Effects of Glubran2 Acrylic Glue on the Subarachnoid Surface in Swine
Preliminary Findings

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Key words: acrylic glue, brain surface, embolization, Glubran2

ABSTRACT – Glubran2 is a cyanoacrylate-based synthetic glue modified by addition of a second monomer. Among its many advantages over traditional cyanoacrylate products, Glubran2 has a much lower thermal polymerization temperature than that of cyanoacrylates used for cutaneous application. For many years, the new glue has been widely used in neuroradiology endovascular treatments. Our study aimed to assess the use of Glubran2 to treat possible complications arising during the embolization of aneurysms or vascular malformations like AVM or fistulae. A complication encountered in some of these cases is rupture of the vessel wall by the microguide or perforation of the aneurysmal sac by the coils used for embolization. This complication could be overcome by injecting Glubran2 into the rupture point but this would put the glue directly in contact with the subarachnoid space and possibly reach adjacent brain tissue. The aim of this experimental study was to place the glue in direct contact with brain tissue to ascertain its immediate compatibility and tolerability in vivo and any ensuing tissue damage. Three swine underwent neurosurgical procedures and survived for different times after which they were slaughtered and their brains explanted and sent for macroscopic and microscopic investigation by the Pathological Anatomy Service. As a whole, Glubran2 was well tolerated in vivo and did not cause major damage in direct contact with brain tissue.

Introduction

Glubran2 (GEM Srl, Viareggio, Italy) is a new class 3 surgical glue for long-term injection (internal and external use) fulfilling the rules laid down by European directive 93/42/EEC. It is a cyanoacrylate-based synthetic glue modified by addition of a second monomer synthetized by the manufacturer. Among the many advantages of the new glue, the monomer gives Glubran2 a lower thermal polymerization temperature (around 45°C) than that of traditional cyanoacrylate products for cutaneous administration. Glubran2 has strong haemostatic and adhesive properties and once solidified constitutes an effective antiseptic barrier against the infectious agents or pathogens commonly encountered in surgical procedures. After a decade of use in different surgical interventions there is evidence that the glue is eliminated resulting in complete clearance of the product by a process of hydrolytic breakdown whose duration depends on the type of tissue affected and the amount of glue injected [3]. Following experimental studies on animals [1], Glubran2 has been used for many years in different endovascular embolization procedures [4,5,12,13,17]. The embolization of particularly fragile vascular malformations like AVM and fistulae requires highly selective catheterization and in some cases may result in rupture of the vessel wall by the microguide. This complication may also arise dur-

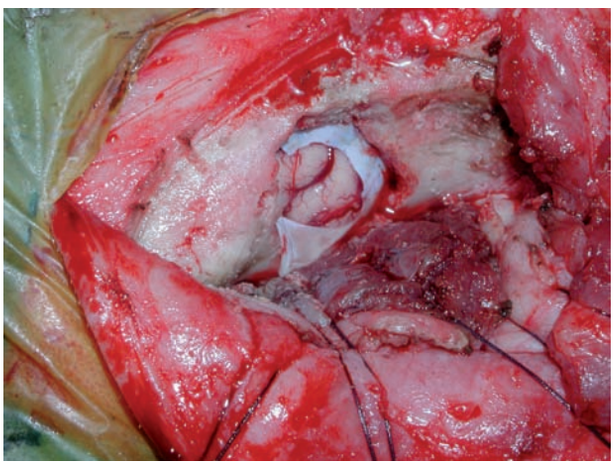


Figure 1 Craniotomy showing the brain surface and cortex with gyri and vessels.

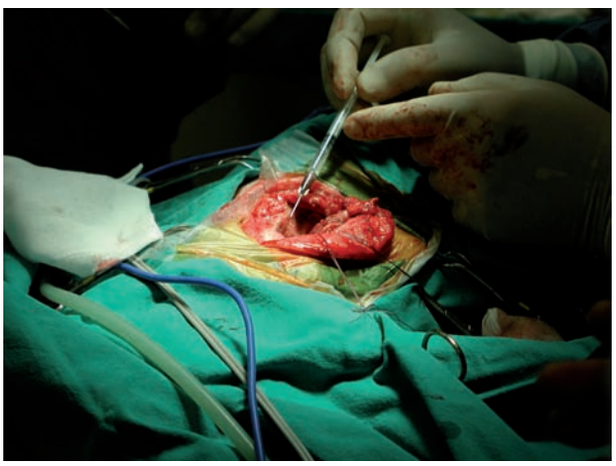


Figure 2 Application of the glue through the syringe.

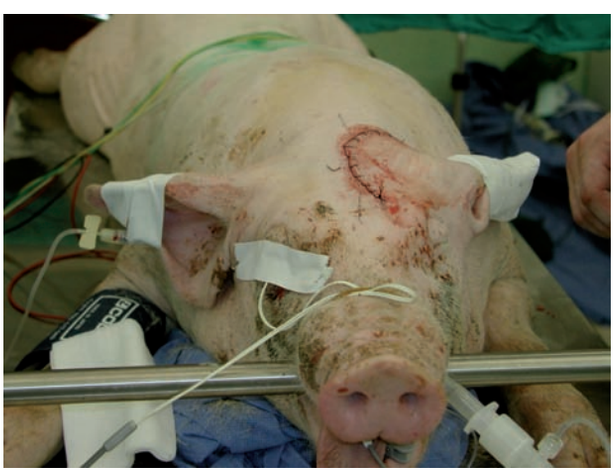


Figure 3 Suture of the epicranial soft tissues after rostrotentorial craniotomy.

ing embolization of brain aneurysms with coils when rupture of the aneurysmal sac is disclosed by leakage of contrast medium into the adjacent perivascular space and invasion of surrounding nerve tissues.

In some cases, this complication could be tackled by injecting Glubran2 into the rupture point on the vessel wall. However, this would place the glue in direct contact with the perivascular area or in the subarachnoid space and possibly hence with the adjacent brain surface: an exemplificative case is shown in figure 7.

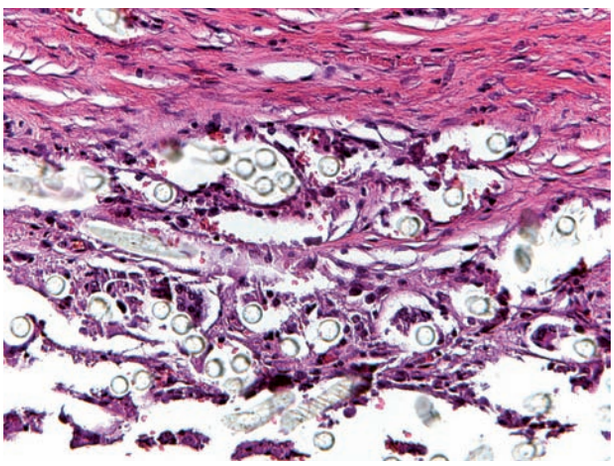
This study aimed to assess the effects of Glubran2 by placing the glue in direct contact with the brain surface and external vessel walls and ascertain its immediate compatibility and in vivo tolerability and any ensuing anatomical or functional damage and histological changes.

Materials and Methods

The experimental protocol was approved by Bologna University Scientific Ethical Committee according to law (D.L. 116/92). Three large white swine weighing between 30 and 60 Kg were used.

After a 24 h solid food fast and 12 h without liquids, the animals were given mixed balanced general anaesthesia including analgesic sedative vagolytic premedication with atropine sulphate, acetylpromazine maleate, azaperone and buprenorphine; induction with thiopental sodium; orotracheal intubation; deep anaesthesia and maintenance with isofluorane in oxygen under controlled respiration; increased analgesics in case of signs of awakening [9].

The swine underwent left lateral rostrotentorial craniotomy six for an area of 4-5 cm^2,



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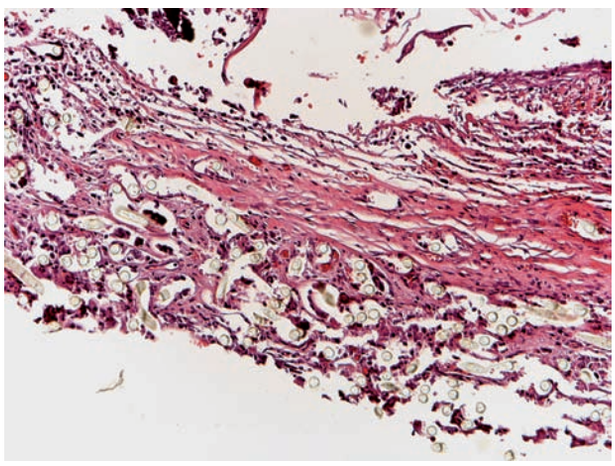

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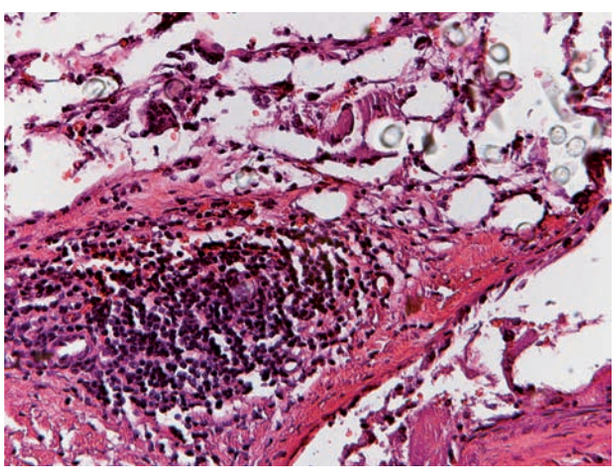

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Figure 4 Swine A (30 day survival). The meningeal membrane shows signs of fibrosis with calcifications and glue residue depicted as a bireflecting crystalline-like substance associated with foreign-body induced chronic inflammation with giant cells. Note the focal signs of subpial spongiosis in the nerve tissue which is largely spared by the pathological process.

durectomy and exposure of brain tissue. A total of 0.1 ml Glubran2 was spotted in droplets to form a thin film of glue over the exposed tissue including the surrounding vessels, followed by closure with the placement of synthetic dura and subsequent repositioning of the bony operculum and suture of the soft epicranial tissues. Antibiotic therapy with enrofloxacin was given postoperatively.

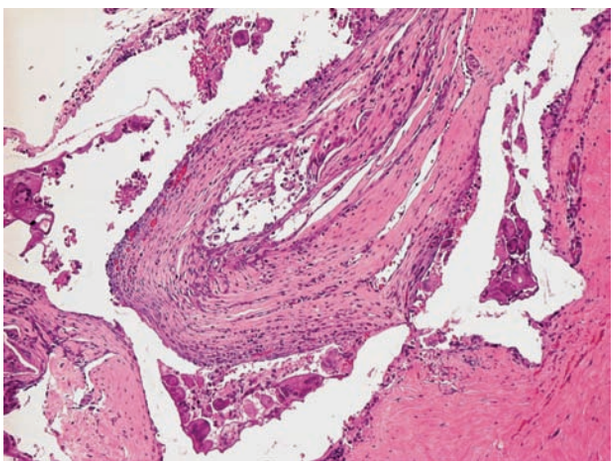
The swine were stabulated at the Clinical Veterinary Department of Bologna University, then killed by induction of general anaesthesia and injection of Tanax, (a product consisting of embutramide, mebenzonium iodide and tetracaine hydrochloride) at 30 days (swine A), 60 days (swine B) and 100 days (swine C) respectively. During stabulation the animals were monitored periodically to assess their general condition, neurological status and well-being using the Glasgow Composite Pain Tool 7 modified for the purpose.

When the swine were slaughtered, brain biopsy specimens were taken for analysis at the Anatomy, Histology and Pathological Cytology Service at Bellaria Hospital, Bologna.

Results

Surgery lasted an average of 60 min after which the swine awoke at normal times and were left to resume their usually position and feed spontaneously without neurological deficits. Clinical follow-up visits during stabulation failed to disclose signs of neurological deficit or suffering.

Anatomopathological tests disclosed the following:



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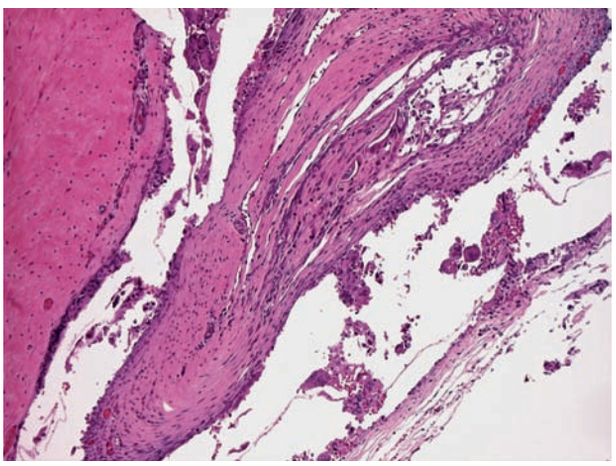

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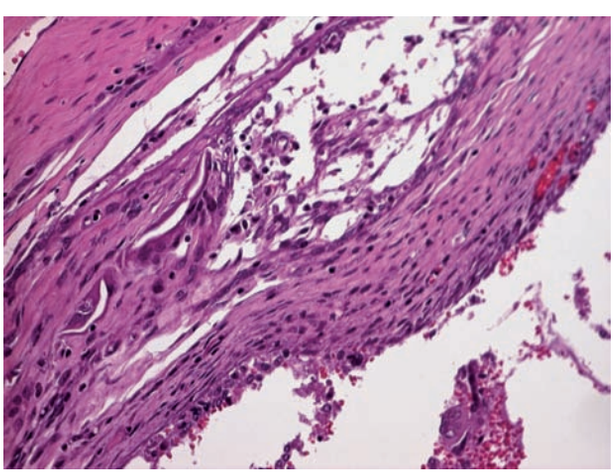

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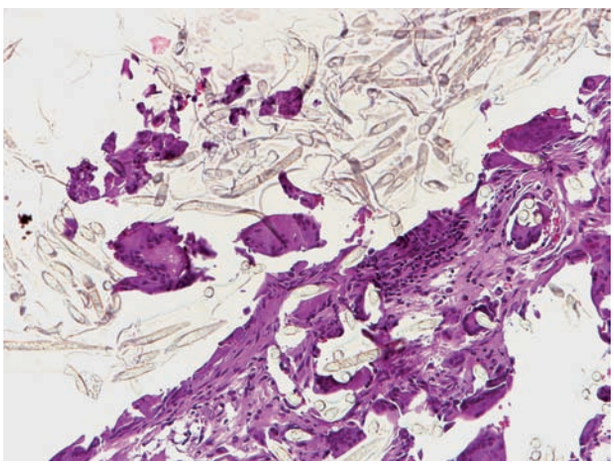
Figure 5 Swine B (60 day survival). The meningeal membrane shows signs of fibrosis with calcifications and glue residue depicted as a bireflecting crystalline-like substance similar to the amount seen in Swine A and associated with foreign-body induced chronic inflammation with giant cells. The nerve tissue shows signs of subpial and focal spongiosis and clusters of macrophages loaded with haemosiderin pigment.

Swine A (killed after 30 days), whose brain weighed 95 g, presented a 2 cm long granular area along the major axis of the treated surface over the left brain hemispherex 1,2 in cui le meningi aderiscono alla corteccia cerebrale. At histological analysis the juxtaposed meningeal membrane showed signs of fibrosis, calcifications and a bireflecting crystalline-like substance associated with chronic inflammation with foreign body-like giant cells. La sostanza-The nerve tissue appeared to be spared except for focal signs of subpial spongiosis. in cui la leptomeninge presenta segni di flogosi cronica con depositi calcifici.

Swine B (killed after 60 days), whose brain weighed 85 g, presented a 2.4 cm long grey-brownish area along the major axis of the treated surface in the left brain hemisphere. At histological analysis the meningeal membrane revealed fibrosis, calcifications and a bireflecting crystalline-like substance associated with chronic inflammation with foreign body-like giant cells. The crystalline-like substance was present in similar amounts to that found in swine A. The nerve tissue showed subpial spongiosis, signs of neuronal ischaemia ("red neurons") and focal clusters of macrophages loaded with haemosiderin pigment. The meningeal vessels appeared slightly congested.

Swine C (killed after 100 days), whose brain weighed 95 g, presented a 1.8 cm long grey-brownish area along the major axis of the treated surface in the left brain hemisphere.

At histological analysis the meningeal membrane revealed fibrosis, calcifications and chronic inflammation with foreign body-like giant cells. Only minimum traces of crystalline-like substance were found. Local subpial in-



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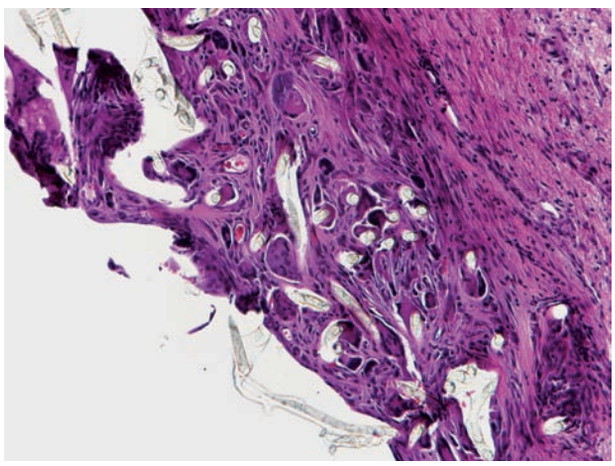

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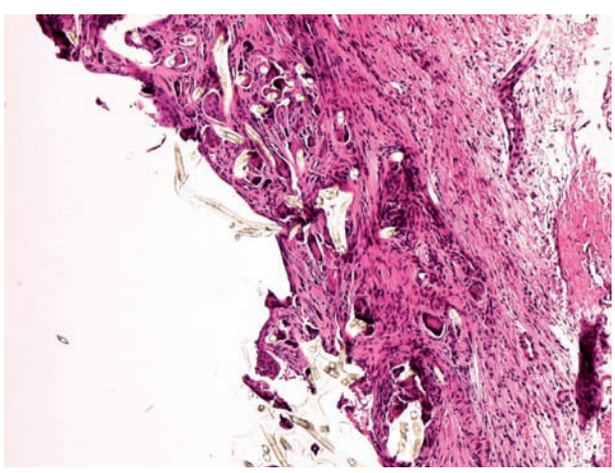

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Figure 6 Swine C (100 day survival). As in Swine A and B, the meningeal membrane shows signs of fibrosis with calcifications and foreign-body induced chronic inflammation with giant cells. Note only the minimum traces of crystalline-like substance and local subpial inflammation of nerve tissue.

flammation involved the nerve tissue which also showed signs of mild neuronal ischaemia ("red neurons").

Discussion

Glubran2 applied to brain tissue and vessels was well tolerated by the animals which showed no evidence of general clinical, neurological or behavioural changes. Macro and microscopic analysis of anatomopathological specimens demonstrated that Glubran2 is readily biodegraded as only minimum traces of the crystalline-like glue were detected 100 days after application. This finding supports previous reports indicating that in due course the glue disappears completely from the focus without leaving any residue [3,10]. Hence it can be reliably assumed that the minimal ischaemic injury detected resulted from the surgical procedure. Histologically, the changes described correspond to a giant cell reaction in the meninges with reactive spongiosis in the subpial nerve tissue following exposure to a foreign body and hence can be deemed (para)physiological [8].

Conclusions

The excellent clinical tolerability of Glubran2 confirmed by a comparative assessment of histological tests in the three swine allow the following conclusions:
1) The amount of crystalline-like bireflecting foreign substance (glue residue) was comparable in the two swine with short and intermediate survival times (Swine A, 30 days; Swine B,

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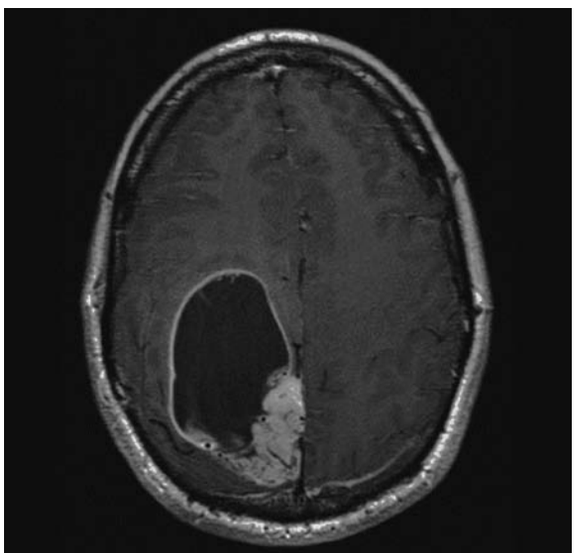

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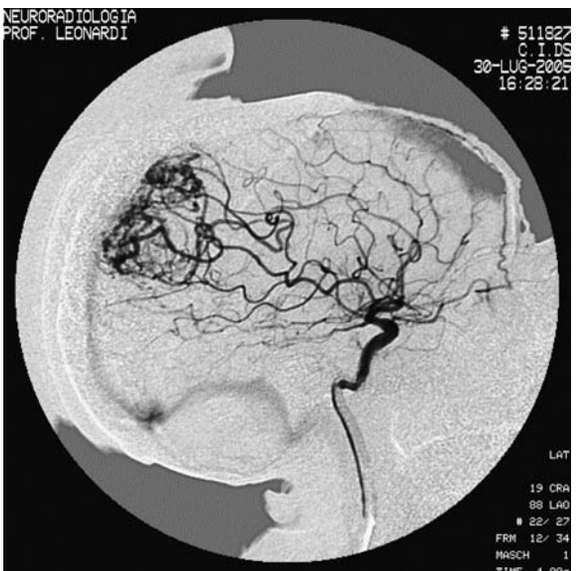
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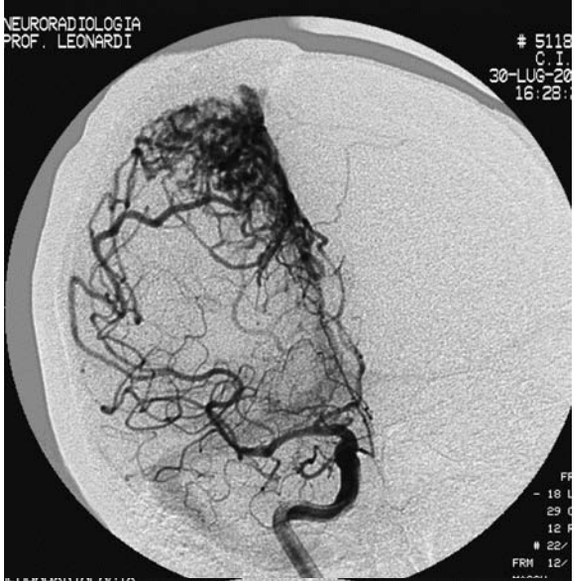
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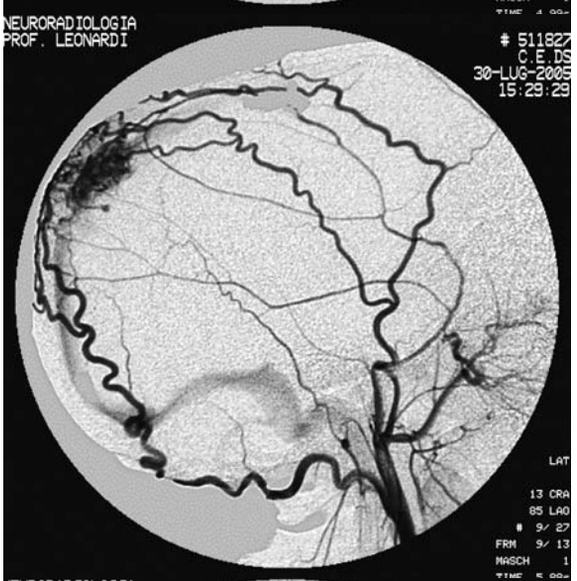
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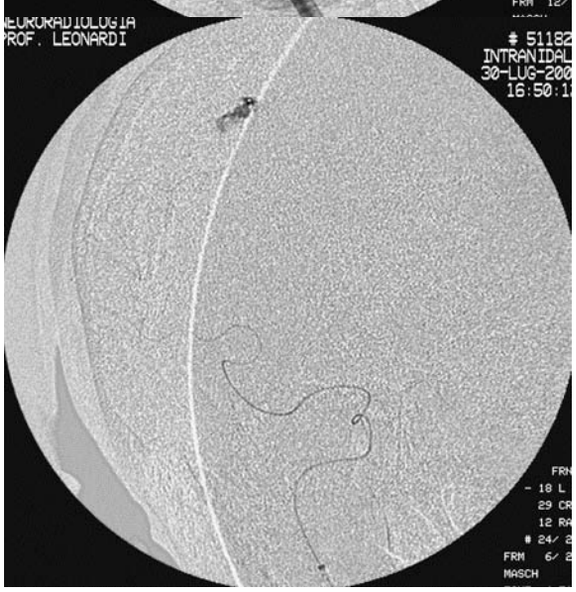
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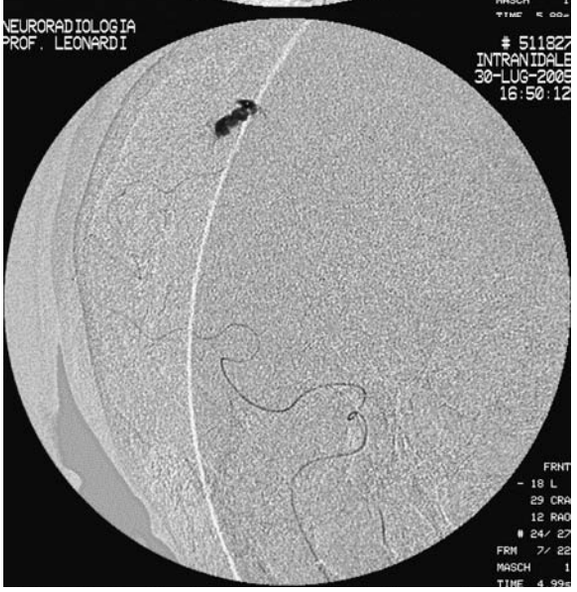
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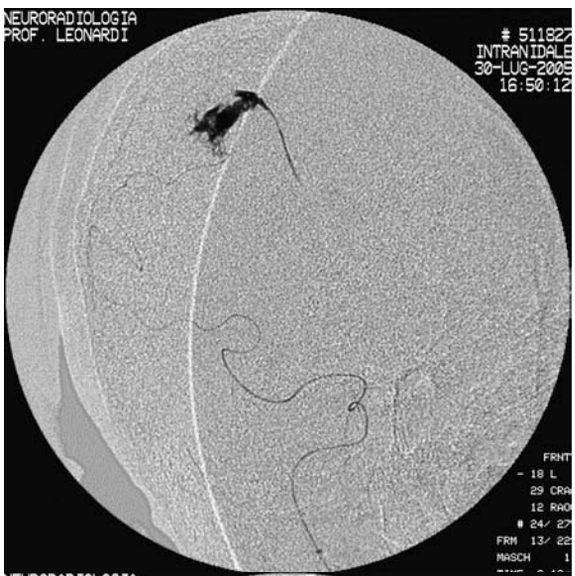
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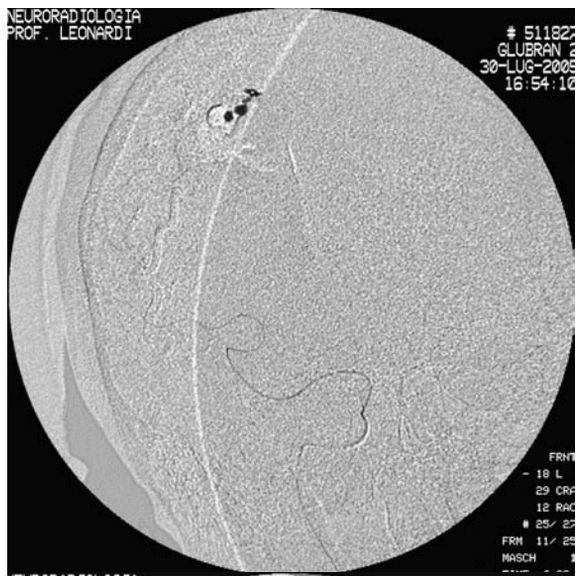
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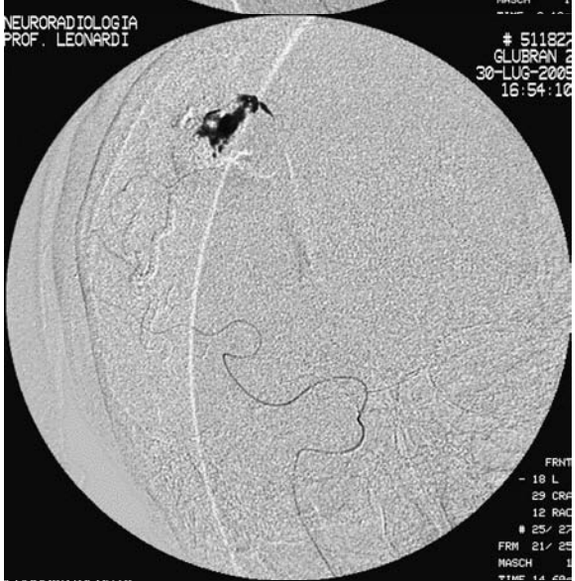
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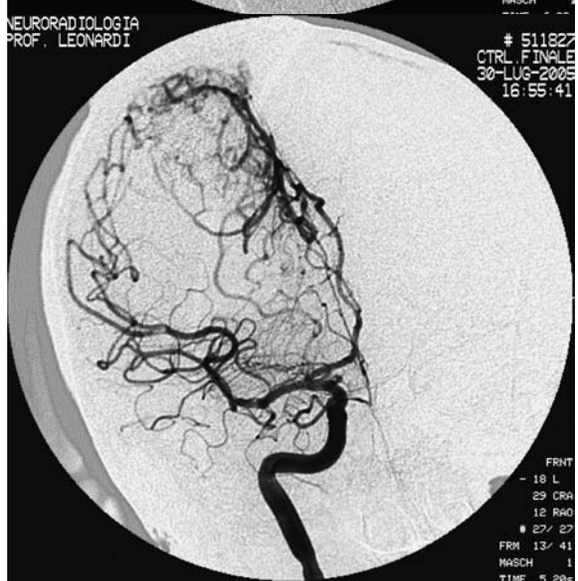
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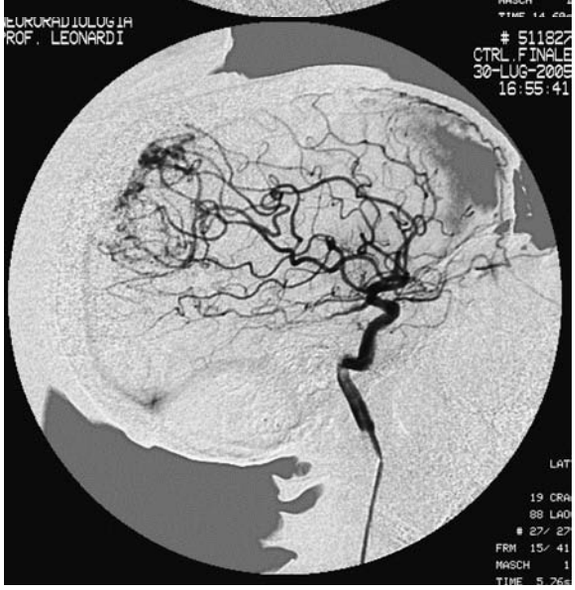
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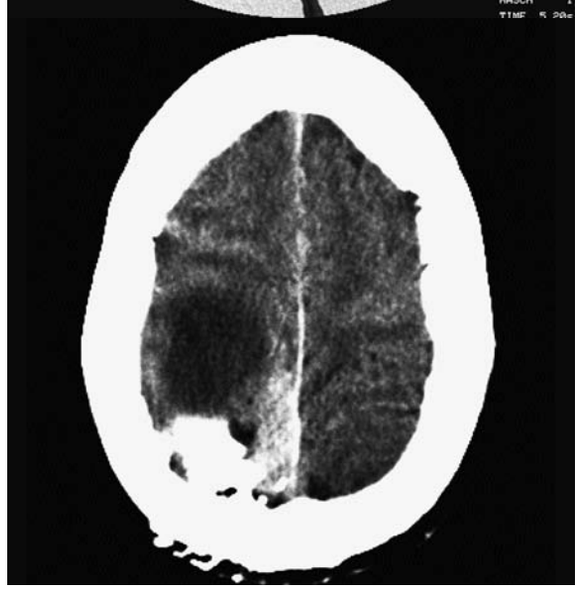

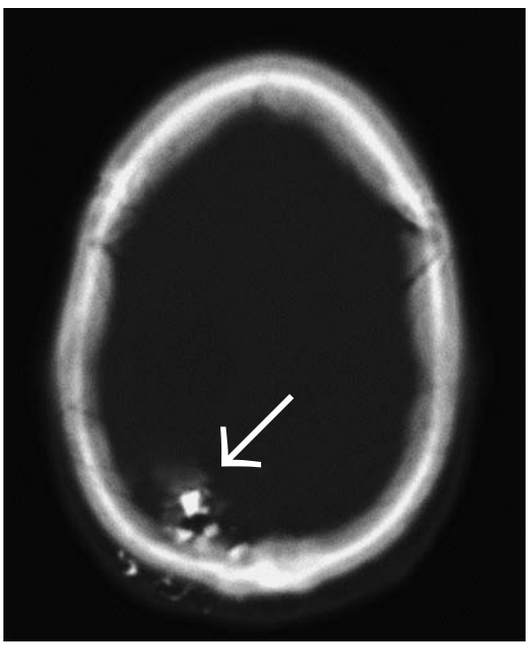

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Figure 7 Male, 28-y o, A) MRI T1w, after injection of contrast medium: frontoparietal cystic tumour with a large hyper-enhancing nodule parasagittal adjacent to the falx cerebri. B-D) Angiographic sequence: large hyper vascularization of the nodule tributary of the external right carotid artery and of the middle cerebral artery. E-G) superselctive catheterisation of the mible cerebral artery, evidence of bleeding from extravasation of contrast medium. H-I) Injection of Glubran2 with occlusion of the leakage point. L-M) Control angiography: no more extravasation of contrast, important reduction of pathological new vessels. N) CT follow up: contrast and blood are evident inside the tumoral cyst (O) with appropriate window is evident the bubble of glue occluding the vessel leakage (arrow).

60 days), whereas it was drastically reduced leaving only minimum traces in the swine slaughtered after 100 days.

2) Chronic meningeal inflammation with foreign body-like giant cells was observed in all animals.

3) The subpial nerve tissue showed signs of spongiosis in all animals.

4) The nerve tissue showed signs of neuronal ischaemia ("red neurons") at the site of surgery in all animals. This finding was more conspicuous in the swine with an intermediate survival (Swine B, 60 days) and confined to the focus in the other two animals.

Glubran2 was completely broken down over time in the swine with the longest survival leaving only minimum sequelae.

This confirms that the glue is biocompatible [14] and not particularly harmful even when placed in direct contact with the brain surface. Breakdown of the glue does not affect its adhesive capacity which evolves in subsequent fibrous scar tissue.

The small number of animals tested precludes statistical analysis, but this study offers further evidence that Glubran2 is well tolerated and can be safely used in the subarachnoid space [1,3,10,14].

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