Endovascular stent-graft placement versus conventional open surgery in infrarenal aortic aneurysm: a prospective study on acute phase response and clinical outcome

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Abstract

Background: For the treatment of aortic aneurysm, stent-graft implantation is an alternative method to open surgery. There is no study comparing both methods with regard to endotoxaemia, the acute phase cascade, and clinical outcome.

Methods: In this prospective study, we enrolled 40 patients (34 males, 6 females; mean age 72.1 ± 7.5 [58–92] years) with infrarenal abdominal aortic aneurysm who underwent aortic surgery. Comparable groups of patients were treated with open (n = 20) or endovascular (n = 20) stent-graft implantation. To characterize the inflammatory response, plasma levels of endotoxin, endotoxin-neutralizing capacity (ENC), interleukin-6 (IL-6), C-reactive protein (CRP), and white blood cell count were determined. In all patients, measurements were performed on admission, skin suture, 4 h and from the first to fifth postoperative day. As parameters for the clinical outcome, we assessed daily temperature, lung function, pain, duration of postoperative hospital stay, and morbidity. Wilcoxon rank test was used for statistical analysis.

Results: In both groups, a significant increase of endotoxin plasma levels and a decrease of ENC was found already after skin incision. IL-6 levels peaked 4 h postoperatively in both groups, whereas CRP rose at the first postoperative day, reaching a maximum at day 2. Conventionally operated patients had significantly higher plasma levels of endotoxin, IL-6, and CRP and lower ENC during and after surgery than patients with stent-graft implantation. Moreover, patients with endovascular stent grafting had significant less postoperative pain, less restriction of total vital capacity, a shorter hospital stay, and a lower morbidity.

Conclusions: Endovascular stent grafting of infrarenal aortic aneurysm seems to be superior not only in terms of the inflammatory response but also in overall clinical outcome. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Endovascular grafts; Aortic surgery; Endotoxin; Acute phase reaction; Inflammatory response

Endovascular treatment of aortic aneurysm is a relatively new minimal invasive method in vascular surgery. This operation is carried out with small instruments under X-ray control and minimal tissue damage leading to small skin incisions and better...
postoperative cosmetic results than open surgery. Moreover, patients postoperatively have less pain and a significantly reduced recovery time than conventionally operated patients. However, although previous studies demonstrated that the endovascular procedure may be the superior alternative [1–6], no study compared the acute phase response and the clinical outcome of both methods.

It is well accepted that patients who undergo surgical procedures can develop leukocytosis, temperature rise, and changes of serum protein and electrolyte levels. These phenomena are summarized as the postoperative acute phase reaction [7,8]. It is well known that after major surgical procedures, interleukin-6 (IL-6) plasma levels increase, triggering the synthesis of acute phase proteins in the liver [9]. There is no study investigating IL-6 levels and mediator release after endovascular aortic stent implantation although these patients may develop an acute phase response. The most potent triggers of IL-6 induction are bacterial lipopolysaccharides, the active part of endotoxins that are thought to play an important pathophysiological role during Gram-negative sepsis [10]. The appearance of endotoxin in the blood circulation was attributed to disturbances of the gut barrier function facilitating endotoxin translocation [8–12].

In the present study, we tested the hypothesis whether endotoxaemia occurs during endovascular treatment of aortic aneurysm compared with the more invasive open surgical method. We further addressed the relationship between endotoxin plasma levels and members of the acute phase cascade during both procedures and compared the morbidity and mortality of both surgical techniques.

1. Methods

1.1. Patients

Forty patients (34 males, 6 females; mean age 72.1 ± 7.5, range 58–92 years) were treated for infrarenal abdominal aortic aneurysm by endovascular (n = 20; mean age 72.8 ± 8.6, range 58–92 years), talent stent prothesis (n = 8), gore stent prothesis (n = 11), corvita stent prothesis (n = 1), bifurcated graft (n = 18), tube graft (n = 2) or open surgery (n = 20; mean age 71 ± 5, range 59–80 years) and investigated with regard to endotoxaemia, the acute phase cascade, and clinical outcome. The study was approved by the local ethical committee of the University of Ulm. Patients were treated between 1996 and 2000 and were comparable in terms of cardiovascular risk factors (endovascular versus open surgery: diabetes mellitus 4/5; hypertension 19/18; dyslipidemia 11/9; smoking 13/8) and other chronic medical disorders (chronic obstructive pulmonary disease 8/9, cholecystolithiasis 2/3, myocardial infarction 3/5, stroke 1/5). Patients with clinical signs of liver cirrhosis, malignancy, immunosuppression, terminal kidney failure, and acquired immune deficiency syndrome (AIDS) or AIDS-related complex (ARC) were excluded from the study. Patients with endovascular treatment had an ASA score (American Society of Anesthesiologists classification system in preoperative evaluation of patients) of 2.9 compared to ASA 3.0 in the conventional group. The diameter of the aneurysm of endovascular patients was 54 ± 5 mm compared to 57 ± 7 mm in the open surgery group.

In all patients, lung function was assessed before surgery and then every day until the third postoperative day using a spirometer. Pain was quantified with the help of a visible pain intensity scale (0 = no pain, 50 = heaviest pain), as recently described [8]. The patients were asked for intensity of pain preoperatively and postoperatively when lying in bed, coughing, and during mobilization.

1.2. Assays

The inflammatory response was characterized by measuring plasma levels of endotoxin, endotoxin-neutralizing capacity (ENC), IL-6, C-reactive protein (CRP), and leucocyte count peri- and postoperatively, as recently described [8]. Heparinized blood was drawn from patients on the following time points: admission (0), after skin suture (1), 4 h after surgery (2), and from the first to the fifth postoperative day (3–7). Blood was collected in sterile heparinized tubes (10 IU/ml of blood) and centrifuged immediately at 2000 × g for 15 min to obtain platelet-free plasma that was stored for up to 5 days at −70 °C until determinations were performed. Endotoxin was specifically measured using the modified limulus-amebocyte-lysate test. IL-6 plasma levels were determined by means of a commercially available ELISA.
test (Quantikine; Biermann, Bad Nauheim, FRG). CRP was determined by nephelometry (Nephelometer 200 Analyzer, Behring, Marburg, Germany).

### 1.3. Statistical analysis

Statistical analysis was performed by comparing the area under the curve (AUC) using the Mann–Whitney U-test. Correlations between variables (Pearson’s correlation coefficient) were assessed using univariate linear regression analysis. \( p < 0.05 \) was accepted as statistically significant. All statistics were carried out using the statistical SPSS for Windows 6.1 software (SPSS, USA).

### 2. Results

#### 2.1. Inflammatory response and mediator levels

The plasma levels of endotoxin, IL-6, and CRP were analyzed pre-, peri-, and postoperatively. Preoperatively, the concentration of endotoxin in the blood was nearly zero in both groups (0.02 endotoxin units [EU]/ml). A statistically significant increase of endotoxin concentration could be detected for the conventional \( p = 0.005 \), but not for the endovascular procedure \( p = 0.3 \). The median endotoxin levels are shown in Fig. 1A. Similar to endotoxin, the conventional group showed significantly higher ENC levels compared to the endovascular procedure \( p < 0.05 \); Fig. 1B.

An intra- and postoperative increase in IL-6 could be detected for both operative procedures reaching the maximum 4 h after surgery with significantly higher peak levels in the conventional group (Fig. 1C). CRP levels increased postoperatively in both groups with maximum values 48 h after surgery. Again, the increase and the absolute CRP values (Fig. 1D) as well as the levels of granulocytes were higher in the conventional operated group.

#### 2.2. Surgical procedure and outcome

The time for the surgical performance differed in both groups (183 min open surgery versus 134 min endovascular treatment, \( p < 0.001 \)). Patients with endovascular treatment received 158 ml contrast medium, whereas patients with open surgery had no intravenous contrast applications. In middle, patients...
with open surgery had to stay 82 h in the intensive care unit compared to 29 h for patients who received endovascular treatment \((p < 0.001\) stent versus open surgery). Postoperative fasting was 1.1 days in the endovascular group with full diet on day 4 compared to 2.2 and 8.0 days in the conventional group \((p < 0.001)\). Patients reached full mobility at day 6 with endovascular treatment and day 8 with conventional surgery \((p < 0.05)\).

The clinical outcome was better in minimal invasive compared with the conventional surgical procedure. In the conventional group, one patient died after the open procedure due to multiorgan failure, five patients developed cardiovascular problems, four patients developed pulmonary problems, and four patients developed renal failure that was treated by hemodialysis. In contrast, in the endovascular group, no patient died, one patient developed cardiovascular problems, and three patients got renal problems. Due to the relatively small number of patients studied, these differences reached no statistical significance. Fifty-four percent of all patients with endovascular treatment developed higher than 38 \(^\circ\)C on the first two operative days compared to only 35% in the conventional group \((p < 0.05)\). Postoperative lung function showed significant differences in both groups. Postoperatively, the vital capacity was reduced by 10% in endovascular patients and by 36% in conventional operated patients \((p < 0.05)\). These differences remained until the end of the observation period. Forced expiratory vital capacity \((FEV1)\) values did not differ between both groups. Patients who underwent endovascular surgery had less pain compared to patients who were conventionally operated. Especially when mobilized and coughing, a significant difference was present between both groups \((p = 0.001)\). The need for analgesic drugs was significantly lower in endovascular treated than conventional operated patients \((p < 0.05)\). Finally, patients with endovascular treatment had to stay 10 days in the hospital as compared to patients with open surgery who were discharged at day 14 \((p < 0.01)\).

3. Discussion

Circulating levels of endotoxin, IL-6, and CRP are acknowledged markers of inflammation [7–12]. In this prospectively randomized study, we determined these inflammatory mediators in patients with infrarenal abdominal aortic aneurysm treated with open or endovascular repair. Our major finding was that patients with endovascular stent-grafting showed both, significantly lower levels of circulating mediators and a better clinical outcome.

Previous studies suggested that endotoxin translocates from the gut thereby triggering the postoperative acute phase reaction [8,10–13]. Under physiological conditions, the normal gut mucosa is a barrier against bacterial endotoxins and endotoxaemia happens only if the permeability of the intestinal mucosa to endotoxins is increased. Endotoxin is released in large amounts when bacteria are destroyed, for example, by antibiotic treatment, and could be transported through intact gut epithelium by vesicle formation [10]. Alternatively, endotoxaemia is also detected without bacteremia due to alterations of endotoxin production and absorption [8]. Endotoxin is a major trigger of inflammatory mediators such as IL-6 and CRP. In our study, this is supported by the time delay of the peak plasma levels of the different mediators and the finding that conventionally operated patients with the higher endotoxin levels also developed higher IL-6 and CRP levels than patients with stent grafting. During endovascular surgery, the smaller skin incisions, the lower tissue damage and the shorter operation time may be major reasons for the lower mediator release observed with this technique. Previous studies provided evidence that the amount of surgical trauma is related to the disturbance of gut barrier function that results in endotoxin translocation and subsequent inflammatory response [8,10,13].

The clinical data of our study clearly demonstrate that patients who underwent endovascular surgery showed a shorter convalescence time and could be discharged earlier from the hospital than conventionally treated patients. This is in agreement with previous studies [1–6] showing that stent-graft repair compares favorably with open surgical repair with a reduced morbidity rate, shortened hospital stays, and satisfactory short-term outcomes. The question arises whether inflammatory mediators such as endotoxin, IL-6, and CRP may predict clinical outcome. In our study, the endovascular group with the minor surgical trauma also showed significantly lower levels of
circuitulating inflammatory mediators as well as a better short-term clinical outcome. On the other hand, patients with postoperative complications revealed higher mediator levels in both surgical groups. However, due to the small number of patients studied, these differences reached no statistical significance. Several previous studies clearly showed that circulating inflammatory markers can predict development of multiorgan dysfunction [14–20].

In summary, our study demonstrates for the first time that patients with endovascular stent grafting showed lower levels of inflammatory mediators, less postoperative pain, minor restriction of total vital capacity, a shorter hospital stay, and a lower overall morbidity than patients with open surgery. We therefore conclude that in aortic aneurysm, endovascular stent grafting may be superior in terms of the acute phase reaction as well as in overall clinical outcome.

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References