

Oral Antibiotic Prophylaxis Can Influence the Inflammatory Response in Aortic Aneurysm Repair: Results of a Randomized Clinical Study

R.G. HOLZHEIMER

Medical Faculty, Martin-Luther University, Halle-Wittenberg, Germany.

Correspondence: René Gordon Holzheimer, M.D., Ph.D., Wallbergstr. 15a, D-82054 Sauerlach, Germany.
Tel +49-8104-887822 - Fax +49-8104-887824 - e-mail: gresser.holzheimer@t-online.de

Summary

The purpose of this prospective, randomized study was to evaluate the effect of oral ofloxacin prophylaxis on endotoxin/cytokine release in aortic aneurysm repair, in 25 patients with infrarenal aortic aneurysm at a University hospital. Outcome parameters included complications after operation; endotoxin and endotoxin neutralizing capacity. All patients had the standard perioperative antibiotic prophylaxis (2 g cefotiam). 12 patients randomly received oral ofloxacin prophylaxis (group 1) the day before the operation (200 mg/2x12h); 13 patients were controls (group 2). Data were analyzed by chi-square analysis, Mann-Whitney and Wilcoxon analysis. Ofloxacin had no effect on the occurrence of complications or on the peripheral endotoxin levels. Ofloxacin-treated patients showed increased endotoxin neutralizing capacity (ENC) 30 min after clamping compared to controls (15.8 ± 15 vs 262.8 ± 709 p=0.005) and increased IL-6 levels preoperatively and 30 min after clamping. Patients with complications had significantly higher IL-6 levels early during the operation and postoperatively (30 min after clamping: 36.4 ± 15.1 vs 18.8 ± 11.9 pg/ml p=0.01; 2nd postoperative day: 768 ± 688 vs 225 ± 322 pg/ml p=0.005). Ofloxacin prophylaxis had no effect on procalcitonin, or neopterin plasma levels. Neither procalcitonin nor neopterin could detect patients with complications. IL-6 plasma levels predicted the occurrence of complications in aortic aneurysm repair. Oral ofloxacin prophylaxis may influence the ENC and IL-6 plasma levels but had no effect on complications, endotoxin and other inflammatory mediators.

Key words: ischemia-reperfusion, aortic aneurysm repair, endotoxin, endotoxin neutralizing capacity, IL-6, procalcitonin, neopterin, portal vein, ofloxacin, translocation.

INTRODUCTION

Antibiotic prophylaxis in vascular surgery has been introduced to avoid prosthetic graft infection ¹. The combination of a broad-spectrum parenteral antibiotic with oral antibiotics in colorectal surgery is considered to reduce the postoperative complications, often caused by Gram-negative pathogens ². Gram-negative infections are associated with the release of endotoxin (LPS) from the disintegrating

cell wall of Gram-negative pathogens ³ and cytokines ⁴. Gut ischemia followed by translocation of endotoxin and bacteria may induce the systemic release of mediators ⁵. Excessive cytokine production can lead to organ dysfunction, organ failure and death ⁶. It is accepted that cytokines may be released in situations described by the term systemic inflammatory response syndrome (SIRS) without established infections ⁷. This may be studied in elective abdominal aortic aneurysm (AAA) repair ⁸

where high levels of TNF- α originating from gut-associated macrophages may be activated by bowel manipulation, ischemia and/or translocated LPS⁹. Ischemia-reperfusion is a complex phenomenon, which may lead to a local and remote tissue injury and, in the case of an excessive immune response, to death¹⁰. This may be associated with a massive release of proinflammatory cytokines into the systemic circulation, contributing to the development of vascular injury by upregulation of adhesion molecules¹¹. Such response may be sufficient to cause organ dysfunction without the presence of pathogens^{12,13,14}. We have recently demonstrated in a clinical study in aortic aneurysm repair that endotoxin release is followed by an increase in pro- and anti-inflammatory cytokines¹⁵. Ofloxacin, a quinolone, with pronounced activity against Gram-negative pathogens¹⁶ may lead to a complete elimination of Gram-negative bacilli in the bowel¹⁷, not affecting the anaerobic microflora¹⁸. Ofloxacin may have an impact on the release of endotoxin and proinflammatory mediators. The purpose of this prospective, randomized study was to investigate the effects of additional oral ofloxacin prophylaxis on endotoxin and proinflammatory mediators in AAA repair.

PATIENTS AND METHODS

Twenty-five consecutive patients undergoing elective infrarenal AAA repair at a university department of surgery were included in this prospective, randomized study, approved by the Institutional Committee on Clinical Research. All patients received i.v. one dose (2g) of cefotetan. The study group (n=12) were given a dose of 200 mg ofloxacin in the morning and the evening of the pre-operative day. The control group (n=13) nil. The aorta was always clamped below the renal arteries after routine systemic heparinization. Colonic mucosal pH or inferior mesenteric artery stump pressures were not recorded.

Plasma samples (venous) were obtained preoperatively (baseline), 30 minutes after incision, 30, 60, 90 and 120 minutes after clamping of the aorta, 4 and 8 hours after operation, and then the first, second and third postoperative day. The samples were kept cool, centrifuged and frozen within 30 minutes. Heparin was used as plasma anti-coagulant. Samples were centrifuged in endotoxin free tubes (Chromogenix, Germany) within 30 minutes and stored at -80°C until processing.

Endotoxin assay

We used the turbidimetric, kinetic LAL-test with internal standardization to measure endotoxin and

endotoxin neutralizing capacity as described by Urbaschek *et al.*¹⁹. The sensitivity of the endotoxin test was 0.5 pg/ml.

IL-6 assay

IL-6 determinations were performed by a commercially available EASIA test (Medgenix Diagnostics, Fleurus, Belgium). The detection limit of the test is 2 ng/ml.

PCT assay

Procalcitonin was determined with LUMITEST PCT (Brahms Diagnostica, Berlin, Germany). Sensitivity of the assay was 0.3 ng/ml. The preliminary reference level for healthy human beings was 0.5 ng/ml. Concentrations above 0.5 ng/ml might indicate an inflammatory process.

Neopterin assay

For neopterin determination the ELITEST NEOPTERIN (Brahms Diagnostica, Berlin, Germany) was used. The reference level for healthy human beings was ≤ 10 nmol/l.

Statistical analysis

The data are indicated as mean and standard deviation. The chi-square, Mann-Whitney and Wilcoxon-test were used for statistical analysis. Differences were considered significant if $p < 0.05$.

RESULTS

Twenty-five patients (2 women, 23 men) with elective aortic aneurysm repair were randomized to receive ofloxacin (n=12) as additional oral prophylaxis the day before surgery (control group: nil n=13). There were three complications in group 1 and two complications in group 2. In group 1 one patient suffered from epileptic seizures. Two patients died: one patient died from severe pneumonia; the other patient died because of cardiovascular failure. In the control group one patient developed a lymph fistula but was discharged after further uneventful follow-up. The second patient had a complicated postoperative course with dissolution of the y-prosthesis due to severe thrombosis and consecutive renal failure, which made a dialysis necessary. After a prolonged hospitalization the patient was discharged.

The patients (Groups 1 and 2) did not differ in age, sex, operation time and clamping time of the aorta, and routine laboratory data. The mean operation time was 288.7 ± 24 minutes for y-prosthesis of the aorta and 133.8 ± 13 minutes for a Dacron graft. Mean clamping time of the aorta was 48.8 ± 10.8

minutes and 45.7 ± 2 minutes respectively. Leukocytes increased significantly on the day of operation ($p < 0.05$) and on the first ($p < 0.01$) and second postoperative days ($p < 0.05$). Thrombocytes decreased significantly on the day of operation and the first postoperative day ($p < 0.01$). The hemoglobin levels decreased significantly intra-operatively, on the day of operation and remained significantly lower than preoperative levels on the first, second and third postoperative days ($p < 0.001$). There was a significant decrease in the hematocrit from preoperative levels on the second postoperative day ($p < 0.001$) and on the third postoperative day ($p < 0.05$). Temperature decreased intra-operatively ($p < 0.001$) and increased significantly on the day of operation and the first postoperative day ($p < 0.001$).

Endotoxin was not detected preoperatively in the patients. The maximum endotoxin level was measured 60 minutes after clamping of the aorta (3 ± 2.9 pg/ml). Endotoxin levels increased significantly 30 minutes after incision and remained significantly elevated when compared to pre-operative levels, until 4 hours after operation ($p < 0.01$). The endotoxin plasma levels on the first, second and third postoperative days did not reach statistical significance when compared to preoperative levels. (Figure 1) There was no difference in endotoxin levels in patients treated with ofloxacin and controls. (Figure 2) Patients with and without complications had a similar pattern of endotoxin plasma levels. Sixty minutes after aortic clamping plasma endotoxin was higher in patients without complications without reaching statistical difference.

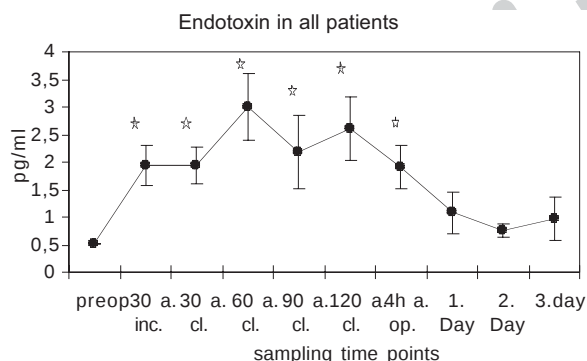


FIGURE 1 - Endotoxin plasma levels in all patients (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): endotoxin is significantly * increased 30 minutes after incision ($p < 0.05$), 30, 60, 90 and 120 minutes after clamping ($p < 0.05$) and 4 hours after operation ($p < 0.05$)

The endotoxin neutralizing capacity declined significantly from the preoperative baseline measurement at 60, 90, 120 minutes after clamping and 4 hours after operation ($p < 0.05$). It increased to maxi-

mum at the first postoperative day (357.6 ± 217.64) and remained at preoperative index levels on day 2 (96 ± 29.48) and day 3 (142.46 ± 49.42) after surgery. (Figure 3) Endotoxin neutralizing capacity levels were almost significantly elevated in preoperative ofloxacin-treated patients when compared to controls ($p = 0.0972$). Ofloxacin-treated patients had significantly elevated endotoxin neutralizing capacity index at 30 minutes after clamping compared to controls (15.8 ± 15 vs 262.8 ± 709.2 $p = 0.0055$). Endotoxin neutralizing capacity levels in ofloxacin-treated patients were almost significantly elevated 30 minutes after incision ($p = 0.0881$), 120 minutes after clamping ($p = 0.0662$) and on the second postoperative day ($p = 0.0849$). (Figure 4) There was no difference in endotoxin neutralizing capacity in patients who had complications and in patients who had an uneventful recovery. (Figure 5)

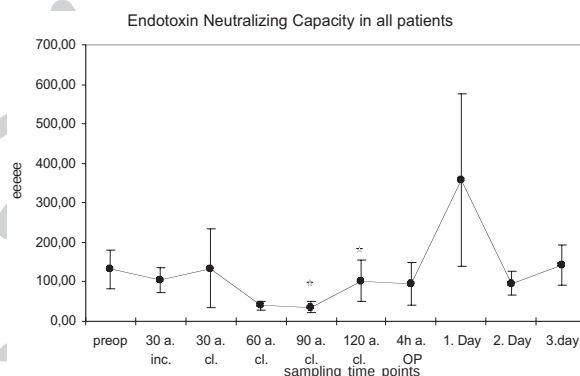


FIGURE 2 - Endotoxin plasma levels in patients with and without oral ofloxacin (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): there is no difference in plasma endotoxin levels of patients treated with or without ofloxacin.

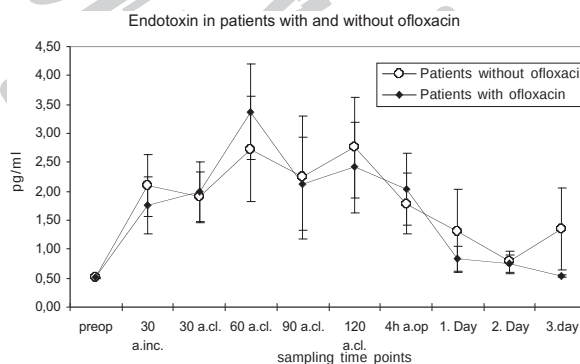


FIGURE 3 - Endotoxin neutralizing capacity (ENC) in all patients (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): ENC is significantly * decreased 90 minutes ($p < 0.05$) and 120 minutes after clamping ($p < 0.05$), 4 hours after operation ($p < 0.05$), and almost significantly 60 minutes after clamping ($p = 0.056$).

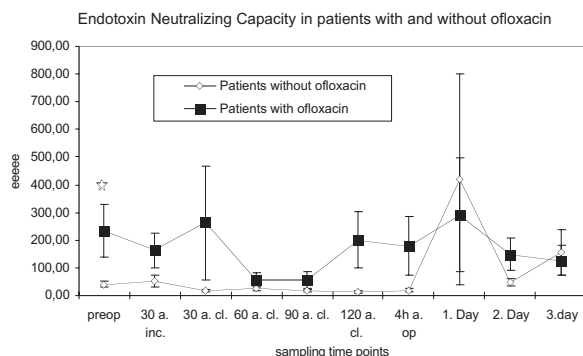


FIGURE 4 - Endotoxin neutralizing capacity (ENC) in patients with and without oral ofloxacin (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): ENC is significantly * increased in ofloxacin-treated patients preoperatively ($p<0.05$), and almost significantly elevated 30 minutes after incision ($p=0.08$), 120 minutes after clamping ($p=0.06$), and the 2. day ($p=0.08$)

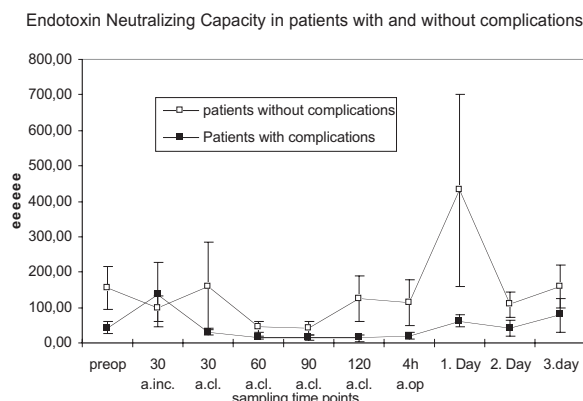


FIGURE 5 - Endotoxin neutralizing capacity (ENC) in patients with and without complications (preop=preoperative, a.inc. = after incision, a.cl. = after clamping): no significant difference detected.

Interleukin-6 (IL-6) concentrations decreased significantly 30 and 60 minutes after clamping when compared to preoperative levels ($p<0.05$). There was a significant increase observed at 60, 90, 120 minutes after clamping, and 4 hours after operation which remained significantly elevated until day 3 after operation ($p<0.001$). Patients who received ofloxacin had almost significantly elevated IL-6 levels preoperatively when compared to controls ($p=0.0866$). Thirty minutes after incision IL-6 levels in ofloxacin-treated patients were significantly higher than untreated controls ($p<0.05$). (Figure 6) Patients with complications had significantly higher IL-6 plasma levels 30, 60, 90 minutes after clamping and on the second postoperative day ($p<0.05$). Plasma IL-6 levels were not quite significantly elevated 120 minutes after clamping and on day 3 after operation. (Figure 7)

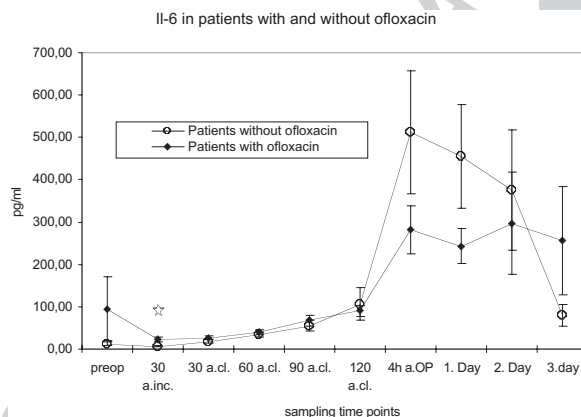


FIGURE 6 - Interleukin-6 (IL-6) plasma concentration in patients with and without oral ofloxacin (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): IL-6 levels are preoperatively ($p=0.08$) almost significantly and 30 minutes after incision ($p=0.01$) significantly * elevated compared to controls *.

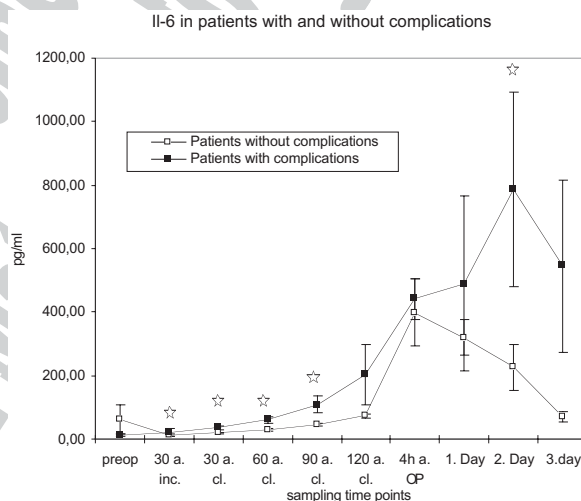


FIGURE 7 - Interleukin-6 (IL-6) plasma concentration in patients with and without complications (preop = preoperative, a.inc. = after incision, a.cl. = after clamping): IL-6 plasma levels are significantly * different in patients with postoperative complications early after incision (30 minutes after incision $p<0.05$; 30, 60, 90 minutes after clamping of the aorta and on day 2 $p<0.05$).

Procalcitonin levels did not remain at their normal preoperative level during the perioperative period. At the first postoperative day procalcitonin increased significantly (0.27 ± 0.03 vs 1.93 ± 0.8 ng/ml) and remained elevated on the second and third postoperative day. Treatment and control groups demonstrated no difference in **PCT** (AUTHORS, DEFINE PCT) levels. Patients with complications tended to have higher PCT levels but maximum PCT levels on the second postoperative day were not significantly different when compared

to patients without complications (6.16 ± 7.76 vs 0.87 ± 1.17 ng/ml $p=0.06$).

Neopterin plasma levels declined at 30 minutes after incision (7.5 ± 4.9 nmol/l) compared to preoperative levels (9.7 ± 6.8 nmol/l). Maximum levels of neopterin were measured on the third postoperative day (15.72 ± 2.29 nmol/l). There was no difference in plasma neopterin levels either in patients who were treated with ofloxacin compared to controls or in patients with and without complications.

DISCUSSION

Endotoxemia is a common finding after vascular operations²⁰. Cohen *et al.* suggest that increased intestinal permeability is associated with supraceliac colic clamping²¹. Aortic aneurysm repair has been associated with ischemia of the bowel²² and endotoxin induces activation of cellular and humoral mediators and endotoxin core antibodies²³. We have recently demonstrated that there is a concomitant release of inflammatory and anti-inflammatory mediators in aortic aneurysm repair which may be induced by endotoxin release from bacterial wall of Gram-negative pathogens in the bowel¹³. Studies on the pharmacokinetics of ofloxacin reveal a high fecal concentration which persists for several days²⁴ and ofloxacin may cause a selective reduction in the normal microflora, mainly aerobic Gram-negative bacteria²⁵. Oral antibiotic prophylaxis is frequently used for bowel surgery and recently it has been suggested that oral prophylaxis with ofloxacin in general surgery may be as effective as intravenous prophylaxis²⁶.

The hypothesis of the present study was that additional oral antibiotic prophylaxis in aortic aneurysm repair might lead to less endotoxin release and a reduced activation of the inflammatory system. This may have an effect on the clinical outcome.

Patients were randomized to receive either 2x200mg ofloxacin orally the day before AAA repair or to be in the control group without oral antibiotic prophylaxis. Endotoxin was detected early in the operative course in all patients and remained elevated postoperatively. The increase in endotoxin plasma concentration was correlated with a concomitant decrease in endotoxin neutralizing capacity. This is in agreement with recently published findings¹³.

Antibiotics may have a distinctive effect on endotoxin release^{27,28}. Orally administered nonabsorbable antibiotics prevented endotoxemia in primates following intestinal ischemia²⁹. Altering the gut contents in a rat model of hepatic failure and coma after liver resection reduced the level of endotoxemia³⁰. In this study, however, patients treated

with ofloxacin did not differ in plasma endotoxin levels; however, there was a significant difference in endotoxin plasma neutralization. *In-vitro* studies revealed that ofloxacin might not reduce TNF-alpha production from LPS-stimulated monocytes *in vitro*³¹. Several factors, which were not determined in this study, may have influenced the determination of endotoxin in plasma. We did not determine intramucosal pH in these patients, which may influence the concentration of endotoxin, TNF, and IL-6 in elective aortic aneurysm patients³². Furthermore, manipulation of the bowel³³ may have a stronger influence than the neutralization of the Gram-negative pathogens by ofloxacin. In other studies it is demonstrated that endotoxin is released in low concentrations and may escape detection by the limulus assay³⁴. Subinhibitory concentrations of ofloxacin are known to enhance the phagocytic killing rate³⁵, which may increase the plasma endotoxin level, whereas diminished bactericidal activity of ofloxacin is associated with the lowest release of endotoxin³⁶. This is in contrast to *in-vitro* data, which elucidated that LPS is released as long as *Escherichia coli* remains structurally intact and is enhanced when the bacterial biomass increases³⁷. Antibiotic-induced endotoxin release in quinolones is influenced considerably by dosage and pharmacodynamics³⁸. Ofloxacin may not reduce sufficiently the amount of anaerobic pathogens in the bowel³⁹ and products from anaerobes may induce limulus amebocyte lysate activation. We observed a significant increase in the endotoxin neutralizing capacity and almost significantly increased levels of IL-6 preoperatively in ofloxacin-treated patients, which suggests that ofloxacin may influence the immune response. The increased endotoxin neutralizing capacity has been observed in surgical intensive care patients treated with ciprofloxacin and imipenem⁴⁰. There are no other reports with regard to the effect of ofloxacin and endotoxin neutralizing capacity available. The situation with decontamination of the gut remains inconclusive even when nonabsorbable antibiotics (polymyxin B, neomycin) are used^{41,42}.

We demonstrated endotoxin in a branch of the mesenteric vein during the operation but before clamping. It may be that endotoxin release is more affected by local microcirculation disturbance induced at the beginning of the operation than by the effect of clamping. Endotoxin and proinflammatory mediators have been detected in the portal vein by several investigators⁴³. Our findings of an early increase in IL-6 levels in the mesenteric vein are in agreement with these reports. The significantly increased IL-6 levels in the mesenteric vein compared to systemic levels support the notion that IL-6 may be locally released by activated gut macrophages. Oxidative stress may have triggered

this release of cytokines and induced the inflammation⁴⁴. Endotoxin may be neutralized by several factors, e.g., plasma proteins, lipids, which may affect endotoxin measurement and the interpretation of results. Other mediators may be easier to determine and may help to provide additional information on the effect of ofloxacin treatment. IL-6, procalcitonin and neopterin, which are known to be increased in SIRS and sepsis,^{45, 46, 47} were not affected by ofloxacin treatment.

The identification of patients at risk for complications may have definite clinical benefit. There were 5 patients with complications (20%) recorded in the study; patients treated additionally with ofloxacin did not experience significantly fewer complications. The efficacy of antibiotic prophylaxis has been recently demonstrated in a multicenter trial⁴⁸.

While endotoxin plasma levels in thoracoabdominal aortic aneurysm repair are correlated with CD11b expression, a marker of neutrophil activation, which predicts postoperative complications,⁴⁹ low concentrations of endotoxin were not associated with complications in this study.

In a recent European multicenter study, surgical intensive care patients with complicated outcome showed significantly decreased endotoxin neutralizing capacity of the plasma compared to controls^{50,50} however, this study did not detect any differences between patients with and without complications, although patients treated with ofloxacin had increased endotoxin neutralizing capacity shortly after clamping of the aorta. IL-6 increased significantly early during the aortic aneurysm repair in patients with complicated follow-up. The increased IL-6 levels in the splanchnic vessel system suggest that the gut and the local proinflammatory cytokine production may have a major impact on the development of septic complications. Local cytokine production and immune compartmentalization are major factors in the development of intra-abdominal sepsis^{51,51}.

Procalcitonin levels did not predict complications in patients in this study. In patients with neuroendocrine tumors high levels of these peptides were detected, indicating that factors other than systemic inflammatory response syndrome (SIRS) alone may influence PCT release⁴⁶. Despite reports that procalcitonin may be an appropriate marker for indicating the early development of severe noninfective SIRS⁵² the predictive value of PCT for a forthcoming multiple organ failure remains to be established⁵³. Neopterin, a marker of macrophage activation⁵⁴ may discriminate between survivors and non-survivors, and between septic and non-septic patients,⁵⁵ which are increased in burn patients⁵⁶ and may be a predictor of shock⁵⁷. In a hemorrhagic traumatic shock model LPS induced a systemic release of

neopterin in septic animals⁵⁸. Most of these studies investigated the release of neopterin in sepsis and severe SIRS. However, in this clinical model of moderate ischemia-reperfusion neopterin failed to demonstrate a difference in clinical complications. However, a significant increase of neopterin may have occurred later as in burn patients three days post-burn⁵⁹.

CONCLUSION

In conclusion, in abdominal aortic aneurysm repair there is an increase of endotoxin-induced proinflammatory mediators. Ofloxacin may have reduced the amount of Gram-negative pathogens but this may have been outweighed by other factors leading to an activation of the limulus amebocyte lysate test system. Ofloxacin treatment increased the endotoxin neutralizing capacity, but did not affect the levels of proinflammatory mediators with the exception of IL-6 levels, at least in this study. Complications were preceded by an early, significant increase of IL-6, which may be released from local gut-activated macrophages. Other mediators, e.g., procalcitonin, neopterin, were not sensitive enough to predict adverse outcome.

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