Vacuum assisted closure versus on-demand relaparotomi in patients with fecal or diffuse peritonitis: A randomized multicenter study (VACOR-Trial)

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Project group

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1. BACKGROUND

Secondary peritonitis due to perforation of a hollow organ is the most common type of peritonitis (1,2). The most common causes of perforation are appendicitis, anastomosis leakage after surgery, intestinal ischemia, peridivericulitis, perforated ulcer or trauma (3-7). Perforation of the colon is most frequent (6-7). Fecal peritonitis is associated with high mortality and morbidity. Hospital mortality is up to 20%, rising to 32% after 6 months (8). Mortality in patients with secondary peritonitis is dependent on age, comorbidity, infection focus, time to intervention and the extent of peritonitis (7,9-14).

The primary treatment is source-control surgery, supported by intensive treatment and antibiotics (15,16). In the aftermath one can choose between several surgical treatment modalities. The first are primary closure of the abdomen with either replarotomy on-demand (ROD) or planned relaparatomy (PR) (17,18). A third is open abdomen (OA) with scheduled abdominal remediation at 2-3-day intervals until the inflammation is under control (5,16,18,19). Then, if possible, the abdominal wall can be closed either gradually or in a single session (2,5).

Van-Ruler et. al showed in their study no significant difference in mortality and morbidity in a randomized study with patients having diffuse peritonitis where PR and ROD were compared. ROD resulted in significantly fewer relaparotomies and reduced medical costs (15,17).

With an OA, a temporary closure (20-22) is used. Open abdomen can be applied in various ways, divided into non-negative pressure wound therapy (non-NPWT) and negative pressure wound therapy (NPWT) (5.23). NPWT, also referred to as Vaccum Assisted Closure (VAC®), is the most widely used procedure with commercially developed and approved equipment routinely used in the clinics (5). Several prospective studies have shown that VAC is a safe treatment option in patients with secondary peritonitis (24-31).

The OA approach to severe secondary peritonitis may be necessary for three different reasons: insufficient control of source of infection, severe physiological deterioration, and prevention of abdominal compartment syndrome (5,25,32,33).

Abdominal sepsis results in a strong immunological response via the release of cytokines into the abdominal cavity (34). Inability to control or disrupt the local inflammatory response is associated with increased mortality in these patients (16). Animal experimental studies suggest that NPTW treatment induces systemic inflammation suppression while counteracting multi-organ failure, by draining the peritoneal fluid, thus reducing cytokine strain (35.36). In the only human study by Kirkpatrick et al. a reduced mortality was observed in the NPWT group, without demonstrating any effect on systemic inflammation, the exact physiological role of NPWT treatment has not yet been adequately elucidated (37).

There are several studies showing decreased mortality and morbidity in peritonitis patients treated with NPWT compared to non-NPWT (23,34,37-40). In the studies mentioned, lower incidence of ventral hernia, entero-atmospheric fistulas and, in addition, lower mortality in the group treated with NPWT are described.

NPWT with "fascial traction" has been found to be superior to conventional NPWT with respect to the closure rate of the fascia and with less risk of formation of entero-atmospheric fistulas (41-43).

NPWT treatment has been used for many years as standard treatment in patients with faecal peritonitis. In spite of this, a definite randomized clinical trial has never been made which investigates possible. advantages and disadvantages compared to the second most commonly used treatment which is primary closure with ROD. Such a study of this character will have great health and economic relevance for patients and communities.

Primary endpoints:

Primary endpoint is to compare peritonitis related complications and Comprehensive Complication Index (CCI) between NPWT treatment (VAC) and conventional treatment (ROD) at 30, 90 days and 1 year.

Secondary endpoints:

- Mortality and peritonitis related complications at 30, 90 days and 1 year
- Quality of life after 3 and 12 months is measured with the SF-36 questionnaire
- Ventral herniation rate after 12 months assessed via clinical examination and CT scan of the abdomen (abdominal wall)
- Cost-effective analysis: Average treatment costs based on the following parameters number of days at ICU, number of days at the ward, radiological interventions (CT-

Abdomen, radiologically guided drainage), number of operations + VAC and number of operations without VAC

Definition of diffuse fecal peritonitis:

Diffuse fecal peritonitis is defined as contamination of 2 out of the 4 abdominal quadrants with fecal contamination starting from the small intestine, colon or rectum.

Definition of peritonitis related complications:

Please see Appendix 1.

2. METHOD

Design

Multicentre randomized non-blinded clinical trial comprising > 4 centres.
The first 15-20 patients will be included from Surgical Department A, Odense University Hospital and Svendborg Hospital before inclusion of other centres. This is to ensure that adjustments/corrections in design or protocol can be introduced with the least inconvenience for other centres.

Randomization

Patients will be included upon suspicion fecal/diffuse peritonitis with focus from the small intestine, colon or rectum and CT scan of the abdomen with free air. Consent will be obtained from the surgical equipoise, after which the project manager will be contacted by phone and randomize the patient web-based via OPEN in blocks of 2, 4 and 6 for primary closure with ROD or application of VAC. Stratification will be carried out for each centre and age above or below 65 years. Patients who cannot be treated according to randomization will be analysed according to intention-to-treat principles in the arm they are randomized to.

Per-operative course

Within the first 24-36 hours after hospitalization, patients must be scored with Acute Physiology and Chronic Health Evaluation II (APACHE II) by the on-call anaesthesiologist. Peroperatively, the abdomen is scored according to Björck's classification, by the operating surgeon.

In patients where the abdomen cannot be closed, i.e. VAC has to be placed or who is scheduled for "second look", they will be as above mentioned analysed according intention-to-treat-principles in the arm they are randomized to. This may be due to inability to close the abdomen, intrabdominal hypertension or non-anatomic post-surgical anatomy (ie, surgically placed permanent packing or bowel that the operating surgeon believes must be left in discontinuity after resection). These patients will be treated according to usual practice. Daily monitoring, scoring, follow-up and registration of peritonitis related complications are done in the same way as the other two randomization arms according to intention-to-treat principles.

How to apply Vacuum Assisted Closure (VAC)

The intestines, including the lateral aspects, were covered by VAC® Abdominal Dressing System, visceral protective layer (protective non-adherent and/or fenestrated layer). The first layer of foam is placed flat in the wound, approximately 5 cm underneath the fascia. A minimum of one piece of foam is folded and placed in the laparostoma above the first layer of foam. Afterwards there will be applied an occlusive drape loosely in 10–15 cm wide strips. During the application of the negative pressure, the facial edges should be approximated manually towards the midline. This is done to make the laparostoma opening as narrow as possible. We used a standard negative pressure of −125 mmHg, but when an anastomosis was performed, the negative pressure was sometimes reduced to as low as −25 mmHg, because lowering the pressure will protect the anastomosis, and a pressure of −25mmHg was high enough to prevent the lateralisation of fascial edges. Each dressing change should be performed at the operation theatre, and in general anaesthesia at maximum relaxation.

How to do primary closure

The abdominal wall is closed according to the Isreaelsson principle where it is sewn continuously in the fascia at a distance between the sutures of 5 mm and the distance to the facade edge of 5-10 mm. Monofilament PDS 0-0 (Ethicon) (or equivalent) is used. The suturing is started cranially and caudally, and the sutures are tied at the end of the continuous thread with self-locking knots. 4 times as much suture material as the length of the wound must be consumed (44).

How the fascia is closed after VAC treatment

The fascia can be closed according to the Israelssons principle as described above or by single interrupted far-near-near-far sutures with Prolene 0-0. However, the method of closure is decided by the surgeon. If the laparastoma cannot be completely closed, we recommend closing the fascia cranially and distally as much as possible successively and placing a new VAC-system until the laparastoma is fully closed, if possible.

When to make relaparotomy-on demand

Relaparotomy should be performed in patients with clinical deterioration or lack of clinical improvement with a probable intra-abdominal cause and/or after exclusion of other infectious foci (e.g. pneumonia) in blood tests and relevant imaging or in surgical emergencies.

- Clinical deterioration is defined as:
    - Increase of SOFA score ≥2 after last operative intervention
- Lack of clinical improvement is defined as the following:
    - Signs of persistent sepsis
    - SOFA score unchanged for at least 48 hours after the index laparotomy or previous relaparotomy or VAC shift

- Surgical emergencies are defined as:

    - Abdominal compartment syndrome
    - Intra-abdominal bleeding with sustained decrease in hemoglobin despite replacement or hemodynamic instability
    - Peritoneal reaction
    - Perforation of a hollow organ in the abdomen
    - Anastomotic leakage
    - Intra-abdominal abscess that cannot drain percutaneously
    - Ischemia or necrosis of a visceral organ.

The clinician should only be guided by the scoring systems. The final decision lies with the attending clinicians.

Postoperative course

- Immediately after the operation the surgeon completes Baseline, Postoperative record and Björck's classification
- All patients should be transferred post-operatively to the intensive care unit
- Patients will be APACHE II and SOFA scored upon arrival at intensive care unit by the anesthesiologist on call
    - When an intensive care doctor assesses that there no need for further intensive care, the patient is transferred to the ward
- Patients should be SOFA scored daily for the first 7 days after the index operation.
    - This should be done by doctors going rounds (applies to both the intensive care unit and the surgical ward)
    - As soon as the patient is transferred to the ward, blood tests should be ordered daily (CRP, d-dimer, procalcitonin, creatinine, bilirubin, platelets)
    - At daily rounds the patients must be GCS scored, a-gas needs to be taken and MAP calculated, which should all be recorded in the journal (in-order to calculate SOFA).
- Responsible physician completes SOFA score sheet, which can be found in the patient's project folder
- Patients randomized to VAC treatment are booked for VAC change after 48 hours by a specialist, where the following events can happen
    - VAC is changed
    - VAC is changed and closure is started
    - The abdomen is closed
    - The peritoneal fluid should be cultured at index operation and at closure
- Patients randomized to primary closure with the ROD of the abdomen will be assessed at the department / intensive care unit of the project manager and a specialist in surgery before the 48-hour surgery, where the following events can happen
    - No operation
    - Re-operation with closure of the abdomen
    - Re-operation with establishment of VAC treatment
    - The peritoneal fluid should be cultured upon closure

After completion of treatment

At the end of treatment all patients are booked for follow-up after 12 months in the outpatient clinic by the project manager. The abdomen is palpated in a standing and supine position with regard to clinical hernias. Prior to the outpatient follow-up, CT will be performed with iv. contrast with and without Valsalva maneuver in order to detect ventral hernia.
The SF-36 questionnaire will be used to measure quality of life at follow-up after 3 and 12 months.

3. STATISTICAL ANALYSIS

Power calculation with the following assumptions:

ROD group with peritonitis-related complications of 40% (17), VAC group with estimated peritonitis-related complications of 25% after review of literature and local numbers (38,42), Power of 80%, Alpha of 0.05, expected dropout of 5% resulted in the need for 150 patients in each group after drop-out of A total of 320 patients are required for 5%.

Peritonitis related complications and Comprehensive Complication Index between NPWT treatment (VAC) and conventional treatment (ROD) will be compared at 30, 90 days and 1 year.
Interim analysis will be done at 25%, 50% and 75% of recruited patients on the peritonitis related complications and mortality parameter, with the aim of detecting significant differences between the groups as early as possible. The interim analyses will only be done on complication outcome and mortality, but not on the cost-effectiveness analysis.

Primarily, superiority analysis will be conducted with the aim of investigating whether VAC treatment is better than primary closure with ROD.

Secondarily, non-inferiority analysis will be performed to investigate whether VAC treatment is not inferior to primary closure with ROD.

Patients who cannot follow the randomized treatment plan will be included in the results and analysed according to the "intention-to-treat" principle.

Univariate analysis will be performed on each type of complication (abscess, leakage, etc.), as well as on complications as a whole (peritonitis related complications). Fisher's exact or Chi2 test will be used to compare treatments depending on the number of observations.

Adjusted analysis by logistic regression, for complications as a whole, as well as for individual complications and outcome, where the following covariate will be adjusted:

- Age
- Performance status
- Co-morbidity

The above analyses will also be performed as subgroup analysis where patients with APACHE-II score> 10 will only be included. This is to evaluate VAC and ROD in the sickest part of the patient population.

Cost-effective analysis where, based on average treatment costs, the costs for the following are calculated and compared this between the treatment groups. T-tests or rank sum test analysis will be performed, depending on whether data are normally distributed (controlled by quantile-quantile plot).

- The number of days at ITA
- The number of days per department
- Radiological interventions
- Number of operations + VAC
- Number of operations minus VAC

Patient characteristics will be summarized by frequencies and proportions (for categorical variables) or by means ± standard deviation, median values, quartiles, range, and minimum and maximum values (for numerical variables). Categorical variables will be compared using a Fisher's exact test and continuous variables with a Wilcoxon's rank sum test.

All of the above analyses will be performed as both intention-to-treat (patients will be analysed according to their randomization group) as well as per protocol analysis (what actually happened).

P values less than 0.05 will be considered statistically significant. Statistical calculations will be performed using Stata software (version 15, Stata Corp LP, Texas, USA).

4. STUDY POPULATION

Patients eligible for enrolment into VACOR are 18+ years of age with suspected secondary peritonitis from intestinal perforation.

Exclusion criteria are;

- Diffuse peritonitis originating from a different focus than the small intestine, colon or rectum
    - Perforated ventricle or doudenal ulcer
    - Perforated gallbladder
    - Necrotizing pancreatitis
    - Salpingitis
    - Peritoneal Dialysis
1. Primary peritonitis
    - Immune-deficient patients
    - Chronic parenchymal liver disease
    - Hemodialysis patients
2. Abdominal trauma
3. Lack of consent
4. Not finding diffuse/fecal peritonitis peroperatively

5. RECRUITMENT OF SUBJECTS AND INFORMED CONSENT

The study has been approved by the Danish Medical Ethics committee with a rather special permission to include patients with a surgical equipoise and afterwards when the subject(s) are in habitual state the informed consent should be obtained.

Consent from the surgical equipoise is obtained before the intervention/surgery is completed. Subjects will not be included to the study until consent from the surgical equipoise and informed consent from patient or guardian is obtained (please see illustration under appendix 3). In addition, consent will be obtained for the storage of biological material in the research biobank. Oral and written consent is obtained during hospitalization as soon as the included patient is in a habitual state, either on the ward or the intensive care unit. The surgical equipoise is appointed according to professional knowledge, first and foremost, it should be a thoracic surgeon who have experience with VAC treatments. At a smaller hospital (not a university hospital) where the trial will take place and where such doctors are not present, a urologist could be appointed as a surgical equipoise.

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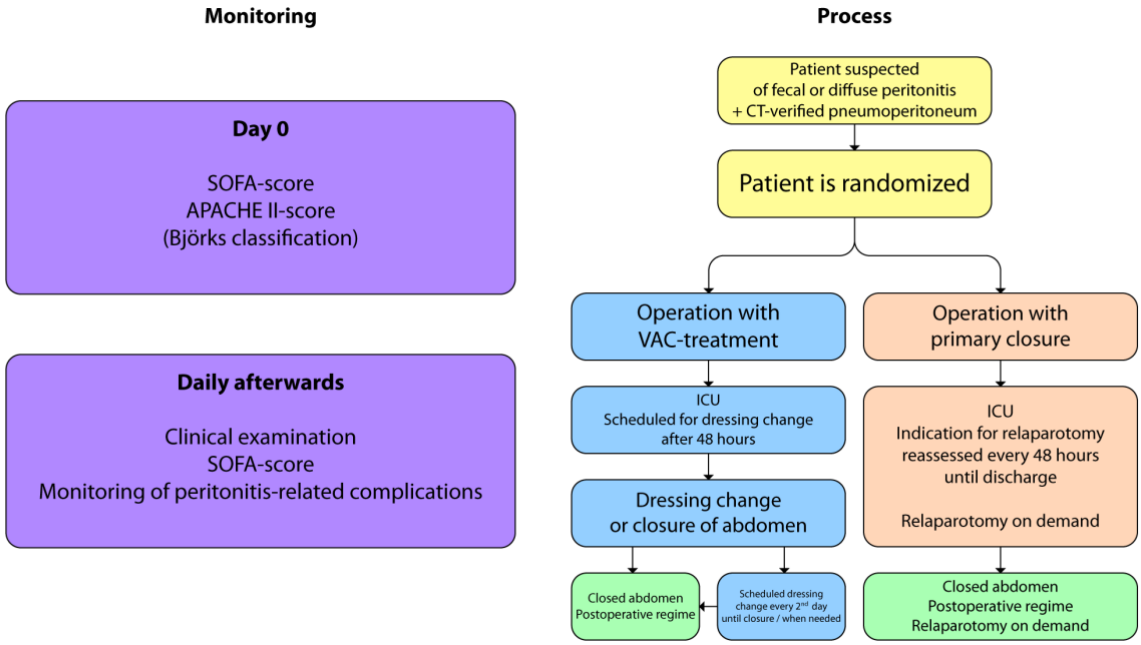
Appendix 1

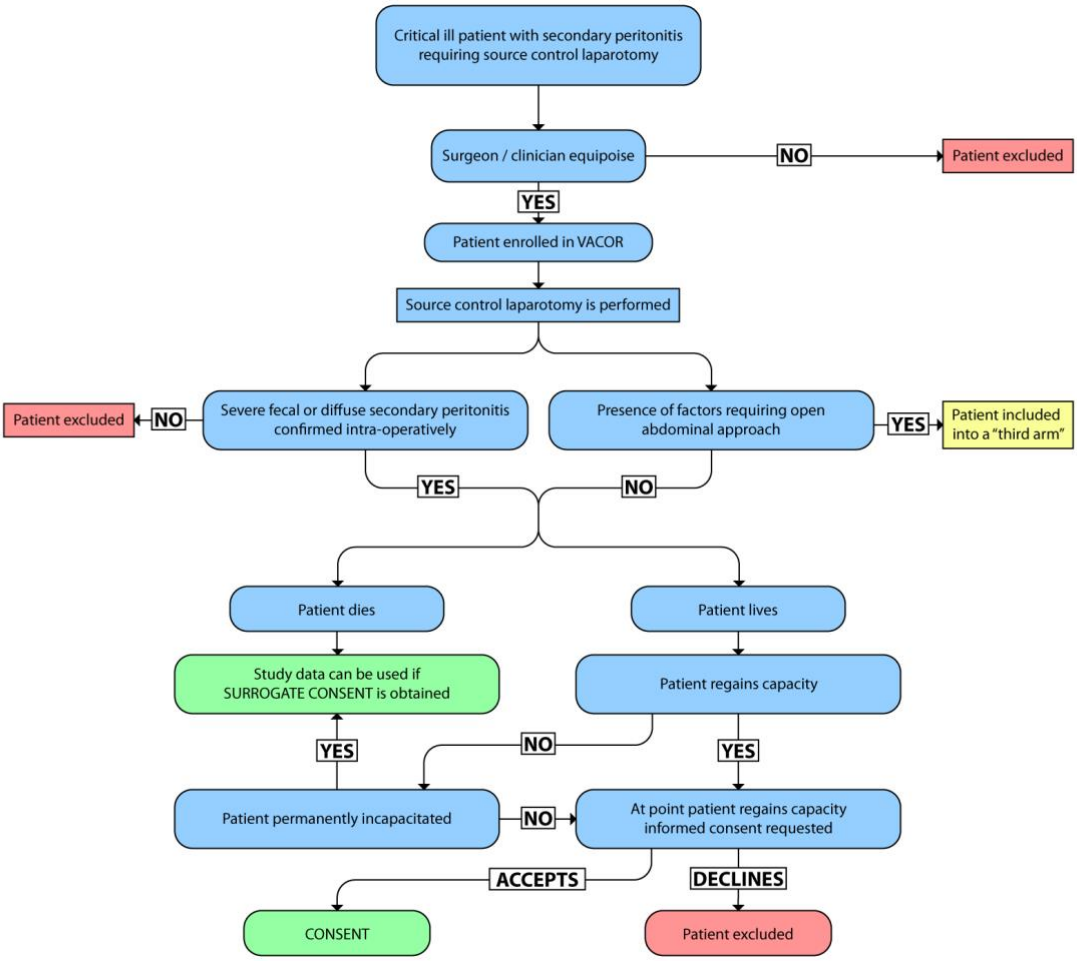
Peritonitis related complications is a combination of all-cause disease-related morbidity in surviving patients within 12-month follow-up after index laparotomy. The complications will be measured after 30, 90 days and 1 year.

- Incisional hernia +/- obstruction
- Incisional hernia without obstruction
- Postoperative ileus due to intra-abdominal adherences or abscess
- Fascial dehiscence
- Failure of closuring the patient's own fascia
- Abdominal compartment syndrome
- Intra-abdominal bleeding or hematoma
- Perforation of intra-abdominal organ confirmed by surgery
- Anastomotic leakage (confirmed by CT and relaparotomy)
- Ischemia or necrosis of intra-abdominal organ
- Enterostomy dysfunction due to prolapse, stenosis or failure
- VAC treatment longer than 8 days
- VAC change sooner than scheduled at 48-hour intervals
- On-demand relaparotomy
- Intraperitoneal abscess
- Enteroatmospheric fistula
- Entero-enteric fistula
- Fistula between hollow organs and cutis or between two hollow organs
- Fistula between hollow organ and other and other

Appendix 2


Monitoring
Day 0
SOFA-score
APACHE II-score
(Björks classification)
Daily afterwards
Clinical examination
SOFA-score
Monitoring of peritonitis-related complications
Process
Patient suspected
of fecal or diffuse peritonitis
+ CT-verified pneumoperitoneum
Patient is randomized
Operation with
VAC-treatment
Operation with
primary closure
ICU
Scheduled for dressing change
after 48 hours
ICU
Indication for relaparotomy
reassessed every 48 hours
until discharge
Relaparotomy on demand
Dressing change
or closure of abdomen
Closed abdomen
Postoperative regime
Scheduled dressing
change every 2nd day
until closure / when needed
Closed abdomen
Postoperative regime
Relaparotomy on demand

Appendix 3


Critical ill patient with secondary peritonitis requiring source control laparotomy
Surgeon / clinician equipoise
NO
Patient excluded
YES
Patient enrolled in VACOR
Source control laparotomy is performed
Patient excluded
NO
Severe fecal or diffuse secondary peritonitis confirmed intra-operatively
Presence of factors requiring open abdominal approach
YES
Patient included into a "third arm"
YES
NO
Patient dies
Patient lives
Study data can be used if SURROGATE CONSENT is obtained
Patient regains capacity
YES
NO
YES
Patient permanently incapacitated
NO
At point patient regains capacity informed consent requested
ACCEPTS
DECLINES
CONSENT
Patient excluded