Impact of Vacuum-Assisted Closure (VAC) Therapy on Clinical Outcomes of Patients with Sternal Wound Infections: A Meta-Analysis of Non-Randomized Studies

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Abstract

Objective: To examine the impact of VAC therapy on mortality of patients with sternal wound infections after cardiothoracic surgery.

Summary Background Data: Controversial results regarding mortality of patients with sternal wound infections were published.

Methods: We performed a systematic search in PubMed and Scopus. Mortality was the primary outcome of the meta-analysis. Recurrences, complications and length of stay were secondary outcomes.

Results: Twenty-two retrospective studies including 2467 patients were eligible for inclusion. Patients treated with VAC had significantly lower mortality compared to those treated without VAC [2233 patients, RR = 0.40, (95% CI 0.28, 0.57)]. This finding was consistent regardless of the study design, the exclusion of studies with positive findings, the criteria for establishment of the compared groups, the time of mortality assessment or the type of infections under study, provided that adequate data was available. VAC therapy was associated with fewer recurrences (RR = 0.34, 95% CI: 0.19–0.59). The meta-analysis did not show any difference in the length of stay (RR = 2.25, 95% CI: −7.52–3.02).

Conclusions: VAC therapy was associated with lower mortality than other surgical techniques in retrospective cohorts of patients with DSWIs following cardiothoracic surgery.

Introduction

Deep sternal wound infections (DSWI), namely mediastinitis and osteomyelitis, are a serious complication occurring in 1% to 5% of patients after cardiothoracic operations in individual studies.[1,2] Intravenous antibiotics and several surgical techniques had been used in the past for their treatment; however, they have been associated with increased short- and long-term mortality.[3] A new technique using topical negative pressure by controlled suction has been introduced in the treatment of wounds achieving wound closure through the formation of granulation tissue. This technique, most commonly applied by vacuum-assisted closure (VAC) wound therapy system, has gradually gained ground and replaced most of the conventional types of wound treatment due to the faster wound healing,[4,5,6] lower length of hospital stay[7,8,9] and the subsequent lower in-hospital cost.[6,10].

Moreover, early studies showed that VAC therapy has the potential to reduce both in-hospital and long-term mortality.[11,12] A meta-analysis published in 2011 showed that patients treated with VAC had shorter duration of hospitalization but no difference in mortality compared to those treated with a non-VAC therapy.[13] Since this publication several new studies became available that expanded our knowledge regarding the effectiveness of VAC application for the treatment of sternal wound infections. We aimed to systematically review and synthesize the available evidence with the methodology of meta-analysis in order to examine the impact of VAC therapy on mortality of patients with sternal wound infections.

Methods

Literature Search

We performed a systematic search in PubMed and Scopus electronic databases in September 2012. The search term that was applied in PubMed was the following: (“negative pressure” OR vac OR “vacuum assisted”) AND (wound) AND (infection). A more conservative search term was applied in Scopus database: (“negative pressure” OR vac OR “vacuum assisted”) AND (sternal wound infection OR dswi OR mediastinitis OR osteomyelitis). In addition, the bibliographies of all relevant articles were searched in
order to identify further potentially eligible studies. Articles written in a language other than English, German, French, Spanish, Italian or Greek were not evaluated. Only published studies were included; abstracts from conferences were excluded.

Study Selection
Articles reporting the comparative outcomes of patients with sternal wound infections treated with VAC versus a non-VAC therapy were considered eligible for the meta-analysis regardless of the study design, patient characteristics, type of surgery and additional used interventions, deep or superficial sternal wound infections. When a patient population was included in more than one published study, only the study with the bigger total study population was included. Studies focusing primarily in sternal wounds without infections or other types of wounds were excluded.

Data Extraction
Data was extracted regarding the major characteristics of the included studies (first author, country, period of the study, study design), number of patients in each treatment arm, group establishment regarding the type of therapy selected, patient co-morbidity regarding the cardiothoracic operations conducted, and time of mortality assessment.

Definitions and Outcomes
Sternal wound infections could comprise both deep and superficial infections developed after a cardiothoracic surgery. The definition of osteomyelitis, mediastinitis and superficial wound infections was based on the definitions provided by the selected individual studies.

The primary outcome of the review was in-hospital mortality. When in-hospital mortality was not provided by the authors of a study, 30-day or 90-day mortality was selected. Secondary outcomes comprised recurrence, as defined by the authors of the included studies, and hospital length of stay (LOS).

Statistical Analysis
The non-randomized studies that were analyzed were considered to be heterogeneous by definition and, therefore, the Mantel-Haenszel random effects model (REM) was applied. Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated regarding all outcomes. Statistical heterogeneity between studies was assessed by using the $I^2$ test ($p<0.10$ was defined to indicate the presence of heterogeneity) and the $I^2$ (for assessing the degree of heterogeneity). The meta-analysis was performed with Review Manager for Windows, version 5.1.

Results
The systematic search in both databases generated 938 articles (754 PubMed, 172 Scopus, 12 hand-searching). The selection process that was followed for the inclusion of the studies is depicted in Figure 1. Twenty-two studies were finally included in the review.[8,11,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33] The characteristics of the included studies are presented in Table 1. Twenty-one studies reported on deep sternal wound infections (16 on mediastinitis,[11,14,15,16,17,18,19,20,21,23,26,27,28,30,32,33] two on osteomyelitis[8,25] and 3 did not specify the type of infections[24,31]). One study included both deep (69%) and superficial (31%) sternal wound infections.[22] In 12 studies, VAC treated patients were compared with a historical control group not receiving VAC therapy.[11,18,19,21,22,23,25,26,27,28,31,32] While in 2 other studies,[8,16] the selection of therapy (VAC or non-VAC) was at the surgeon’s discretion, as both types of therapy were simultaneously available. Six studies did not provide the criteria for the selection of therapy in the enrolled patients.[14,15,20,24,30,33] Twelve studies provided data for in-hospital mortality,[8,14,15,16,18,20,21,26,27,31,32,33] 2 on 30-day,[28,30] and 2 studies on 90-day mortality,[11,19] while 4 studies did not determine when mortality was assessed.[22,23,24,25,26,27,28,30,31,32].

Pooling of all 20 studies that provided data on mortality showed that patients treated with VAC had significantly lower mortality compared to those treated with a non-VAC therapy, [Figure 2, 2233 patients, RR = 0.40, (95% CI: 0.28, 0.57)]. Heterogeneity was not observed in this analysis ($I^2 = 16$%). In addition, mortality was lower among patients receiving VAC therapy after the exclusion of studies that showed significantly lower mortality [1058 patients, RR = 0.60, (95% CI: 0.41–0.89)]. Lower mortality was found among patients treated with VAC among studies using a historical non-VAC control group [1476 patients, RR = 0.32 (95% CI: 0.20, 0.50)]. Heterogeneity was not observed in this analysis ($I^2 = 5$%). Similarly, lower mortality was observed for VAC therapy in the studies that did not provide the criteria for the selection of therapy [655 patients, RR = 0.45 (95% CI: 0.23, 0.88)]. No difference was found between the compared groups when the selection of the type of therapy was at the surgeon’s discretion [102 patients, RR = 0.99, (95% CI: 0.21, 4.65)].

In-hospital mortality was lower among patients treated with a VAC compared to those treated with a non-VAC therapy, [Figure 3, 1186 patients, RR = 0.40, (95% CI: 0.26, 0.62)]. Heterogeneity was not observed in this analysis ($I^2 = 13$%). On the other hand, no difference in 30-day [193 patients, RR = 2.28 (95% CI: 0.30, 17.25)] and 90-day mortality [191 patients, RR = 0.21 (95% CI: 0.03, 1.30)]; a small number of patients were included in these 2 analyses. Finally, in the studies that did not provide the time of mortality assessment a trend towards lower mortality was observed [663 patients, RR = 0.39 (95% CI: 0.14, 1.05)].

Patients with mediastinitis and/or undetermined deep sternal wound infections treated with VAC therapy had lower mortality compared to the respective patients treated with a non-VAC therapy, [Figure 4, 1534 patients, RR = 0.38 (95% CI: 0.24, 0.66)] and [117 patients, RR = 0.21 (95% CI: 0.06, 0.73)] respectively. Heterogeneity was not observed in the abovementioned analyses ($I^2 = 23$% and $I^2 = 0$, respectively). No difference in mortality was found between the compared groups among patients with osteomyelitis [58 patients, RR = 1.78 (95% CI: 0.35, 9.04)]. Last, 1 study including both deep and superficial sternal wound infections showed lower mortality among patients treated with VAC therapy than those treated with a non-VAC therapy [524 patients, RR = 0.36 (95% CI: 0.18, 0.73)].

Only 4 of the 20 studies provided data regarding funding; 1 was industry-funded.[22] 2 were funded by universities[11,32] while 1
study was not funded.[18] Therefore, potential bias arising out of funding could not be adequately investigated.

Recurrences, Complications and Length of Stay

Ten studies provided data on recurrence of DSWIs (1197 patients).[11,17,21,22,25,27,28,30,31,32] Pooling of these studies showed that recurrence was less common among patients treated with VAC compared to those treated with a non-VAC therapy, [RR = 0.34 (95% CI: 0.19, 0.59)]. Moderate heterogeneity was detected in this analysis (I² = 48%). Data on complications was available within 4 studies.[11,14,21,31] Different types of complications were reported in the individual studies including remote infections, sepsis, cardiovascular/neurological/gastrointestinal complications, renal failure, bleeding, multiple organ failure, fistula, empyema, dehiscence, skin graft requirement, skin necrosis, seroma, discharging sinus, partial flap loss, new atrial fibrillation. However, only one study presented the total number of complications patients in each treatment arm,[14] while the remaining three studies presented the individual complications in each arm.[11,21,31] Therefore, the data could not be further analyzed.

Finally, ten studies provided data on LOS (983 patients).[8,11,14,16,19,21,27,29,31,33] Pooling of the outcomes of these studies showed that there was no statistically significant difference in LOS between patients treated with VAC and those treated with a non-VAC therapy, [RR = −2.25 (95% CI: −7.52, 3.02)]. Considerable heterogeneity was detected in this analysis (I² = 82%) and individual studies showed that VAC was associated with both significantly lower and higher duration of hospitalization.

Discussion

The currently available data from retrospective cohort studies suggest that the use of VAC therapy was associated with lower mortality than non-VAC therapy for the treatment of patients with DSWIs after cardiovascular surgery. This finding was consistently present regardless the study design, the inclusion of studies with positive findings, the criteria for establishment of the compared groups, the time of mortality assessment or the type of infections under study, provided that adequate data was available. In addition, VAC therapy was associated with fewer recurrences of infections. On the contrary, this meta-analysis did not show any difference in the duration of hospitalization.

The main limitation of the current meta-analysis is the retrospective nature of the available data. No randomized controlled trial has been published yet and one protocol had been registered –to our knowledge? regarding the effectiveness and safety of VAC therapy for the treatment of patients with DSWIs in...
Table 1. Characteristics of the studies included in the meta-analysis.

| First author | Year | Study design; period, country | Number of analyzed patients (VAC vs non-VAC) | Patient co-morbidity | Group establishment | System of VAC used | Mortality assessed at | Funded or non-funded study |
|--------------|------|--------------------------------|-----------------------------------------------|----------------------|---------------------|---------------------|----------------------|---------------------------|
| Deniz        | 2012 | Retrospective cohort; 2000–2011, Turkey | 90 (47 vs 43) | 60% coronary artery bypass revascularization, isolated | 2000–2003: non-VAC 2003–2011: VAC | KCI system | 90-day | NR |
| Fleck        | 2012 | Retrospective cohort; 1995–2011, Austria | 524 (326 vs 198) | Cardiac operations (VAC group: 62% aorto-coronary artery bypass, 39% VR, 17% congenital surgery or aortic surgery or heart transplantation) | 1995–2001: non-VAC 2002–2011: VAC | KCI system | Undetermined | KCI, USA |
| Risnes       | 2012 | Retrospective cohort; 1997–2010, Norway | 104 (64 vs 66) | CABG | 1997–2002: non-VAC 2002–2006: both non-VAC and VAC 2006–2010: VAC | KCI system | 30-day | NR |
| Rodriguez Cetina Biefer | 2012 | Retrospective cohort; 1999–2008, Portugal | 159 (105 vs 54) | 51% CABG, 18% isolated valve, 18% CABG+valve, 14% other procedures (thoracic aneurysms, aortic dissections, congenital repair procedures) | According to the surgeon’s discretion; VAC available for use at the clinic after 2002 | NR | NA | NR |
| Simek        | 2012 | Retrospective cohort; 2002–2007, Czech Republic | 62 (34 vs 28) | 76% CABG, 6% valve, 18% CABG+valve | 2002–2004: non-VAC 2004–2007: VAC | KCI system | In-hospital | NR |
| Steingrimsson | 2012 | Retrospective cohort; 2000–2010, Iceland | 43 (20 vs 23) | 63% CABG, 16% AVA+CABG, 7% aortic valve replacement alone | 2000–2005: non-VAC 2005–2010: VAC | KCI system | In-hospital | Landspitali University Research Foundation |
| Vos          | 2012 | Retrospective cohort; 2000–2011, Netherlands | 132 (89 vs 43) | 81% CABG, 75% LIMA, 21% RIMA, 22% AVR, 8% MVR | VAC or non-VAC; no reasons are reported | NR | In-hospital | NR |
| Assmann      | 2011 | Retrospective cohort; 2004–2008, Germany | 154 (82 vs 72) | 68% CABG | VAC or non-VAC; no reasons are reported | KCI system | In-hospital | NR |
| De Feo       | 2011 | Retrospective cohort; 1979–2009, Italy | 200 (55 vs 145) | 57% coronary artery bypass, 26% valve surgery, 18% other procedures | 1979–2002: non-VAC 2002–2009: VAC | KCI system | In-hospital | Non-funded |
| Kobayashi    | 2011 | Retrospective cohort; 2001–2007, Japan | 16 (9 vs 7) | 44% CABG, 19% AVR, 31% thoracic aortic surgery, 6% cardiac trauma | 2001–2003: non-VAC 2003–2007: VAC | NR | Undetermined | NR |
| Morisaki     | 2011 | Retrospective cohort; 1991–2010, Japan | 59 (8 vs 51) | 58% CABG, 20% single-valve surgery, 8% OPCAB, 5% modified Bentall procedure, 5% thoracic aneurysm operation, 5% combined operations, 5% other, 2% CABG+infarct exclusion | 1991–2006: non-VAC 2006–2010: VAC | NR | In-hospital | NR |
| Baillot      | 2010 | Retrospective cohort; 2002–2007, Canada | 149 (125 vs 24) | (8) IMA | VAC or non-VAC; no reasons are reported | NR | In-hospital | NR |
| De Feo       | 2010 | Retrospective cohort; 2000–2009, Italy | 75 (45 vs 30) | Cardiac surgery | VAC or non-VAC; no reasons are reported | KCI system | NA | NR |
| Petzina      | 2010 | Retrospective cohort; 2004–2009, Germany | 118 (69 vs 49) | 84% CABG ± valve procedure | 2004–2006: non-VAC 2006–2009: VAC | NR | In-hospital | NR |
| First author | Year | Study design; period, country | Number of analyzed patients (VAC vs non-VAC) | Patient co-morbidity | Group establishment | System of VAC used | Mortality assessed at | Funded or non-funded study |
|--------------|------|-------------------------------|---------------------------------------------|----------------------|---------------------|-------------------|----------------------|--------------------------|
| Eyileten     | 2009 | Retrospective cohort; 2000–2007, Turkey | 65 (33 vs 32) | 75% CABG, 9% MVR, 5% MVR+CABG, 5% AVR, 2% AVR+CABG, 2% Bentall procedure | 2000–2004: non-VAC 2005–2007: VAC | KCI system | In-hospital | NR |
| Fuchs        | 2005 | Retrospective cohort; 1998–2003, Germany | 68 (35 vs 33) | Bypass operations, heart valve replacements | 1998–2000: non-VAC 2000–2003: VAC | KCI system | Undetermined | NR |
| Immer        | 2005 | Retrospective cohort; 1998–2003, Switzerland | 55 (38 vs 17) | 76% CABG, 58% unilateral mammarian artery, 15% bilateral mammarian artery, 1% reoperation | VAC or non-VAC; no reasons are reported | KCI system | Undetermined | NR |
| Segers       | 2005 | Retrospective cohort; 1992–2003, Netherlands | 63 (29 vs 34) | 64% CABG, 14% valve surgery, 21% CABG+valve surgery, 2% other | VAC or non-VAC; no reasons are reported | KCI system | 30-day | NR |
| Sjögren      | 2005 | Retrospective cohort; 1994–2003, Sweden | 101 (61 vs 40) | 72% CABG, 28% other procedures | 1994–1998: non-VAC 1999–2003: VAC | NR | 90-day | County of Skåne Medical Science Fund, University Hospital of Lund Donation Funds |
| Domkowski    | 2003 | Retrospective cohort; 1997–2002, United Kingdom | 102 (96 vs 6) | Cardiac surgery | VAC or non-VAC; no reasons are reported | NR | In-hospital | NR |
| Doss         | 2002 | Retrospective cohort; 1998–2000, Germany | 42 (20 vs 22) | 69% CABG, 14% CABG+AVR, 5% CABG+carotid endarterectomy, 5% CABG + concomitant left ventricular aneurysm resection, 5% isolated AVR, 2% CABG + concomitant AVR+mitral valve repair | 1998–1999: non-VAC 1999–2000 both non-VAC and VAC, according to the surgeon’s discretion | KCI system | In-hospital | NR |
| Berg         | 2000 | Retrospective cohort; 1989–1997, Netherlands | 60 (31 vs 29) | 35% CABG with venous graft, 58% CABG with IMA, 5% valve replacement, 2% CABG+valve replacement | VAC or non-VAC; according to the surgeon’s discretion | NR | In-hospital | NR |

*For patients treated for sternal wound infections between 1997 and 2001, no mortality data was available and therefore, they were not included in the analysis.

1 In this study, in a few patients, despite the availability of the VAC, a non-VAC therapy has been chosen due to the poor quality of the sternum (fractured, white aspect, fragile) or on the clinical situation with incontrollable infection and hemodynamic instability.

doi:10.1371/journal.pone.0064741.t001

Table 1. Cont.
which mortality is the primary end-point.[34] In addition, only one of the included studies performed a multivariate analysis to identify independent predictors for survival; VAC therapy was not introduced into this model and methicillin-resistant *Staphylococcus aureus* was the sole independent predictor for mortality.[26] Therefore, only unadjusted data were available for comparisons.

A variety of techniques were used for the management of DSWIs in the control groups of both the individual studies and between studies; in addition, VAC was not the sole intervention applied in the VAC group of patients in all studies. As this clinical heterogeneity was expected, a random effect model was selected for all comparisons prior to the implementation of the meta-analysis. On the other hand, statistical heterogeneity was not observed in any of the performed analyses and all subgroup analyses consistently confirmed the results of the primary analysis, thus strengthening the validity of the results of the meta-analysis. Data regarding the offending bacteria and corresponding antibiotic treatment was not available. Finally, outcomes regarding the way of using VAC (i.e. pressure or duration) were not available within the included studies.

A recent international consensus conference suggested certain non-surgical interventions that are documented as decreasing
mortality after a cardiac surgery and need further study[35]; administration of insulin, levosimendan, volatile anesthetics, statins, chronic beta-blockade, early aspirin therapy, the use of preoperative intra-aortic balloon counterpulsation are encountered among them. VAC therapy could be also included in this list if the lower mortality finding is confirmed in randomized studies.

VAC therapy is not approved officially for the treatment of DSWIs. However, the positive findings of early studies showing lower mortality (although not uniformly) or decreased duration of hospitalization,[8,11,12,16] in addition to better outcomes in favor of VAC therapy from RCTs in other patient populations, prompted the experts in the field to recommend the wider use of VAC for Treatment of Sternal Wound Infections.

Figure 3. Forest plot depicting the risk ratios (RR) of mortality of patients according to the time of mortality assessment. (Vertical line = “no difference” point between the two regimens. Squares = risk ratios; Diamonds = pooled risk ratios for all studies. Horizontal lines = 95% CI.)

doi:10.1371/journal.pone.0064741.g003
of VAC for the treatment of patients with DSWIs.[1,2] It should be noted that VAC is recommended “before primary closure, as preparation for secondary closure with vascularised tissue and as an adjunct to flap healing”. [1,2]

data regarding recurrent DSWIs and even fewer for systemic or related to the surgical interventions complications. VAC therapy was associated with fewer recurrences than conventional treatment in the meta-analysis. Data regarding complications could not be further analyzed and adverse events following VAC and non-VAC therapy were not studied in this meta-analysis. In face of potentially lower mortality, the development of complications and adverse events seems
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negligible. However, surgeons should be aware of them in order to improve the quality of life of their patients. Complications of VAC treatment include bleeding (although sometimes its presence can be attributed to factors other than the VAC itself),[36] decrease of cardiac output when it is applied directly on the heart,[37] and adhesion formation,[38] and can occur after the application of vacuum.[2] Advisory panels also warn against the use of VAC therapy when the patient has excessive or uncontrolled bleeding or uses anticoagulants that result in international normalized ratio over 2, untreated or undrained osteomyelitis, and chest or pulmonary malignancy.[2]

Infections are among the major complications that prolong hospitalization. Controversial results were reported regarding this outcome in the studies included in the meta-analysis; six studies reported that LOS was significantly lower in patients receiving VAC therapy, while two reported that LOS was significantly prolonged. The meta-analysis including 10 studies showed no difference in the LOS when VAC was used, but considerable statistical heterogeneity was found. Therefore, it is difficult to draw conclusions regarding LOS. A recently published meta-analysis concluded that LOS was shortened with the use of VAC,[13] This meta-analysis included data from 6 studies; 3 of them were also included in the present meta-analysis. One did not provide the mean and standard deviation,[7] one provided the mean but not the standard deviation,[30] and one provided separate data for two groups of patients receiving VAC;[24] since we did not contact with the corresponding authors to request additional data, these data could not be included in the meta-analysis. Since hospital cost is associated mainly with LOS, these findings question the cost-effectiveness of VAC therapy in this patient population. Different findings in favor or against VAC regarding cost-effectiveness have been published.[38,39,40,41]

In conclusion, the currently available data suggest a lower mortality and support the use of VAC therapy for the treatment of patients with DSWIs following cardiothoracic surgery. The retrospective design of the studies included in the meta-analysis and the lack of adjusted data highlighting VAC as an independent predictor of survival suggest that a well designed RCT is warranted to study the effects of VAC therapy, alone or in combination with other techniques, on mortality of patients with DSWIs. The effect of VAC on LOS and the related cost should be further investigated in this patient population.

Author Contributions

Conceived and designed the experiments: MEF. Analyzed the data: MEF GST AK KZV. Wrote the paper: MEF GST AK KZV. Drafting the article or revising it critically for important intellectual content: MEF GST AK KZV. Final approval of the version to be published: MEF GST AK KZV.

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