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Fibrinolytic response to retinal detachment surgery under general or local anesthesia

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PURPOSE. *To evaluate perioperative changes in fibrinolysis in patients undergoing retinal detachment surgery under general or local anesthesia.*
PATIENTS. *Prospective study of 81 patients (43 male, 38 female), aged from 15 to 82 (mean 50.7 SD = 17.8) years, undergoing retinal detachment surgery (encirclement with scleral buckling) under general anesthesia (group A), and 14 patients (6 male, 8 female) aged from 15 to 78 (mean 52.9, SD =19.8) years, operated under local anesthesia (group B). Excluded were patients with venous or arterial disease or other factors that could change the parameters investigated.*
METHODS. *Blood was sampled from a cubital vein one day before surgery, immediately after induction of anesthesia but before surgery, immediately after completion of the operation but before the termination of anesthesia and after the operation (on days 1 and 4). In patients' citrated plasma, tissue plasminogen activator antigen (t-PA-Ag), plasminogen activator inhibitor type 1 antigen (PAI-1 Ag) and activity (PAI-1), fibrin-fibrinogen degradation products (FDP) and euglobulin lysis time (ELT) were measured.*
RESULTS. *The pattern of changes in perioperative fibrinolytic activity was similar in both groups. Intraoperative levels of FDP were significantly higher and ELT shorter than preoperatively. In both groups t-PA Ag concentration was significantly increased on the first postoperative day. There were no changes in PAI-1 in both groups. Postoperatively, the FDP concentration was reduced and ELT prolonged.*
CONCLUSIONS. *Retinal detachment surgery induces intraoperative activation of fibrinolysis in the systemic circulation regardless of the type of anesthesia. (Eur J Ophthalmol 2001; 11: 66-72)*

KEY WORDS. *Fibrinolysis, Retinal detachment surgery, Anesthesia, Tissue plasminogen activator and inhibitor*

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INTRODUCTION

There is an evidence that after injury and major surgery there is an early, marked increase in blood fibrinolytic activity and subsequent fibrinolytic suppression with finally, progressive normalization (1). Disturbing the balance between profibrinolytic activity and inhibition of fibrinolysis may result in either a bleeding or a thrombotic tendency.

The results presented in a previous report indicate that scleral buckling surgery, like major surgery, can cause significant fibrinolytic sequelae, influencing the values of systemic fibrinolysis (2). During retinal detachment surgery fibrinolytic activity markedly increases. Intraoperative values of tissue plasminogen activator antigen (t-PA Ag), and fibrin-fibrinogen degradation products (FDP) were significantly higher and euglobin lysis time (ELT) was shortened. Postoperatively,

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fibrinolytic activity was reduced (decreses in t-PA Ag and FDP and prolongation of ELT). The significance of these findings was not certain as all the procedures in that study were performed under general anesthesia – an important factor which could have affected the fibrinolytic activity. On the basis of these observations it would be difficult, even impossible, to discriminate between the influence of anesthesia and the influence of retinal detachment surgery alone. It would therefore be interesting to know whether the same changes occurred during retinal detachment surgery under local anesthesia.

Earlier studies, however, supported surgery as the main cause of hemostatic changes, since patients undergoing minor surgery (smaller than cholecystectomy) under general anesthesia showed none of the changes in hemostasis seen after major surgery (3).

The purpose of this study was to compare the changes in blood fibrinolysis during and after retinal detachment surgery in patients operated under general or local anesthesia and to check whether this type of surgery, like major surgery, really causes activation of fibrinolysis.

PATIENTS AND METHODS

We studied 81 patients with rhegmatogenous retinal detachment, undergoing retinal detachment surgery under general anesthesia (group A) and 14 patients operated under local anesthesia (group B). Group A comprised 43 males and 38 females aged from 15 to 82 years (mean age 50.7, SD 17.8). Group B consisted of 6 males and 8 females, aged from 15 to 78 years (mean 52.9, SD 19.7).

Exclusion criteria were other illness, medical treatment additional to retinal detachment, surgery during the past two years, tobacco smoking, pregnancy in the past two years, menopause with the last menstruation not longer than a year ago, diabetes mellitus, previous or present venous thrombosis in the patient or close relatives. None of the patients received any medication that might affect the hemostatic mechanism in the 30 days before the study, intraoperatively or in the postoperative period (eg, aspirin, anticoagulants, steroids, non-steroid antinflammatory agents, oral contraceptives, vasoactive drugs, calcium channel bockers). No perioperative thromboembolic prophylaxis was used.

The operations, performed by two retinal surgeons, included encircling combined with the segmental scleral buckling procedure, cryopexy and subretinal fluid drainage. General anesthesia was standardized, it was induced with fentanil, atropine, and succinylcholine, and maintained with O_2, NO_2 and vecuronium.

Local anesthesia was preceded by premedication with midazolam, and was induced using 5 ml of 0.5% bupivacaine with 5 ml of 2% lignocaine mixed in the same 10-ml syringe of which 3 ml were given as a retrobulbar injection and the remainder as a facial block. Fentanil was administered during surgery.

All patients gave their written informed consent before they were included in this study. The study had been approved by the Ethics Committee of the Faculty of Medicine, University School of Medical Sciences of Bydgoszcz.

Blood sampling

Venous blood samples were taken between 09.00 and 10.00 h from the cubital vein and placed in sodium citrate solution (9:1), at the following times: 24 h before operation, immediately after induction of anesthesia but before surgery, and immediately after completion of the operation, but before the termination of anesthesia (usually between 11.00 and 12.00 h), on the 1st and 4th postoperative days. Subsequent days when blood was collected are marked throughout the paper as follows: day –1, oper –0, oper +0, day 1, day 4. All venepunctures were done using minimal venostasis after a rest period of 15 min in a recumbent position. Except on the days of the operation, a light hospital breakfast was given between 1 and 1.5 h before blood was taken.

Fibrinolytic studies

In the citrated plasma the following were determined by immunosorbent assay (ELISA):

1) The concentration of tissue plasminogen activator antigen (t-PA Ag) (Imulyse, Biopool) with monoclonal antibodies as described by Kominger et al and Ranby et al (4, 5).

2) The concentration of plasminogen activator inhibitor type 1 (PAI-1 Ag) (Imulyse, Biopool), as described by Ranby et al (6).

3) The activity of plasminogen activator inhibitor type 1 (PAI-1 activity), with an amidolytic method (Spectrolyse, Biopool) according to Chmielewska et al (7).

4) The concentration of fibrin-fibrinogen degradation products (FDP) according to Merskey et al (8).

5) The euglobulin lysis time (ELT) according to Kowarzyk et al (9).

Because of financial restraints, each parameter was evaluated in different numbers of eyes (Table I).

TABLE I - SIZES OF THE GROUPS AND PARAMETERS EVALUATED

	Number of eyes Anesthesia	
Parameter	**General**	**Local**
t-PA Ag	30	11
PAI Ag	49	12
PAI-1 activity	20	10
FDP	58	14
ELT	59	7

Statistical analysis

Results of normally distributed data are expressed as mean and standard deviation. For normally distributed data an additional t-test was used to compare the two samples. Repeated measures analysis of variance (ANOVA) was used to compare the results at different time points in both groups. Parameters with non-Gaussian distribution are presented as the median and interquartile range. The Mann-Whitney U-test was used to compare unpaired data (between groups). The Wilcoxon matched signed rank test was used for paired data (day-to-day variations). A p-value below 0.05 was considered statistically significant.

RESULTS

In the two groups of operated patients the distribution of sex (43/38 vs 6/8), age (50.7, SD 17.8 vs 52.9, SD 19.7), and the duration of the operations (75.2, SD 20.4 min vs 69.4, SD 20.7 min) were similar. All operations were completed without complications. patients were discharged from hospital on the 4th postoperative day.

TABLE II - PERIOPERATIVE CHANGES IN VARIABLES IN PATIENTS UNDERGOING RETINAL DETACHMENT SURGERY UNDER GENERAL OR LOCAL ANESTHESIA

Time*	**Anesthesia**	**-1 Median (interquartile range)**	**-0 Median (interquartile range)**	**+0 Median (interquartile range)**	**+1 Median (interquartile range)**	**+4 Median (interquartile range)**
tPA Ag (ng/ml)	general	8.9 (10.5)	6.6 (9.0)	9.6 (8.6)	8.4 (10.2)	6.7 (6.4)
	local	9.8 (6.1)	8.2 (9.8)	10.4 (11.1)	12.6 (14.3)	11.2 (7.6)
PAI-1 Ag (ng/ml)	general	19.0 (16.4)	13.8 (9.5)	14.5 (10.5)	15.7 (10.0)	17.7 (14.7)
	local	12.3 (15.3)	16.5 (13.7)	15.0 (9.7)	9.7 (7.1)	16.6 (15.5)
PAI-1 (IU/ml)	general	12.5 (11.8)	15.8 (12.3)	14.0 (11.5)	19.3 (17.8)	15.0 (12.0)
	local	4.7 (6.7)	4.1 (1.7)	1.8 (3.8)	4.0 (3.6)	6.0 (5.3)
FDP (µg/ml)	general	0.0 (5.0)	5.0 (5.0)	5.0 (5.0)	0.0 (5.0)	0.0 (5.0)
	local	5.0 (5.0)	5.0 (5.0)	10.0 (10.0)	7.5 (10)	2.5 (5)
ELT (min)	general	95 (50)	90 (60)	55 (35)	110 (70)	95 (70)
	local	170 (45)	155 (90)	100 (60)	135 (70)	192 (115)

*for time points, see section headed “Blood sampling”; tPA Ag = tissue plasminogen activation antigen; PAI-1 Ag = plasminogen activator inhibitor type 1 (concentration); PAI-1 = plasminogen activator inhibitor type 1 (activity); FDP = fibrin-fibrinogen degradation products; ELT = euglobin lysis time

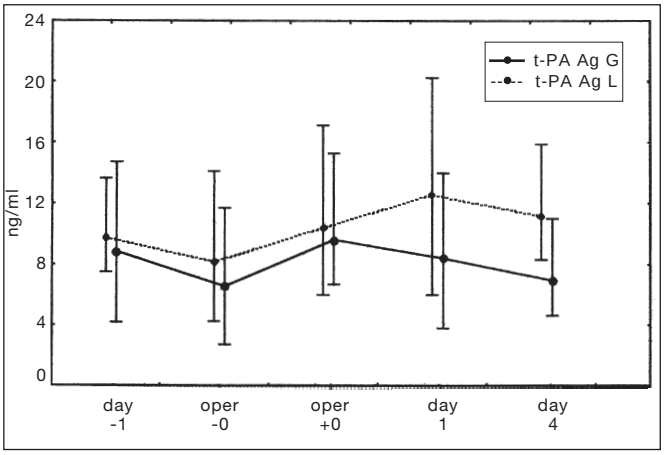

Fig. 1 - *Perioperative values of tissue plasminogen activator (t-PA Ag) in patients undergoing retinal detachment surgery under general (G) or local (L) anesthesia.*

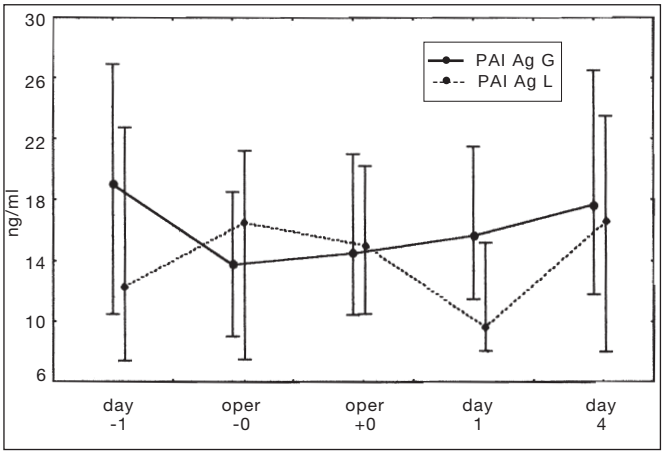

Fig. 2 - *Perioperative concentration of plasmin activator inhibitor type 1 (PAI-1 Ag) in patients undergoing retinal detachment surgery under general (G) or local (L) anesthesia.*

t-PA Ag

The pattern of changes in t-PA Ag was similar in both groups, the concentrations rose during surgery and on the first day after the operation were significantly higher than just before surgery (oper –0 vs day 1, $p < 0.05$). The concentration of t-PA Ag the day before surgery and on the first postoperative day were similar and remained within the normal range (day –1 vs day 1) (Fig. 1).

PAI-1 Ag

The concentration of PAI-1 Ag decreased significantly after the induction of general anesthesia, before surgery began, and remained low during surgery (day-1 vs oper –0, $p<0.05$). In both groups there were no significant changes during surgery and on the first postoperative days. In the local anesthesia group PAI Ag rose on the fourth postoperative day (Fig. 2).

PAI-1 activity

There was no difference in the pattern of changes in PAI-1 activity in the two groups. The activity of PAI-1 decreased during surgery, but not significantly. On the other days no significant difference was detected (Fig. 3).

FDP

The concentration of FDP changed similarly in both groups. It rose significantly after the induction of anesthesia but was not affected by the technique (day –1 vs oper –0, $p<0.05$). On the frist postoperative day the level was significantly higher than before surgery (day –1 vs oper +0, $p=0.02$), and dropped on the first day after surgery (oper –0 vs day 1, $p<0.01$). FDP was similar before and after surgery and remained within the normal range (Fig. 4).

ELT

In both groups the pattern of changes in values of ELT was similar. There was a significant decrease during surgery (oper –0 vs oper +0, $p<0.02$) but on postoperative day 1 this was reversed (oper +0 vs day 1, $p<0.02$), and by the fourth postoperative day ELT was no longer significantly different from the initial results (Fig. 5). Table II summarizes the findings of the study.

DISCUSSION

After major surgery there are phasic changes of fibrinolytic activity, with early activation during or immediately after surgery, subsequent fibrinolytic suppression, and finally progressive normalization (1). Similar hemostatic events are reported after retinal detachment surgery (2). It is also an established opinion that not only surgical stress but other factors, such as anesthesia, may influence fibrinolytic activity (9, 10).

Anesthetic agents and techniques can influence the hemostatic response to surgery through a number of mechanisms: the membrane-stabilizing effects of local anesthetics, the direct cellular effects of volatile

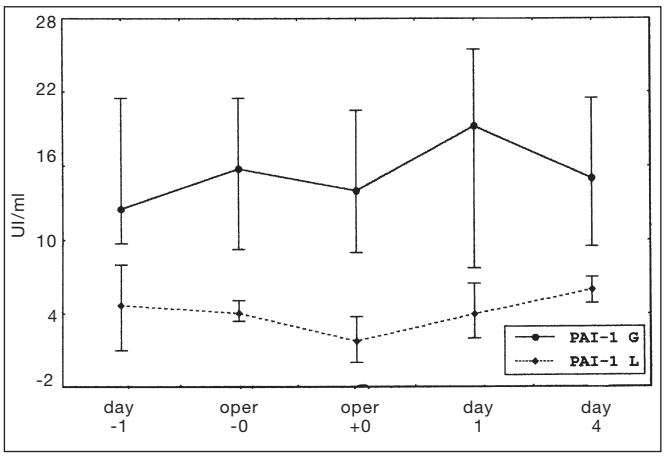

Fig. 3 - *Perioperative activity of plasminogen activator inhibitor type 1 (PAI-1) in patients undergoing retinal detachment surgery under general (G) or local (L) anesthesia.*

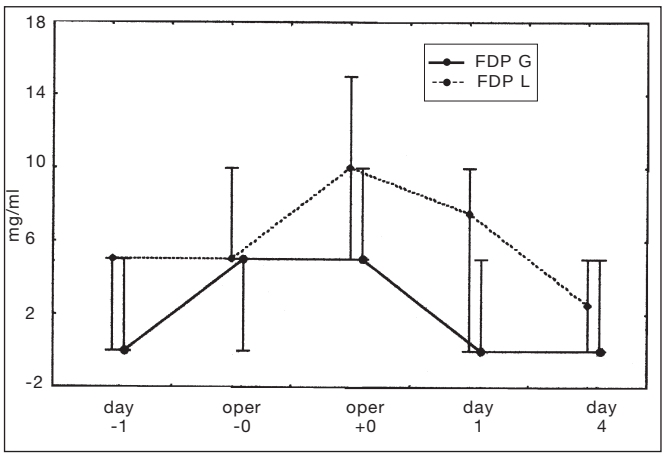

Fig. 4 - *Perioperative levels of fibrin-fibrinogen degradation products (FDP) in patients undergoing retinal detachment surgery under general (G) or local (L) anesthesia.*

anesthetics, the modification of the neuroendocrine response to surgery (9-18). It is difficult to distinguish the influence of anesthesia from that of surgery alone.

Possible anesthesia-induced changes in coagulation and fibrinolysis have been investigated and there are reports of activation of the coagulation system during different surgeries under general anesthesia (9, 15). These studies, however, cannot exclude a major influence of the surgical procedure on the activation of the hemostatic system.

Loick et al, presuming a minimal effect of elective ophthalmic surgery on the variables determined, concluded that none of the anesthetic procedures induced platelet activation and fibrinolysis (15). There was some support for these data but this conclusion contrasts with other reports of a considerable increase in fibrinolytic activity during routine anesthesia and surgery (9, 10). Different surgical procedures may be responsible for these conflicting observations.

It has been noted that regional anesthesia attenuates the cortisol and catecholamine responses to surgery. In some studies lumbar epidural analgesia caused less postoperative inhibition of fibrinolysis and a smaller increase in coagulation factors than general anesthesia (16). Other authors, however, reported no changes in hemostasis, whether general anesthesia was used or not (9, 19).

As fibrinolysis may be accelerated with the stress of major surgery, the stress of anesthesia may have affected hemostatic patterns. Changes have been described after the induction of anesthesia (general, epidural or cervical block), even before surgery began (19). This was in some degree confirmed by the present study, in which we noted a significant decrease in PAI-1 Ag after induction of general anesthesia and increase in FDP after general or local anesthesia.

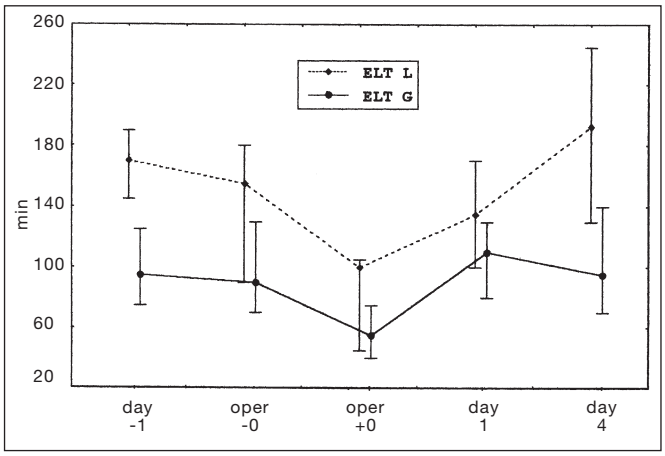

Fig. 5 - *Perioperative euglobulin lysis time (ELT) in patients undergoing retinal detachment surgery under general (G) or local (L) anesthesia.*

In this study the direct effects of the anesthetic technique on systemic fibrinolysis are probably of less importance than the response to retinal surgery. So the present results confirm the assumption that changes in fibrinolytic activity shortly after retinal detachment surgery are evoked by the surgery alone. The patterns of changes of t-PA Ag, PAI-1 Ag, PAI-1 activity, FDP and ELT were similar in both groups. These

results agree with some previous studies that found no significant differences in the parameters of hemostasis in patients having different forms of anesthesia (19). Gold found the decrease in activated clotting time was of the same magnitude in patients receiving regional (cervical plexus block) or a combination of regional and general anesthesia (19). Roussi et al checked the effects of a general anesthetic procedure on hemostasis in pigs and observed no difference before and under general anesthesia, indicating that the anesthetic procedure itself did not modify pig hemostasis (20).

According to Niemi et al general anesthesia does not result in any clear activation and release of fibrinolytic factors, which originate in the vascular endothelium (14). ELT is sensitive to the level of circulating plasminogen activator, and we found that ELT was shortened by the retinal detachment operation and prolongated postoperatively. There was no difference in the pattern of perioperative changes of ELT in relation to the type of anesthesia.

The present study suggests that retinal surgery induced the release of t-PA Ag. In the two groups t- PA Ag levels were significantly elevated on the first postoperative day, compared to preoperative values. In the general anesthesia group there was a significant intraoperative increase in t-PA Ag but in the local anesthesia group this increase was less pronounced. There are many factors causing t-PA Ag release, including exercise, stress, trauma, venous occlusion, or catecholamines. Premedication used before local anesthesia, presumably through its anxiolytic effects, suppresses the t-PA Ag release by modifying the stress response. From our laboratory results it seems that local anesthesia slightly modifies the pattern of t-PA Ag changes.

Since the assay of t-PA Ag gives data about the concentrations of active and non-active forms the results must be clarified by perioperative assessment of t-PA activity. Active t-PA and its active inhibitor are both released into the circulation, where they can influence each other's activity. It has already been demonstrated that patients undergoing major surgery showed enhanced t-PA activity during the operation but, despite this increase no plasminogen activation could be demonstrated in these patients. This was explained by an increase in plasma t-PA inhibitor (PAI-1 Ag) and its activity at this point. Patients with more advanced surgery had higher levels and a more marked increase in the PAI-1 Ag concentration (21). An analysis of the postoperative period revealed simultaneous increases in t-PA Ag, PAI-1 Ag and PAI-1 activity (22-24). This was not the case in our study. The PAI-1 Ag concentration fell after the induction of general anesthesia but there were no intraoperative changes in either group.

PAI-1 activity is a consequence of the formation of a complex between PAI Ag and t-PA Ag. In both groups subsequent measurements of PAI-1 activity also showed no significant alterations.

FDP levels rise in many patients after major surgery (21). There was no difference between patients with respect to the perioperative changes in FDP, but both groups had significantly higher FDP levels at the end of the operation.

Although the groups were different sizes, there is a strong statistical indication that retinal detachment surgery has an effect on perioperative blood fibrinolysis. Our results suggest that the fibrinolytic system was markedly activated by this surgery and that there are some similarities in perioperative fibrinolysis changes with major surgery and retinal detachment surgery.

Underactivity of the fibrinolytic system on one hand, and overactivity on the other, are primary or secondary factors in a number of disease processes and may lead to critical complications such as bleeding or thrombosis (1, 3, 11, 16). Understanding the mechanism underlying the fibrinolytic response during surgery may thus be very important.

In summary, the present study found that perioperative changes in blood fibrinolysis after retinal detachment surgery were not affected by the type of anesthesia, thus suggesting that retinal surgery itself is a major cause of phasic changes in perioperative fibrinolytic activity.

From our laboratory results, it seems that patients undergoing retinal detachment surgery are at risk of perioperative changes in blood fibrinolysis comparable with those after major surgery so the possibility of systemic side effects should not be underestimated.

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REFERENCES

1. Murphy WG, Davies MJ, Eduardo A. The haemostatic response to surgery and trauma. Br J Anaesth 1993; 70: 205-13.
2. Malukiewicz-Wiśniewska G, Kotschy M, Kaluzny J. The influence of retinal detachment surgery on perioperative blood fibrinolysis. Curr Eye Res 1999; 19: 123-30.
3. Mansfield AO. Alteration in fibrinolysis associated with surgery and venous thrombosis. Br J Surg 1972; 59: 754-7.
4. Kominger C, Speiser W, Wojta J, Binder BR. Sandwich ELISA for t-PA antigen employing a monoclonal antibody. Thromb Res 1986; 41: 527-35.
5. Ranby M, Nguyen G, Scarabin PY, Samana M. Immunoreactivity of tissue plasminogen activator and it's inhibitor complexes: Biochemical and multicenter validation of a two site immunosorbent assay. Thromb Haemost 1989; 61: 409-14.
6. Chmielewska J, Wiman B. Determination of tissue plasminogen activator and its fast inhibitor in plasma. Clin Chem 1986; 32: 482-5.
7. Merskey C, Zalezari P, Johnson AJ. A rapid, simple, sensitive method for measuring for fibrinolytic split-products in human serum. Proc Soc Exp Biol Med 1969; 131: 871-9.
8. Kowarzyk H, Buluk K. Postepy badan nad krzepnieciem krwi. Postepy Hig Med Dosw 1950; 2: 1-9.
9. Bredbacka S, Blomback M, Hagnevik K, Irestedt L, Raabe N. Per- and postoperative changes in coagulation and fibrinolytic variables during abdominal hysterectomy under epidural or general anaesthesia. Acta Anaesthesiol Scand 1986; 30: 204-10.
10. Davis F. M, McDermott E, Hickton C, et al. Influence of spinal and general anaesthesia on haemostasis during total hip arthroplasty. Br J Anaesth 1987; 59: 561-71.
11. Bertha BG, Folts JD, Nugent M, Rusy BF. Halothane, but no isoflurane or enflurane, protects against spontaneous and epinephrine-exacerbated acute thrombus formation in stenosed dog coronary arteries. Anesthesiology 1989; 71: 96-102.
12. Fauss BG, Meadows JC, Bruni CY, Qureshi GD. The *in vitro* and *in vivo* effects of isoflurane and nitrous oxide on platelet aggregation. Anesth Analg 1986; 65: 1170-4.
13. Fyman PN, Triner L, Schranz H, et al. Effect of volatile anaesthetics and nitrous oxide-fentanyl anaesthesia on bleeding time. Br J Anaesth 1984; 1198-200.
14. Niemi T T, Kuitunen H, Vahtera EM, Rosenberg PH. Haemostatic changes caused by i.v. regional anaesthesia with lignocaine. Br J Anaesth 1996; 76: 822-8.
15. Loick HM, Goener-Radig C, Ostermann H, Theissen JL, Zander J. The influence of different procedures of general anaesthesia on platelet function, coagulation and fibrinolysis system. Acta Anaesthesiol Scand 1993; 37: 493-7.
16. Rosenfeld BA, Beattle C, Christopherson R, et al. The effect of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Anesthesiology 1993; 79: 435-43.
17. Sharrock NE, Go G, Williams-Russo P, Haas SB, Harpel PC. Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty. Br J Anaesth 1997; 79: 29-34.
18. Simpson PJ, Radford SG, Forster SJ, Cooper GM, Hughes AO. The fibrinolytic effects of anaesthesia. Anaesthesia 1982; 37: 3-8.
19. Gold MS. The effect of epidural/general and cervical plexus block anaesthesia on activated clotting time in patients undergoing vascular surgery. Anesth Analg 1993; 76: 701-4.
20. Roussi J, Andre P, Samama M, et al. Platelet functions and haemostasis parameters in pigs: absence of side effects of a procedure of general anaesthesia. Thromb Res 1996; 81: 296-305.
21. Mellbring G, Dahlgren S, Wiman B. Plasma fibrinolytic activity in patients undergoing major abdominal surgery. Acta Chir Scand 1985, 151: 109-14.
22. Aramoto H, Shigematsu H, Tetsuichro M. Perioperative changes in coagulative and fibrinolytic function during surgical treatment of abdominal aortic aneurysm and arteriosclerosis obliterans. Int J Cardiol 1994; 47: 55-63.
23. Dabrowiecki S, Rosc D, Jurkowski P. The influence of laparoscopic cholecystectomy on perioperative blood clotting and fibrinolysis. Blood Coagul Fibrinolysis 1997; 8: 1-5.
24. Kluft C, Verfheijen JH, Jie AFH, et al. The postoperative fibrinolytic shutdown a rapidly reverting acute phase pattern for the fast acting inhibitor of tissue-type plasminogen activator after trauma. Scand J Clin Lab Invest 1985; 45: 605-10.