

Dynamics of Inflammatory Parameters After Endovascular and Open Infrarenal Abdominal Aneurysm Repair

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ABSTRACT

Background: The aim of this study was to investigate the dynamics of inflammatory parameters in patients after infrarenal abdominal aneurysm surgery.

Methods: The retrospective study included patients with operated infrarenal abdominal aneurysm, divided into two groups: (i) patients receiving endovascular aneurysm repair (EVAR); (ii) patients that had open surgery. General data and inflammatory parameters (CRP, leukocytes, platelets and fibrinogen) were taken during hospitalization, compared mutually and analyzed.

Main findings: All inflammatory parameters, observed preoperatively, were close to the referent range. Serum CRP values leukocyte counts in EVAR patients raised after operation, but returned to the reference range more quickly. Around the middle of their hospital stay and at day of discharge, the open surgery group had statistically significantly higher platelet values than the EVAR group. During the preoperative period and in the middle of hospitalization, the open surgery group showed higher fibrinogen values, while at day of discharge, the EVAR group showed statistically significantly higher fibrinogen values.

Principal conclusions: Observed serum inflammatory parameters (CRP, leukocytes, fibrinogen and platelets) in different phases of hospitalization were lower and closer to the reference value in patients with infrarenal abdominal aneurysm who received EVAR compared to patients receiving open surgery. All observed parameters other than fibrinogen returned to the reference value faster in EVAR patients.

Key words: abdominal aortic aneurysm, endovascular aneurysm repair, inflammatory parameters

Article processing history:

Received March 25, 2023

Revised May 28, 2023

Accepted June 23, 2023

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Cite this article as: Stipić J, Rastović P, Bogdan G. Dynamics of Inflammatory Parameters After Endovascular and Open Infrarenal Abdominal Aneurysm Repair. Annals of Biomedical and Clinical Research. 2023;2:126-134.

<https://doi.org/10.47960/2744-2470.2023.2.2.127>

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INTRODUCTION

The aortic aneurysm is defined as a localized and irreversible increase of 50 % in diameter compared to normal aorta diameter values. An aneurysm can occur in any artery, but the aortic aneurysm is the most common location, especially the infrarenal part (1). There are true and false aneurysms, relating to layers of the artery wall (2). It is estimated that between 4% and 8% of men, and between 0.5% and 2% of women over the age of 60, have an abdominal aortic aneurysm (AAA) (3).

The etiology of abdominal aneurysms is multifactorial and ultimately leads to thinning of the artery wall due to a lack of elasticity which, combined with blood pressure, tends to lead to growth and fatal rupture (4). It has been observed that aneurysms and atherosclerosis are connected, since they coexist and share the same risk factors. However, unlike atherosclerosis, inflammatory processes are more common with aneurysms and dilated blood vessels. A feature of aneurysm is the loss of elastin and collagen, which is directly connected to metalloproteinases activity and, furthermore, apoptosis of smooth muscle cells and inflammatory infiltration of the vessel wall. Other risk factors are similar to atherosclerotic risks, including an unhealthy lifestyle, physical inactivity, a cholesterol-rich diet, smoking and endogenous factors such as age, sex and immunological status (5,6). The most important reversible cause of the aneurysm is smoking, while the most important irreversible cause is genetics. The risk of AAA increases if it is present in the first generation of a family and it is more often associated with diseases such as hypertension, hypercholesterolemia and diabetes mellitus (7,8). An aneurysm can also be related to Ehlers-Danlos and Marfan syndromes in younger people (9,10).

In the majority of patients with abdominal aneurysms, discovery is coincidental. A smaller proportion of patients experiences symptoms such as pain arising from compression of surrounding structures or from

circulatory insufficiency of abdominal aortic branches. In countries with AAA screening programs, at-risk groups are screened carefully. Aneurysms are proven by radiological examinations, the Color Doppler test (CD), Multi-Slice Computed Tomography (MSCT angiography) and sometimes via Magnetic Resonance Imaging (MRI) (11).

The definitive treatment of AAA is surgical, primarily depending on its size. The main approaches are open surgery, where a synthetic graft is implanted, and endovascular aortic repair (EVAR), involving endovascular insertion of the graft into the lumen of the vessel (12). Post-implantation syndrome (PIS) is a term used to encompass a clinical entity characterized by systemic inflammation following the treatment of an abdominal aneurysm with a synthetic graft. Its significance for recovery and prognosis is still unclear (13,14). The main features of PIS include persistent pyrexia despite antibiotic therapy, negative culture results in terms of microbiological processing/tests, leukocytosis and/or coagulation disorders (15,16). The frequency of PIS varies greatly, between 3% and 60% for AAA-operated patients (17). The increase in other inflammatory parameters after aortic surgery is soon recognized and occurs both after open surgeries and after EVAR. A significant increase in almost all known measurable inflammatory parameters has been demonstrated, including C-reactive protein (CRP), leukocytes, tumor necrosis factor, interleukin-8, complementary components and coagulation factors (14). Interestingly, the level of inflammatory parameters in PIS corresponds to severe inflammatory conditions, such as sepsis, but does not have the same clinical significance. By taking and analyzing blood and body fluid samples for microbiological tests, the cause of elevated inflammatory parameters is generally not found; hence, these tests are not routinely performed after abdominal aneurysm surgery (18). A high postoperative inflammatory response raises concerns about postoperative morbidity, particularly in high-risk patients

including older people who have several comorbidities. In most cases, PIS is generally well tolerated, but even so, it can result in a more demanding postoperative recovery leading to prolonged hospitalization and therefore it can be considered a moderate complication of aortal repair (19).

The aim of the present study was to investigate the dynamics of inflammatory parameters (CRP, leukocytes, platelets and fibrinogen) in patients after infrarenal abdominal aneurysm surgery and to compare the values between those receiving open surgery and those receiving EVAR.

MATERIALS AND METHODS

Participants

The study group comprised patients with an infrarenal aneurysm of the abdominal aorta who underwent surgical treatment at the Department of Surgery and the Department of Radiology of the University Clinical Hospital Mostar during the period of March 15th 2016 to March 15th 2022. The patients were divided into two groups: those who received EVAR and patients who received open aortic bypass surgery with a synthetic graft.

Methods

Patient data were obtained retrospectively from the institutional Health Information System database and medical paper records. Studied parameters were: age, sex, type of treatment, diameter of the abdominal aneurysm, status of the aneurysm, type of implanted graft, leukocytes (impedance and volumetry, no./L), CRP (immunoturbidimetry, mg/L), fibrinogen (g/L), platelets (109/L) and length of hospital stay in days. Blood samples were obtained the day the patients were hospitalized, the day after surgery, during the middle of their hospital stay and on day of discharge.

Statistical analysis

For statistical analysis of the obtained data, the statistical package IBM SPSS Statistics v.21 was used. Percentages and frequencies are shown for those data with categorical variables, while continuous variables are shown using descriptive parameters (median, arithmetic mean and standard deviation). The chi-square test and Fisher's exact test were used to compare categorical variables, Student's t-test was used to test differences between continuous variables and Wilks' lambda test was used to compare dependent variables. Differences of $p < 0.05$ were taken as statistically significant and p-values that could not be shown to three decimal places were shown as $p < 0.001$.

RESULTS

There were 84 patients included in the study, with significantly more men ($n=77$) than women ($n=7$). The most frequently operated were the unruptured aneurysms of the infrarenal part of the abdominal aorta. In the postoperative period, there were mostly no confirmed infections, which occurred more often in patients receiving open surgery. Survival was very high and there were no differences between the two groups (Table 1). The mean (SD) age of all patients was 67.85 ± 6.92 years (range 52-85 years). There was no significant difference in age between open surgery patients (66.96 ± 7.12 years) and EVAR patients (68.92 ± 6.61 years). There was no statistically significant difference in aneurysm diameter between open surgery patients (6.79 ± 1.97 cm) and EVAR patients (6.18 ± 1.25 cm). Open surgery patients had a longer postoperative hospital stay than EVAR patients (13.28 ± 4.09 days vs. 7.08 ± 2.48 days).

Table 1. Demographic and clinical characteristics of patients (n=84) with infrarenal abdominal aneurysm who underwent surgery

	Group				χ^2	p
	Open surgery		EVAR			
	n	%	n	%		
Sex					0.070	0.696*
Male	43	93.5	34	89.5		
Female	3	6.5	4	10.5		
Aneurysm status					7.323	0.017*
Unruptured aneurysm	33	71.7	36	94.7		
Ruptured aneurysm	10	21.7	2	5.3		
Threatening rupture	3	6.5	0	0.0		
Infection during treatment					8.461	0.004*
Not confirmed infection	35	76.1	38	100.0		
Confirmed infection	11	23.9	0	0.0		
Outcome					0	1*
Survival	45	97.8	38	100.0		
Death	1	2.2	0	0.0		

*Fisher's exact test

All preoperative observed inflammatory parameters were close to reference ranges in both groups. Serum CRP, leucocytes, platelets and fibrinogen values were compared between the groups at four time periods: preoperatively, the first postoperative day, in the middle of their hospitalization and on day of discharge. At all examined time periods, these parameters were statistically significantly higher in the open surgery group, except for the preoperative period where there was a statistically significant difference between leukocytes and CRP, and at day of discharge, where EVAR patients had higher fibrinogen serum level values (Table 2).

The level of the serum value of CRP in open surgery patients changed significantly during hospital stay, with the peak value recorded in the middle period of hospitalization. Similar dynamics of serum CRP values were observed

EVAR patients. In both groups, the differences were statistically significant even after comparison within the same group with regard to periods of hospitalization (Table 3).

The level of leukocytes in the peripheral blood in open surgery patients changed significantly during hospital stay, with the peak value recorded in the period of the first postoperative day. In EVAR patients, the highest values were recorded in the middle of their hospitalization period. In both groups, the differences were statistically significant in most cases and after comparison within the same group with regard to periods of hospitalization (Table 4).

The value of platelets in peripheral blood in open surgery patients changed significantly during hospital stay, with the biggest drop recorded on the first postoperative day.

Table 2. Inflammatory parameters at different time periods of hospitalization in relation to type of infrarenal abdominal aneurysm surgery

	Group				t	p
	Open surgery		EVAR			
	$\bar{X}$	SD	$\bar{X}$	SD		
CRP preoperative	10.378	19.377	4.279	6.345	2.008	0.049
Leukocytes preoperative	9.351	4.338	6.084	0.777	5.010	<0.001
Fibrinogen preoperative	3.572	0.538	3.461	0.525	0.955	0.342
Platelets preoperative	220.870	52.591	210.658	30.668	1.108	0.271
CRP first postoperative day	100.772	52.070	26.949	12.001	9.321	<0.001
Leukocytes first postoperative day	12.996	3.862	9.726	2.123	4.913	<0.001
Fibrinogen first postoperative day	3.570	1.004	2.774	0.449	4.826	<0.001
Platelets first postoperative day	165.087	53.875	165.184	21.735	0.011	0.991
CRP mid-hospitalization	162.080	62.203	121.358	25.247	4.054	<0.001
Leukocytes mid-hospitalization	9.426	3.300	9.780	1.984	0.606	0.546
Fibrinogen mid-hospitalization	5.491	1.156	4.961	0.689	2.605	0.011
Platelets mid-hospitalization	194.630	75.329	145.158	19.197	4.289	<0.001
CRP day of discharge	70.559	43.116	55.000	17.528	2.234	0.029
Leukocytes day of discharge	8.207	2.321	7.229	1.140	2.513	0.014
Fibrinogen day of discharge	5.057	1.044	5.510	0.404	2.710	0.009
Platelets day of discharge	291.500	106.719	188.579	28.995	6.267	<0.001

Table 3. Dynamics of CRP values at different time periods of hospitalization

Group	$\bar{X}$	SD
Open surgery ^a	Preoperative	10.38 19.38
	First postoperative day	100.77 52.07
	Mid-hospitalization	162.08 62.20
	Day of discharge	70.56 43.12
EVAR ^b	Preoperative	4.28 6.34
	First postoperative day	26.95 12.00
	Mid-hospitalization	121.36 25.25
	Day of discharge	55.00 17.53

^a Wilks' $\lambda=0.129$; $F(3; 43)=96.924$; $p<0.001$; partial $\eta^2=0.871$ ^b Wilks' $\lambda=0.035$; $F(3; 35)=324.567$; $p<0.001$; partial $\eta^2=0.965$

Table 4. Dynamics of leukocyte (Le) values at different time periods of hospitalization

Group	$\bar{X}$	SD
Open surgery ^a	Preoperative	9.35 4.34
	First postoperative day	13.00 3.86
	Mid-hospitalization	9.43 3.30
	Day of discharge	8.21 2.32
EVAR ^b	Preoperative	6.08 0.78
	First postoperative day	9.73 2.12
	Mid-hospitalization	9.78 1.98
	Day of discharge	7.23 1.14

^a Wilks' $\lambda=0.382$; $F(3; 43)=23.220$; $p<0.001$; partial $\eta^2=0.618$ ^b Wilks' $\lambda=0.178$; $F(3; 35)=53.750$; $p<0.001$; partial $\eta^2=0.822$

In EVAR patients, the greatest drop was recorded in the middle of their hospitalization period. In both groups, the differences were statistically significant in most cases and after comparison within the group with regard to

periods of hospitalization, with the exception of open surgery patients, where there was no significant difference before surgery and after discharge (Table 5).

Table 5. Dynamics of platelets in peripheral blood at different time periods of hospitalization

Group		$\bar{X}$	SD
Open surgery ^a	Preoperative	220.87	52.59
	First postoperative day	165.09	53.87
	Mid-hospitalization	194.63	75.33
	Day of discharge	291.50	106.72
EVAR ^b	Preoperative	210.66	30.67
	First postoperative day	165.18	21.74
	Mid-hospitalization	145.16	19.20
	Day of discharge	188.58	29.00

^a Wilks' $\lambda=0,244$; $F(3; 43)=44,412$; $p<0,001$; partial $\eta^2=0,756$

^b Wilks' $\lambda=0,091$; $F(3; 35)=116,083$; $p<0,001$; partial $\eta^2=0,909$

Table 6. Dynamics of serum fibrinogen values at different time periods of hospitalization

Group		$\bar{X}$	SD
Open surgery ^a	Preoperative	3.57	0.54
	First postoperative day	3.57	1.00
	Mid-hospitalization	5.49	1.16
	Day of discharge	5.06	1.04
EVAR ^b	Preoperative	3.46	0.52
	First postoperative day	2.77	0.45
	Mid-hospitalization	4.96	0.69
	Day of discharge	5.51	0.40

^a Wilks' $\lambda=0,285$; $F(3; 43)=36,001$; $p<0,001$; partial $\eta^2=0,715$

^b Wilks' $\lambda=0,025$; $F(3; 35)=447,951$; $p<0,001$; partial $\eta^2=0,975$

The value of serum fibrinogen in open surgery patients changed significantly during hospital stay, with the peak value recorded in the period in the middle of their hospitalization. In EVAR patients, the highest values were recorded on day of discharge. In both groups, the differences were statistically significant in most cases and after comparison within the group with regard to periods of hospitalization, with the exception of open surgery patients, where there was no significant difference before surgery and on the first postoperative day (Table 6).

DISCUSSION

To our knowledge, our study is the first to analyze the dynamics of inflammatory parameters in this manner and to compare the same dynamics between patients operated on by the classic open surgery method and via EVAR. In the first measurement of observed inflammatory parameters, despite all being close to referent range, there were statistically higher values of CRP and leukocytes. These results were because patients with ruptured AAA had the highest values of CRP and leukocytes, but we did not compare this group of patients because of their small number.

There were significantly more male patients than female patients. The most frequently operated condition was the unruptured aneurysm of the abdominal part of the aorta. The average age of the patients was 68 years old. Patients who received open surgery had a longer stay in hospital. CRP values were significantly higher in open surgery patients at all points of examination. Leukocyte values were also significantly higher in open surgery patients at all periods except in the mid-point of their hospital stay. Platelet values were significantly higher in the open surgery group in the middle of their hospital stay and on day of discharge. Fibrinogen values were higher at all examined periods in open surgery patients, except at the preoperative period, when there was no statistically significant difference, and after discharge, when EVAR patients had higher values.

However, compared to the healthy population, some inflammatory parameters such as CRP, leukocytes, circulating cytokines and immunoglobulins can be basically elevated in patients with abdominal aneurysm (20). The growth of inflammatory parameters immediately after surgery, the reaching of peak values and the gradual decrease and approach of a reference range in this sample was obvious, as well as the differences between patients receiving open surgery and patients receiving EVAR. Generally speaking, EVAR patients had, on average, serum values of the observed parameters that were closer to the reference range and they approached this point faster. Tissue damage in ruptured aneurysms raises serum CRP values through the mechanism of an aseptic inflammatory process. Since EVAR is a less aggressive treatment, there is less operative trauma to the entire organism and CRP values are lower compared to patients receiving open surgery. The results of Tambyraj et al. support these claims; however, they did not find significant differences in CRP values between patients who survived surgery and those who did not, and it therefore remains unclear how important CRP is as a prognostic factor in the

postoperative period. They also did not find any other reason in their sample for elevated CRP except PIS. (21). When comparing CRP values in EVAR patients in regard to the presence of an endoleak (blood extravasation after stent placement), it was found that patients with a larger endoleak have significantly higher CRP values. The mass of the mural thrombus itself, which is formed during the endoleak, is a factor that increases many inflammatory parameters such as CRP and leukocytes (22). Similarly to CRP, leukocytes acting as inflammatory indicators in patients after abdominal aneurysm surgery also show a significant increase, which is not related to possible inflammatory processes and complications (21).

After trauma, which includes aneurysm surgery, leukocytes migrate into the circulation and traumatized tissue, and change the surface expression of adhesion molecules. This process has also been recorded after less traumatic vascular procedures such as balloon dilation of a blood vessel. It is believed that one of the mediators in this reaction is the tumor necrosis factor alpha (TNF- α) released from local tissue (23). Clot formation after vascular surgery is a necessary part of the normal hemostatic process and without which more complications such as bleeding would occur. Abdominal aneurysm surgeries are associated with a procoagulant state, high production and activity of thrombin, fibrinogen and other components of coagulum.

In the process of forming a fresh clot, some components such as platelets are quickly consumed and slowly renewed and, therefore, a decrease can be observed. Three months after the procedure, almost normal coagulation factor values can be observed, although they never reach the reference range. It is believed that the prosthetic material itself provokes a procoagulant state, although it lacks the endothelial fibrinolytic activity of the blood vessel and therefore is at risk of occlusion and consequent circulatory insufficiency. Activities and values of coagulation factors are also

associated with thrombus size, extent of surgery and the status of the aneurysm (24).

In contrast to classic surgery, EVAR patients are expected to be hospitalized less often after treatment. In centers where this procedure is routinely performed, there is almost no need for follow-up in the intensive care unit (ICU); patients only stay for a few hours in the ICU and up to four days on the hospital ward. It is necessary to consider various early and late complications after EVAR, most of which have to be addressed by open surgery. The global trend is to use EVAR where it is not contraindicated (25). Monitoring inflammatory parameters after abdominal aneurysm surgery can point towards complications if their dynamics are not in accordance with expected values and, therefore, they can be a useful indicator in clinical work. In patients whose inflammatory parameters do not decrease or do not return to the reference range with the expected dynamics, it is necessary to look for additional causes of infection and complications, as the cause is not post-implantation syndrome (26).

In the present research, we could not include all patients operated on in the given period. Many were excluded due to non-continuous monitoring of parameters and did not have the necessary laboratory tests. For future studies, we suggest continuous monitoring of all patients, since it is necessary to carry out laboratory tests every other day in order to gain insight into the continuity of the parameters and to investigate other inflammatory parameters such as interleukins and complement components. The purpose of this monitoring would be to try to determine which level and dynamics of inflammatory parameters are acceptable after abdominal aneurysm surgery. All patients with a confirmed infection or complication should be excluded from future work.

ACKNOWLEDGMENTS

None

FUNDING

The author(s) received no financial support for the research, authorship and/or publication for this study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

JS: acquisition of data, literature review, contribution to study conception and design; PR and GB: contribution to study conception and design, literature review, supervision, interpretation of data, critical revision of the paper.

ETHICAL BACKGROUND

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: We deny any restrictions on the availability of data, materials and associated protocols. Derived data supporting the findings of this study are available from the corresponding author on request.

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