PREventing Surgical Site occurrences using negative pressURE wound therapy

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Primary Objective: Primary objective of this trial will be to determine whether iNPWT reduces the number of patients with clinically relevant* SSOs after (potentially) contaminated ventral hernia repair

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Abdominal hernias and other abdominal wall conditions
Study type	Interventional

Summary

ID

NL-OMON56300

Source
ToetsingOnline

Brief title
The PRESSURE Trial

Condition

- Abdominal hernias and other abdominal wall conditions
- Bacterial infectious disorders
- Skin and subcutaneous tissue therapeutic procedures

Synonym
incisional hernia, Ventral abdominal wall hernia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: De studie betreft een investigator-initiated studie. De onderzoeksgroep krijgt het materiaal kosteloos verstrekt.

Intervention

Keyword: contaminated abdominal wall reconstruction, incisional negative pressure wound therapy, surgical site occurrences, ventral hernia repair

Outcome measures

Primary outcome

Primary outcome of the PRESSURE trial will be the percentage of patients with clinically relevant* SSO <30 days after surgery.

*A SSO is considered clinically relevant when the attending physician considers the SSO of being of such severity that it needs further action for purposes of clinical diagnosis (other than clinical examination) or treatment, such as ultrasound/CT, antibiotics, drainage or surgery. Imaging will only be counted if followed by an intervention. The term *attending physician* is interpreted to mean the surgeon(s), infectious disease specialist, other physician on the case, emergency physician or physician*s designee (nurse practitioner or physician*s assistant).

For the primary outcome, the following complications are considered SSO:

• Superficial SSI as defined by the CDC, but with the minor modification that opening of the wound doesn*t count as SSI when not being proven by culture. Cultures are imperative upon opening of the wound by clinicians58:

Infection of skin and subcutaneous tissue of the incision

AND the patient has at least one of the following:

a. Purulent drainage from the incision

b. Organisms identified from an aseptically obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment. Patients will be instructed by the investigators to inform their clinical caretakers that their wounds may ONLY be opened when an aseptically obtained specimen is taken from their incision as well.

AND

The patient has at least one of the following signs of symptoms: pain

or

tenderness; localized swelling; erythema; or heat. A culture or

non-culture

based test that has a negative finding does not meet this criterion.

d. Diagnosis of a superficial incisional SSI by the attending physician

or other designee.

When superficial SSI is diagnosed it is determined whether the superficial SSI is accompanied by clinically relevant dehiscence or not, which is registered afterwards.

• Deep incisional SSI defined by the CDC, but with the minor modification that opening of the wound doesn*t count as SSI when not being proven by culture. Cultures are imperative upon opening of the wound by clinicians58:

Infection involves deep soft tissues of the incision (e.g., fascial and muscle layers)

AND

Patient has at least one of the following:

a. Purulent drainage from the deep incision.

b. A deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, attending physician or other designee and organism is identified by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (e.g., not Active Surveillance Culture/Testing (ASC/AST). Cultures are imperative upon opening of the wound. When a wound dehisces and culture is negative it will be recorded not as SSI but as wound dehiscence.

AND

Patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture or non-culture based test that has a negative finding does not meet this criterion.

c. An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical, histopathologic exam, or imaging test

• Wound cellulitis

Defined as wound erythema treated with antibiotics without requiring manipulation or opening of the incision

• Wound dehiscence

Defined as the splitting apart of the margins of the wound in the absence of meeting SSI criteria, for which action has been undertaken (e.g. surgery)

• Enterocutaneous fistulae

Defined as a connection between bowel and abdominal wall not deliberately created during surgery

• Seroma

Defined as a seroma for which action has been undertaken (e.g. drainage/imaging, etc)

• Hematoma

Defined as a hematoma for which action has been undertaken (e.g. drainage/imaging, etc)

• Skin ischemia/necrosis

Defined as signs of ischemia (the six P*s: pain, pallor, pulseless, paraesthesia, paralysis, poikilothermia (not being able to regulate temperature)

SSO monitoring

Monitoring will take place with active patient-based surveillance by a combination of ante- and post-discharge surveillance methods:

• Examination by the physician during admission and after discharge in the outpatient clinic at post-operative day 30

• Review of medical records

• In case of suspicion of SSO after discharge the patient will be assessed in the outpatient clinic. Control patients will undergo the same amount of planned evaluations for SSO as the intervention group in order to prevent bias.

Secondary outcome

The following secondary outcomes will be assessed in the outpatient clinic at 30 and 90 days and 1 year after surgery:

• The individual components of SSO at <30, <90, <1 year after surgery as defined above

• Recurrence at 1 year after surgery (= hernia recurrence + bulging)

Clinically relevant bulging will be defined as bulging, in absence of incisional hernia recurrence, of such a severity that it is an indication for surgery. For hernia recurrence we propose using the definition of the European Hernia Society (EHS): **any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging.** Hernia recurrence will be proven upon clinical suspicion using ultrasound or CT imaging as is current standard practice.

• The percentage of patients with any signs of SSO yes/no on photographs

Patients will be asked to take photos of their abdomens and wound upon removal of the iNPWT/conventional dressing at post-operative day 7 and every week thereafter and when they present themselves for assessment using standardized instructions (allows for blinded outcome assessment).
Smartphone ownership is suspected to be high among patients. Furthermore, smartphone camera quality has been shown to be comparable to regular consumer level digital cameras in the last several years.59 The photos will be uploaded using the Castor electronic data capture system63, which is a fully certified data center (ISO 27001:2013, ISO 9001 and NEN7510), and is the same electronic data capture system that will be used for the rest of the data collection.

• Peri-incisional SSO

Defined as surgical site occurrences, as defined for our primary outcome, of the incisional area only.
It seems logical to assume iNPWT mainly acts on tissue in proximity of the iNPWT, while further lateral in the abdominal wall there is no to little effect. This notion is also substantiated by a retrospective study from our institute where the effect of the intervention was predominant in tissue beneath the iNPWT dressing.63 This is important to consider because abdominal wall surgery frequently involves surgery of abdominal wall areas unable to receive iNPWT, increasing the risk of developing SSO in these areas. By looking only at overall SSO, SSO in these areas may cloud detection of the effect of iNPWT on the tissue that actually received treatment with the investigational

intervention.

• Skin closure at post-op day 30 on photograph

Skin closure will be defined as complete re-epithelialization throughout the incision.

• Scar quality on photograph at 1 year postoperative using a Visual Analog Score and blinded outcome assessment60

• Frequency and type of procedures related to SSO

Surgical procedures, percutaneous drainage, diagnostic procedures (e.g. CT/ultrasound, wound culture) will be registered as a way to quantify wound morbidity.

• Hospital stay after surgery in days

• Emergency department visits after discharge

• Readmission within 30 days, 90 days and within a year for any complication

• 30-day, 90-day, in-hospital and 1-year mortality

• Non SSO-complications

Complications as pneumonia, ileus, AKI, IAH/ACS and thrombo-embolic events will be registered as well and graded according to the Clavien-Dindo classification as modified by the European Hernia Society.

• Quality of life pre-operatively and at 1 year postoperatively using the EQ5D-5L questionnaire

• Cost-effectiveness 1 year after surgery (see cost protocol)

Study description

Background summary

In a 2010 article, the Ventral Hernia Working Group stated that primary outcomes in ventral hernia repair are considered to be hernia recurrence as well as surgical site occurrences (SSO), because of their significant influence on recurrence.1 With an incidence of 38% and 49% in Ventral Hernia Working Group grade 3 and 4, SSOs are an excessively frequent problem in abdominal wall reconstruction.2 Unfortunately, SSOs lack a clear definition in the literature.3 Nevertheless, in the chapter *Managing Complications of Open Hernia Repair* of the recently published book *Hernia Surgery - Current Principles* from Novitsky4, the following short term complications regarding the surgical site are mentioned:

• SSI as defined by the CDC5
• SSI as in wound cellulitis (as in wound erythema treated with antibiotics without requiring manipulation or opening of the incision, falls out of the current CDC SSI criteria)
• Wound dehiscence
• Enterocutaneous fistulae
• Seroma
• Hematoma
• Skin ischemia/necrosis

Of these SSOs, SSI has been shown to be the most significant predictor of recurrence, with recurrence of up to 80% compared with 34% for those without SSI.6,7 It is also the most common reason for hospital readmission following open ventral hernia surgery.8-10 Although data about the costs of SSO as a whole are lacking, a Centers for Disease Control and Prevention health care survey found roughly 157,500 SSI*s associated with inpatient operations of the general population in 2011 in the United States.11 With an average attributable financial cost of SSI of $20,785 per case, this leads to an overwhelming $3,273,637,500 annually for the United States alone.12 Strikingly, SSI is associated with mortality, which is 3% in all of surgical patients. Because of the frequent co-morbidities in this field, it is likely to be much higher in ventral hernia repair. Furthermore, studies with long-term follow-up have demonstrated a dramatic increase in recurrence rate after SSI.9,13,14 Another particular frustrating complication following ventral hernia repair are seromas, with a prevalence proven to be as high as 100% on routine ultrasound exams postoperatively.15 Although not all seromas are clinically relevant, seromas can be a bothersome postoperative problem. Furthermore, seromas may prevent the ingrowth of mesh and thus add to the risk of recurrence, and may become inoculated with bacteria through the surgical wound or iatrogenically from repeat fluid aspirations.15

Since 2006, negative pressure wound therapy (NPWT) has been applied on surgical incisions (incisional NPWT, in short iNPWT) in order to reduce the amount of SSOs, with promising results in the literature.16-21 iNPWT is also known as prophylactic negative pressure wound therapy (pNPWT) and closed incision management (CIM).

Although to some it might seem counter-intuitive to apply negative pressure wound therapy to a primarily *closed* wound, one should consider that strictly seen, the wound is still open. Indeed, no matter how perfectly restored the underlying tissues may be, a wound should be considered to be really closed only if restoration of an intact epidermal barrier, called *re-epithelialization*, has been established.22 To ascertain this, wound healing occurs through several overlapping phases: hemostasis, inflammation, proliferation and maturation.23 Only in the proliferative phase, which just starts on day two after injury and normally lasts up to 3 weeks in the normal cutaneous wound, re-epithelialization occurs.22

Considering this, primary *closed* surgical incisions are actually open wounds for a considerable amount of time, albeit relatively small ones compared to non-surgically closed wounds, for which NPWT was used originally.24 Yet, for the past decades, the mainstay of incisional wound care has been an simple adhesive gauze based dressing, and it currently still is (although use of wound glue as a dressing is rising in the UK).25,26 Remarkable in this context, one study has shown that bacteria are able to penetrate even up to 64 layers of gauze dressing.27

iNPWT devices generally consist out of foam, adhesive drapes and a vacuum pump with connected tubing. The working mechanism roughly consists of two components: on the one hand by applying subatmospheric (also called *negative*) pressure on the wound, on the other by creating a barrier between the wound and the external environment with the adhesive film.

The negative pressure has several supposed working mechanisms: it approximates the underlying tissue and skin edges, thus reducing any dead space (which makes the micro-environment of the wound less susceptible for microbial proliferation). Furthermore, the negative pressure reduces lateral stress28, reducing the risk of dehiscence. Perfusion has been measured to be increased, possibly providing in the raised need for oxygen in a healing wound.29 Moreover, it removes any excess fluid, which benefits oxygenation and healing as well30, and results in less, and smaller seromas.31

Additionally to the benefits of negative pressure, the barrier provided by the adhesive film reduces the risk of external contamination into the wound, resulting in less contamination with skin flora.32 The barrier also prevents evaporation, thus keeping the wound moist, which is thought to accelerate healing.33
Altogether, it seems that iNPWT is a promising technique for reducing surgical site complications, hospitalization length, as well as costs. Nonetheless, although several randomized controlled trials have been conducted in clean orthopedic surgery34-38, no RCTs have compared iNPWT with conventional dressings in contaminated surgery up to our knowledge.

We hypothesize that iNPWT reduces the incidence of SSOs, length of stay, readmission and costs in contaminated abdominal wall reconstruction.

Study objective

Primary Objective:

Primary objective of this trial will be to determine whether iNPWT reduces the number of patients with clinically relevant* SSOs after (potentially) contaminated ventral hernia repair <30 days after surgery.

*A SSO is considered clinically relevant when the attending physician considers the SSO of being of such severity that it needs further action for purposes of clinical diagnosis (other than clinical examination) or treatment, such as ultrasound/CT, antibiotics, drainage or surgery. Imaging will only be counted if followed by an intervention. The term *attending physician* is interpreted to mean the surgeon(s), infectious disease specialist, other physician on the case, emergency physician or physician*s designee (nurse practitioner or physician*s assistant).

Secondary Objective(s):

Secondary objectives are:
- to determine whether iNPWT reduces the amount of SSOs and its individual components <90 days and 1 year after surgery
- to investigate whether it leads to less clinically relevant bulging or hernia recurrence 1 year postoperatively
- to investigate if it reduces the need of interventions for SSO
- to investigate whether iNPWT reduces length of stay after surgery, emergency department visits and readmissions after discharge
- to investigate whether it leads to a better quality of life for hernia patients 1 year after surgery.
- to investigate whether it is cost-effective in contaminated abdominal wall reconstruction

Study design

STUDY DESIGN

This study will be a investigator-initiated, multinational, multicenter, randomized controlled clinical trial in our collaborative international network with superiority design, in which eligible patients will be randomized to receive iNPWT or a wound dressing as according to local hospital policy (a pragmatic approach) using block randomization and stratification based on hospital site while using an open label design for the primary outcome (presence of SSO <30 days). Prolonged follow-up will be at <90 days and <1 year postoperative.

Apart from the open label primary outcome, we propose blinded outcome assessment of photographs taken from the abdomens of patients for assessment of SSO as can be judged by photograph. For example, patients may be instructed to take a photograph of their abdomen every following week after surgery (post-op day 7, 14, etc) for up to one month, and when they present themselves for assessment. If these results point in the direction of the open label primary outcome results this will be a strong argument for our study.

The duration of the study is estimated to be 2,5 years.

It will be ensured that the study protocol will adhere to the SPIRIT statement regarding interventional trials. Trial registration will occur at Clinicaltrials.gov as well as TrialRegister.nl.

Intervention

Patients participating in this trial will be randomized to:

Treatment group A

The intervention group will receive a commercially available Prevena* Incision Management System (Kinetic Concepts Inc. (Acelity), San Antonio, TX, USA), placed in sterile conditions after closure of the skin during surgery. The interventional product will remain in situ for 7 consecutive days postoperatively at -125 mm Hg continuous subatmospheric pressure, irrespective of hospital discharge.

This device has been tested both in non-clinical as clinical studies and is already in use in the coordinating center (Academic Medical Center - The Netherlands) in patients undergoing abdominal wall reconstruction.

Any concern about the wound or device will require removal of iNPWT earlier than planned and will be recorded as a secondary endpoint of the trial.

Treatment group B

The control group will receive conventional wound dressings, defined as a simple, sterile, gauze based dressing, as is locally available and routinely used at the participating center.

Moreover, participating sites and patients will be instructed to not manipulate or touch the wound when not strictly indicated for clinical purposes, and to not remove the dressing (e.g. for inspection) unless it is clearly indicated, or soaked by wound exsudate.

By demanding the dressing to be a simple gauze based dressing, we presume no large confounding factors will be present. Moreover, according to a Cochrane review recently updated in December 2016, there is no evidence to conclude one wound dressing is superior over any other in preventing SSI at this moment.43 Nonetheless, advanced dressings (e.g. vapour-permeable films, hydrocolloid dressings, fibrous hydrocolloid dressing, polyurethane matrix hydrocolloid, wound glue or antimicrobial dressings) are excluded. Furthermore, realizing a uniform dressing for all patients may prove difficult because this will be an international trial in various hospitals whose material departments may not have the same dressing available.

Study burden and risks

In general, iNPWT is tolerated well by patients and is considered to be safe.13

Although one study36 has described blister formation after the application of iNPWT, no other studies have reported replicating this finding. With an adequate placement technique, blisters have not been seen.

In theory it is also possible that placement of iNPWT amplifies bleeding in case of inadequate hemostasis at the incisional site. However, in case of bleeding, the iNPWT will be removed immediately. Furthermore, the iNPWT units

contain an acrylic adhesive coating and a skin interface layer with silver, which may present a risk of an adverse reaction in patients who are allergic or hypersensitive to acrylic adhesives or silver. Additionally, the iNPWT dressing contains silver that may impair visualization with certain imaging modalities. The dressing may also impair visual inspection during the first 7 days.

Nevertheless, iNPWT has been shown to be a safe intervention in several systematic reviews, where the risks described above were not designated to be a problem.14,57 However, iNPWT does appear to decrease SSI, and possibly other SSO as well.57

Patients will be asked to take photographs of their abdomen and wound 7 days after surgery and every week thereafter the first month, when they present themselves for assessment, as well as after three months and after 1 year.

Participants will be asked to fill out the EQ5D questionnaire pre-operatively, one and three months postoperatively and 1 year postoperatively. Furthermore, after three months and after one year patients will be asked to fill out two questionnaires to assess cost-effectiveness.

Patients will also be asked to fill out the POSAS 2.0 questionnaire 1 month, 3 months and 1 year postoperatively.

Clinical evaluation of patients for SSO and hernia recurrence is part of routine clinical care and therefore is not viewed as a study procedure.

Outside of the procedures described above, no invasive procedures, laboratory tests or psychological/psychiatric evaluations will be performed outside of routine clinical care.

Informed consent will be obtained from every patient.

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

In order to participate in this trial, a subject must meet the following criteria:
• >=18 years
• Informed consent
• Pre-operative CT available (< 12 months of surgery)
• Scheduled for elective, open abdominal wall reconstruction*, And one of the following:
• A stoma** or enterocutaneous fistula and an abdominal wall defect*** of >6 cm**** on CT
• Violation of the gastrointestinal tract and an abdominal wall defect of >6 cm on CT
• Infected or exposed mesh (any size)
• Open abdomens with contamination***** (any size), * Operative treatments may include transversus abdominis release, endoscopic external oblique release or open external oblique release, as long as the abdominal wall reconstruction is open. Reconstructions incorporating the pedicled or free transfer of tissue (e.g. an antero-lateral thigh or latissimus dorsi flap) are included as well.
, ** This includes jejunostomy, ileostomy, colostomy and Bricker stomata. ,
*** Abdominal wall defect is defined as:
**any abdominal wall gap with or without a bulge perceptible by imaging*
This definition is a modification of the definition proposed by the EHS for incisional hernia recurrence., ****In case of parastomal hernia and the patient is candidate for ostomy takedown or relocation, the resulting defect in the abdominal wall should be taken for this measure, ***** Contamination is defined as CDC Surgical Wound Class II (potentially contaminated) to IV

(dirty/infected).

Exclusion criteria

• Patients <18
• Parastomal hernias planned for reconstruction using a local (or laparoscopic) approach without a laparotomy*, *In case of a patient scheduled for reconstruction of both incisional hernia and a parastomal hernia, the reconstruction of the incisional hernia will be eligible for randomization. If a parastomal hernia is approached through a laparotomy, the laparotomy incision will be eligible for randomization.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-09-2018
Enrollment:	190
Type:	Actual

Medical products/devices used

Generic name:	incisional negative pressure wound therapy
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	18-04-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2021

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

ID: 22141
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL60054.018.16
OMON	NL-OMON22141