxylin & Eosin (Merck, Darmstadt, Germany). Representative slides from the centre of the lesion were selected from each group at each time point and evaluated blind by a neuropathologist.

All procedures were carried out in accordance with the UK Animals (Scientific Procedures) Act 1986, and adequate measures were taken to minimise pain and discomfort.

RESULTS

At Day 7 there was an extensive acute inflammatory reaction with Tisseel® but there was a mild response in the Adherus® and Bioglue® groups, which was comparable to control. At Day 14 there was no evidence of acute inflammation in the control group but all other groups showed a mild acute neutrophil infiltration. There was no evidence of acute inflammation at Day 28 in any group. (See Table 1)

At Day 7 there was a mild lymphocytic infiltrate at the surgical site in the control group and in the Tisseel® group, compared to a moderate lymphocytic infiltrate in the Adherus® and Bioglue® groups. At Day 14 the control group had a mild lymphocytic infiltrate at the surgical site but all the other groups had a moderate infiltrate. By Day 28 all groups had a mild lymphocytic infiltrate at the surgical site.

At Day 7 there was a single/rare foreign body giant cell reaction in the control group and with Adherus®. However, the Tisseel® group showed an extensive and the Bioglue® group showed a moderate reaction. By Day 14 the control group showed a moderate foreign body giant cell reaction but all the other groups had an extensive reaction. By Day 28, however, the foreign body giant cell reaction had settled down in the control and Tisseel® groups but there were single/rare cells in the Adherus® group and a moderate reaction in the Bioglue® group.

At Day 7 there was a moderate fibroblastic reaction in the control group and also in the BioGlue® group. Tisseel® and Adherus® showed a severe reaction. However, at 14 days, there was a mild fibroblastic reaction in the control group and a moderate reaction in the Tisseel® group but a severe reaction in the Adherus® and Bioglue® groups. By Day 28 the fibroblastic reaction in all groups was mild and comparable to control.

The control and Tisseel® groups showed only focal inflammation in the cord at all time points. However, in the Adherus® and Bioglue® groups there was evidence of spinal cord degeneration (Figure 2)

The control and Tisseel® groups did not show any histological evidence of mass effect on the cord at any time point. The Adherus® and BioGlue® groups showed

evidence of cord compression from the glue mass at Days 7, 14 and 28 but the rats in these groups did not have an obvious neurological deficit when they were observed.

One BioGlue® rat failed to wake up at the end of the procedure. Two BioGlue® and one Adherus® rat developed a left hemiplegia. (Figure 3) One rat in the Adherus® group developed a left hind limb paresis. There were no such complications in the control and Tisseel® groups.

DISCUSSION

Fibrin glues have been used for over thirty years in neurosurgery and have a number of applications. [2,3] A number of safety studies were conducted before they became established.[4,5] However, little is known of the histological effects of newer compounds, such as BioGlue® and Adherus® on CNS tissues. We undertook this study to compare the effects of Tisseel®, BioGlue® and Adherus® on spinal cord using a rat brachial plexus repair model.

All implanted materials are expected to undergo tissue responses when placed *in vivo*. The inevitable injury that results leads to an acute inflammatory response characterised by neutrophil polymorphs. Neutrophils have a lifespan of days and disappear from the exudate more rapidly than macrophages, which can persist from days to months. The chronic inflammatory response is characterised by macrophages but includes monocytes and lymphocytes. Inflammation with the presence of mononuclear cells is referred to as chronic inflammation, whereas the foreign body reaction with granulation tissue development is often considered the normal healing response to implanted materials. The proliferation of fibroblasts and vascular endothelial cells leads to the formation of granulation tissue. The foreign body reaction is composed of foreign body giant cells and components of granulation tissue, which include macrophages and fibroblasts. The end stage healing response to biomaterials is generally fibrosis or fibrous encapsulation.

Tisseel® is a fibrin glue established neurosurgery for over 30 years. It's main role is to obtain dural closure but other applications include treating cerebrospinal fluid leaks,[14] nerve repair,[15] reinforcing muscle wrapping around aneurysms[16] and as a protective agent for intracranial nerves during skull base surgery.[1]

Tisseel® has been successfully used for intradural brachial plexus repair in primates and clinical practice. [6,7,17] A histological safety study to assess the safety of fibrin glue on intact nervous tissue showed a strong acute inflammatory reaction with Tisseel® on day 7 but by day 28 the inflammatory reaction had ceased, suggesting that fibrin glue does not induce extra brain or intracranial nerve damage in a rat model.[4] Muhammed et al.[5] showed that although there was an acute inflammatory response and angiogenesis after placement of fibrin glue into rat brain, surrounding neuronal and glial elements were unaffected. Our results are similar in that they show a severe acute inflammatory response at Day 7 when Tisseel® is applied, more so than the control and other groups. However, by Day 14 the acute inflammatory response was mild in all groups and by Day 28, as would be expected, there was no acute inflammation present in any of the groups.

Although there was a mild to moderate chronic lymphocytic infiltrate at the surgical site in all the groups across all the time points this was no different to the control group at Day 28 in all groups. All groups displayed a moderate to severe fibroblastic reaction at Days 7 & 14 but by Day 28 the reaction was mild and comparable to control.

BioGlue® has been successfully used as a dural sealant and for reconstruction of the sellar floor following transphenoidal procedures. It solidifies rapidly on application and the manufacturers suggest it should be avoided in confined spaces because it can cause neural compression. In the first major study investigating BioGlue® in neurosurgery it was used as a dural sealant in 114 supratentorial, 53 infratentorial, 41 transphenoidal and 8 spinal procedures with no serious complications and only two CSF leaks in patients undergoing posterior fossa craniotomies. In another study by Kaye et al BioGlue® was safely used following 32 transphenoidal procedures. [8, 18]

An *in vivo* study to investigate the biocompatibility of BioGlue® on the cerebral cortex demonstrated that an inflammatory infiltrate was found overlying the pia-arachnoid but did not expand into the brain parenchyma except in instances of mechanical disruption. Although an increase in gliosis at the application site was detected this was not significant. [19] In our model there may have been some disruption at the pia-arachnoid interface between the nerve and spinal cord and consequently the

BioGlue® and Adherus® may have penetrated the spinal cord and lead to gliosis and necrosis of the cord, as was seen at all time points to varying degrees.

A laboratory study with BioGlue® demonstrated that up to 2 months post-operatively it did not induce a chronic inflammatory response in vascular tissue. However, rarely in some specimens it did show a minor foreign body reaction but neither fibrosis or multinucleated giant cells were seen. [12] However, other cardiac, thoracic and vascular studies have reported inflammatory responses, [20-22] fibrosis, [21-23] tissue necrosis [20] and foreign body reaction [24] with the use of BioGlue®. Other clinical studies have suggested an increased risk of wound infections when BioGlue® is used as dural sealant in cranial surgery, due to a pyogenic and chronic inflammatory response. [25-27]

Adherus® is an activated PEG and polyethyleneimine hydrogel. PEG hydrogels have been frequently used in medical implants due to their ease of use and potential cytocompatibility. [28] A number of studies support the notion that local environment may play a role in augmenting an inflammatory response to these hydrogels. [29-31] Bjugstad et al [32] demonstrated that the inflammatory response to PEG-based hydrogels was complex and depended on the degradation rates of the hydrogel. Their study suggests that PEG based hydrogels, when implanted in to the brain may attenuate the acute and chronic inflammatory responses. Preul et al. [33,34] observed various types of inflammatory cells within the dura mater, arachnoid and pia in chronic stage animals. However, in the study by Bakar et al [35] although there was an acute inflammatory response in damaged brain tissue in the Adherus® group there was no polymorphonuclear response in the chronic stage. They suggested that Adherus® was not neurotoxic, did not delay healing or lead to degenerative changes.

A foreign body giant cell reaction represents the healing response to implanted materials. Our results suggest that there was a severe foreign body giant cell reaction with Bioglue® at Day 14 but this had become moderate by Day 28. There was a mild foreign body giant cell reaction in the Adherus® group at Day 28 but there was no foreign body reaction in the Tisseel® and control groups at this time point. In our study at Day 28 Adherus® produced a mild foreign body response compared to BioGlue® which produced a moderate response. However, although the foreign body giant cell reaction with Tisseel® was severe at Days 7 & 14, by Day 28 there was no foreign body giant cell reaction in this group.

Importantly, the Tisseel® and control groups only showed focal spinal cord inflammation at the surgical site suggesting that the application of Tisseel®, irrespective of whether the pia-arachnoid interface had been damaged or not, did not produce inflammation more so than in the control group. However, the Adherus® and BioGlue® groups showed evidence of gliosis and spinal cord degeneration although the majority of these rats did not have any obvious neurological deficit. (Figure 2) However, it is not clear whether the degeneration of the spinal cord in these two groups was due to a pressure necrosis, ischaemic injury to the cord or toxicity of the compounds or a combination of these effects.

The control and Tisseel® groups showed no evidence of spinal cord compression as seen on the histology, at any time point. However, in the Adherus® and BioGlue® groups spinal cord compression of varying degrees was noted at days 7, 14 and 28 in all sections. However, the majority of rats in these groups did not show any obvious neurological deficit as a result of the compression.

Two rats in the Bioglue® group developed a left sided weakness. Sections showed a large amount of amorphous material with inflammatory infiltrate compressing the spinal cord, resulting in marked spinal cord degeneration. There was a severe acute inflammatory reaction as well as a marked lymphocytic infiltration at the surgical site. There was a moderate soft tissue necrosis and fibroblastic reaction. (Figure 2) Other researchers have suggested that BioGlue® can cause nerve injury and have attributed this to the glutaraldehyde component. They have suggested that direct contact with nerves should be avoided. [13]

One Adherus® rat developed a delayed complete hindlimb paralysis due to compression of the cord with glue mass. The other Adherus® rat that developed a hemiparesis also had compression of the left hemicord. Whether these were due to inadvertent application of a large amount of sealant or due to expansion of the hydrogel *in vivo* is unclear. Indeed there are studies suggesting that there was delayed cauda equina compression after spinal dura repair with BioGlue®, possibly due to expansion of the hydrogel after application.[36]

In the above complications the exact mechanism of cord injury remains uncertain but it would be advisable to follow manufacturers guidelines and not apply BioGlue® and Adherus® in confined spaces in close proximity to neural tissue.

CONCLUSION

Tisseel® may be used without significant problems on the spinal cord and CNS tissues. BioGlue® and Adherus® may be applied thinly to the outside of the dura to create a watertight closure but intradural use and contact with spinal tissue should be avoided. If there is a risk of BioGlue® or Adherus® leaking inside the dura, for example with a non-uniform dural laceration, we recommend that these synthetic glues should not be used.

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Table 1. Table showing the histopathological response to the spinal cord following application of Tisseel®, Adherus® and BioGlue® at days 7, 14 and 28.

Figure 1. Image taken using operating microscope. The hemilaminae of C7 and T1 have been removed. The dura has been opened and hitched and the spinal cord is visible. The C8 dorsal root (a) has been transected and lifted laterally. Broken lines shown direction of dorsal root before it was cut.

Figure 2. Representative images of Haematoxylin & Eosin (H&E) stained sections at Day 28. **a & b)** Low and medium power images of the control group. The dorsal root, region of transection of the dorsal root, the spinal cord (arrows) and paraspinal muscles are indicated. Medium power image **(b)** shows a focal inflammatory infiltrate on the surface of the spinal cord (arrow). **c & d)** Low and medium power images of the Tisseel® group showing only a mild inflammatory infiltrate in the cord. There is no evidence of spinal cord degeneration and the Tisseel® has been absorbed. **e & f)** Low and medium power images of the BioGlue® group. BioGlue® (B) can be seen as an amorphous, acelluar material which has not been broken down by day 28. There is evidence of spinal cord degeneration (arrows, D) with a eosinophilic infiltrate at the inferior margin of the glue. **g & h)** Low and medium power images of the Adherus® group. Adherus® (A) can be seen compressing the spinal cord. There is an area of spinal cord degeneration (arrows, D) with a eosinophilic chronic inflammatory infiltrate in the cord.

Figure 3. a) Large quantity of BioGlue® caused significant compression and pressure necrosis of the left side of the spinal cord. b) At high power a marked inflammatory infiltrate, characterised by the eosinophilic infiltrate, is apparent and the area of marked spinal cord degeneration is identified. The amorphous acellular material of BioGlue® is infiltrated with eosinophilic cells at the inferior border and is compressing the spinal cord.