PERIODICUM BIOLOGORUM
VOL. 111, No 2, 193–196, 2009

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Original scientific paper

Immune response to surgical stress in spinal anaesthesia

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Key words: spinal anaesthesia, cytokines, immunology

Received April 8, 2004.

Abstract

Background and Aims: *Surgical stress and anaesthesia cause immunosuppression that can predispose patients to postoperative infections and other complications. Anaesthesia may indirectly affect the immune system of surgical patients by modulating neurohormonal stress response. The aim of the study is to establish whether the examined cytokines either individually or in certain correlations may characterise regional (spinal) anaesthesia.*

Patients and Methods: *Nine (9) patients with American Society of Anaesthesiologist status I or II who were scheduled for TURP (transurethral resection of the prostate) were anaesthetised in spinal anaesthesia. .Peripheral venous blood samples were collected 2 hours before surgery, on the first, third and fifth postoperative days. We measured pro-inflammatory cytokines (IL-1α; IL-1β; TNF-α; IL-6; IL-8; MCP-1; VEGF; EGF), anti-inflammatory cytokines (IL-4; IL-10), and cytokines which are secreted by Th 1 helper lymphocytes (IL-2; IFN-γ) in order to establish differences in patients before and after surgery.*

Results: *Serum concentration of pro-inflammatory cytokines (IL-1α; IL-1β; TNF-α;IL-8; MCP-1; VEGF; EGF), anti-inflammatory cytokines (IL-4; IL-10), and cytokines which are secreted by Th 1 helper lymphocytes (IL-2; IFN-γ) show no statistically different values before and after surgery. Only serum concentration of IL-6 was significantly ($P < 0.05$) increased on the first postoperative day and than decreased on the third postoperative day.*

Discussion and Conclusion: *Regional techniques, such as epidural or spinal anaesthesia, with an afferent neural block by local anaesthetics profoundly inhibit hormonal and metabolic stress response. Surgery – related postoperative release of the proinflammatory cytokine IL-6 was increased in patients after spinal anaesthesia with no increased levels of the typical Th1 cytokine IFN-γ and no increase of cytokines such as IL-10 and IL-4, which are associated with T-helper type 2 (Th2)-like immune response. Spinal anaesthesia results in less immunosuppression, i.e. maintains the number of Th1 cells, thus stimulating the cell immunity.*

INTRODUCTION

Injury, surgery or trauma is connected with acute disorder of the immunological system, which manifests as increased inclination to infection *(1)*. However, until today it has not been clearly shown to what extent the type of anaesthesia influences the immune system *(2, 3)*. This phenomenon is primarily characterised by disorder of cell immu-

nity and function of macrophages *(3)*. According to knowledge so far, the relation between Th 1 and Th2 cytokines is increased in spinal anaesthesia, without significant changes in general anaesthesia *(4)*. The purpose of this study was to define the value of pro-inflammatory cytokines (IL-1α; IL-1β; TNF-α; IL-6; IL-8; MCP-1; VEGF; EGF), anti-inflammatory cytokines (IL-4;IL-10), and cytokines which are secreted by Th 1 helper lymphocytes (IL-2; IFN-γ) in order to establish differences in patients before and after surgery *(4, 5)*.

PATIENTS AND METHOD

The study included 9 patients after their informed consent had been obtained. The patients were American Society of Anaesthesiologists (ASA) status I or II, scheduled for Transurethral Resection of Prostatae (TURP). Patients were anaesthetised in regional (spinal) anaesthesia.

Patients with signs of infection, temperature or who had received blood transfusion were excluded from the study.

Peripheral venous blood samples were collected 2 hours before surgery, on the first, third and fifth postoperative days.

The following was determined from the blood samples: preoperative and postoperative values of pro-inflammatory cytokines (IL-1α; IL-1β; TNF-α; IL-6; IL-8; MCP-1; VEGF; EGF), anti-inflammatory cytokines (IL-4; IL-10), cytokines which are secreted by Th 1 helper lymphocytes (IL-2; IFN-γ), leucocytes, CRP and fibrinogen.

Biochip Array Technology is used to perform simultaneous quantitative detection of multiple analytes from a single patient sample. The core technology is the Randox Biochip, a solid-state device containing an array of discrete test regions of immobilised antibodies specific to different cytokines and growth factors. A sandwich chemiluminescent immunoassay is employed for the cytokine array. Increased levels of cytokine in a specimen leads to increased binding of antibody labelled with horseradish peroxidase (HRP) and thus an increase in the chemiluminescent signal emitted.

Anaesthetic management

All patients were administered premedication of 7.5 mg midazolamum p.o. one hour before entering the operating room (operating theatre).

We applied local anaesthetic to patients – 3 ml 0.5% levobupivacaine ((15 mg) with a 24 Gy Whitacre/Quincke spinal needle in the L3–L4 subdural area. Before application, the skin in the area was infiltrated with 2% lidocain (20 mg).

Continuous infusion of electrolytic solutions (5 ml/kg /h) were carried out during the operation. Monitoring included heart frequency, systolic and diastolic blood pressure, medium arterial pressure and saturation.

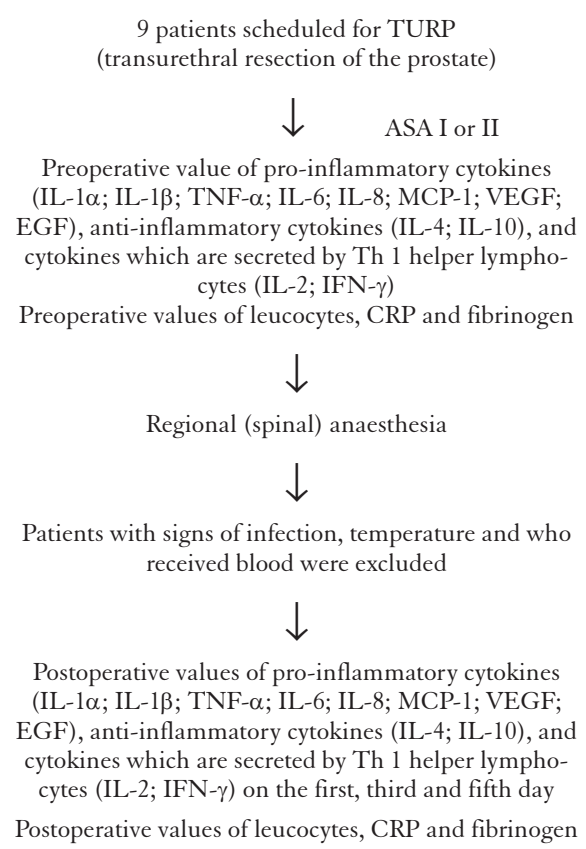

Figure 1. *Flow diagram – Study protocol.*

RESULTS

The patient characteristics and operative details are shown in Table 1. There were no significant differences between the patients. None of the patients received blood transfusions during the (perioperative) (preoperative) period. All the patients were discharged from the hospital without any major complications.

The immune response (as measured by a variety of parameters) was examined in patients undergoing transurethral resection of the prostate (TURP) for benign disease.

There was no significant differences in the duration and severity of surgical trauma.

TABLE 1

Patient characteristics (results are expressed as mean +/–SD or median).

Group	Spinal anaesthesia (n=10)
Mean Age (years)	70,2 (+/– 5,5)
Mean body high (cm)	175,9 (+/– 5,5)
Mean body weight (kg)	78,1 (+/– 11,2)
Duration of surgery (min)	62,1 (+/– 23,9)

TABLE 2

Features of the acute phase response (results are expressed as mean +/–SD or median).

Group	Spinal anaesthesia ((*n*=10)
Preoperative leucocytes	7,36 (+/–1,8)
Postoperative leucocytes	8,1 (+/–1,4)
Preoperative fibrinogen	3,0 (+/–1,1)
Postoperative fibrinogen	3,3 (+/–0,7)
Preoperative CRP	6,56 (+/–3,5)
Postoperative CRP	14,43 (+/–7,9)

Tissue damage induced by this type of surgery has probably less effect on the immune system as compared with extensive abdominal or orthopedic surgery *(8)*.

Table 2 shows features of the acute phase response (results are expressed as mean +/– SD or median). Preoperative CRP 6.56 (+/– 3,5) to postoperative CRP 14,43 (+/– 7,9) ratios in patients receiving spinal anaesthesia increased. Preoperative to postoperative values of leucocytes 7,36 (+/– 1,8)/8,1 (+/– 1,4) and fibrinogen 3,0 (+/– 1,1)/3,3 (+/– 0,7) show no significant changes.

Table 3 shows preoperative and postoperative values of cytokines. Statistical analysis of data obtained from consecutive blood samples was performed with Friedman test for paired samples. Results are presented as median (range). The level of significance was set at $P<0.05$.

The main result of the present study is that the surgery – related postoperative release of the proinflammatory cytokine IL-6 ($P < 0.05$) increased in patients after spinal anaesthesia.

Serum concentration of pro-inflammatory cytokines (IL-1α; IL-1β; TNF-α; IL-8; MCP-1; VEGF; EGF), anti-inflammatory cytokines (IL-4; IL-10), and cytokines which are secreted by Th 1 helper lymphocytes (IL-2; IFN-γ) show no statistical difference in values before and after surgery.

DISCUSSION

The immunological system in humans is an extraordinary complex and adaptable system, able to recognise and eliminate manifold strange cells and molecules *(1)*. The role of immunoreaction is defence against infections, defence against tumour and maintenance of gene and antigen homeostasis *(3)*. Injury, whether surgical or

TABLE 3

Preoperative and postoperative values of cytokines.

Pg/ml	IL-2	IL-4	IL-6	IL-8	IL-10	VEGF
Preoperative value	8,0600 (6.615-15.325)	2,4200 (1.895-3.245)	1,4500 (0.970-2.77)	19,9200 (7.805-232.56)	,81 (0.36 -2.00)	201,8300 (155.96-443.28)
First day Value	7,4800 (5.445-10.495)	2,2700 (1.93-3.99)	13,3800 (11.78-126.62)	11,0500 (4.29-61.32)	1,5000 (0.905-5.215)	202,100 (176.41-241.57)
Third day Value	8,81 (6.13-9.450)	2,4200 (1.93-4.145)	8,1800 (5.06-20.29)	9,030 (5.255-362.17)	,8400 (0.37-1.135)	218,7600 (133.59-284.10)
Fifth day Value	7,2900 (5.745-8.715)	2,4200 (1.89-2.49)	4,0400 (2.26-10.04)	8,9400 (4.25-19.17)	,7700 (0.34-1.935)	329,5600 (161.74-451.87)
P value	,269	0,68	**0,00**	0,35	0,1	0,25

Pg/ml	IFNG	TNF-alfa	IL-1alfa	IL-1beta	MCP1	EGF
Preoperative value	4,5200 (1.85-23.76)	7,1700 (2.825-10.490)	,5600 (0.295-0.965)	,7000 (0.445-0.365)	329,9200 (243.04-358.19)	158,5100 (58.10-255.51)
First day value	3,8100 (1.68-23.76)	7,1100 (5.085-12.155)	,2800 (0.220-0.40)	,4200 (0.275-1.415)	278,42 (237.93-586.73)	117,1100 (84.30-224.44)
Third day value	1,8200 (1.30-2.85)	3,9200 (2.880-5.980)	,3400 (0.30-0.37)	,5500 (0.345-0.855)	265,8000 (214.63-299.79)	129,5000 (24.77-195.48)
Fifth day value	3,6600 (2.19-5.18)	7,8200 (5.27-10.00)	,3000 (0.28-0.41)	,4700 (0.305-0.860)	269,100 (244.69-325.10)	147,9600 (50.93-267.06)
P value	0,73	0,28	0,21	0,74	0,64	0,44

traumatic, is connected with acute disorder of the immunological system which is manifested as increased inclination to infections. This phenomenon is primarily characterised by disorder of cell immunity and function of macrophages *(5)*. In serious infections and extensive injuries there is reduced production of Th1 cytokine and increased production of Th2 cytokine, which is connected with immunosuppression (5). General or regional anaesthesia alone, without operation, has periodical and minimum effects on the immunological system. However, this changes during the operation *(6, 7, 8)*. It has been established that various anaesthesiological procedures during the same operation cause a various trend of alteration in the cytokine level in serum *(9)*. Spinal anaesthesia results in less immunosuppression, i.e. maintains the number of Th1 cells, thus stimulating cell immunity *(4)*. Serious disorder of the immunological system may cause complications, as there are disorders in wound healing, increased number of infections, inadequate response to stress, multiorganic suppression and increased incidence of metastases *(10, 11)*.

CONCLUSION

The main result of the present study is that the surgery – related postoperative release of the proinflammatory cytokine IL-6 was increased in patients after spinal anaesthesia.

Serum concentration of pro-inflammatory cytokines, anti-inflammatory cytokines and cytokines which are secreted by Th 1 helper lymphocytes showed no statistical difference in values before and after surgery.

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