Protocol - Cardiac general

Delayed primary versus late secondary wound closure in the treatment of postsurgical sternum osteomyelitis

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Summary

Sternal osteomyelitis and poststernotomy mediastinitis is a severe and life-threatening complication after the cardiac surgery. The incidence ranges up to 3% with a mortality rate up to 29%. In addition, postoperative infections after sternotomy are associated with prolonged hospital stay, increased healthcare costs and impaired quality of patient life, representing an economic and social burden. The emergence of increasing antimicrobial resistant bacteria augments the importance of postsurgical infections since the antimicrobial choices are becoming limited. Furthermore, the incidence of infection is an indicator for the quality of patient care in the international benchmark studies. Although several therapy strategies are nowadays present in clinical practice, there is a lack of evidence-based surgical consensus for treatment of this surgical complication. In most cases the poststernotomy mediastinitis involves surgical revision with debridement, open dressing and/or vacuum-assisted therapy. After the granulation tissue on open chest wound is achieved, secondary closure and/or reconstruction with vascularized soft tissue flaps, such as omentum or pectoral muscle is performed. It seems there is a need for more effective surgical treatment of poststernotomy wound infections, which may address the prolonged hospitalization and reduce the number of surgical interventions and with this also the perioperative morbidity. In light of this we propose a randomized study comparing new delayed primary closure of the sternum to the secondary vacuum-assisted closure.

Keywords: Surgical site infections; Mediastinitis; Poststernotomy infection; Surgical complications

1. Etiology of poststernotomy infections

Many mechanisms have been proposed to explain the development of sternal wound infection. These theories include inadequate sternal fixation leading to instability and dehiscence of the overlying skin incision and inadequate surgical drainage. Further theories suggest a localized ischemic osteomyelitis. This theory suggests that sternal wires become loose, leading to sternal instability, which ultimately leads to skin dehiscence and osteomyelitic infection. The most commonly cultured organism is Staphylococcus aureus.

From the literature the incidence ranges between 1 and 3% [1, 2] with a mortality rate from 19 to 29% [1, 3]. The most devastating complication of the open sternum is the laceration of the right ventricle which has a very high mortality. Open sternum results in additional destabilizations of the thoracic cage. Prolonged immobilization or substantial surgical trauma are further complications of the conventional strategy [4].

Several retrospective and prospective studies have identified factors relating to increased risk of sternal dehiscence. Patient risk factors include obesity, diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic cough from tobacco abuse, steroid therapy, hypertension, immunosuppression and advanced age. Operative risk factors include single or bilateral internal mammary artery (IMA) harvesting (which significantly decreases blood supply to the ipsilateral hemithorax), prolonged operation, excessive hemorrhage, reoperation, break in sterile technique, and the use of an intra-aortic balloon pump.

2. Objectives

2.1. Study hypothesis

The optimal treatment of sternum osteomyelitis has not yet been defined. The aim of this randomized study is to compare the treatment outcome of the delayed primary closure with short-term vacuum-assisted closure (VAC)-therapy (48–72 hours) with the late secondary closure with long-term VAC therapy (> 14 days).

We hypothesize that the delayed primary closure will have a better outcome than late secondary closure regarding parameters:
- cure rate (> 80% vs. < 60%)
- length of hospitalization (≤ 6 weeks vs. > 6 weeks)
2.2. Aims

Primary
To compare the treatment outcome (hospital stay, morbidity, mortality and surgical stress load) of the delayed primary closure approach with the late secondary closure.

Secondary
To evaluate side effects of both treatment approaches, and treatment expenses.

3. Study population

3.1. Inclusion criteria

We will include all patients:

- eighteen years of age or more
- who has been operated on the open heart and received a total or partial median sternotomy
- informed consent has been obtained, the subject is willing to follow protocol study treatment regimen, and comply with all planned follow-up assessments
- no self-determined patients are included

3.2. Exclusion criteria

We will exclude patients:

- after heart transplantation or other orthotopic transplantation procedure
- superficial wound infections (see definition under 4.1)
- sterile open wound dehiscence without any sign of local or systematic infection.

3.3. Ethical aspects

The permission from the Local Ethical Committee will be obtained before beginning the study. This study will be also registered with www.ClinicalTrials.gov. Patients will be enrolled before randomization 1:1 into each study arm; in each group we will randomly include 20 patients. The randomization is not blind and will be performed by one of the principal investigators. In the absence of the principal investigators this may be performed by co-investigators. Surgical procedures in both arms should be standardized. In this way it is essential that all the interventions will be performed by the main investigator and the co-investigator.

Arm A: in this group the patients will be treated with the standard surgical treatment. The details of the procedure are described under 4.4.

Arm B: in this group the patients are treated according to the new concept of the delayed primary sternal closure. The procedure is described under 4.5. See also Fig. 1.
4. Procedures and methods

4.1. Definition of the sternal infection

Median sternotomy wound complications vary from sterile wound dehiscence to suppurative mediastinitis. Sternotitis, mediastinitis, wound complication and wound infection have been used synonymously to denote deep sternal wound infection. For the sake of consistency in comparing data from various reports, definitions of sternal wound complications are as follows [5–7].

Ad 1) Mediastinal dehiscence: median sternotomy wound breakdown in the absence of clinical or microbiological evidence of infection.

Ad 2) Mediastinal wound infection: clinical or microbiological evidence of infected presternal space and sternal osteomyelitis, with or without mediastinal sepsis and with or without unstable sternum. Subtypes include:

A) superficial wound infection: wound infection confined to the subcutaneous tissue.

B) Deep wound infection (mediastinitis): wound infection associated with sternal osteomyelitis with or without infected retrosternal space. Deep sternal wound infections, or mediastinitis, are classified into four subtypes based on the time of first presentation, the presence or absence of risk factors and whether previous attempts at treating the condition have failed (Table 1).

4.1.1. Sternal wound infection

The definition of mediastinitis has been established by the Centers for Disease Control and Prevention in the USA [8]. According to these guidelines, diagnosis of mediastinitis requires at least one of the following:

Ad 1) an organism isolated from culture of mediastinal tissue or fluid;
Ad 2) evidence of mediastinitis seen during operation;
Ad 3) one of the following conditions: chest pain, sternal instability, or fever (>38.8 °C), in combination with either purulent discharge from the mediastinum or an organism isolated from blood culture or culture of mediastinal drainage.

4.2. Outline of the surgical procedures

Patients with suspected sternal osteomyelitis will be hospitalized and the following diagnostic procedures will be performed: laboratory blood tests [leukocytes, C-reactive protein (CRP), creatinin, aspartate aminotransferase (AST), alanine transaminase (ALT), creatine kinase (CK)], computed tomography (CT) of the sternum, wound swab.

After the diagnosis is secured the patients will receive an information consent form for the study. Subsequently, they will be randomly included in one of the surgical arms.

4.3. Current treatment strategy of poststernotomy infections

During the past years, VAC wound therapy has emerged as a treatment for open septic wounds. It is a non-invasive system that helps promote wound healing by delivering negative pressure, the application of this subatmospheric form of treatment has several advantages as compared to the conventional treatment. VAC therapy allows open drainage that continuously absorbs exudate with simultaneous stabilization of the chest and isolation of the wound. This therapy induces the building of the granulation tissue which in the majority is a result of the reduced edema and increased blood flow in the adjacent tissue. Furthermore, VAC therapy approximates the wound edges and provides a mass filling effect with a low degree of surgical trauma, without establishing a new wound (e.g., abdominal wound in omental flaps) [9, 10]. In the recent literature the mean hospitalization of the patients being treated with the VAC therapy was 25 ± 20 days with overall mortality of 15% [11].

4.4. Arm A: secondary closure with the vacuum-assisted system (VAC)

Nowadays after the diagnosis of the poststernotomy wound infection is established the clinical procedure is obtained as follows: first the empiric antibiotic therapy with vancomycin is induced. The laboratory samples including bacteriology tests are obtained. The initial surgical revision is done within 24 hours. Intraoperatively from the surgical field tissue samples are sent for bacteriology investigation to determine the antibiotic pattern resistance. All sternal wires are removed. Surgical debridement is made until occurrence of tissue bleeding. Careful and extensive cleaning of the wound is performed using saline solution at 37 °C and a solution of 50% betadine and saline solution (1:1 betadine:H₂O). Finally, VAC sponge is implanted with a negative suction pressure of 75 mmHg. Postoperatively a chest X-ray is obtained, in the first 24 hours the laboratory samples with CRP and white blood cell count are performed. The first revision with a second look and debridement is usually made in 72 hours. Subsequently, in the following days the wound is stepwise revised, during VAC changes a sharp spoon and necrotic bone is removed when necessary, but extensive sternectomy is avoided. At each revision tissue samples are obtained for microbiological investigations.

According to the patients’ general situation they are extubated immediately after VAC therapy initiation and stay on the intensive care unit (ICU) for about 24 hours. The patients undergo the surgical procedures five to seven.
times at time intervals of 72 hours. Subsequently, when
the last three bacteriology samples are negative a delayed
primary closure or rectus abdominal muscle flap may be
done. When the antibiotic is known, the specific antibi-
otic therapy is induced (Fig. 1).

4.5. Arm B: surgical procedure by delayed primary closure

As compared to the previous therapy modalities mentioned
under 2.2 and 1.3 the new method has an advantage on the
surgical wound healing due to delayed primary intention.

In the first step, after the diagnosis of the infection is
done and the empiric antibiotic therapy is induced with
vancomycin in the first surgical intervention, the sternal
wire is removed, the mediastinum is explored and extensive
surgical debridement is performed until occurrence of
tissue bleeding. Careful and extensive cleaning of the
wound is performed using saline solution at 37 °C and a
solution of 50% water peroxide and saline solution (1:1
H2O2:H2O), at least three samples (tissue biopsies) are
taken for microbiology. The patients will receive treatment
delivered through the VAC system in the first 48 hours
following the first surgical intervention. Subsequently, the
wound is closed (Fig. 1).

We begin with the dissection and elevation of the pector-
alis major muscle and corresponding subcutaneous flap
through diathermy. Dissection is performed from the medi-
an line along the costal grid, up to two-thirds of the
anterior chest wall, preserving the humeral insertion, one
thoracoacromial vascular bundle and the pectoralis minor
muscle. Note in this area there are very important vascular
anastomosis areas between the internal thoracic artery,
acromial artery and the lateral thoracic artery which should
be preserved. At the inferior plane, the pectoralis major
muscle will be raised – including the anterior rectus fascia –
down to the xiphoid process. The upper segment of the
anterior rectum will be raised with the pectoralis major
muscle. The intercostal perforating arterial branches will
also be preserved. A silicon drain tube is placed in the
retrosternal space if this is possible. In patients with
fracture or asymmetry of the sternum incision, osteosyn-
thesis is performed using the Robiscek technique. Then two
suction drains are placed below the muscular plane upon
the costal grid for drainage of the large area of detachment
of the musculoaponeurotic layer.

The suture of the pectoral fascia should be tension free,
using a continuous suture with resorbable material (Vicryl
3-0). The subcutaneous tissue is closed over the drainage,
with a separate subcutaneous suture. The skin is closed
with an unresorbable suture similar to the Allgöver tech-
nique. These sutures are removed between the 12th and
14th postoperative days.

Thus, the results of the bacteriology are known in most
cases after the first 48 hours of the specific antibiotic
therapy.

4.6. General considerations

Contraindication for closure of the chest:
wounds with active purulence require extensive debride-
ment prior to flap coverage and/or rigid fixation. Additional
contraindications for sternal reconstruction are found in
patients who are unstable for surgery, including those with
poor pulmonary function, poor cardiac reserve, or terminal
illness. Hemodynamic stability is required for surgical inter-
vention in patients with sternal dehiscence.

4.7. Early perioperative management in the first 48 hours

4.7.1. Transfer to the ICU

After each definitive sternal closure the patients will be
transferred to the ICU for the hemodynamic observation in
the first 24 hours. The following are considered as indica-
tions to transfer on ICU: preoperative sepsis, intraoperative
hemodynamic instability and/or need for catecholamines,
intraoperative need for massive transfusion, rupture of the
ventricular cavities (left or right), the need for emergency
cardiopulmonary bypass.

4.7.2. Transfer to intermediate care

Hemodynamic and pulmonary stable patients will be extu-
bated in the operating room, and will be transferred to the
intermediate care unit of the department of cardio-
vascular surgery.

4.7.3. General considerations

Independently of both investigation groups Arm A and
Arm B an X-ray of the thorax will be obtained post opera-
tively after the transfer. In the first 24 hours, the laboratory
samples will be obtained (CRP, anticoagulation, white blood
cell (WBC) count, hemoglobin, hematokrit, AST, ALT, gamma-
glutamyl transeptidase (GGT), creatinin, urea, and anti-
coagulation tests partial thromboplastin time (PTT), pro-
thrombin time (PT)). Respiratory physiotherapy will be
obtained 24 hours after the surgical revision.

Open chest patients should not be mobilized out of bed,
however, chest elevation and mobilization of 45–90° is
allowed.

After definitive closure of the chest the patient may be
fully mobilized after the first 48 hours, or after the transfer
to the ward.

4.8. Outcome evaluation

Late postoperative management after 48 hours for both
investigation groups.

Ad 1) during the hospitalization the patients will be visited
by the surgeon and the responsible infectiologist every
48 hours. The clinical signs for infection, sternal instability,
and laboratory blood testing controls (white blood cell
count with differential, CRP level AST, ALT, GGT, creatinin,
urea, and anticoagulation tests PTT, PT) will be performed
every 48 hours. The vital signs and the temperature will
be recorded according to the standard flow charts on the
ward and are determined three times in 24 hours during
the whole hospitalization. X-ray of the thorax will be
performed on day of admission after closure of the chest
and after the seventh postoperative day. If there is a
suspicion for local infection or recidivism a CT-scan will be
performed.
Ad 2) after admission and at three, six and 12 months, the subjects will be evaluated clinically, and laboratory parameters will be assessed. The end of therapy (EOT) will be assessed three months after admission and test of cure (TOC) 12 months after study inclusion. At each follow-up visit, clinical signs and symptoms of infection, adherence to antimicrobial treatment protocol, and possible significant side effects of antimicrobials will be recorded. In addition, laboratory blood testing (WBC count with differential, CRP level) and plain radiography will be performed.

4.8.1. Success
Successful outcome is defined as normal laboratory test results and absence of clinical signs of infection. The presence of the unstable sternum or creation of the pseudarthrosis is defined either as treatment failure (if clinical signs and symptoms, laboratory tests, or radiographic signs suggest relapse of device-associated infection) or failure due to other reasons (aseptic failure or reinfection with a different pathogen).

4.8.2. Safety
Safety will be assessed for the entire study period from the inclusion into the study through the everyday visits. Safety endpoints include laboratory analyses, vital signs, concomitant medications and physical examination findings. All patients will be monitored for elevations in temperature, CRP and WBC count with a differential. Patients with unexplained temperature (T > 38.5 °C) or with elevated CRP > 70 and/or signs of new postoperative wound infection will be evaluated with a chest CT-scan. If this investigation or the clinical signs of infection are confirmed the patients will be excluded from the study and will be treated with the standard VAC therapy described in detail in 4.3.

4.9. Outline of the antibiotic procedures
Preoperatively, no antibiotics will be given in order to obtain representative microbiology during first debridement. After first surgery (debridement), imipenem 4 × 500 mg i.v. + vancomycin 2 × 1 g i.v. will be administered as empirical therapy. After closure of the wound and removal of the VAC, targeted antibiotic therapy will be started for two to three weeks, followed by oral antibiotics for a total of six weeks. CRP must be normal for four weeks before stopping antibiotics and will be determined weekly. The targeted highly active antibiotic therapy will be given according to the microbiology susceptibility testing.

5. Conclusions
The protocol for randomized study may be conducted if there are sufficient centers who agree to participate. Thus, we would like to invite readers to participate in a multicenter study.

References