Single-arm, open-label, multicenter study to evaluate the safety and performance of Dura Sealant Patch in reducing CSF leakage following elective cranial surgery

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The objective of the study is to clinically assess the safety and performance of the Dura Sealant Patch as a means of reducing intra- as well as post-operative CSF leakage in patients undergoing elective cranial intradural surgery with a dural...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nervous system, skull and spine therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON48601

Source
ToetsingOnline

Brief title
ENCASE

Condition

- Nervous system, skull and spine therapeutic procedures

Synonym
brain fluid, CSF leakage

Research involving
Human

Sponsors and support

Primary sponsor: Polyganics BV, Groningen

Source(s) of monetary or material Support: Polyganics BV

Intervention

Keyword: dura mater, leakage, sealant

Outcome measures

Primary outcome

The primary endpoint is a combined endpoint of any neurosurgical events defined as:

Safety

1. Incidence of wound infection confirmed by increase of CRP and positive cultures up to 30 days after surgery;

Performance

2. Incidence of intra-operative CSF leakage after patch application at 20 cmH2O of Positive End Expiratory Pressure (PEEP);

3. Incidence of percutaneous CSF leak confirmed by *-2 transferrin test up to 30 days after surgery.

Secondary outcome

Safety

* Incidence of device related AEs throughout the study up to 90 days after surgery

* Incidence of device related AEs throughout the study up to 360 days after surgery

* Incidence of wound infection confirmed by increase of CRP and positive cultures up to 90 days after surgery

Performance

* Incidence of percutaneous CSF leak confirmed by *-2 transferrin test up to 90 days after surgery

* Incidence of pseudomeningocele with the need of puncture, external lumbar drainage or surgical evacuation as assessed by treating physician up to 90 days after surgery

* Incidence of pseudomeningocele >20 cc as confirmed on MRI

* Thickness of dura mater and Dura Sealant Patch (combined) in mm analyzed with MRI

Study description

Background summary

The dura mater is the dense, leathery membrane covering and protecting the brain and spinal cord. The dura is a collagenous connective tissue consisting of numerous collagen fibres, fibroblasts, and few elastic fibres arranged in a parallel form. Opening of the dura can be caused by several reasons. It occurs in 30% of neurosurgical procedures, both intracranial as spinal. Also, accidentally during some spinal procedures, where after surgery this defect needs to be closed. Finally, trauma capitis or spinal trauma may damage the dura mater.
The dura is marginally perfused with blood. Dura behaves totally different than other, better-perfused tissue, like muscle or fascia.During surgery, the temporary dry environment and the heat of the operation microscope cause the dura to shrink. This makes stitching the dura to close it often difficult which leads to suboptimal postoperative regeneration of the defect or even absence of regeneration. Especially in the elderly, dura can be paper thin and impossible to handle without damage. In case the dura is not closed watertight this can potentially cause complications. First, the Cerebrospinal Fluid (CSF) can accumulate under the skin (pseudomeningocele) which can hamper proper wound healing and cause complaints like pain. Secondly, it can leak outside through the wound (CSF leakage). This makes normal wound healing impossible. Both complications often lead to an extra intervention and longer stay of the patient in the hospital.

CSF leakage is one of the most common neurosurgical complications, occurring in 4-32% of surgical cases with a higher incidence in complicated skull base

surgery, intradural spine surgery and surgery of the posterior fossa.The likelihood of CSF leakage as a surgical complication can also depend on age, indication, location of surgery, and underlying pathology. Most patients with CSF leakage necessitate a prolonged hospital stay, antibiotic treatment for meningitis, external lumbar drainage, reoperation, or a combination of these measures. CSF leakage leads to significant patient burden and expense, with an estimated cost of 10,000*15,000 US dollars per patient per leakage.
The use of a dural sealant as an adjunct to primary dural closure is often assumed to have value for preventing CSF leakage; yet, few empirical reports describe such an effect.

In a systematic review on all available data in literature, twenty articles were included; ten of these were comparative studies (sealant versus no sealant) including 3 randomized controlled trials. In the 20 articles, a total of 3682 surgical procedures were reported. The number of CSF leakages in general did not differ between the sealant group (8.2%) and control group (8.4%), RR 0.84 (0.50-1.42), I2=56%. Exclusion of non-RCT*s did not alter the results. Meta-analyses for secondary outcomes showed no difference between number of incisional CSF leakage, RR 0.30 (0.05-1.59), I2=38% and pseudomeningocele formation, RR 1.50 (0.43-5.17), I2=0%. Surgical site infection was less seen in the sealant group (1.0%) compared to the control group (5.6%), RR 0.25 (0.13-0.48), I2=0%.

Closure of the dura involves several steps. First, the neurosurgeon tries to primarily close the dura with continuous or interrupted stitches. This is possible in 60-70% of intracranial cases and almost 95% of spinal intradural cases (only not in meningioma surgery where the dura is excised or in operations were surgeons on purpose had to increase the intradural space). Watertight closure of the dura is, without any augmentation, per definition not possible because of the puncture holes of the sutures. However, the dura has to be closed as watertight as possible. No protocols exist when to apply an extra substitute over a primarily closed dura instead of suturing only, this is dependent on personal feeling of the operating surgeon. If primary closure is impossible, an autograft (pericranium or muscle) [6] or allograft, xenograft or synthetic substitutes are sometimes sutured in the defect to reduce openings in the dura which are subsequently closed with a sealant. Native autologous tissue grafts can perform as good as dural substitutes because they do not provoke severe inflammatory or immunological reactions. Potential drawbacks in using autografts are: difficulty in achieving a watertight closure, formation of scar tissue, insufficiently accessible graft materials to close large dural defects, and potential additional incisions for harvesting the graft.
As alternative to the use of an autograft, a non-autologous (allograft) dural substitute can be used. Various xenografts have been studied for this purpose, including bovine and ovine pericardium, porcine small intestinal submucosa, and processed collagen matrices. However, these non-resorbable xenografts are often associated with adverse effects, such as graft dissolution, encapsulation, foreign body reaction, scarring, and adhesion formation.

If the quality of dural closure is improved, complications associated with CSF leakage, including meningitis, pseudomeningocele, impaired wound healing, and subgaleal fluid collection, could be reduced. CSF leakage leads to increased morbidity, prolongation of hospital stay, surgical revision, and enhanced costs as well as possible surgical revisions.

In daily practice, in approximately 25-50% of all intradural neurosurgical procedures, any adjunct to dural sealing with or without graft is used to prevent CSF leakage and to allow the dura to heal after surgery. This comes down to, in the Netherlands only, 4000-10.000 procedures per year (estimated).

Polyganics BV (medical technology company, Groningen, The Netherlands) has developed in close cooperation with the Brain Technology Institute (Neurosurgical Research Institute, Utrecht, The Netherlands) the Dura Sealant Patch for watertight dural closure after cranial surgery. This study will be conducted, first time in humans, to clinically assess the safety and performance of Dura Sealant Patch as a means to reduce CSF leakage after dural closure in patients undergoing cranial surgery.

Study objective

The objective of the study is to clinically assess the safety and performance of the Dura Sealant Patch as a means of reducing intra- as well as post-operative CSF leakage in patients undergoing elective cranial intradural surgery with a dural closure procedure.
Intra-operative CSF leakage is defined as:
CSF leakage after closure of the dura before placement of the bone flap while an elevated CSF pressure is induced.
Post-operative CSF leakage is defined as:
* percutaneous CSF leakage; leakage of CSF through the wound from the moment the wound is surgically fully closed until 90 days post-operative, and
* pseudomeningocele; accumulation of CSF under the skin from the moment the wound is surgically fully closed until 90 days post-operative.

Study design

This study will be conducted, first time in humans, to clinically assess the safety and performance of Dura Sealant Patch as a means to reduce CSF leakage after dural closure in patients undergoing cranial surgery.
The study will be conducted as an open-label, single-arm, multicenter study with a 360 days follow up. Up to 40 patients will be enrolled at up to 3 sites in Europe.

Intervention

Each subject will receive one (1) Dura Sealant Patch after closure of the dura

mater. The dura mater will be closed with suturing. If deemed necessary by the surgeon, a substitute (galea only) can be used.

Study burden and risks

Anticipated clinical benefits
In the current treatment of closure of dural opening after cranial surgery, there is no defined standard of care within neurosurgery. Both sealants as well as suturing only are treatments used. The added values of these different treatments are often assumed, but rarely well described in the literature. This is also reflected in no defined standard of care.
The investigational device adheres to the dura mater and provides a watertight closure bridging small gaps. This adhesion avoids posterior CSF leakage. Complications associated with CSF leakage, including meningitis, pseudomeningocele and impaired wound healing could be reduced.
The clinical benefit may be the reduction of the accompanied complications with CSF leakage. Another benefit may be the ease of use of the device as it can be applied directly out of the package without extra actions regarding preparation.
Anticipated adverse device effects
During the preclinical testing in animals (pigs), there were 2 observations in regards to a possible relation to the device, but had no clinical consequences to the animals.
Adverse device effects in humans could occur, which are not yet known.
Residual risks associated with the investigational device
Even though this is a novel medical device with regards to safety and use in the intended area, there is minor risk for extremely rare or unknown side effects developing from the treatment.
The individual components of the device are well known and used in other marketed products. The specific combination of components for the intended use of this product has been extensively tested through in vivo, in vitro and chemical testing.
However, there is still a residual risk that the barrier function of the device might not be sufficient to reduce occurrence or recurrence of CSF leakage. This residual risk will be mainly covered by lot release of the device, to ensure proper adhesion to the dura mater; as well as various validations such as packaging and sterilization, to ensure no loss of adhesion properties overtime.
Risks associated with participation in clinical investigation
The risks of the surgical procedure include post-operative complications, as well as any potential complications during the surgery which is performed under anesthesia. The risks include but are not limited to, infection, inflammation, discomfort at the surgical site, and neurological complications resulting from the procedure (none device related).
In terms of application of the device, the potential risks are mainly associated to untrained personnel, which will be covered by a device training to be completed by all participating surgeons and general personnel, clear labelling and by the provided IFU, before start of the study.
Possible interactions with concomitant medical treatment

Interactions with concomitant medications in humans are not known. However, in the in-vivo studies no interactions were reported.
Risk mitigation
Pre-clinical studies demonstrate the device performs as intended and meets the performance specifications including biological testing. This biological testing demonstrated that the product is biologically safe for implementation in humans and can be used as intended.
The clinical protocol incorporates several procedures to minimize the risks to subjects and to ensure the benefits of the clinical study outweigh its potential risks. These include:
* Subjects in the study will undergo frequent visits and routine medical follow-up to help detect any abnormal changes and to provide appropriate treatment if necessary.
* The study will be monitored to ensure the identification, documentation and analysis of adverse events; and to ensure compliance with the protocol and procedures that are in place for conducting research to protect the safety and well-being of all subjects.
* Surgeons will be experienced with dural closure methods and will receive training form the sponsor on device specific protocol.

Risk-to-benefit rationale
Based on preclinical studies, as well as the current known risks of dural closure methods, the risk to benefit ratio for using the Dura Sealant Patch is within reason for foreseeable risks. However, preclinical studies do not always predict the side effects humans may experience. Additionally, complications due to individual subject response to an implanted device may necessitate future dural closure procedures. Close observation and follow-up of patients is required as outlined in the protocol.
As previously mentioned, training procedures, lot release testing and various validations will minimize the risks to patients and ensure the benefits of the clinical use outweigh its potential risks. Since there is a low risk for safety issues related to the use of the device and the risk of CSF leakage can be reduced with this device post-operatively, the general safety risks associated with a surgical intervention are outweighed by the benefit of absence of post-operative CSF leakage.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Preoperative; Subjects who are able to provide a written informed consent prior to participating in the clinical investigation. Subjects who are * 18 years old. Subjects who are able to comply with the followup or other study requirements. Subjects who are planned for an elective intracranial intradural surgery in whom a dural incision of at least 2 cm in length is necessary, which will be closed. Female subjects of child bearing potential must agree to use any form of contraception from the time of signing the informed consent form through 90 days post-surgery. Intraoperative;
Surgical wound classification Class I/Clean. Minimally 5 mm of dural space surrounding dural opening.

Exclusion criteria

Preoperative; Female subjects who are pregnant or breastfeeding. Subjects with an assumed impaired coagulation due to medication or otherwise. Subjects suspected of an infection requiring antibiotics. Subjects with any type of dural diseases in planned dural closure area. Subjects requiring re-opening of planned surgical area within 90 days after surgery. Subjects requiring local radiotherapy in planned surgical area. Subjects with a known allergy to any of the components of the Dura Sealant Patch. Subject who previously participated in this study or any investigational drug or device study within 30 days of screening. Subjects with a presence of hydrocephalus. Subjects with contra-indication to MRI. Intraoperative; Subjects in

whom elevation of PEEP or pCO2 has a potential detrimental effect. Subjects who will require a CSF or wound drain, electrodes or other devices passing the dural layer or extra to intracranial bypass surgery. Primary closure of the dura mater with synthetic, non-autologous or autologous material other than galea. A gap > 3 mm after primary closure of the dura mater.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-10-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	Dura Sealant Patch
Registration:	No

Ethics review

Approved WMO Date:	16-08-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-03-2019
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03566602
CCMO	NL64477.041.18

Study results

Date completed:	29-04-2020
Actual enrolment:	31

Summary results
Trial is onging in other countries