Prospective, multicenter study to evaluate the Safety and performance of a syntHetic tissue sealant in reducing fluid lEakage following elective hepatobiLiary anD pancreatic Surgery

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The primary objective of the study is to demonstrate safety and performance in reducing intra- and post-operative leakage (bile and pancreatic juices) by using the Sealing Device in patients undergoing elective hepatic resection or distal...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON55236

Source
ToetsingOnline

Brief title
SHIELDS

Condition

- Hepatobiliary therapeutic procedures

Synonym
Fluid leakage following elective hepatobiliary and pancreatic surgery / leakage of bile and pancreatic juices after surgery

Research involving
Human

Sponsors and support

Primary sponsor: Polyganics BV, Groningen
Source(s) of monetary or material Support: Polyganics BV

Intervention

Keyword: Hepatobiliary & pancreatic surgery, Pre CE Mark, Reducing fluid leakage, Synthetic tissue sealant

Outcome measures

Primary outcome

Liver group

Incidence of post-operative bile leakage (ISGLS Bile leakage Grading Scale) [up

to day 30]

Pancreas group

Incidence of post-operative pancreatic juice leakage (ISGPS Grading Scale) [up

to day 30]

Secondary outcome

• Assessment of intra-operative control bleeding (Validated Intraoperative

Bleeding Scale developed by Lewis et al., 2016)

• Incidence of leak-associated comorbidities

• Incidence of re-intervention, transfusion, hospital stay, mortality

• Ease of use and application of Sealing Device

Additional for liver group

• Incidence of post-operative bile leakage [up to day 90 and 180]

• Incidence of post-operative bleeding (PHH) [up to day 30]

Additional for pancreas group

• Incidence of post-operative pancreatic juice leakage [up to day 90 and 180]

• Incidence of post-operative bleeding (PPH) [up to day 30]

Study description

Background summary

During and after Hepato-Pancreato-Biliary (HPB) surgery, surface related complications can occur such as leakage of bile and pancreatic juices and bleeding (Koyabashi 2016; De Boer 2012). During surgery, uncontrolled bleeding is one of the major complications that can influence both the surgeon*s ability to succeed in the surgery and the patient*s recovery (Schuhmacher 2015). Major complications post-operatively are leaking of bile and pancreatic juices into the abdominal cavity, which are directly related to other morbidities and mortality causing enlarged health care need. In the clinical field, the most important complications associated with HPB surgery are considered to be post-operative pancreatic juice leakage in pancreas surgery, post-operative bile leakage in liver surgery and intra-operative bleeding in liver surgery (Koch 2011; Koyabashi 2016). The most optimal management for treatment of bile leakage and bleeding associated with HPB surgery is still not defined (Fischer 2011).

Bile leakage can be classified into 3 grades (grade A or biochemical leak, grade B and grade C) depending on treatment requirement of the defect (Koch 2011). A bile leakage is defined as clinically relevant by Koch et al. if the bilirubin levels in the drained fluid is 3 times higher than the baseline in serum. Biochemical leak, previously known as grade A bile leakage, causes no change in patients* clinical management, while Grade B and C require respectively active therapeutic intervention or bile leakage relaparotomy (Koch 2011).
Pancreatic juices leakage is described and graded by Bassi et al. (2017). Their definition of clinically relevant pancreatic leakage is *a drain output of any measurable volume of fluid with an amylase level >3 times the upper limit of institutional normal serum amylase activity, associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula* and graded into biochemical leaks and Grade B and C pancreatic fistula*s, in which Grade B and C fistula*s require medical intervention (Bassi 2017). Bile or pancreatic leakage is currently mostly aimed to be prevented by administration of a sealant to the defect (Koyabashi 2016). Known fibrin sealants are considered ineffective as of the interference of the leaking fluids with the sealant components (i.e. ineffective sealing caused by

breakdown of the sealant and/or ineffective tissue adherence) (Figueras 2007). The interference of the leaking fluids with the hemostatic agents may lead to ineffective control of possible post-operative bleeding after placement (Schuhmacher 2015; Figueras 2007).

The solution would be a device to be placed on the wound surface of the liver or pancreas that prevents leakage of fluids (e.g. bile, pancreatic juices, blood) into the abdominal cavity. It should therefore withstand the interference of bile and pancreatic fluids that exits the damaged fluid channels in and around the liver and the resected surface of the pancreas. In this way minimal-moderate post-operative bleedings can be controlled as well. Polyganics has therefore developed the Sealing Device: a bioresorbable device that can reduce the leakage of fluids into the abdominal cavity after liver surgery and control minimal-moderate bleeding after HPB surgery. The primary mode of action of this device is the reduction of leakage of fluids from the site of surgery into the abdominal cavity after surgery. In addition, the product controls minimal to moderate bleeding after application. Target group for this device are currently patients scheduled for HPB surgery, which is represented by elective liver and pancreas surgery. The device should at least provide support during the critical wound healing period (up to 10 days after surgery).

Polyganics BV (Groningen, The Netherlands) , in close collaboration with University Hospital-Eppendorf (UKE) Hamburg, has developed the Sealing Device for use in hepato-pancreato-bilary (HPB) surgery to reduce leakage of fluids from the site of surgery into the abdominal cavity and as an adjunctive hemostatic device to control minimal to moderate bleeding at the surgical site. The Sealing Device has been challenged in pre-clinical testing (laboratory and in-vivo work), but has not been evaluated for safety and performance in humans.

This investigation will be conducted to clinically assess the safety and performance of Sealing Device as a means to reduce bile and pancreatic juice leakage in HPB surgery. Secondarily, the control of minimal to moderate bleeding will be assessed. To achieve adequate representation of the primary objective, the study will contain two separate surgical patient groups: Liver and Pancreas.

Study objective

The primary objective of the study is to demonstrate safety and performance in reducing intra- and post-operative leakage (bile and pancreatic juices) by using the Sealing Device in patients undergoing elective hepatic resection or distal pancreatectomy.

Study design

This first-in-human feasibility study will be conducted, first time in humans, to clinically assess the safety and performance of Sealing Device as a means to reduce intra- and post-operative leakage (bile, pancreatic juices and blood) in patients undergoing hepatobiliary or pancreatic surgery.
The study will be conducted as an open-label, single-arm, multicenter study with a 16 months follow up. Up to 80 patients (40 liver and 40 pancreas patients) will be enrolled at up to 7 sites in Europe. The first 10 patients (5 liver and 5 pancreas patients) will be part of the first phase (first-in-human) and will be enrolled sequentially with at least 72 hours between the surgeries. These 72 hours need to be free of device-related SAEs. In case a device-related SAE occurs, enrolment will continue after this SAE has been resolved. After the 10th patient has been discharged, an initial analysis of safety and performance will be performed up till the Discharge follow-up and communicated to the applicable authorities before enrolment is continued in Germany.
The list of participating sites will be maintained by Polyganics during the execution of the study, with the final list being part of the Clinical Study Report.
This study has been designed primarily to demonstrate safety and performance of the investigational device in HPB surgery to support the design dossier approval for CE-marking.
In this study, each subject will receive a maximum of three (3) Sealing Devices (10 x 5cm) on either liver or pancreas in one (1) procedure. The defect will be closed with standard of care method.
The assessments performed in this study as well as the time points are described in the flowchart (see section 1) and the accompanied description in section 6.2.
Based on clinical considerations and literature, a 30 day follow-up is widely regarded as a standard follow up period for most liver- and pancreatic operations and assessments. In order to add a safety margin on this standard follow up and considering the resorption profile of this device of 15 months, a total follow up period of 16 months is planned (15 months + 1 month safety margin). Follow-up of the subjects will be performed at 3 days, discharge, 30 days, 90 days, 180 days and 16 months after surgery.

Intervention

All surgeries must be recorded by video, to be able to assess bleeding rates and correct application of the devices. The following instructions for placement of the Sealing Device are mandatory for a successful result with the Sealing Device:

Pre-operative
1. Take the package with the Sealing Device out of the freezer at least 10 minutes and maximum of 8 hours, before use.
2. Immediately remove the outer box and keep the pouch closed until Sealing Device can be applied. For sterile transfer of the Sealing Device: only the product inside the transparent blister is sterile.

3. Per procedure, it is allowed to use up to 3 Sealing Devices of 10 x 5 cm simultaneously to cover the defect(s).

A. Intra-operative - liver
NOTE: The procedure should be filmed.
1. Liver defect should be closed with standard everyday method of the hospital, which should comply to the state of the art.
2. Rinse the liver surface from particles with physiological saline.
3. Liver surface should be moist (remove excessive fluid if applicable).
4. In case of bleeding, this should be controlled up to mild to moderate bleeding.
5. Open both the aluminum pouch and the inner blister (both are non-sterile).
6. DO NOT apply manual pressure on the Sealing Device before application (the white foam layer should not be compressed since it will not expand after being compressed and this impacts the adhesive function).
7. If the size of the liver defect is smaller than the Sealing Device, cut to the required size with an additional margin of at least 1 cm (this size is needed to ensure overlap of the device with the defect to ensure adhesive function).
8. NOTE: In case the defect is larger than the patch(es), apply the Sealing Device to the area(s) where you expect a bile leak with at least 1 cm overlap into the non-critical area. This critical area should be determined according to the standard practice at the hospital. At least approximately 80% of the total treated area should be covered with the device material (up to 3 devices maximally).
9. Cutting should be done by using a dry and sterile instrument (e.g. scissors).
10. Place the white side of the dry Sealing Device against the liver defect, without pre-moistening the patch.
a. Place on the liver defect
b. Cover at least 1 cm beyond the margins of the critical defect at all edges.
c. In case of misplacing, do not re-position the device but remove the device gently and use another immediately.
11. To position the Sealing Device correctly, compress the Sealing Device with the fingers onto the tissue; compression of the foam fixates the patch and is necessary for adhesion.
12. For an equal pressure distribution;
a. Use gauze and cover the complete Sealing Device with this gauze.
b. Hold down the Sealing Device with light pressure; for a minimum of one (1) minute.
13. Remove the light pressure and gauze carefully after at least one (1) minute. There is no residual product which needs to be removed since the entire Sealing Device will fully resorb.
14. In case the Sealing Device is (slightly) dislocated during application or partly insufficient pressure was applied, it might partly not adhere to the surface. In that case, the Sealing Device should be gently removed and replaced with a new Sealing Device.
15. Wrap up the surgery and close the wound with standard every day method of

the hospital, which should comply to the state of the art.

B. Intra-operative - advised application pancreas
NOTE: The entire procedure should be filmed.
1. The pancreatic stump should be closed with standard every day method of the hospital, which should comply to the state of the art. Please assess whether the margin between the defect and the portal vein is >=1 cm. If the margin is < 1 cm, the patient should be excluded.
2. Rinse the pancreatic stump resection surface from particles with physiological saline.
3. Pancreatic stump resection surface should be moist (remove excessive fluid if applicable).
4. In case of bleeding, this should be controlled up to mild to moderate bleeding.
5. Open both the aluminum pouch and the inner blister (both are non-sterile).
6. DO NOT apply manual pressure on the Sealing Device before application (the white foam layer should not be compressed since it will not expand after being compressed and this impacts the adhesive function).
7. If the size of the pancreatic stump resection defect is smaller than the Sealing Device, cut to the required size, with an additional margin of at least 1 cm (this size is needed to ensure overlap of the device with the defect to ensure adhesive function)
8. Cutting should be done by using a dry and sterile instrument (e.g. scissors).
9. Place the white side of the dry Sealing Device against the pancreatic stump resection surface, without pre-moistening the patch.
a. Place on the pancreatic stump resection surface, fold it from retro pancreatic over the stump and attach it to the pancreatic tissue directly.
b. Wrap a second patch around the first parch and the stump from ventral to dorsal side, adhering to the first patch and thus securing the edges of the patch.
c. Cover at least 1 cm beyond the margins of the defect at all edges.
d. In case of misplacing, do not re-position the device but remove the device and use another immediately.
10. To position the Sealing Device correctly, compress the Sealing Device with the fingers onto the tissue; compression of the foam fixates the patch and is necessary for adhesion.
11. For an equal pressure distribution;
a. Use gauze and cover the complete Sealing Devices with this gauze.
b. Hold down the Sealing Devices with light pressure; for a minimum of one (1) minute.
12. Remove the light pressure and gauze carefully after at least one (1) minute. There is no residual product which needs to be removed since the entire Sealing Device will fully resorb.
13. In case the Sealing Device is (slightly) dislocated during application or partly insufficient pressure was applied, it might partly not adhere to the surface. In that case, the Sealing Device should be removed and replaced with a

new Sealing Device.
14. Wrap up the surgery and close the wound with standard every method of the hospital, which should comply to the state of the art.

Study burden and risks

A risk analysis according to the ISO 14971:2007 - Application of risk management to medical devices, has been conducted. Risks are minimized or eliminated through appropriate design control, confirmed by pre-clinical bench, laboratory and animal testing.

In the current treatment of closure after liver or pancreas surgery, there is no defined standard of care within general surgery. Adjuncts as well as suturing, stapling or other methods are treatments used for closure of resected organ surfaces after liver- or pancreas surgery. The added values of these different treatments are often assumed, but rarely well described in the literature as outcomes are inconclusive. This is also reflected in no Consensus with regards to defined standard of care for closure of resected organ surfaces in liver- or pancreas surgery.
The clinical benefit of the Sealing Device for the patient is expected to be the reduction of post-operative leakage after HPB surgery and therefore accompanied complications such as inflammation and fever. This is achieved by formation of a physical barrier after applying the Sealing Device on the surgical wound. This is supported by pre-clinical animal (porcine) study results with a bile leakage model and a pancreas leakage model developed by the University of Hamburg and a modified hemostasis model in the liver. Briefly, the bile leakage study demonstrated that in 16,7% of the animals a bile leak was observed compared to 83.3% of the animals in the control group (Veriset, Medtronic) after 7 days follow-up. The pancreas leakage study demonstrated that no clinically relevant leakage was observed as there were no signs of pancreatitis, severe adhesion or hematoma in the Sealing Device group, which were however observed in the control group (Veriset, Medtronic) during necropsy after 14 days follow-up. The hemostasis study indicated that the Sealing Device outperformed the controls (Veriset, Medtronic and Tachosil, Takeda/Baxter) in a heparinized porcine bleeding model for intra-operative bleeding control as well as post-operative bleeding control (72 hours follow-up). There were no device-related Adverse Events regarding the Sealing Device in both studies. Another benefit is the ease of use of the device as it can be applied directly out of the package without extra actions regarding preparation, which has been confirmed in a usability study addressing application of the Sealing Device in open (manual) fashion.

The potential risks of the device are covered through the harm list in the table below, describing the residual occurrence of each potential effect to the patient.
Harm Severity Residual occurrence
1 Allergic reaction Severe Improbable

2 Carcinoma formation Severe Improbable
3 Infection Severe Improbable
4 Organ fluid leakage Severe Remote
5 Re-bleeding Severe Improbable
6 Inflammation/irritation Moderate Remote
7 Systemic toxicity Moderate Remote
8 Lengthened procedure Limited Improbable
9 Pain Limited Improbable
10 Tissue adhesions Limited Improbable
11 Customer dissatisfaction Negligible Occasional
12 No effect Negligible Remote
13 Unknown Unknown Occasional

Although this is a novel medical device with regard to safety and intended area of use, there is minor risk for side effects developing from the treatment.
The individual components of the device are developed and selected to be biocompatible and the specific combination of components for the intended use of this product has been and is currently being extensively tested through in vivo, in vitro and chemical testing.
During preclinical testing in an intramuscular rabbit implantation model, the Sealing Device showed a moderate tissue reaction compared to high density polyethylene (HDPE) controls after 4, 13, 26, 40 67 weeks. When compared with the control Tachosil®, the Sealing Device demonstrated no reaction to the tissue after 4 weeks, slight reaction after 13 weeks and moderate reaction after 26 and 40 weeks. The Sealing Device displayed comparable moderate signs of resorption at 4 and 13 weeks, while it appeared slightly more resorbed at 26 and 40 weeks. These differences in tissue reaction can be expected, as Tachosil® is a collagen that is prone for assimilation (scaffolding) as opposed to the Sealing device, which is a biodegradable product. At 67 weeks, it was markedly degraded with more than 90% material degradation. Slight to moderate mineralization at 13 and 26 weeks was observed. However, a trend toward reversibility of the mineralization was observed at 40 weeks and the reversibility was confirmed after 67 weeks of implantation. The signs of mineralization were localized, not extensive, temporary, and not coupled with remarkable degenerative, fibrotic and encapsulation process. Similar extent of dystrophic mineralization was also observed with the control article at 4 weeks before being completely resorbed with no side effects left. Intramuscular implantation is associated with more intense tissue reaction than subcutaneous implantation. Comparable degradation was observed in an in vivo degradation study in a superficial liver defect model (Aachener mini pig) after 56 weeks follow-up. Next to the possibility of some local tissue reaction generally associated with implants, other anticipated adverse device events are those generally recognized for implantable devices such as allergic reactions and procedure related infections.
There is a residual risk that the Sealing Device is not functioning as intended. From a design point of view, this residual risk will be mitigated and controlled by lot release of the device and design verification, including

stability testing and animal performance testing as previously described to ensure proper adherence and barrier functionality.
At the same time, from an application point of view, the physicians will be properly trained before being allowed to use the device. The device will be accompanied by a clinical IFU and label.

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, leakage, 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 leading to improper placement or use of the device, which will be mitigated by device training to be completed by all participating surgeons and general personnel, clear labelling and by the provided IFU, before study start.

As previously mentioned, training procedures, lot release testing and various device validations will minimize the risks to patients and ensure the benefits of the clinical use outweigh those potential risks. Since there is a low risk for safety issues related to the use of the device and the risk of post-operative leakage (bile, pancreatic juice and blood) can be reduced with this device, the general safety risks associated with a surgical intervention are outweighed by the benefit of reducing of post-operative leakage (bile, pancreatic juice and blood) in HPB surgery.

Contacts

Public
Polyganics BV, Groningen

Rozenburglaan 15A
DL Groningen 9727
NL
Scientific
Polyganics BV, Groningen

Rozenburglaan 15A
DL Groningen 9727
NL

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 follow-up or other study requirements
- Subjects who are planned for an elective hepatic resection surgery or elective distal pancreatectomy surgery

Intraoperative
- Patch is applied manually (during open procedure, conversion procedure, or laparoscopic assisted procedure)

Exclusion criteria

Preoperative
- Female subjects who are pregnant and/or breastfeeding
- Subjects with a known allergy to any of the components of the Sealing Device (Polyurethane sheet with DC-Green #6 dye and Polyurethane matrix foam with 8-Arm-PEG40k succinimidyl carbonate adhesive and Disodium Hydrogen Phosphate)
- Subjects with bleeding disorders requiring anti-coagulation medication (except acetylsalicylic acid)
- Subjects who receive double-anti coagulation
- Subjects who receive peritoneal dialysis
- Subjects with a presence of systemic infection
- Subjects who previously participated in this study, or in any investigational drug- or device study within 30 days of screening
- Subjects who previously required liver transplantation

- Subjects undergoing a procedure requiring an anastomosis (e.g. Klatskin tumours or Whipple)

Additional for liver group
- Subjects with liver cirrhosis Grade C on the Child-Turcotte-Pugh score

Intraoperative
- Subjects with multivisceral resections, except resection of spleen

NOTE: multivisceral resections are defined when, in addition to resection of liver or pancreas, any of the following organs are resected:
- Intestine/bowel
- Liver (if resection is more than a biopsy), when patient is to be included in the pancreas group
- Pancreas (if resection is more than a biopsy), when patient is to be included in the liver group

- Not able to apply the patch(es) according to the instructions for use
- Total surgery requiring > 3 HPB Sealing Devices of 10 x 5 cm (which equals a resection surface of more than 88 cm2)

Additional for liver group
- Subjects with a Grade 3 or 4 bleeding after liver transection (Lewis 2016)
- Subjects with liver cirrhosis Grade C on the Child-Turcotte-Pugh score

Additional for pancreas group
- A margin of <1 cm between the defect and the portal vein

NOTE: The margin is intended to ensure sufficient normal tissue is left of the pancreatic stump to be able to have a 1 cm overlap of the device on the tissue of the pancreas. There is no contra-indication of the device with regards to placement on veins, as indicated in the Instructions For Use where no contra-indications for the device have been identified. Therefore, as long as there is 1 cm tissue on the pancreatic stump left for overlap of the device, the patient can be included into the study based upon this criterium.

Study design

Design

Study type: Interventional
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-02-2021
Enrollment:	12
Type:	Actual

Medical products/devices used

Generic name:	Sealing Device
Registration:	No

Ethics review

Approved WMO Date:	15-01-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NCT04024956
CCMO	NL71140.018.20