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SHORT COMMUNICATION

Histological and magnetic resonance imaging assessment of Liqoseal in a spinal in vivo pig model

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Polyganics b.v.

Abstract

Background: Liqoseal (Polyganics, B.V.) is a dural sealant patch for preventing postoperative cerebrospinal fluid (CSF) leakage. It has been extensively tested preclinically and CE (*Conformité Européenne*) approved for human use after a first cranial in-human study. However, the safety of Liqoseal for spinal application is still unknown. The aim of this study was to assess the safety of spinal Liqoseal application compared with cranial application using histology and magnetic resonance imaging characteristics.

Methods: Eight female Dutch Landrace pigs underwent laminectomy, durotomy with standard suturing and Liqoseal application. Three control animals underwent the same procedure without sealant application. The histological characteristics and imaging characteristics of animals with similar survival times were compared to data from a previous cranial porcine model.

Results: Similar foreign body reactions were observed in spinal and cranial dura. The foreign body reaction consisted of neutrophils and reactive fibroblasts in the first 3 days, changing to a chronic granulomatous inflammatory reaction with an increasing number of macrophages and lymphocytes and the formation of a fibroblast layer on the dura by day 7. Mean Liqoseal plus dura thickness reached a maximum of 1.2 mm (range 0.7–2.0 mm) at day 7.

Conclusion: The spinal dural histological reaction to Liqoseal during the first 7 days was similar to the cranial dural reaction. Liqoseal did not swell significantly in both application areas over time. Given the current lack of a safe and effective dural sealant for spinal application, we propose that an in-human safety study of Liqoseal is the logical next step.

1 | INTRODUCTION

Cerebrospinal fluid leakage is a frequent complication after neurosurgical interventions, and is associated with prolonged hospital stay and increased healthcare costs.[1,2] To prevent CSF leakage, watertight closure of the dura mater is thought to be the most important step. Various products are used to augment this process, including approved sealants and off-label use of fibrin glues,[3] but their effectiveness has not yet been proven.[4]

Therefore, a biodegradable synthetic dural sealant, Liqoseal, has been developed (Polyganics B.V.) (Figure 1).[5] The device consists of two layers: the watertight blue top layer is a biodegradable poly(ester) ether urethane and the white bottom adhesive layer is made out of poly(DL-lactide-co-ε-caprolactone) copolymer and multiarmed NHS functionalized

FIGURE 1 Liqoseal characteristics. Length 8 cm, width 8 cm, thickness ~5 mm and weight 1600–2000 mg. Reproduced with permission from the copyright owner[7]: Van Doormaal TPC, Germans MR, Sie M, Brouwers B, Fierstra J, Depauw PRAM, Robe PA, Regli L. Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Performance of Dura Sealant Patch in Reducing Cerebrospinal Fluid Leakage Following Elective Cranial Surgery: The ENCASE Trial Study Protocol. Neurosurgery. 2020 Feb 1;86 (2):E203-E208. Website URL: https://journals.lww.com/neurosurgery/Fulltext/2020/02000/Single_Arm,_Open_Label,_Multicenter_Study_to.36.aspx. Neurosurgery is the official journal of the Congress of Neurological Surgeons. The Creative Commons license does not apply to this content. Use of the material in any format is prohibited without written permission from the publisher, Wolters Kluwer Health, Inc. Please contact permissions@lww.com for further information.

polyethylene glycol (PEG-NHS).[5-7] Liqoseal has been CE (*Conformité Européenne*) certified (2030288CE06) for cranial use since January, 2020.

Previous ex vivo experiments showed that Liqoseal provides a stronger watertight barrier than competitors in models mimicking cranial and spinal application situations.[5] However, Liqoseal is currently not approved for spinal use in humans. It is not clear if cranial results can be extrapolated to spinal application. Despite being a continuous membrane, there are differences between the spinal dura and cranial dura.[8] The spinal dura mater consists of the inner layer of the cranial dura mater, whereas the second, outer endosteal/periosteal layer of the cranial dura mater continues as periosteum at the level of the spinal cord.[8] The thickness of the dura mater is different at various levels along the spinal cord.[8]

For this study we hypothesized that the acute (up to 7 days) dural reaction to Liqoseal on spinal porcine dura resembles the cranial porcine reaction. To evaluate this hypothesis we implanted Liqoseal spinally in 8 animals and compared histological results and the thickness of dura plus sealant assessed using magnetic resonance imaging (MRI) with the results of Liqoseal implantation in a cranial porcine in vivo model at similar survival times.[9]

2 | METHODS

This study was approved by the Animal Experiment Committee (DEC) Utrecht, the Utrecht Animal Welfare Body (IVD) and the Central Animal Experiments Committee affiliated to the Dutch National Institute for Public Health and the Environment (Approval Nos AVD1150020184784 and AVD115002016457).

2.1 | Intervention

The surgical model, including the anesthesiology protocol and improvements in spinal stabilization in pigs, has been described extensively in a previous publication.[10] In short, a lumbar laminectomy and durotomy was performed in 11 female Dutch Landrace pigs with a mean weight of 78.3 (±4.5) kg (Figure 2A). Dura was closed using interrupted sutures (vicryl 5.0; Ethicon). In 8 animals Liqoseal was subsequently applied (Figure 2B) and 3 were used as control. In the Liqoseal group, a 2×1 cm piece of the sealant was cut and applied dry. Subsequently we applied manual pressure of approximately 1 kg using moist gauze for 2 min. Intraoperatively we did not perform further leakage tests to avoid disturbing the histological reaction and dural adherence. For comparison with the cranial model study[9] we included 8 implantation animals with survival times similar to the cranial model: 3 that survived up to 3 (±1) days and 5 that survived 7 (±1) days. Two control animals with spinal durotomy that survived 7 (±1) days were included (Table S1). The distribution of animals across survival groups is unequal due to initial postoperative complications which led to early termination of three animals. This was resolved by adjustments made to the surgical model for subsequent animals.[10] The planned survival time for this group was originally 7 days.

2.2 | MRI assessment

Before termination, a spinal contrast enhanced MRI was made in the prone position under anesthesia. After the MRI the animals were euthanized with an overdose of pentobarbital. The thickness of the sealant combined with dural thickness was measured in millimeters (mm) using Horos™, version 2.2.0. software on T2-weighted MRI without gadolinium for the 8 spinal implantation animals. Thickness was measured at its maximum using the length tool at the first (most cranial) surgical level. When no clear distinction could be made between postoperative hematoma/edema and the sealant combined with dura, no measurement was taken.

2.3 | Histological assessment

For histological analyses the operated region of the vertebral column was cut out *en bloc* with a 1 cm margin around the surgical area and thus included the vertebra, appendicular process joints, skeletal muscle, meninges, spinal cord and spinal nerves.

The blocs were put in 10% neutral buffered formalin for fixation. After fixation, the sample was decalcified with Formical-4 (Statlab Medical Products Inc.) at room temperature. On average, decalcification of the sample took 14 days. The decalcification process was evaluated daily by X-ray (Pathvision 23×29 cm, Faxitron Bioptics, LLC). After decalcification, the sample was routinely processed using isopropyl alcohol for

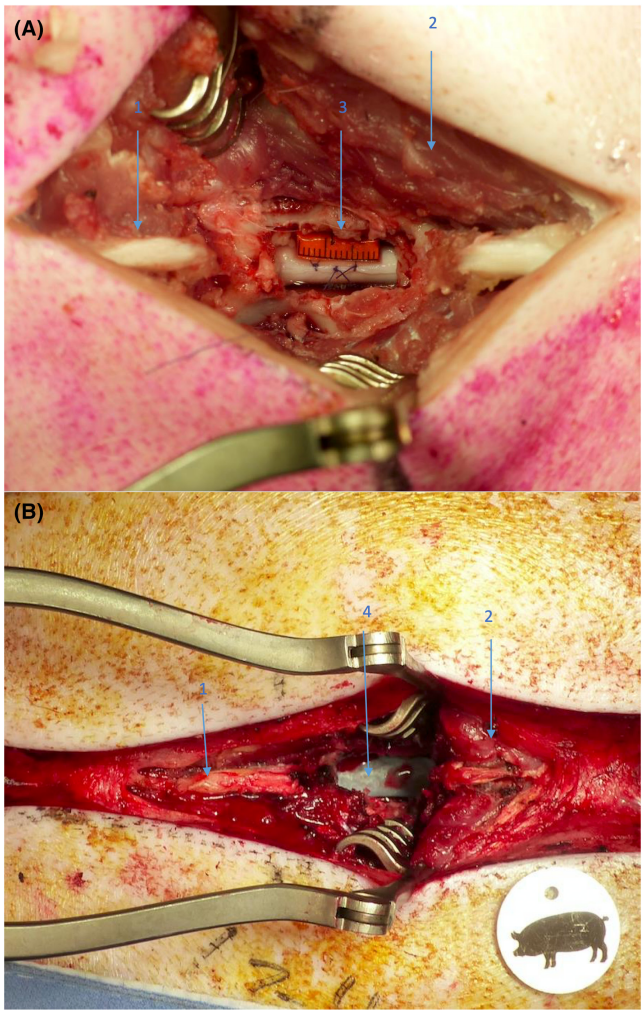

FIGURE 2 (A) Dorsal view of interlaminar decompression on one level, showing the spinal cord (1) with sutured durotomy of 1.5 cm (3) and surrounding muscle tissue (2). (B) Dorsal view of interlaminar decompression after the implantation of Liqoseal over the sutured durotomy (4).

dehydration and embedded in paraffin. Slices 0.4 mm thick were then cut with a microtome and stained with hematoxylin and eosin.

Histological features scored were (1) inflammatory response, (2) necrosis, (3) neovascularization and (4) fibrosis. This analysis was performed by a board-certified veterinary pathologist (W.B).

2.4 | Comparison group

In a previous study,[9] the cranial reaction to Liqoseal was compared with those to DuraSeal and Tachosil in a cranial in vivo model up to 12 months postoperatively. In this earlier study a total of 32 domestic pigs, of mean weight 66 (±5.7) kg, underwent craniotomy plus durotomy. This study showed that the foreign body reaction to Liqoseal was equivalent to the reactions to DuraSeal and Tachosil, which were in use clinically at that time.[9]

The histology and MRI results in the current study were compared with the data from this previous Liqoseal study in a cranial porcine model with similar survival groups to minimize the number of animals used. We included all animals with similar survival times ($N = 8$) from this previous study as a comparison group. These 8 animals included 4 Liqoseal implantation animals, of which 2 survived for 3 days and 2 for 7 days. The other 4 pigs were control animals, of which 2 survived for 3 days and 2 for 7 days. An MRI was obtained on the day of termination.[9]

For those cranial samples, the calvaria were cut out *en bloc* with a 1 cm margin around the bone flap and fixed in 10% neutral buffered formalin for 1 week. Thereafter coronal sections of 5–8 mm were created. Decalcification and processing for histological evaluation was performed as described for the spinal samples.[9]

3 | RESULTS

3.1 | Histology

In all 4 groups (spinal control, spinal Liqoseal, cranial control, cranial Liqoseal) the histologic reaction in all 4 categories ((1) inflammatory response, (2) necrosis, (3) neovascularization and (4) fibrosis) was similar (Table 1).

3.1.1 | Day 3 spinal

In the animals in the spinal group that survived up to 3 (±1) days, the histological analysis showed hemorrhages and neutrophilic infiltration within the sealant (Figure 3A). Within the dura a moderate predominantly neutrophilic infiltration was visible. At day 3 a mild fibroblast proliferation was seen. No adhesion of the spinal cord to the dura mater or the sealant was visible. Within the spinal cord either no changes were seen or mild to severe Wallerian degeneration in the dorsal up to all funiculi was present. Occasionally hemorrhages were also present in the spinal cord.

3.1.2 | Day 3 cranial

For the cranial group the reaction consisted of hemorrhages with mild-to-moderate neutrophilic infiltration within the sealant (Figure 3B). Furthermore, multifocally bone spicules, caused by the creation of burr-holes during the cranial surgical procedure, were visible, with a mild-to-moderate fibroblast proliferation with few macrophages and multinucleated giant cells. The multinucleated giant cells were occasionally seen within the sealant. Within the dura mater there was predominant neutrophilic inflammation with a mild fibroblast proliferation. Additionally, significant amounts of eosinophils were visible. The histology in the cranial control animals was comparable to that in the animals with Liqoseal implantation. No adhesions were visible between the nervous tissue and the dura mater or the sealant. Both in control and Liqoseal pigs the underlying nervous tissue showed multifocally a mild lymphoplasmacytic meningitis, mild cortical edema and moderate poliomalacia with demyelination of the corresponding white mater. Furthermore, occasionally a cell poor vasculitis was visible in the leptomeninges and cortex.

TABLE 1 Overview of histological results.

Up to 3 (±1) days	7 (±1) days	
Spinal		
Sealant	Hemorrhages Neutrophilic infiltration	Moderate amounts of macrophages Few multinucleated giant cells Moderately thick fibroblast layer
Dura	Mild acute inflammatory reaction; neutrophilic infiltration	Moderate subacute to chronic granulomatous inflammatory reaction
Cranial		
Sealant	Hemorrhages Neutrophilic infiltration Mild to moderate fibroblast proliferation Few multinucleated giant cells	Moderate subacute to chronic granulomatous reaction against the sealant. Moderate thick fibroblast layer
Dura	Mild acute inflammatory reaction; neutrophilic infiltration Significant amounts of eosinophils Mild fibroblast proliferation	Moderate subacute to chronic granulomatous reaction Mildly thick fibroblast layer

3.1.3 | Day 7 spinal

In the spinal samples the number of macrophages increased at 7 (±1) days, with moderate numbers of macrophages and the presence of multinucleated giant cells (granulomatous inflammation) (Figure 3C). At 7 days the fibroblast proliferation between the sealant and the dura mater had started to become a moderately thickened fibrotic layer. The number of inflammatory cells in the dura and between the dura and the leptomeninges was small to moderate and changed from more acute, with neutrophils present, to a subacute-to-chronic infiltrate with lymphocytes, plasma cells and macrophages. In one Liqoseal pig suspected adhesion between the leptomeninges and the dura mater was seen. Within the spinal cord either no changes were seen or mild Wallerian degeneration in different funiculi was present in both control and Liqoseal animals.

3.1.4 | Day 7 cranial

The reaction in the cranial samples showed a distinct granulomatous inflammation redirected to the sealant. Furthermore, formation of a fibroblastic layer between the sealant and the dura mater was observed. Within the dura mater and between the dura mater and the leptomeninges an inflammatory infiltrate shifting from a more acute to a subacute inflammation was again visible (Figure 3D). No adhesions of the cerebral tissue to either the dura mater or the sealant were visible. In both control and Liqoseal pigs multifocally a cell-poor vasculitis with occasional fibrin thrombi in both the leptomeninges and the cerebral cortex was seen, as well as a lymphoplasmacytic and histiocytic leptomeningitis with fibroblast proliferation, cerebral edema and poliomalacia and demyelination of the corresponding white matter.

3.2 | MRI

The sealant appeared hyperintense on T2-weighted images (Figure 4A–D). The combined thickness of dura and sealant was determined in 5 out of 8 animals in the spinal Liqoseal group. In 3 animals no clear distinction could be made between the sealant and postoperative edema and hematoma.

Spinal MRI measurements in this study were not significantly different compared to earlier cranial measurements in a porcine model. The measured mean thickness of the sealant on MRI in all samples was 1.0 mm (range 0.7–2.0 mm). The mean thickness of the dura and sealant up to 3 (±1) days postoperatively was 0.8 mm (range 0.7–0.9 mm). The mean thickness of the dura and sealant at 7 (±1) days postoperatively was 1.2 mm (range 0.7–2.0 mm).

In the cranial model the mean thickness of dura and sealant was 0.9 mm (range 0.7–1.1) at 3 days and 1.1 mm at 7 days.[9] The overall mean thickness of dura and sealant was 1.0 mm (range 0.7–1.1) in the cranial model.

4 | DISCUSSION

We compared the foreign body reaction of spinal Liqoseal implantation to cranial implantation by combining histological and MRI assessments.[9] The histological reaction to Liqoseal observed in the spinal porcine in vivo model is comparable to the reaction found in the cranial porcine in vivo model in the first 7 post-operative days. MRI assessments showed no indication of clinically significant swelling of Liqoseal and spinal dura up to day 7 (±1) postoperatively.

Over time in the spinal model we observed a foreign body reaction consisting of neutrophils and reactive fibroblasts up to day 3 (±1), changing to a subacute granulomatous inflammatory reaction with increasing numbers of macrophages and lymphocytes and the formation of a fibroblastic layer on the dura by day 7 (±1). This reaction was comparable to that in the cranial model, except for the less pronounced presence of eosinophils and the absence of multinucleated giant cells in the spinal model. This difference was probably caused by bone spicules present in the cranial samples which were the result of the creation of burr-holes and trepanation, as opposed to laminectomy performed with rongeurs.

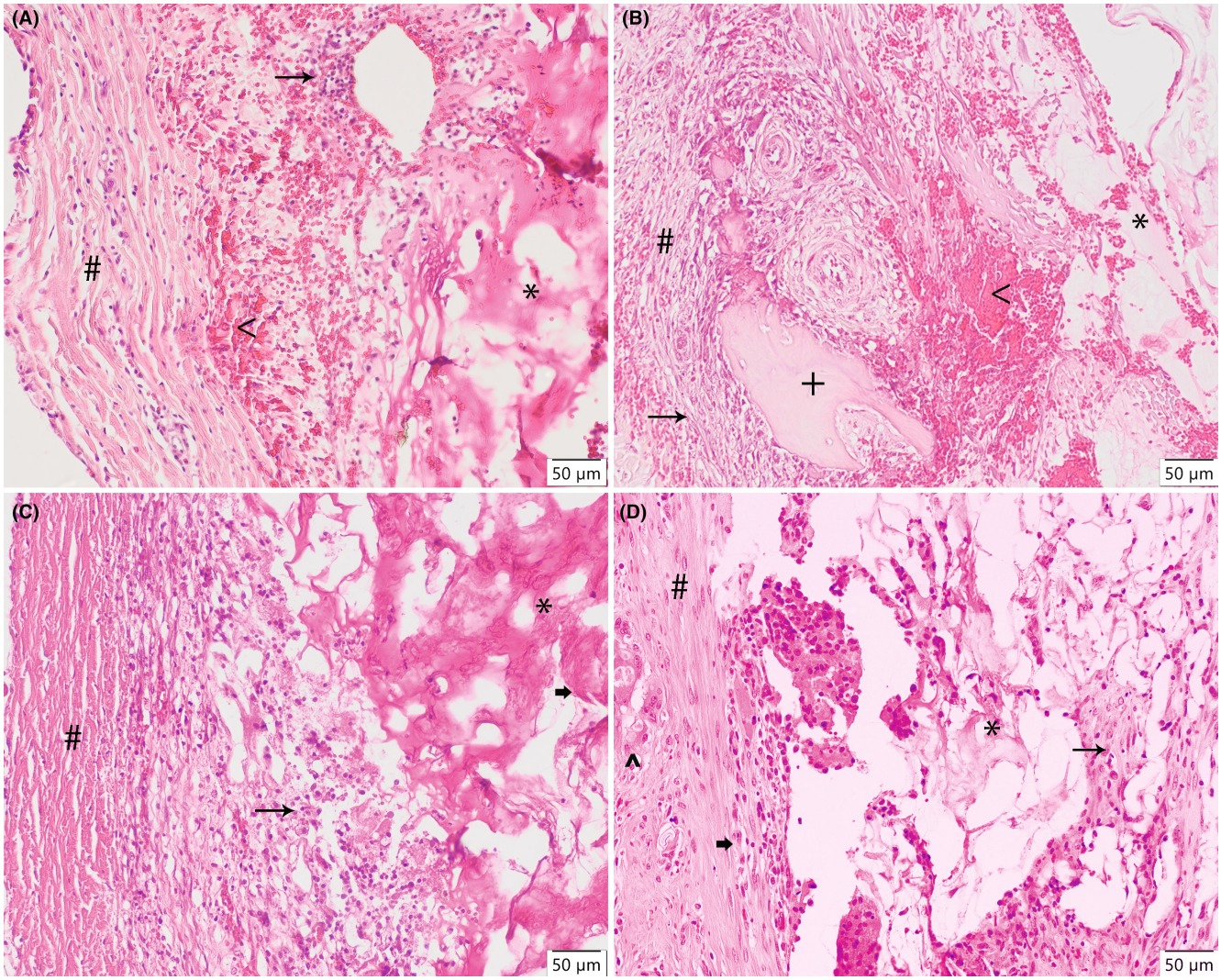

FIGURE 3 (A) Pig with a spinal sealant, 3 days post-surgery. Between and in the dura mater and the sealant are hemorrhages (<) and neutrophils (→) visible. (B) Pig with a cranial sealant, 3 days post-surgery. Between the dura mater and the sealant and in the sealant are hemorrhages (<) visible. The arrow points to fibroblast proliferation and macrophages surrounding a bone spicule (+). (C) Pig with a spinal sealant, 7 days post-surgery. Between and in both the dura mater and the sealant a granulomatous inflammation is visible (→). (D) Pig with a cranial sealant, 7 days post-surgery. Between the dura mater and sealant and within the sealant a granulomatous inflammation is visible (thin arrow). The thick arrow points to a layer of newly formed fibroblasts. The arrow head (^) points to a granulomatous reaction directed at suture material. #Dura mater; *sealant.

In the previous cranial study which also included animals with longer survival times, Liqoseal appeared to be fully resorbed between 6 and 12 months compared to DuraSeal (Integra LifeSciences) and Tachosil (Corza Health), which were fully resorbed within 3 months.[9] The slower degradation properties of Liqoseal may allow the dural defect to heal completely while maintaining a watertight closure. The histological assessment of animals with longer survival times in the cranial study showed a decrease in inflammatory response from 1 month onwards, with only a minimal reaction present at 12 months.[9] Based on the similarities between the histological reactions in the spinal and cranial models in the short survival groups presented in the current study, we expect that the histological reaction will progress similarly to that presented in our previous cranial model with longer survival times.[9]

The first in-human single-arm trial ENCASE showed that Liqoseal is safe and easy to use in cranial surgery.[6,7] None of the patients in this trial had intra- or postoperative CSF leakage. MRI imaging gave no indication of clinically significant swelling of the device throughout the follow-up, comparable to the current study. At day 7 dura and sealant thickness was 3.5 mm (0.8–8.1 mm) and at 3 months it was 2.1 (0.8–7.4 mm), compared to a pre-implantation and compression thickness of 5 mm.[6]

Swelling leading to spinal cord/nerve compression is a complication of concern with the use of DuraSeal, which has been FDA (Food and Drug Administration) approved for spinal use. The hydrogel can swell up to 50% and cases of neurological deficit as a result have been reported.[3,11,12,13,14] Similarly, this complication has also been reported for off-label use of fibrin gluel.[15] Thus, a sealant which does not swell after application has an important advantage. Swelling of the device, measured using MRI, should be an important safety measure in any future studies investigating the application of sealants in spinal surgery.

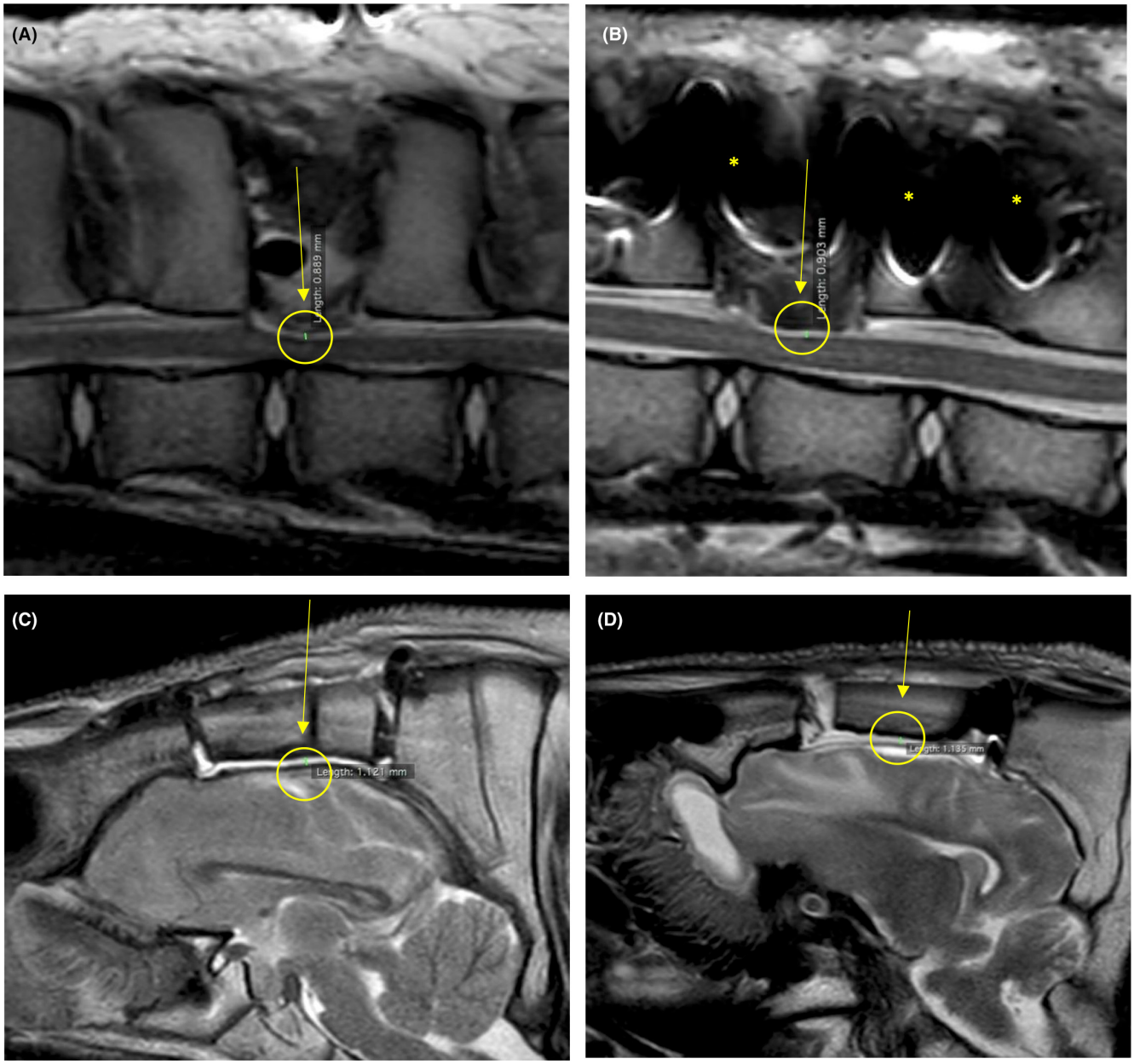

FIGURE 4 Measurement of sealant and dura thickness by MRI, indicated by arrows. (A) Spinal group up to 3 days. (B) Spinal group at 7 days (artifacts (*) due to the screws used for fixating the Lubra plates (Veterinary Orthopedic Implants Inc) still facilitate assessment of the spinal cord and dura). (C) Cranial group up to 3 days. (D) Cranial group at 7 days.

At this point, there is no effective and safe sealant for spinal use available. Systematic review of the existing literature showed no significant difference in CSF leakage rate between cases in which currently available sealants for spinal use were used in addition to suturing compared to cases where only primary suturing of the dura was performed.[4] The CSF leakage rate in both groups was substantial at an average of 11%, with secondary complications associated with CSF leakage being potentially life-threatening.[4]

The current study is limited by the small sample size and short survival times of the animals in the spinal in vivo model. The study was terminated before the planned sample sizes and termination times could be achieved for two reasons: 1. Difficulties with the model required various alterations to the surgical protocol throughout the study. 2. There was insufficient financial support to continue this costly study, following the adaptations that had to be made. Postoperative complications causing neurological deficit in the first animals required their early termination. Adaptations to the surgical model, with fixation of the spine, resolved this issue allowing survival to 7 days in subsequent animals.[10] For these reasons the numbers of intervention versus control animals across the different survival time groups vary.

In addition, the MRI measurements of the sealant and dura thickness could only be performed on a limited number of animals because of difficulty distinguishing between sealant and dura on MRI

scans and postoperative edema or hematoma in some cases. This limited sample size does not allow for statistical comparison of the measurements between groups.

Despite the limited sample size of the spinal in vivo study, we believe that a comparison of the results of the current study with those of previously published cranial in vivo studies provides valuable evidence for the use of Liqoseal in spinal surgery and contributes to reducing unnecessary animal research. Preclinical safety data for future spinal in-human trials may be obtained from these results instead of setting up a larger spinal animal study with longer survival times.

In conclusion, this study shows that the spinal dural histological reaction to Liqoseal during the first 7 days is similar to the cranial dural reaction and Liqoseal does not significantly swell in both application areas over time. Furthermore, no safety issues were reported in the first in human cranial study (ENCASE).[6]

Combined with previous data, this study suggests that Liqoseal can be safely applied on spinal dura. Given the current lack of safe and effective dural sealant for spinal surgery and burden of disease caused by CSF leakage, we propose that an in-human study investigating the safety and efficacy of Liqoseal in spinal surgery is the logical next step.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Tristan van Doormaal, Bart de Boer, Wilhelmina Bergmann, Saskia Redegeld and Sander van Thoor, Ahmet Kinaci and Emma Slot. The first draft of the manuscript was written by Emma Slot and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

TPCvD is a consultant for Polygancis b.v, AK received a research grant through Polyganics b.v., EMHS receives a research grant through Polyganics b.v. The other authors report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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