The Inflammatory Response Following Treatment of Abdominal Aortic Aneurysms: a Comparison Between Open Surgery and Endovascular Repair

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Objectives: to compare the inflammatory response following endovascular and conventional AAA repair.

Design: prospective study.

Patients and methods: ten patients were selected for open surgery (OPEN) and ten for endovascular (ENDO) AAA repair. Leukocytes, platelets, myeloperoxidase, lactoferrin, β-thromboglobulin, C-reactive protein (CRP), interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α) and complement activation products were measured before, during and after surgery.

Results: in the OPEN group the median hospital stay was longer (6 vs. 12 days, \( p = 0.001 \)) and more patients required transfusion \( (p = 0.02) \). IL-6 and CRP increased postoperatively, most in OPEN \( (p < 0.01) \). Platelet counts decreased after the first angiography in ENDO \( (p < 0.01) \) and before aortic cross-clamping in OPEN \( (p < 0.05) \). The decrease was larger in OPEN \( (p = 0.02) \). Leukocyte counts decreased after the first angiography in ENDO and thereafter increased \( (p = 0.001) \). An equivalent increase was observed in OPEN after declamping \( (p = 0.001) \). Leukocyte and platelet degranulation products increased after the first angiography in ENDO and after declamping in OPEN. Changes in complement activation products were small. TNF-α did not change significantly.

Conclusion: endovascular AAA repair caused significant leukocyte and platelet activation. Based on the timing of activation this could be caused by radiographic contrast media.

Key Words: Aortic aneurysm; Endovascular graft; Inflammation; Leukocytes; Platelets; Contrast media.

Introduction

Inflammation is a normal reaction to tissue injury and infection, permitting defence and subsequent healing. If inappropriately activated, however, the inflammatory mechanisms may cause thrombosis or bleeding, oedema formation and organ dysfunction. Both conventional surgery and endovascular repair of infrarenal abdominal aortic aneurysms (AAA) induce unwanted systemic inflammatory responses. There is evidence of neutrophil recruitment, adhesion to graft material, consumption, and degranulation. Decreases of platelet counts after stent-graft placement and adhesion of platelets to graft material have also been noted. Patients with AAA have an activated coagulation system, with even higher levels of activation observed during open surgery. Activation of the complement system has been demonstrated both during conventional and endovascular operations. Increased concentrations of C-reactive protein (CRP) and cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) were observed after both procedures, and increases in TNF-α and IL-6 have also been registered preoperatively. There are indications that manipulation of the aneurysms during stent graft placement with release of thrombotic contents may initiate cytokine production with resultant intraoperative hypotension.

During endovascular placement of stent grafts it is necessary to inject radiographic contrast medium to achieve exact positioning and to check for leakage after the procedure. Data on the ability of non-ionic contrast media (CM) to induce inflammatory responses...
are inconclusive. CM have effects on platelet degranulation but not on adhesion or aggregation.\textsuperscript{20-24} There are reports that CM stimulate production of cytokines such as TNF-\(\alpha\).\textsuperscript{25} Some authors have shown activation of complement with consumption of C3 and C4 and production of C3b and C5a.\textsuperscript{26-28} Others have found no activation or even inhibition of complement.\textsuperscript{29-32} CM are reported to give increased numbers of neutrophils, but no degranulation.\textsuperscript{30,33,34}

It is anticipated that the operative trauma following endovascular AAA repair will be smaller than following open surgery. Thus, endovascular treatment should theoretically lead to less extensive systemic inflammation than conventional surgery. Some earlier studies have questioned this hypothesis.\textsuperscript{4,6,18,19} The aim of the present study was therefore to compare inflammatory reactions during and after conventional open surgery and endovascular treatment for infrarenal abdominal aortic aneurysms.

Patients and Methods

Twenty consecutive patients with asymptomatic infrarenal AAAs were included in the study. Indications for treatment were determined by the size of the aneurysm (diameter >50 mm) and the patient’s general medical condition. All patients were considered fit for open surgery and there were no differences in preoperative risk factors between the groups. The protocol was based on a previous pilot study including three patients treated by endovascular technique, performed to evaluate the sampling time points. Both the pilot and the final study were approved by the local ethics committee. All patients gave informed consent.

Endovascular group

Ten consecutive patients with infrarenal abdominal aneurysms considered anatomically suitable were treated with a transfemorally placed polyester/nitinol stent graft (Vanguard, Boston Scientific, Oakland, NJ, U.S.A.) as previously described.\textsuperscript{35,36} Bifurcated grafts were used in all patients. Nine were operated on under regional anaesthesia.\textsuperscript{37} One patient had general anaesthesia because he was on warfarin. All patients received 5000 IU of heparin i.v. after exposure of the common femoral artery, and butylscopolamine 20 mg was administered before the first angiography. The first dose of radiographic CM (Omnipaque 200 mg/ml, Nycomed Amersham, Oslo, Norway) was given before start of the surgical procedure in the groin (two patients) or within 7-30 min thereafter. If necessary, i.v. nitroglycerine was given to reduce systolic blood pressure below 130 mmHg during deployment of the main part of the stent graft into the aorta.

Conventional surgery group

Ten consecutive patients considered anatomically unsuitable for stent-grafting were included in the “OPEN” group and treated with conventional surgery. The aneurysm was replaced with a gelatine-coated polyester graft (Braun Unigraft, B. Braun Melsungen AG, Melsungen, Germany) through a midline laparotomy incision. The exclusion criteria for endovascular treatment were mainly a short infrarenal neck and/or dilated common iliac arteries.\textsuperscript{39} Cross-clamping was performed below the renal arteries in all patients. Three patients had tube, seven bifurcated grafts. All patients were given general anaesthesia and received 5000 IU of heparin i.v. before cross-clamping of the aorta.

In both groups, the patients received 2 g cephalothin (Keitin, Eli Lilly, Indianapolis, IN, U.S.A.) before the operation and then 1 g every 8 h for 2 days. All patients received 500 ml dextran 70 (Macrodex, Pharmalink, Spånga, Sweden) on the day of implantation, the first postoperative day and every other day thereafter until mobilisation.

Blood sampling

Blood samples, with or without anticoagulants (see below), were drawn at the following time points: in the morning before anaesthesia; after exposure of the common femoral artery (ENDO) or the abdominal aorta (OPEN); 10 min after the first angiography (ENDO) or after declamping of the aorta (OPEN), at the end of the operation, 8 h after the operation, and every morning at 08:00 during the hospital stay. Due to different technique, not all the blood sampling points were equal. The measured parameters in the two groups were therefore compared using maximal values or increases, avoiding direct comparisons at the different time points. Samples for standard haematology analysis were stored for a maximum of four hours at 4-8 °C. All other samples were stored for a maximum of 8 h on ice (plasma) or at room temperature (serum) before centrifugation. Plasma or serum was stored at \(-70\) °C until analysis.
Laboratory tests

Haemoglobin (Hgb), haematocrit and platelet and leucocyte counts were determined in an automated haematology instrument (Coulter STKS, Coulter Corp., Miami, FL, U.S.A.). CRP, bilirubin, haptoglobin, lactate dehydrogenase (LD), activated partial thromboplastin time (APTT), and fibrinogen were measured by standard laboratory methods. Granulocyte activation was assessed by concentrations of the degranulation products myeloperoxidase (MPO) and lactoferrin (LF) in ethylene–diamine–tetraacetic acid (EDTA) containing plasma, measured in enzyme immunoassays (EIA) as previously described.38,39 Platelet degranulation was assessed by determination of β-thromboglobulin (BTG) closure because of bleeding from the proximal anastomosis. He underwent reoperation again the next day with resection of a short segment of small bowel because of ischaemia, and was discharged from hospital after 45 days. No other major complications were observed in the OPEN group. There was no early mortality (<30 days) in either group.

Acute-phase indicators

In both groups IL-6 increased significantly from the termination of the operation to the last sample drawn (first postoperative morning). The maximal increases were 134 pg/ml (102–209 pg/ml) (ENDO) and 379 pg/ml (216–915 pg/ml) (OPEN) (intergroup difference: p<0.01). The body temperature increased postoperatively in both groups. The maximal temperatures were 38.3°C (38.2–38.4°C) (ENDO) and 38.3°C (37.9–38.6°C) (OPEN) (intergroup difference: p = 0.91).

Leukocytes

The leucocyte counts (Fig. 1) decreased from 4.9 × 10⁹/l (4.1–6.3 × 10⁹/l) to 4.4 × 10⁹/l (3.6–6.1 × 10⁹/l) after the first angiography in the ENDO group (p<0.01), and thereafter increased (p<0.001). In the OPEN group, leucocyte counts started increasing after declamping of the aorta (p<0.001). In both groups, the counts were comparable to baseline on the fifth postoperative day. The maximal increase from baseline was 3.7 × 10⁹/l (2.5–4.7 × 10⁹/l) (ENDO) and 5.1 × 10⁹/l (3.9–5.9 × 10⁹/l) to open surgery. Two patients had early endoleaks into the aneurysmal sac. In one patient a leak from the left iliac artery was treated with coiling of the internal iliac artery and extension of the stent graft to the external iliac artery. This patient later developed retrograde filling of the aneurysm from the inferior mesenteric and lumbar arteries and the aneurysm diameter increased slowly. Coiling of the inferior mesenteric artery did not stop the growth and a laparoscopic ligation of the artery was recently assessed by concentrations of the degranulation products myeloperoxidase (MPO) and lactoferrin (LF) in ethylene–diamine–tetraacetic acid (EDTA) containing plasma, measured in enzyme immunoassays (EIA) as previously described.38,39

Statistics

Results are presented as medians with 95% non-parametric confidence intervals due to non-normal distribution of several variables. Data were analysed by two-way repeated measures analysis of variance (ANOVA), in most cases after rank transformation to achieve appropriate model fit. Subsequent within-group comparisons were performed with Friedman’s test, and between-group comparisons with the Mann–Whitney U-test. Correlations between maximal MPO, LF, and BTG concentrations and total contrast dose were analysed using Spearman’s rank-correlation coefficient. p-Values below 0.05 were considered significant.

Results

Patient characteristics are given in Table 1. In the ENDO group no patients experienced intra- or postoperative hypotension and there were no conversions
Inflammatory Response Following AAA Repair

Table 1. Patient and treatment data for ten patients treated with endovascular repair (ENDO) or open surgery (OPEN) for AAA. (Medians with 95% non-parametric confidence intervals).

<table>
<thead>
<tr>
<th>Data Description</th>
<th>ENDO</th>
<th>OPEN</th>
<th>p-Value¹</th>
</tr>
</thead>
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<tr>
<td>Age (years)</td>
<td>73 (68–77)</td>
<td>69 (64–76)</td>
<td>0.74</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>7</td>
<td>1.00</td>
</tr>
<tr>
<td>Aneurysm diameter (mm)</td>
<td>58 (53–63)</td>
<td>57 (53–67)</td>
<td>0.82</td>
</tr>
<tr>
<td>Graft type (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tube</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Bifurcated</td>
<td>10</td>
<td>7</td>
<td>0.21</td>
</tr>
<tr>
<td>Radiographic contrast volume (ml)</td>
<td>300 (239–361)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Operating time (min)</td>
<td>175 (150–201)</td>
<td>215 (184–316)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>6 (5–9)</td>
<td>12 (8–26)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of patients transfused (n)</td>
<td>1</td>
<td>7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

¹ p-Values are calculated by Mann–Whitney U-test or Fisher’s exact test.

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Fig. 1. Leukocyte counts (×10⁹/l, medians and 95% non-parametric confidence intervals) during endovascular (open squares) and open (filled squares) AAA treatment. Time points are before anaesthesia, after exposure of common femoral artery or abdominal aorta, ten minutes after first angiography (arrowhead) or after aortic declamping, at termination of the operation (arrow), 8 h postoperatively, first, second, and fifth postoperative morning (note change of scale on x-axis). Intergroup difference in maximal increase: p = 0.06.

(open) (intergroup difference: p = 0.06). A similar pattern was seen for neutrophil counts, but the differences between the groups were smaller (data not shown).

MPO increased in the ENDO group after the first angiography (p<0.01) and in the OPEN group after declamping of the aorta (p<0.001) (Fig. 2). The maximal increases in MPO were 682 µg/l (497–1471 µg/l) (ENDO) and 645 µg/l (419–948 µg/l) (OPEN) (intergroup difference: p = 0.55).

LF showed the same pattern as MPO with an in-
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Fig. 2. Myeloperoxidase (µg/l, medians and 95% non-parametric confidence intervals) during endovascular (open squares) and open (filled squares) AAA treatment. Time points are before anaesthesia, after exposure of common femoral artery or abdominal aorta, ten minutes after first angiography (arrowhead) or after aortic declamping, at termination of the operation (arrow), 8 h postoperatively, first, second, and fifth postoperative morning (note change of scale on x-axis). Intergroup difference in maximal increase: $p = 0.55$.

crease after the first angiography in the ENDO group ($p<0.05$) and after declamping in the OPEN group ($p<0.001$). The maximal increases in LF were 388 µg/l (246–666 µg/l) (ENDO) and 490 µg/l (328–684 µg/l) (OPEN) (intergroup difference: $p = 0.43$).

Platelets

Platelet counts (Fig. 3) decreased in both groups starting after exposure of the aorta and before cross-clamping in OPEN ($p<0.05$) and after the first angiography in ENDO ($p<0.01$). The maximal decreases were $47 \times 10^9$/l (30–63 $\times 10^9$/l) (ENDO) and $84 \times 10^9$/l (58–116 $\times 10^9$/l) (OPEN) (intergroup difference: $p = 0.02$), and the counts were comparable to baseline on the fifth postoperative day.

BTG started increasing at the termination of the operation in ENDO ($p<0.001$) and after declamping in OPEN ($p<0.05$) (Fig. 4). The maximal BTG increases were 87 IU/ml (45–136 IU/ml) (ENDO) and 63 IU/ml (22–97 IU/ml) (OPEN) (intergroup difference: $p = 0.23$).

Complement

There were no significant changes in the complement activation products C3bc and TCC (data not shown). C5a-des-Arg decreased non-significantly during the operation in both groups, probably due to haemodilution. Postoperatively, there was a significant increase in C5a-des-Arg in both groups ($p<0.001$), and concentrations remained elevated until discharge. The maximal increases were 20.2 ng/ml (11.4–29.5 ng/ml) (ENDO) and 8.9 ng/ml (4.7–14.6 ng/ml) (OPEN) (intergroup difference: $p = 0.02$).

TNF-α and TNF receptors

There were no significant changes in TNF-α in either group (data not shown). The concentrations of TNF receptor I (p55) increased slightly until the last sampling point on the first postoperative morning in both groups ($p<0.001$). The maximal increases were 2.4 ng/ml (1.1–6.4 ng/ml) (ENDO) and 3.7 ng/ml (2.3–9.2 ng/ml) (OPEN) (intergroup difference: $p = 0.21$). There was a small postoperative increase in TNF receptor II...
Fig. 3. Platelet counts ($\times 10^9/l$, medians and 95% non-parametric confidence intervals) during endovascular (open squares) and open (filled squares) AAA treatment. Time points are before anaesthesia, after exposure of common femoral artery or abdominal aorta, ten minutes after first angiography (arrowhead) or after aortic declamping, at termination of the operation (arrow), 8 h postoperatively, first, second, and fifth postoperative morning (note change of scale on x-axis). Intergroup difference in maximal increase: $p=0.02$.

Fig. 4. $\beta$-Thromboglobulin (IU/ml, medians and 95% non-parametric confidence intervals) during endovascular (open squares) and open (filled squares) AAA treatment. Time points are before anaesthesia, after exposure of common femoral artery or abdominal aorta, ten minutes after first angiography (arrowhead) or after aortic declamping, at termination of the operation (arrow) and 8 h postoperatively. Intergroup difference in maximal increase: $p=0.23$. 

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(p75) without intergroup differences (p = 0.9) (data not shown).

**Haemoglobin and transfusions**

Haemoglobin concentrations decreased from 12.0 g/dl (10.9–13.1 g/dl) to 10.5 g/dl (9.3–11.5 g/dl) (ENDO) and from 13.1 g/dl (12.2–14.2 g/dl) to 10.6 g/dl (10.1–11.0 g/dl) (OPEN) on the fifth postoperative day. The maximal Hgb decrease was larger in the OPEN group (p = 0.02). In the OPEN group seven patients received a median of three (0.5–5) units of packed red cells as opposed to one patient (two units) in the ENDO group (Table 1).

**Coagulation, fibrinolysis, and haemolysis**

The APTT was increased in both groups at termination of the operation (p<0.001). The increase from baseline was larger in ENDO (110 sec (75–151 s)) than in OPEN (36 s (13–76 s)) (p = 0.01) in keeping with the higher heparin doses given. The APTT was normalised 8 hours postoperatively.

Fibrinogen concentrations decreased slightly but still remained within normal limits until 8 hours postoperatively (p<0.01) in both groups, then increased equivalently in both groups (p<0.001) and remained slightly elevated throughout the hospital stay. The concentrations on the fifth postoperative day were 5.8 g/l (5.0–6.7 g/l) (ENDO) and 5.8 g/l (4.9–6.9 g/l) (OPEN).

There were no signs of haemolysis as measured by changes in haptoglobin and bilirubin (data not shown). LD concentrations increased significantly in both groups (p<0.05) to 337 U/l (289–528 U/l) (ENDO) and 442 U/l (358–592 U/l) (OPEN). The maximal increase was larger in OPEN (p = 0.02).

**Contrast volume**

The patient groups were small, and we found no significant correlations between total contrast volume given and maximal MPO (ρ = 0.653, p = 0.057), LF (ρ = 0.453, p = 0.242), or BTG (ρ = 0.471, p = 0.201) concentrations.

**Discussion**

Some of the biochemical indicators (IL-6, CRP and platelet counts) used in the present investigation show that the operative trauma was more pronounced with open surgery compared to endovascular AAA repair. Both the operating time and the hospital stay were significantly longer following open operations, although the patients in the ENDO group stayed in hospital between one and three days more than necessary for their condition, to have various blood tests and a computed tomography scan performed before discharge. The OPEN group also needed more blood transfusions. The higher concentrations of LD in the OPEN group probably reflected tissue damage rather than haemolysis, since there were no significant changes in haptoglobin or bilirubin concentrations.

In keeping with previous observations, the acute phase indicators IL-6 and CRP increased more in the OPEN group than in the ENDO group. IL-6 is a cytokine secreted by mononuclear phagocytes, endothelial cells and T-lymphocytes. It induces production of acute-phase proteins such as fibrinogen and CRP in the liver. IL-6 secretion takes place both during open surgery and endovascular treatment for AAA as well as following ischemia/reperfusion injury and after exposure of leukocytes to vascular graft materials. Swartbol et al. have shown high concentrations of IL-6 in supernatants from AAA thrombotic contents.

Even the patients undergoing endovascular repair showed evidence of a significant inflammatory reaction intra- and postoperatively. In the ENDO group an initial decrease in leukocyte counts was followed by an increase. This pattern is typical for systemic granulocyte activation, where an increased adhesion and entrapment in the peripheral circulation is followed by a reactive recruitment from bone marrow and spleen. In the OPEN group no initial decrease was observed and the increase was higher. The release of MPO and LF was comparable in both groups.

The decrease in platelet counts was more pronounced in the OPEN group, but activation of platelets measured by the release of BTG was not significantly different in the two groups. On the contrary, BTG concentrations tended to remain higher postoperatively in the ENDO group. Thus, endovascular treatment neither reduced granulocyte nor platelet activation as compared to conventional surgery.

In the ENDO group the activation of both leukocytes and platelets was seen following the first angiography, and before cross-clamping of the actual lower limb. This could indicate that the injection of contrast media (CM) played a major part in inducing activation. Several investigators have shown degranulation of platelets induced by non-ionic CM, but not degranulation of granulocytes. In the OPEN group
the increases of platelet and leukocyte degranulation products were seen mainly after declamping, and not following exposure of the aorta. This supports the view that the relatively minor surgery connected with endovascular repair did not induce degranulation. Heparin was given before angiography and is known to activate platelets and prime neutrophils, but not, alone, to lead to neutrophil degranulation. Furthermore, ischaemia/reperfusion injury could not explain the degranulation, since the actual lower limb was reperfused at a later time. However, the blood sampling points during operations are not directly comparable between the two groups, due to the different techniques.

In the OPEN group the activation could be explained by multiple factors. These patients were also given heparin. The tissue damage was more extensive. Finally, activation of platelets and leukocytes are induced by the inserted vascular graft material and ischaemia/reperfusion injury.

There were only small changes in complement-activation products in our study. Other investigators have shown such complement activation by different graft materials, even gelatine-coated polyester grafts. We do not know why our data differ from these earlier studies. However, we conclude that both of the procedures used in this protocol showed a high degree of complement compatibility.

In the present study there was no increase in TNF-α, but a minor increase in the circulating TNF receptor p55 was seen in both groups. Neutrophils shed TNF receptors in the early stages of activation and this could be regarded as a regulatory mechanism both prohibiting higher levels of free TNF-α and extensive granulocyte activation, which might have harmful effects to the patient. Other investigators have found an increase in TNF-α following endovascular AAA repair. This has been explained as a consequence of IL-6 release from thrombotic contents because of mechanical manipulation during stent graft deployment. IL-6 in turn stimulates secretion of TNF-α which could be responsible for the episodes of decreased blood pressure observed. We did not see any episodes of significant hypotension in our patients treated by endovascular technique.

In conclusion, the present study confirms that endovascular AAA repair is less traumatic than open surgery. However, the endovascular technique caused significant leukocyte and platelet activation. The timing of activation suggests a relationship to the administration of radiographic CM. The contribution to activation from CM compared to graft-material reactions, tissue damage and ischaemia/reperfusion injury warrants further investigation.

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