CLINICAL INVESTIGATIONS

A combinative effect of low-molecular-weight heparin and intermittent pneumatic compression device for thrombosis prevention during laparoscopic fundoplication

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Key words: *laparoscopic fundoplication; tissue factor pathway inhibitor.*

Summary. *Background. Venous thromboembolism is known to be an important social and health care problem because of its high incidence among patients who undergo surgery. For instance, 20–30% of patients develop this problem after general surgical operations, while 5.5% of patients have this complication when laparoscopic fundoplications are performed without any prophylaxis. The aim of our study was to evaluate the hypocoagulation effect of the following treatments during and after laparoscopic fundoplication: a) intermittent pneumatic compression (IPC) and b) combination of low-molecular-weight heparin (LMWH) and IPC.*

Material and methods. The study was performed on 20 consecutive patients who were randomized into two groups. The first group received IPC during operation, the second group received IPC during operation and LMWH before operation. Plasma prothrombin fragment F1+2 (F1+2), thrombin-antithrombin complex (TAT) – markers of thrombogenesis – and plasma free tissue factor pathway inhibitor (fTFPI) – a marker of hypocoagulation effect – were measured 1 h before, during, and after the laparoscopic operation.

Results. In the IPC group, plasma F1+2 and TAT levels increased significantly during and after laparoscopic gastrofundoplication. In the IPC+LMWH group, F1+2 and plasma TAT levels did not change during or after the operation. fTFPI levels significantly increased during and after the operation in the IPC+LMWH group; however, fTFPI levels did not change during or after the laparoscopic operation in the IPC group.

Conclusions. A combination of low-molecular-weight heparin and intermittent pneumatic compression during laparoscopic fundoplication caused hypocoagulation effect in the patients, which was not observed in the patients who were treated with intermittent pneumatic compression alone.

Introduction

Laparoscopic fundoplication has rapidly become the operation of choice for gastroesophageal reflux disease, caused by a hiatal hernia. We already know that laparoscopic operations (cholecystectomy, fundoplication, colon resections, etc.), compared with open ones, have demonstrated a reduction in postoperative pain, a decrease in hospital stay, and earlier returns to everyday work and improved cosmetic effect. The increased intra-abdominal pressure associated with pneumoperitoneum and reverse Trendelenburg position during surgery generate venous stasis in the lower limb, which was already present due to the general anesthesia, by compressing the retroperitoneal vena cava and iliac veins during the laparoscopic fundoplication (1). A variety of mechanical techniques and devices (compression bandages, passive exercise, electrical calf stimulation, intermittent pneumatic compression) have been used in an attempt to reduce this stasis during surgery. In our previous study (1), we demonstrated that intermittent pneumatic compression (ICP) is the most effective tool in reducing venous stasis during laparoscopic fundoplication.

Stasis alone does not cause thrombosis, but the combination of stasis, hypercoagulability, and endothelial damage allows thrombus to develop (2). Some studies demonstrated (3–8) that laparoscopic cholecystectomy leads to postoperative activation of

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the coagulation system, which is one of the factors for postoperative thromboembolic complications. These changes can also be present in laparoscopic fundoplications. The incidence of thromboembolic complications after laparoscopic fundoplication is unknown, and we could not find the reported studies on intraoperative and postoperative changes of coagulation during laparoscopic fundoplications.

The aim of this study was to evaluate the hypocoagulation effect of intermittent pneumatic compression (IPC) or the combination of low-molecular-weight heparin (LMWH) and IPC during and after laparoscopic fundoplication.

Materials and methods

This was a prospective randomized clinical study, where 20 consecutive patients undergoing elective laparoscopic fundoplications because of gastroesophageal reflux disease, caused by hiatus hernia, were studied. All patients gave their written informed consent, and the local ethics committee approved the study. The patients were randomized into two groups, with 10 patients in each group. The first group received IPC during laparoscopic fundoplications (IPC group). The IPC was performed using a special apparatus "Vasoflow Gradient 200." This apparatus includes a compressor and special stockings, constructed from three parts. Firstly, the pressure in the lower part was raised up to 60 mm Hg; secondly, the pressure in the middle part was raised up to 48 mm Hg; and finally after that, the pressure in the upper part was raised up to 36 mm Hg. The second group received 40 mg of LMWH enoxaparin (Clexane, Aventis Pharmaceuticals, Germany) subcutaneously 1 h before the operation and IPC during the laparoscopic fundoplication (IPC + LMWH group). All operations were performed under standardized endotracheal anesthesia. After the operation, all patients were extubated in the operating room.

Three experienced surgeons performed all the operations (Nissen fundoplication). The antireflux wrap was formed by rolling 2.5-cm gastric fundus behind the abdominal portion of the esophagus, thus reinforcing the lower esophageal sphincter. The wrap was then fixed to the esophagus and suturing the stomach to the front of the esophagus.

Blood collection and processing

Plasma prothrombin fragment F1+2 (F1+2) and thrombin-antithrombin complex (TAT) – markers of thrombogenesis – were evaluated. The hypocoagulation effect was evaluated by measuring plasma free

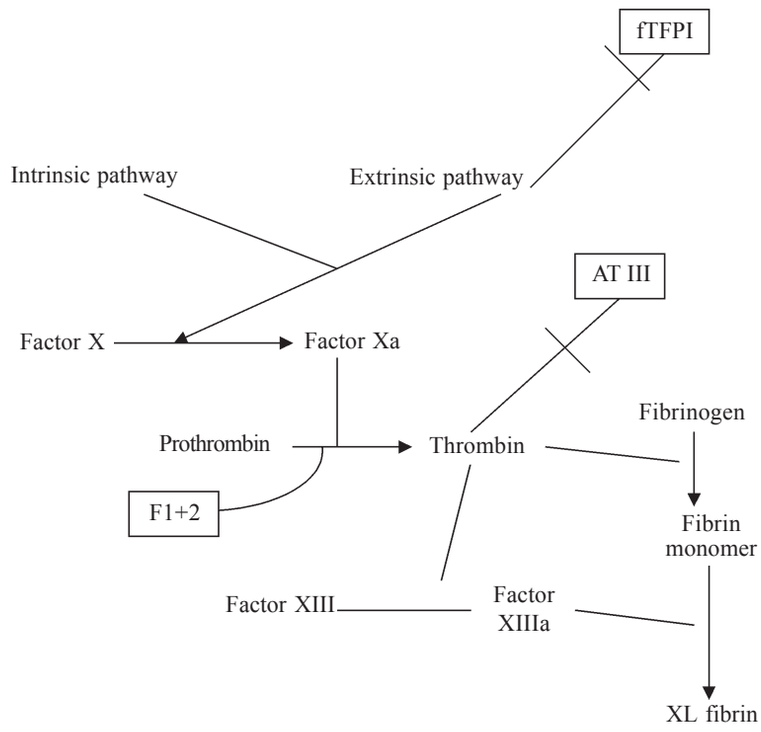

Fig. The schematic diagram of the coagulation pathway
F1+2, prothrombin fragment 1+2; AT III, antithrombin III; fTFPI, free tissue factor pathway inhibitor; XL fibrin, cross-linked fibrin.

tissue pathway factor inhibitor (fTFPI). Figure shows the schematic diagram of the coagulation pathway.

Blood sampling. Venous blood samples were taken from the forearm vein three times:

1. Before the operation and before LMWH injection;
2. 1 h after the introduction of the laparoscope;
3. 10 min after extubation.

Blood was drawn by a clean venipuncture following a double-syringe technique and placed into Vacutainer® tubes containing 3.9% (0.129 M) trisodium citrate (Becton Dickinson Vacutainer® Systems, Plymouth, UK) in the ratio of one part of citrate to nine parts of whole blood. The samples were then centrifuged at 2500*g* for 15 min to obtain platelet-poor plasma (PPP).

F1+2 and TAT concentrations in plasma samples were measured by a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) (Enzygnost® F1+2 and Enzygnost® TAT microenzyme immunoassay, Dade Behring, Germany). fTFPI measurements were performed by an ELISA technique (Diagnostika Stago, France) according to the manufacturer's instructions.

Statistical analysis

Statistical evaluation was conducted using descriptive analysis: the normality test (Shapiro-Wilk *W* test), the unpaired Mann-Whitney *U* test to compare data from two study groups (IPC and IPC+ LMWH), Wilcoxon test to investigate differences in F1+2, TAT, and fTFPI in each group of patients. Data were expressed as the median with minimum and maximum values. $P<0.05$ was considered significant.

Results

The patients in the two groups were similar in terms of age, weight, height, gender, duration of surgery, and American Society of Anesthesiologists (ASA) class (Table 1). There were no clinical signs of deep vein thrombosis in all 20 patients before and after operation.

Plasma F1+2 levels increased significantly after laparoscopic gastrofundoplication in the IPC group. In the IPC + LMWH group, plasma F1+2 levels did not change significantly during or after the operation (Table 2). Plasma TAT levels also increased significantly during and after the operation in the IPC group; however, TAT levels did not change significantly in the IPC + LMWH group (Table 3).

Plasma fTFPI levels significantly increased during and after operation in the IPC + LMWH group; however, plasma fTFPI levels did not change significantly during or after the laparoscopic operation in the IPC group (Table 4).

Discussion

Laparoscopic surgery leads to postoperative activation of the coagulation system, which is a prerequisite for thromboembolic complications. As a result, venous thrombosis may occur when procoagulant stimuli overwhelm the natural protective mechanisms. Procoagulant stimuli include the excessive activation of coagulation, particularly when protective pathways are compromised by thrombophilic abnormalities, vessel wall damage, or stasis. Therefore, venous thrombosis may lead to pulmonary embolism, which can be fatal, and to postphlebitic syndrome.

Table 1. Demographic data

Variable	IPC group (n=10)	IPC + LMWH group (n=10)	*P* value
Age, years	67.5 (45–78)	68.5 (57–80)	NS
Gender, n			
male	4	5	NS
female	6	5	NS
Weight, kg	73.4 (66–95)	78.2 (70–91)	NS
Height, cm	171 (168–186)	175 (164–181)	NS
ASA class, n			
I	2	1	NS
II	6	8	NS
III	2	1	NS
Duration of surgery, min	102 (90–154)	110 (85–162)	NS

Values are expressed as median (range) unless otherwise indicated.
ASA, American Society of Anesthesiologists; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; NS, not significant.

Table 2. Changes of plasma prothrombin fragment F1+2 levels in the IPC and IPC + LMWH groups

Group	Plasma level of prothrombin fragment F1+2, nmol/L		
	Before operation (baseline)	1 h after introduction of laparoscope	10 min after extubation
IPC group (n=10)	1.07 (0.89–1.23)	1.0 (0.73–1.26)	1.85 (1.31–5.36)[ab]
IPC + LMWH group (n=10)	1.11 (0.83–1.94)	1.01 (0.77–1.93)	1.44 (0.89–2.17)

Values are expressed as median (range).
IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin.
[a]$P<0.0001$ vs baseline.
[b]$P<0.0001$ vs 1 h after introduction of laparoscope.

Table 3. Changes of plasma thrombin-antithrombin complex levels in the IPC and IPC + LMWH groups

Group	Plasma level of thrombin-antithrombin complex, μg/L		
	Before operation (baseline)	1 h after introduction of laparoscope	10 min after extubation
IPC group (n=10)	1.5 (1.2–2.5)	6.5 (2.7–9.5)[a]	9.1 (1.4–45.2)[bc]
IPC + LMWH group (n=10)	2.5 (1.2–7.3)	4.8 (1.3–20.1)	4.7 (1.3–7.1)

Values are expressed as median (range).
IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin.
[a]$P<0.0001$ vs baseline.
[b]$P<0.0001$ vs baseline.
[c]$P<0.0001$ vs 1 h after introduction of laparoscope.

Table 4. Changes of plasma free tissue pathway factor inhibitor levels in the IPC and IPC + LMWH groups

Group	Plasma level of free tissue pathway factor inhibitor, ng/mL		
	Before operation (baseline)	1 h after introduction of laparoscope	10 min after extubation
IPC group (n=10)	13.7 (7.2–22.3)	13.7 (7.3–20.1)	11.3 (7.9–15.2)
IPC + LMWH group (n=10)	13.4 (8.3–20.4)	27.9 (20.6–43.6)[a]	21.3 (11.5–32.3)[b]

Values are expressed as median (range).
IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin.
[a]$P<0.001$ vs baseline.
[b]$P<0.05$ vs baseline.

Laparoscopic surgery may potentially predispose to thrombosis, although to a lesser degree than open surgery, since it alters the venous flow and coagulability and causes endothelium injuries (3). The incidence of thromboembolic complications after laparoscopic fundoplication is unknown, and we could not find as well studies on the dynamics of intraoperative and postoperative coagulation during laparoscopic fundoplications.

A series of highly sensitive and specific immunochemical tools have been developed that can quantitate the levels and activities of various steps of the hemostatic mechanism in vivo at the subabnormal level. These include prothrombin F1+2, which measures the cleavage of prothrombin molecule by factor Xa and TAT complexes reflecting the vivo thrombin generation process. The increases in plasma prothrombin fragment F1+2 and thrombin-antithrombin complex indicate an increased formation of thrombin. In this study, plasma prothrombin fragment F1+2 and TAT complex were used as markers of activation of the coagulation pathway.

Coagulation is regulated at several levels. Key inhibitors include tissue factor pathway inhibitor, antithrombin, and the protein C pathway. The inhibition of the factor VIIa/tissue factor complex (extrinsic coagulation pathway) is effected by TFPI (9). TFPI acts in a two-step manner (9). In the first step, TFPI complexes and inactivates factor Xa to form a TFPI/factor Xa complex. The TFPI within this complex then inactivates tissue factor-bound VIIa as the second step. As the formation of the TFPI/factor Xa complex

is a prerequisite for the efficient inactivation of factor VIIa, the system ensures that some factor Xa generation occurs before factor VIIa-mediated initiation of the coagulation system. In this study, plasma free tissue factor pathway inhibitor as a marker of the hypocoagulation effect was used.

The antithrombotic effect of IPC is thought to be the result of increased venous velocity and stimulation of endogenous fibrinolysis. However, the results of several studies on the enhancement of hypocoagulation effect by an IPC have been controversial (10–13). Cahan et al. (11) showed that external pneumatic compression devices did not enhance systemic fibrinolysis or prevent postoperative shutdown either by decreasing plasminogen activator inhibitor-1 activity or by increasing tissue plasminogen activator activity. Their data suggest that external pneumatic compression devices do not prevent deep venous thrombosis by fibrinolytic enhancement; effective prophylaxis is achieved only when the devices are used in a manner that reduces venous stasis in the lower extremity. Jacobs et al. (12) reported that sequential gradient intermittent pneumatic compression induced prompt, but short-lived, alterations in fibrinolytic function, and the values quickly reverted to baseline on the termination of compression. Okuda et al. (8) reported that the intermittent compression boot did not prevent increased intravascular thrombogenesis and platelet activation through significant increases of plasma D-dimer and β-thromboglobulin after laparoscopic cholecystectomy. Killewich et al. (10) also reported that enhanced regional fibrinolysis in the lower extremities could not be detected with the use of external pneumatic compression devices, as measured with the tissue plasminogen activator and plasminogen activator inhibitor-1 activity in common femoral venous blood samples obtained from patients undergoing abdominal surgery. On the other hand, Comerota et al. (13) reported that external pneumatic compression devices induced a significant decrease in plasminogen activator inhibitor-1 activity in normal volunteers.

As it is showed above in our study, the use of IPC alone during laparoscopic fundoplication did not prevent an increase in the intravascular thrombogenesis although significant increases of plasma F1+2 and TAT were observed during and after laparoscopic fundoplication.

Giddings et al. (14) reported that IPC led to highly significant falls in factor VIIa, associated with increased levels of tissue factor pathway inhibitor in nonsmoking volunteers. Chouhan et al. (15) investigated the effect of IPC on the tissue factor pathway in 6 normal subjects and 6 patients with postthrombotic venous disease. Their study results demonstrated that the IPC results in an increase in plasma TFPI and a decline in FVIIa in both groups. Authors speculated that the inhibition of tissue factor pathway, the initiating mechanism of blood coagulation, is a possible mechanism for the antithrombotic effect of IPC. The results of our study demonstrate that IPC solely used did not increase TFPI in plasma and did not produce a hypocoagulation effect during laparoscopic fundoplication.

Most circulating TFPI is bound to lipoproteins. TFPI is also found in platelet α-granules and on the endothelial cell surface (9). TFPI bound to the endothelium is released with therapeutic doses of heparin or low-molecular-weight heparin, suggesting that TFPI binds to the endogenous glycosaminoglycans on the endothelial wall surface (9).

LMWH has been showed to be safe and effective for the prevention and treatment of venous thrombosis in a large number of randomized clinical trials. Therefore, we administered LMWH enoxaparin together with IPC 1 h before operation to prevent postoperative venous thromboembolism in the second group of the patients.

The focus of our study was to examine effect of the combined treatment (IPC + LMWH) on sensitive markers of hypercoagulation versus IPC alone. Therefore, we evaluated only clinically evident deep-vein thrombosis, the rate of which is very low after laparoscopic surgery.

Although we do not know whether the combined treatment (IPC + LMWH) reduces the rate of deep-vein thrombosis diagnosed by Duplex examination and that it is more effective than IPC alone, based on our data, we can only conclude that hypercoagulable state is present during and after laparoscopic fundoplication when the patients were treated with IPC alone for prevention of deep-vein thrombosis. Our data indicated that the combination of IPC and LMWH caused hypocoagulation during the operation. We suggest that this combined treatment could be considered for preventing deep-vein thrombosis during laparoscopic fundoplication.

Conclusions

Our study results demonstrate that combination of low-molecular-weight heparin and intermittent pneumatic compression generates hypocoagulation effect and is more effective than intermittent pneumatic compression alone to prevent deep-vein thrombosis during and after laparoscopic fundoplication.

Mažos molekulinės masės heparinų ir kintančios pneumokompresijos kojinių hipokoaguliacinis efektas laparoskopinių fundoplikacijų metu

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Raktažodžiai: laparoskopinė fundoplikacija, audinių kelio faktoriaus inhibitorius.

Santrauka. *Įvadas*. Kojų giliųjų venų trombozė yra sveikatos apsaugos ir socialinė problema. Giliųjų venų trombozė pasireiškia 20–30 proc. ligonių po atvirų pilvo chirurgijos operacijų bei 5–6 proc. ligonių po laparoskopinių pilvo ertmės operacijų. Šio tyrimo tikslas – įvertinti ir palyginti mažos molekulinės masės heparinų (MMMH) ir kintamos pneumokompresijos kojinių galimą hipokoaguliacinį poveikį laparoskopinių fundoplikacijų metu.

Tirtųjų kontingentas ir tyrimo metodai. Atlikta atsitiktinių imčių klinikinė studija. Tiriamieji suskirstyti į dvi grupes: pirmos grupės ligoniams laparoskopinės fundoplikacijos metu buvo naudojamos kintamos pneumokompresijos kojinės; antros grupės ligoniams – kintamos pneumokompresijos kojinės operacijos metu plius MMMH, kuris sušvirkštas į poodį 1 val. prieš operaciją. Plazmos protrombino fragmentas F1+2 (F1+2), trombino-antitrombino kompleksas (TAT) – trombogenezės žymenys bei laisvas plazmos audinių kelio faktoriaus inhibitorius (fTFPI) – hipokoaguliacijos žymuo buvo tiriami 1 val. prieš operaciją, operacijos metu ir baigus operaciją.

Tyrimo rezultatai. Pirmoje grupėje F1+2 ir TAT koncentracija kraujo plazmoje statistiškai reikšmingai padidėjo operacijos metu bei ją baigus. Antroje grupėje F1+2 ir TAT koncentracija operacijos metu nekito. fTFPI koncentracija kraujo plazmoje statistiškai reikšmingai padidėjo operacijos metu antroje grupėje, o pirmoje grupėje ji nekito.

Išvada. MMMH ir kintamos pneumokompresijos kojinės derinys, vartojamas laparoskopinių fundoplikacijų metu, sukėlė hipokoaguliacinį poveikį, kurio nepastebėta naudojant tik kintamas pneumokompresines kojines.

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