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# Hemostatic Agents in Neurosurgery

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## 1. Introduction

Adequate hemostasis is a prerequisite in neurosurgery, to prevent dramatic postoperative bleedings and their consequences. Different sorts of local hemostatic agents have been developed, with a variable efficacy. Some of them have been used for years, none being perfect.

The residual presence of these agents may behave as foreign bodies, and induce inflammation, infection, and even delayed bone growth.

Safety is an other concern since most of modern agents contain more or less human and animal components.

We are going to review the history of those agents, their different categories, compare them and try to establish some guidelines when using them, with their different indications.

## 2. Hemostasis (basis)

Hemostasis comes from the coordinated activation of platelets and plasma clotting factors to form a platelet fibrin clot. Two processes, primary and secondary hemostasis activation of the clotting cascade is done by collagen for the intrinsic pathway, and the extrinsic pathway is activated by the release of tissue factors from the damaged zone. The two converge into the common pathway which begins with the conversion of Factor X to Xa, the conversion of prothrombin to thrombin, which is integral in clot stabilization via fibrin. This common pathway is facilitated by Factor V (Hawiger 1987).

## 3. History

From the beginning of the neurosurgical practice, local hemostatic agents have proved to be very useful completing the more classical use of the electrocoagulation whatever its type, mono or bipolar or sometimes laser.

### 3.1 First attempts

#### 3.1.1 Auto or hetero-muscle application

Until the early 1950, neurosurgeons used as topical hemostatic agents fresh chicken breast which was delivered to the operative theatre just before the beginning of the operation. Electrocoagulation device was not very good, and they often had to apply the chicken flesh

on the brain during ten minutes while washing the field with warm serum, and removed it before closing the dura.

Fresh muscle harvested from the temporal site or the thigh is still commonly used for extradural dural hemostasis and may be left in situ.

At the same times, bone wax was used and is still used for bone hemostasis (Grant 2007). Bone wax was created by Sir Victor Haden Horsley (1857-1916) from beewax in 1892. Since this period different components were added to wax, but the common name remained "Horsley wax".

### 3.2 Hydrogen peroxide

It has been used for decades as a hemostatic agent and is believed to establish hemostasis through its vasoconstrictive properties, and is also credited to create a disruption of the blood-barrier and an aggregation of the platelets and neutrophils leading to thrombus formation. The free diffusion of H<sub>2</sub>O<sub>2</sub> through the vessel walls and its conversion to water and O<sub>2</sub> leads to intra-luminal bubbles, micro-embolisms and vessels obstruction.

### 3.3 Modern evolution

Multiple local hemostatic agents now exist (Abaut & Basle 2003, Grant 2007)

#### 3.3.1 Fibrin sealants

The better understanding of hemostasis mechanisms brought new perspectives for the conception of other local agents. The first discussion for topical agents is due to Bergen who emphasized the role of fibrin in hemostasis. Secondary, this will move to the preparation of fibrin sealants, the first combination of bovine thrombin with human plasma for topical use. In 1938, purified thrombin became available, with obtention of new fibrin sealants used in 1940, as reported in the literature, even for nerve repair. In 1944, their use was reported to optimize skin-grafts survival and adhesion of skin grafts, in severe burn injury during the war by Cronkite. Richard Upjohn Light 1945 reviews the different existing helps to improve hemostasis in neurosurgery, and Fincher 1946 reports the uses of gelatin foam .

But the technics used in those times only led to preparations being the potential source of transmission of viral hepatitis. So bovine thrombin was substituted for human thrombin to minimize the risk of viral transmission. But some patients developed coagulopathies due to the use of bovine thrombin related to immune-mediated production of thrombin and factorV inhibitors.

All these difficulties led to abandon the fibrin sealants for years.

In the late 1960, isolation and concentration of clotting factors from human plasma became possible, and in 1972, Matras produced the first item of modern fibrin sealants. The first commercially fibrin sealant was approved in Europe in 1982, and Later in USA in 1990.

In 1998, Tisseel and Hemascel sealants were approved by FDA, and the first sealant with entirely human components called Crosseals was made in 1993. Surgical use widely spread in nearly all specialities.

### 3.3.2 Gelatin hemostatic agents

They were introduced in 1940 such as Gelfoam and Surgifoam.

Gelfoam is a purified pork skin gelatine with hemostatic properties which may come from its physical features, and not from an effect on the clotting cascade. It may be used with saturated thrombin.

They exist as sponges and have a capacity to expand up to 200% in vivo, which may be a negative property in some deep fields specially in neurosurgery.

Floseal combines human derivated thrombin with bovine derivated gelatin matrix granules which are mixed at the time of use, and also exists as a liquid device minimizing the expansion property, allowing its application in minimal invasive surgery and neurosurgery.

### 3.3.3 Cyanoacrylate adhesives

They were developed by Dr H Coover in 1942. It consists cyanoacrylate monomers which polymerize in long chains in the presence of hydroxyl ions.

### 3.3.4 Oxyfied regenerated glucose

Is a plant -based topical hemostatic introduced in 1960. It is made by regenerating a pure plant-derived cellulose secondary knitted and oxidized. It acts as a scaffold for clot formation. On post-operative imaging, it may mimic an abcess or some residual tumor.

### 3.3.5 Microfibrillar collagen

This substance (Avitene) was introduced in 1970. Microfibrillar applied collagen products come from the purification of bovine collagen, followed by microcristallisation. It is presented as a powder, and is more effective than gelatine based hemostasis, since it is able to activate the clotting cascade.

## 3.4 Thrombin and fibrinogen (fibrin glue)

Are the most recently appeared.

Fibrin glues contain thrombin and fibrinogen: when combined, the fibrinogen is activated by thrombin and converted into fibrin monomere which form an adhesive glue at the tissues applied.

The fibrin monomere interacts with the patient's own factor VIII and calcium to convert the final product into a fibrin polymer that allows for platelets activation and aggregation with subsequent hemostasis.

They are presented with a dual chamber syringe that allows for the combination of the thrombin and fibrinogen when the plunger is depressed. They also can be used in spray. Many commercial products are now on the market: Tisseel (Baxter), Evicel formerly called Crosseal (Johnson and Johnson)...Tisseel is now bovine free.

4. Classification of existing products

4.1 Surgical local hemostatic agents with an aspecific effect on the clotting cascade

*Hemostatic agents with a natural origin*

Are medical devices of Class III, and may be extracted from animals (calf, ox, pig or horse) or plants (wood, cotton, alga, potatoe-starch)

*Mecanism of efficacy*

Collagen and gelatine induce the platelet aggregation leading to a clot when in contact with blood

Oxidized cellulosis allows absorption of blood. Glycuronic acid diminishes the PH, induces vasoconstriction, and the creation of hematin film, and in vitro shows an bactericid effect.

Alginates release the Ca++ ions , with a platelet activation followed by a fibrinoformation. Alga fibers reinforce the clot structure.

Starch acts like a filter which concentrate the blood cells and the proteins such as thrombin, albumin and fibrinogen, with an hemostasis occurring in a few minutes.

*Different products*

Composition	origin	product	presentation
Collagen	Calf	Pangen	compress
	Ox	Avitene	
	Pig	Surgicol	
	Horse	Antema (Biomet)	
Gelatin	Ox	Tissufleece (Baxter)	Gel
		Gentafleece (Baxter)	
		Septocoll ( Biomet) + gentamycin	powder, gel, pad
		Collatemp (Inocoll)	
	Pig	Floseal (Baxter) + Thrombin	gel
		Gelitaspon (Caps recherche)	
Oxidized cellulosis	Pig	Surgiflo Johnson & Johnson)	Powder
		Spongostan (Johnson & Johnson)	
	Wood	Gelita (Pouret)	Plugs
		Surgicel (Johnson&Johnson )	
Alginates	Cotton	Gelitacel (Caps recherché)	Compress
	Laminaria	Algosterile	
Starch	Hyperborea		Powder
	Potatoe	Arista (Medafor)	

*Hemostatic agents with a synthetic origin*

Their classification depends on their chemical category

- Aldehyds associated with gelatine (GRF) or albumin (Bioglue –Gamida-)
- Glycol polyethylens (Coseal –Baxter- and pleuraseal)
- Cyanoacrylates (Glubran and Omnex)

*Mechanism of efficacy*

Their aim is the constitution of a film to obtain water tightness and prevent the risk of hemorrhage

They won't be developed here their use being contraindicated in neurosurgery.

**4.2 Hemostatic agents with a specific effect on hemostasis cascade**

Concern four products containing all fibrinogen and thrombin, their difference is due to the different associated coagulating factors leading to product the last stage of the coagulation (Silver, Wang & AL 1995, Jackson 2001). Experimental studies have compared the properties and efficacy of the different fibrin sealants (Dickneite, Metzner & Al 2003) in correlation with their components. They emphasized the necessity of Factor XIII as the key of a good efficacy for clotting. All tested fibrin sealants performed well on individual parameters, but Beriplast (Aventis Behring) was the foremost fibrin sealant in consistently providing early hemostasis.

These products are the Tissucol, the Beriplast, the Quixil and the Tachosyl.

Each one contains other coagulation factors (Factor XIII, fibronectin, plasminogen), and an antifibrinolytic.

The Quixil contains no substance from animal origin, but transnenamic acid and subsequently must never be in contact with nervous tissues.

**Tissucol (Baxter)**

- Can exist as a solution or a spray
- \*Powder and reconstitution solution I
- Contains human components: fibrinogen (90mg/ml), Factor XIII(10UI/ml), fibronectin(5,5mg/ml), plasminogen0,08mg/ml), bovine aprotinin (3000 UIK/ml)
- \*Powder and reconstitution solution II
- Contains human thrombin (500 UI/ml)
- \*The excipient of powder and reconstitution I
- Contains glycin, human albumin, sodium nitrate, tyloxapol
- \*The excipient of powder and reconstitution solution IIContains Glycin, Sodium chlorure, reconstitution solution EPPI, Calcium chlorure
- Must be kept in refrigerator, can be kept for 2 years
- After reconstitution remains stable for 4 hours

**Beriplast (Nycomed)**

- Same presentation
- \*Powder and reconstitution solution I

- Contains human components: Fibrinogen (90mg/ml), Factor XIII( 60UI/ml), with bovine aprotinin (1000UIK/ml)
- \*Powder and reconstitution II
- Contains human thrombin (500UI/ml)
- \*Powder and reconstitution solution
- Contains human thrombin (500UI/ml)
- \*Powder and reconstitution solution I
- Contains Isoleucin, Arginin, Sodium glutamate, human albumin, Sodium citrate, reconstitution EPPI, Sodium chlorure
- Can be kept for one year at room temperature, and 2 in refrigerator
- Remains stable for 24 hours after preparation.

### **Quixil (Johnson & Johnson)**

We don't detail its composition for the previously related reason.

### **Tachosil (Nycomed)**

Presents as compress

- \*The white side is covered with human fibrinogen( 5,5mg/cm<sup>2</sup>)
- \* The yellow side with human thrombin (2UI/cm<sup>2</sup>)
- The excipients associate horse collagen, human albumin, Riboflavin, sodium chlorure, sodium citrate, L-Arginin.
- Can be kept for three years at room temperature

### **Autolog fibrin:Vivostat system (Vivolution)**

- Is a medical device whose the European autorisation has been given in 2000.
- This automatized system can provide autolog from the patient blood in 23 minutes.
- It associates a processor, a Kit preparation and a spray system.
- It contains no animal component so it eliminates all risks of viral transmission
- Nowadays, it is mainly used in cardiac and thoracic surgery, in vascular and abdominal surgery, but not in neurosurgery.

## **5. Patches and pads**

Those non-invasive hemostatic closure devices as described by Hirsch, Reddy & Al 2003 are mainly used to obtain hemostasis of percutaneous arteriotomy sites of arterial catheterization. This type of patch comes from the studies confirming the hemostatic properties of a high-molecular -weight polysaccharide the poly-N-acetyl-glucosamine (p-Glc-Nac).

Its use is mostly in cardiac surgery and in interventional radiology.

### **5.1 Choice of the device and indications**

First we shall remind that some specialities are contra-indicated in neurosurgery: cyanoacrylates, Quixil, alginates. H<sub>2</sub>O<sub>2</sub> must only be used out of the dura mater.

The choice of the product and the strategy for local hemostasis are correlated with the type of neurosurgery, the sources of the bleeding, and the neurosurgeon practice, and the financial supplies.



No one must expect from local hemostatic products whatever their quality to be a substitute for the classical bipolar electrocoagulation hemostasis, and more widely for the respect of the tissues.

### 5.1.1 Type of bleeding

#### *Arterial bleeding*

Bipolar coagulation must be used and gives a perfect adequacy to the needs if associated with irrigation.

#### *Bleeding from a venous sinus*

The suture remains the best mean when possible, possibly reinforced with a muscle or aponevrotic patch. If the bleeding is close to the vault, the suspension of the dura mater to the bone with interposition of a patch of muscle, oxidized cellulosis or both is the solution.

Anterior cavernous sinus bleeding can be controlled by injection of fibrin glue with a good hemostasis. However of the series reported by Sekhar, Natarajan & Al 2007, of the 20 patients who had an injection in the superior petrosal sinus, 2 experienced complications caused by occlusion of veins draining the brainstem. The 46 whose anterior cavernous sinus had been injected had no complications.

#### *Diffuse bleeding "cloth-bleeding"*

A global hemostasis disturbance must be searched.

Local hemostatic agents are indicated, the most often oxidized cellulosis (surgical) will be applied, as well as tissucol (solution or spray).

#### *Bone bleeding*

Bone wax remains the most commonly used device, with a good efficacy. However, large amounts must be avoided for they will stay there for ever as a foreign body, and may be the cause of chronic infection, and a secondary removal.

When skull base surgery is performed, surgical, muscle can be on the bleeding site. According to the concerned neurosurgeons, the most effective product is the Floseal (powder).

#### *Dura mater water-proof*

Prevention of cerebro-spinal fluid (CSF) leaks must be done by the tight closure of the dura mater, reinforced if necessary by application of Surgicel.

Large defects require a graft which can also be sutured, the suture of which may be reinforced in the same way.

In large defects of the dura mater or on the skull base, most of the neurosurgeons will fill the defect with autolog fat tissue (easily indentified on post-operative CT-scan or MRI pictures) associated with glue (Tissucol or Bioglue). An external lumbar CSF derivation will be added in the most difficult cases.

N-B: A local hemostatic agent will never by itself be sufficient to give a definitive water-proof security.



## 5.2 Main uses in daily practical practice

### *Skull and brain injuries*

The surgery of the skull base defects requires in most of the cases the filling of bone defects with tailed bone grafts, followed by the suture and/or grafting of the dura mater and as previously described the application of a local agent, Surgicel being the most widely used.

Brain contusions require after excision of the necrotic tissues to apply some Surgicel if any small bleeding goes on, the best option being to obtain a very good hemostasis with nothing left in the remaining cavity.

Opened cranio-cerebral wounds must be cleaned with a non-aggressive product, and H<sub>2</sub>O<sub>2</sub> is still indicated in such circumstances.

### *Transphenoidal surgery*

Bleeding during pituitary surgery with a transphenoidal approach can lessen visibility, and this confined narrow route does not allow the use of electrocoagulation. The use of oxidized cellulose or glue is very useful. Ellgala, Maartens & Al 2002 have tested the use Floseal during 293 with a satisfying result.

### *Endoscopic surgery*

The endoscopic treatment of CSF leaks of the anterior skull base whatever their aetiology, includes the identification of the defect, the filling of the defect with a fragment of the medial turbinate fixed with bioglue followed by appliance of the rest of the pedicled turbinate below and oxidized cellulose (Surgicel) packing.

Same procedures using muscle or turbinate may be used if a leak occurs during an hypophysis surgery procedure, Surgicel being commonly used to maintain the devices and /or to reinforce hemostasis.

Some devices such as catheters are very useful in those deep tight fields.

### *Spine and spinal cord surgery*

Vertebral plexus are better controlled with local hemostatic agents. Fibrin glue is effective when the more common appliance of Surgicel is not effective (Sekhar, Natarajan & Al 2007)

Spinal cord tumors must be approached through laminotomy, the lamina section being done with a craniotomy. After retraction of the posterior arch flap, the extradural hemostasis must be perfect sometimes difficult due to epidural veins. Bipolar coagulation of the veins will be completed by appliance of small fragments of Surgicel, and bone wax on bone section the opening of the spinal cord is done under magnification. Surgicel application will help for hemostasis, the coagulation use being as restricted as possible.

After the tumour removal, no hemostatic agent should be left intradurally. The closing of the dura mater is seldom absolutely waterproof, and Surgicel and glue are commonly used to improve its quality (Lapierre 2009).

In other intra-dural spinal surgery one must avoid to let in situ any agent.

*Brain surgery*

From the extra-dural stage to the ending of the extradural hemostasis after the dura mater closure, local hemostatic agents have their place all along the procedure, to protect the brain, and to complete local hemostasis (Federspiel, Josephson & Al). In brain tumours, oxidized cellulose (surgical) is widely used, during the ablation of the tumour and at the end of the procedure to prevent and stop any bleeding in the remaining cavity whatever the type of tumor. One must be aware that it is still illegal to let products like Surgicel inside brain cavities, and inside the dura mater. Many physicians however will not take this in account considering the appliance of local agents on previously bleeding walls a better security for the patient. Tschan & Al 2010 have also evaluated the efficacy and safety of micropolysaccharide hemispheres (MPH) with no reported adverse effect. As soon as postoperative day 1, MPH were not detected anymore. There was no tumor mimicking enhancement. Many publications and everyone experience however report signal anomalies on post operative imagery mimicking residual tumour or early recurrence, or even an abcess, or a cotton pad when using Surgicel or gelatine sponge (Maurer, Ekholm & Al 1986)...This has led to some iterative unuseful surgery and even legacy. The histologic study only shows granuloma.

In aneurisms surgery, before the development of interventional radiology, aneurisms who could not be clipped were wrapped with muscle and hemostatic agents, unsuccessfully. Nowadays, surgery of aneurisms only requires hemostatic agents during the procedure to protect the brain and stop the faint bleedings coming from the neighbouring. Appliance of some small Surgicel pieces to the aneurism neck and clip may help to maintain the clip parallel to the vessel direction when releasing the retractors.

*Spinal surgery*

Local hemostatic agents have many indications in spinal surgery of all types, especially to ensure the epidural veins hemostasis.

They must not be left in contact with nerve roots intra or extradurally, due to the possibility of granuloma formation. Their presence is credited of the appearance of post-operative pain.

In case of epidural spontaneous hematomas they are very useful particularly if they are due to anti-coagulant accidents.

A randomized study performed in 127 patients by Renkens, Payner & Al 2001 comparing Floseal, microfibrillar collagen (Aviten) and fibrin glue showed the control of hemostasis in ten minutes for 97% of the cases with Floseal, and for 71% with the other agents.

## 6. Listing of main complications

*Stroke*

Is only reported when using hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). Mut, Yemisci & al 2009 reported one case in a patient, after which they performed an experimental study on mice brains using 3% H<sub>2</sub>O<sub>2</sub> solution. When H<sub>2</sub>O<sub>2</sub> was applied on the cortex, a vasoconstrictive response of all arteries and arterioles of the treated zone was observed, and after 15 seconds of exposure to H<sub>2</sub>O<sub>2</sub>, multiple bubbles were observed within the lumen of all subpial arteries when pial layer had been destroyed, or not.

Histology revealed the production of peroxynitrite, and the diffusion of H<sub>2</sub>O<sub>2</sub> through the superficial cortical layers. The addition of peroxide and H<sub>2</sub>O<sub>2</sub> resulted in platelet aggregation and acute thrombus formation. The combination of NO and H<sub>2</sub>O<sub>2</sub> is cytotoxic, and mediated by generated NO radicals. Among them, peroxynitrite is a potent and destructive oxidant, which may disrupt the blood-brain barrier.

Those data confirm that H<sub>2</sub>O<sub>2</sub> must only be used in the extra-dural space.

#### *Peripheral nerve impairment*

The potential effect of hemostatic agents on peripheral nerve function was suspected by clinical experience of postoperative local deficit or pain after the appliance of hemostatic agents in situ.

Experimental studies have been performed by Nagamatsu, Podratz & al 1996 and Alkan, Inat & al 2007.

The first used oxycel (OC) (Deseret medical, Becton Dickinson and Company, Sandy, Utah) for studies in vitro and in vivo in rats. In vitro, neurite outgrowth of the dorsal root ganglion neuron was inhibited after 15 minutes exposure

In vivo, the pH was lowered in the subperineurium, and remained low for 2 hours. The acidity of the oxidized cellulose is involved in the development of experimental neuropathy by OC. The direct application of OC to peripheral nerves must be avoided.

The second studied the effect of oxidized regenerated cellulose, gelatine sponge, bone wax and bovine collagen on the sciatic nerve of the rat, embedded in each substance. The compound action potential (CAP), and the nerve conduction velocity (NCV) were studied one hour and four weeks after the operation. In the bovine collagen and bone wax groups they were no statistically significant differences compared with initial control group.

In the gelatine sponge group, CAP was increased statistically significantly 4 weeks after surgery.

In the oxidized regenerated cellulose, NCV was significantly reduced, and the CAP increased 1 hour after surgery. No significant difference was seen after 4 weeks, but partial necrosis and walking disturbances were seen on the operated legs after 1 to 3 weeks.

Bovine collagen seems the most adapted for direct appliance to the nerves.

Intra-spinal retained Surgicel can induce radiculopathy (Partheni, Kalogheropoulou & Al 2006) and MRI studies could not exclude a post-operative hematoma, leading to reoperate the patient

#### *Granulomatous formations*

When left in the operative field, hemostatic agents may induce early or late tissue reactions and the formation of granulomas especially oxidized cellulose ( Voormolen, Ringers & Al 1987) . Kaymaz, Tokgoz & al 2005, in an experimental study in the rabbit brain report the modifications due to the application of oxidized cellulose and gelatine sponge. They observe on MRI a perilesional oedema in both series, while histopathology a tissue-degeneration more marked with the gelatine sponge use 24 hours after operation. In a rat brain neurosurgical model (228 animals), Erath, Schaff & Al 2008 studied Arista, Surgicel, Avitene,

Floseal or Kaolin (positive control) and showed the presence of residual material in all animals with Avitene, Surgicel and Floseal at day 14. Avitene and Floseal demonstrated a propensity for causing granuloma formation.

Apel-Sarid, Cochrane & Al 2010 report a pediatric case series of 3 patients: the 3 cases had intra cerebral surgery (2 for tumors ablations, and one focal dysplasia treatment). The local hemostatic used agent was microfibrillar collagen haemostat (Avitene). The three had a second surgery for new or recurrent seizures, and MRI exploration suspected either a tumour recurrence or an abscess. Histologically, the mixed inflammatory infiltrate was typified by the presence of Avitene-centric necrotizing granulomas surrounded by a palisade of macrophages and often several eosinophils.

So long, one must remain aware that the best behaviour is to remove any local hemostatic agent before closing the dura, if possible.

#### *Viral transmission*

With purified products, the risk of viral transmission has become very weak but is not totally missing, since all the products contain bovine components except for Vivostat. No recent report has been published yet. Virally inactivated human thrombin has replaced now bovine thrombin in most European products. (Buttusil 2003)

#### *Antibodies formation and immunologic concerns*

In the series of Renkens, Payner & Al 2001, at 6-8 weeks post operative evaluation of antibodies again bovine thrombin and bovine FactorVa demonstrated no statistical significance in the differences between treatment and control groups.

There was no evidence of antibody-related coagulopathy in either group. However, immunology mediated coagulopathy associated with exposure to bovine thrombin or to fibrin sealants containing this component is widely recognized. This component had to be replaced by human thrombin (Buttusil 2003). Bovine aprotinin (BA) may induce severe anaphylactic reactions, especially in patients previously treated with such products, suggesting that the use of a test dose should be proposed.

Crosseal A containing traneximic acid (TA) eliminates this risk, but is contraindicated for neurosurgery.

## **7. Financial point of view for hemostatic agents**

The most sophisticated they are, the most expensive. Anyway, the most daily used of all remain the oxidized cellulose, and the cost remains important. I should dare to add considering the glues that during the 15 years of my practice they did not exist. When they were available I have been using them for the ten following years.

After some warning about security, I stopped. The results remain identical during these three consecutive periods.

In developing countries, the price remains prohibitive, and in other countries, the local hemostatic agents are probably widely over-used. The indispensable devices remain electrocoagulation, Horsley wax, associated with a cautious and accurate surgery. The indication of local hemostatic agents must be evaluated in terms of risk-benefit for the

patient, and not considered as a comfort for the surgeon. Of course local hemostatic agents are useful in some cases, but must not be considered as compulsory in the daily practice.

## 8. Disclosure

The authors report no conflict of interest concerning the materials and devices described in this paper.

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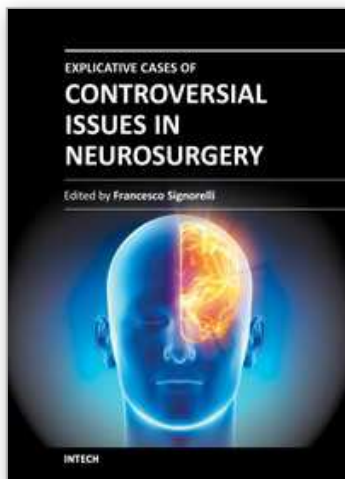
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