

**SHORT THESIS FOR THE DEGREE OF DOCTOR OF
PHILOSOPHY (PhD)**

**Evaluation of thrombotic risk and prevention of venous
thromboembolism after radical prostatectomy**

by Mátyás Benyó, MD

Supervisor: Tibor Flaskó, MD, PhD



**UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF CLINICAL MEDICINE**

Debrecen, 2013

EVALUATION OF THROMBOTIC RISK AND PREVENTION OF VENOUS
THROMBOEMBOLISM AFTER RADICAL PROSTATECTOMY

by Mátyás Benyó, MD

Supervisor: Tibor Flaskó, MD, PhD

Head of the Examination Committee:

Prof. András Berta MD, DSc

Members of the Examination Committee:

Prof. János Kappelmayer, MD, DSc

Endre Holman, MD, PhD

The examination takes place at the Department of Ophthalmology, Medical
and Health Science Center, University of Debrecen

11:00 a.m. 17th December, 2013

Reviewers:

Prof. Zoltán Boda, MD, DSc

György Tóth, MD, PhD

Head of the Defense Committee:

Prof. András Berta, MD, DSc

Members of the Defense Committee:

Prof. János Kappelmayer, MD, DSc

Endre Holman, MD, PhD

Prof. Zoltán Boda, MD, DSc

György Tóth, MD, PhD

The PhD defense takes place at the Lecture Hall of Building “A”, Department
of Internal Medicine, Medical and Health Science Center, University of
Debrecen

13:00 p.m. 17th December, 2013

1. Introduction

The hemostatic system secures the constant blood flow and prevents bleeding from the vascular system. The imbalance between procoagulant and anticoagulant activity – caused by conditions, or medical interventions – will lead to thromboembolism or hemorrhage. The severity of the disease will determine the severity of the changes in the hemostatic system.

Advanced age, malignancy and pelvic operation are the factors exposing patients to increased risk of thrombotic events after surgical treatment of prostate cancer.

Pharmacological and mechanic ways of thrombosis prophylaxis are available nowadays, but there is a lack of randomized trials comparing the different prophylactic methods regarding urological procedures, furthermore the most recent results are not promoted by the European urological guidelines.

The present dissertation provides overview of the presence of thrombotic complications, the increased thrombotic risk after urological procedures focusing on radical prostatectomy and its prevention. It gives results of assessing increased hypercoagulability after prostate cancer surgery with the aid of laboratory methods and evaluates the present practice of thrombosis prophylaxis at Hungarian urological departments.

2. Literature review

2.1. Importance and risk assessment of venous thromboembolism

Worldwide 52% of hospitalized patients are judged to be at risk of thrombotic events including deep venous thrombosis (DVT) or pulmonary embolism (PE), which were adjudicated as the most common cause of death after pelvic cancer surgery –like radical prostatectomy (RP)– according to a prospective observational study. Most contemporary RP series report rates of thromboembolic complications ranging from 0.8% to 6.2% (with the use of various prophylactic measures), so there is no doubt that RP carries a significant risk of potentially fatal venous thromboembolism (VTE).

The risk of VTE is determined by patient's age, length of the operation, extent of incision and way of anesthesia in case of surgical interventions. This can be modified by co-morbidities, body characteristics and general condition of the patient.

Low risk is stated in cases of patients younger than 40 years undergoing minor operations without comorbidities. Patients between 40 and 60 years or <40 years but with comorbidities have moderate thrombotic risk. High risk is considered >60 years or patients 40-60 years with diseases affecting hemostatic system. Very high risk is stated when more comorbidities are

present: malignancy, hypercoagulability, VTE event in history, hip or knee prosthesis, polytrauma or spinal cord injury.

3.2. Methods of thrombosis prophylaxis

There are several methods available for the prevention of thrombotic events in the perioperative period. The most common pharmacological prophylaxis is the low molecular weight heparin (LMWH) and unfractionated heparin (UFH). These block hemostatic factors II and X in order to prevent hypercoagulability.

The most cost efficient mechanic prophylaxis is early mobilization (on the first postoperative day). Intermittent pneumatic compression (IPC) or pneumatic compression boots (PCB) are based on the same mechanism: pneumatic boots are applied for the length of immobilization, which contains inflatable chambers supporting venous flow from the lower limbs towards the heart. Graduated compression stocking (GCS) are also useful on the first few postoperative days.

3.3. Laboratory methods of detection of hypercoagulability

Coagulation-time tests are suitable for testing the humoral part of the hemostatic system. Prothrombin time (PT) presents the extrinsic way of

hemostasis. Activated partial thromboplastin time (APTT) provides information about extrinsic part of hemostasis. Thrombin time (TT) is suitable for detection of fibrinogenemias, presence conventional heparin or disseminated intravascular coagulation (DIC). Testing fibrinogen (FNG) level detects failure or lack of FNG. Measuring D-dimer is provides information about demolition of bounded fibrin. It is suitable for testing consumption coagulopathies and thromboembolism.

Recent trials measuring thrombin generation by fluorescent substrate assay proved that this is a suitable method for estimating the risk of thrombotic events under appropriate sample handling and laboratory conditions. Elevated basal peak thrombin generation was associated with a 74% increased risk of VTE published in prospective LITE data.

3.6. The presence of malignant prostate cancer

Prostate cancer is the most common solid male neoplasm among men in Europe and in Hungary with an incidence of 513/100000 outnumbering lung and colorectal cancers. The mortality is high in cases of advanced disease, but with early detection the 5 years cancer specific survival can exceed 90%. Due to the efficient screening programs these patients can be diagnosed in time and proper treatment can be indicated. Radical prostatectomy has shown promising results regarding outcomes in cases of localized prostate cancer

against conservative treatment options. The ratio of complication has dropped dramatically and life quality outcomes are gaining more and more attention with the increasing experience of this treatment option.

3.7. Objectives

The aims of this study were the followings of study phase I:

- (1) Verification of thrombotic risk after radical prostatectomy with laboratory methods.
- (2) Comparison of sensitivity of thrombin generation assay and conventional clotting tests.

The objectives of study phase II were

- (3) Assessment of preferred methods of thrombosis prophylaxis at the Hungarian departments of urology before and after urological operations focusing on radical prostatectomy.
- (4) Studying modification of ongoing antiplatelet and anticoagulation treatment before and after urological surgeries.
- (5) Evaluation of ratio of venous thromboembolism in the postoperative period of prostate cancer surgery detected by urologists.

4. Patients and methods

4.1. Patients and inclusion criteria of the study phase I.

In our prospective study, 24 patients with histology proven localized prostate cancer were selected (mean age 61, range 50–70 years), and followed up after laparoscopic radical prostatectomy. Patients with any anticoagulant medication or any medical condition potentially affecting coagulation assessment and any other kind of malignancy or previous treatment of prostate cancer were excluded from the study. For comparison 20 male age matched controls (mean age 60, range 42–76 years) without prostate cancer and with the same exclusion criteria as for the patients were recruited at the urology outpatient service. The prostate cancer was excluded by the following inclusion criteria: total Prostate Specific Antigen (tPSA) level ,1.5 ng/ml, digital examination of prostate negative. Written informed consent was obtained from each participant. The local ethics committee of the University of Debrecen (Debrecen, Hungary) approved the study protocol.

4.2. Brief protocol and statistical methods of study phase I.

Low molecular weight heparin (LMWH) administration (40 mg or 4000 IU anti-Xa/day) was started one day prior to the surgical intervention and was continued for 5 weeks after the laparoscopic procedure according to the guidelines of the American Urological Association (AUA). Patients were mobilized on the first postoperative day.

Blood was collected from the antecubital vein into the appropriate Vacutainer tubes 1 day prior, at 1 hour, 6 days, 1 and 10 months after radical prostatectomy. Sampling was performed at least 12 hours after LMWH administration to obtain heparin free plasma from patients under therapy.

The following parameters were evaluated: prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, D-dimer, factor Xa, antithrombin III, hematologic parameters, prostate specific antigen and thrombin generation.

For statistical analysis the patients were divided into subgroups according to the followings: tumour stage (PT2, n= 19; PT3, n =5) additional lymphadectomy (n= 12); narcosis time (<230 min, n= 12 and \geq 230 min, n= 12); body mass index (BMI, <25, n= 8 and \geq 25, n= 16). Preoperative data were compared to controls and the results of the postoperative samples were

compared to the preoperative ones (day-1). Statistical tests were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego CA, www.graphpad.com). P,0.05 is considered to indicate statistical significance.

4.3. Brief protocol of study phase II.

A questionnaire was posted to every department of urology (n=37) having surgical activity in Hungary. In a covering letter the head of the division was requested to report retrospectively the number of the performed radical prostatectomies, the preferred approach, the surgeons' experience and the length of the postoperative hospital stay. The number of the transurethral, pelvic (anti-incontinence and reconstructive), laparoscopic and open procedures were also evaluated. Thrombotic risk assessment, the way and the length of different prophylactic methods, modification of previous anticoagulant therapy were also reported. The departments were asked to report the number of experienced thrombotic events after radical prostatectomy of the previous year

The responders were asked either to present their result by filling the questionnaire electronically or post the form back. All data was entered into a

computer database and analyzed in an anonymous fashion. During the analysis Microsoft Office Excel statistics were used.

The ethics committee of the Health Scientific Committee of the Ministry of Health approved the study protocol (case number: 24098-0/2010-1018EKU).

The Hungarian Association of Urology morally supported the present research.

5. Results

5.1. Results of study phase I.

5.1.1. Oncological and life-quality outcomes

Based on the preoperative PSA values (mean: 8 ng/mL) and histology of the prostate biopsy specimens, radical prostatectomy was combined with regional lymphadenectomy in 12 out of 24 cases. The mean narcosis time was 233 minutes (range 140–335). Mean blood loss was 314 mL (range 50–700) which correlates with the changes in the RBC levels. No severe intra- or postoperative complications occurred.

Histological examinations revealed prostate cancer in stages between pT2a and pT3b in one case with a single lymph node metastasis (Gleason Score 5–

9). The median value of PSA was reduced to the limit of detection. Salvage irradiation therapy and 6 month hormone therapy was given to 2 patients from the 6th postoperative week. No relapse of malignancy was experienced in any patient in the first ten postoperative months. Eighty-three percent (20/24) of the study population was continent, and 42% (10/24) of the patients had erection with or without medication at 10 months. No thrombotic complications occurred during the observational period.

5.1.2. Changes of the laboratory parameters

White blood cell counts were elevated one-hour postoperatively and normalized afterwards. Platelet counts were the highest on the sixth postoperative day and lowered afterwards. Prothrombin time and TT were prolonged in the one-hour postoperative samples and then returned back to the preoperative value, and activated partial thromboplastin time was prolonged preoperatively compared to the controls and shortened after the operation, however these changes were minor. Conventional clotting tests remained in the reference range after surgical procedure. Reference ranges in our laboratory are: PT: 7.5–12.8, APTT: 26.5–37.7 and TT: 15.4–23.4 [sec]. Fibrinogen levels decreased first, then doubled and decreased almost to the preoperative value at one month. D dimer level was high at one-hour

postoperatively, further elevated by the sixth day and normalized afterwards. Thrombin generation measured by TGA was evaluated by the peak thrombin concentration (nM), the area under the curve. AUC), the lag phase, the peak time and the velocity index (Vindex;). Compared to the controls, peak thrombin and AUC were elevated in the patients' preoperative samples, while the other parameters of the thrombin generation remained unchanged. The peak thrombin levels were further elevated in the early postoperative period, reaching a maximum by the sixth day, as did AUC, and normalized by the end of the first month. Significant differences in the lag phase, peak time and velocity index were seen in the postoperative onehour samples. None of the TGA parameters correlated with the changes in fibrinogen levels except AUC on the sixth day ($p = 0.0038$, Pearson correlation). No correlation between conventional clotting times and changes in the thrombin generation parameters were found, except for PT and TT on the sixth day, where the correlation with the lag phase was significant. Decreased antithrombin (AT) levels may increase the thrombin generation thus we assessed its changes in the study samples. Compared to the baseline, AT-levels were reduced one hour postoperatively, which however was not significant. As patients had been under prophylactic LMWH treatment and the presence of LMWH in plasma is expected to decrease peak thrombin level and AUC. The inhibitory

effect of LMWH on FXa (aFXa activity) in the plasma samples was measured and found to be below the limit of detection in each of the samples.

5.1.3. Group analysis

The patients' data was analyzed retrospectively for correlation between different clinical parameters and peak thrombin levels. Neither pathological tumor stage (pT) nor additional lymphadenectomy did alter TGA results significantly. Longer narcosis resulted in increased peak thrombin levels in the first postoperative sample ($p=0.024$, unpaired t test with Welch's correction). Baseline plasma peak thrombin levels of patients with elevated body mass index (BMI.25) were similar to the normal BMI patients, however a significant difference was found on the sixth postoperative day ($p=0.011$, Mann Whitney test).

5.2. Results of study phase II.

A total response rate of 59% (22 departments) was achieved. The departments of all four Hungarian medical universities have filled the questionnaire.

5.2.1. Radical prostatectomy

5.2.1.1. Number and approach of radical prostatectomies

A total response rate of 59% (22 departments) was achieved. Eight departments do not perform RP, so they were excluded from this part of the study. The reported number of radical prostatectomies was 506 performed by the departments who filled the form, among these 41.9% (n=212) was laparoscopic, 0.8% (n=4) was perineal and 57.2% (n=290) was retropubic RPs. The high volume centers (radical prostatectomies >50/year) performed 314 radical prostatectomies (62.0% of all). More than 70% of the procedures were performed by a single surgeon in 93% of the institutes. The average length of hospital stay was 10 days ranging from 8 to 16.

5.2.1.2. Risk assessment and way of thrombosis prophylaxis

Pharmacological thromboprophylaxis with LMWH once daily was preferred by 100% of the departments, but the practice was different. 80% of the patients are under LMWH administration from the 1st day prior RP to the end of the 4th postoperative week. None of the institutes reported the use of

UFH. Graduated support stockings were applied by 37% of the patients. Although pneumatic compression boots were available by 29% of the institutes, they didn't use them. Early mobilization was the most common way of mechanic prophylaxis. One low volume department reported the method of planned hemodilution during the surgical procedure for the purpose of thrombosis prophylaxis.

Although dose adjustment of LMWH is performed in 93% of the departments and by 91% of the patients, risk assessment was reported only by 11 institutes. In the high-volume centers this is the task of the anesthesiologist, but in the smaller institutes it is a due of the urologist.

5.2.1.3. Modification of ongoing anticoagulant treatment

Acetylsalicylic acid drugs were stopped by 97% of the patients (n=487), and in 58% (n=287) they were replaced by LMWH. In case of thienopyridins these drugs were switched to LMWH in 82% (n=416). Kumarins were replaced in 100%. The highest variation was experienced regarding the timing of modification of ongoing anticoagulant treatment of the patients. The responders reported stopping the therapy in the range of 10th to 1st day prior to surgery, and the drugs were re-administered in the range of 1st to 30th postoperative day.

5.2.1.4. Thrombotic events

According to the self-report of the institutes clinical thrombotic events were experienced in 1.4% of the cases (7 patients): 4 were deep vein thrombosis (DVT) and 3 were pulmonary embolism (PE). Two DVT events occurred during the 4th postoperative week, the others were experienced within two weeks after the surgical procedure. Two thrombotic events were reported by high volume center (>50 RP/year) and two by low - volume department (<20 RP/year). Six patients were under constant LMWH prophylaxis at the time of the thrombotic event. The start of the pharmacological prophylaxis varied from 1 day prior surgery to the first postoperative day. GSS was also applied in the first few postoperative days by 5 patients. Five patients underwent risk assessment and dose adjustment prior surgery, 3 of them were rated as high risk, the others as very high risk patients. One of the 7 events was fatal (0.2% referring to the whole study population) and this event was reported by a low volume department (3 weeks of LMWH + GSS).

5.2.2. Transurethral operations

All participating departments perform transurethral operations. Nineteen institutes reported the annual number of transurethral surgeries, The number was between 110 and 600 per year (total 6166). Pharmacological thromboprophylaxis with LMWH once daily was administered by 91% (n=20) of the departments. Dose adjustment of LMWH is performed in 100% (n=21) of the departments and risk assessment in 85% (n=17). Dose of LMWH is determined by anesthesiologist in 60% (n=12), by urologist in 25% (n=5) and according to common decision in 15% (n=3). The institutes start the LMWH prophylaxis on th 1st preoperative day in 80% (n=16), on the day of the operation in 20% (n=4). None of the institutes reported the use of unfractionated heparin or pneumatic compression boots. Graduated compression stockings was applied by 68% (n=15) of the departments from the 1st preoperative day to the mobilization of the patient. This was performed on the 1st postoperative day in 86% of the institutes (n=19).

Modification of ongoing thrombosis prophylaxis (cixlooxigenaze inhibitors, or thyenopyridines) or therapy (kumarins) is heterogeneous among the departments in case of transurethral operations as well as before pelvic or

open surgeries. Acetylsalicylic acid was stopped 2-10 days before interventions. Clopidogrel and ticlopidin was administered during transurethral operation in one institute. The practice regarding kumarins is much more unified, these drugs are replaced by LMWH from the 5th preoperative day to the postoperative 10th day.

5.2.3. Pelvic (anti-incontinence and reconstructive) surgery

According to the questionnaires 91 % (n=20) of the departments perform pelvic surgeries ranging 17 to 1010 per year. This data was not given by 3 institutes. Total number was 1761. Pharmacological thromboprophylaxis with LMWH once daily was administered by 100% (n=20) of the departments. Dose adjustment of LMWH is performed in 95% (n=19) of the departments and risk assessment in 85% (n=17). Dose of LMWH is determined by anesthesiologist in 50% (n=10), by urologist in 32% (n=7) and according to common decision in 14% (n=3). The timing of LMWH is very heterogeneous. Graduated compression stockings was applied by 70% (n=14) of the departments from the 1st preoperative day to the mobilization of the patient. This was performed on the 1st postoperative day in 85% of the institutes (n=17).

5.2.4. Laparoscopic operations

According to the questionnaires 64 % (n=14) of the departments perform laparoscopic operations ranging 8 to 201 per year. This data was not given by an institute. Total number was 820. Pharmacological thromboprophylaxis with LMWH once daily was administered by 93% (n=13) of the departments. Dose adjustment of LMWH is performed in 86% (n=12) of the departments and risk assessment in 64% (n=9). Dose of LMWH is determined by anesthesiologist in 60% (n=8), by urologist in 15% (n=2) and according to common decision in 15% (n=2). One institute did not report the dose adjusting person. The timing of LMWH is very heterogeneous. Graduated compression stockings was applied by 50% (n=14) of the departments from the 1st preoperative day to the mobilization of the patient. This was performed on the 1st postoperative day in 86% of the institutes (n=12).

5.2.5. Open procedures

According to the questionnaires 95 % (n=21) of the departments perform laparoscopic operations ranging 10 to 1800 per year. This data was not given by two institutes. Pharmacological thromboprophylaxis with LMWH once daily was considered by 100% (n=21) of the departments. Dose adjustment of

LMWH is performed in 95% (n=20) of the departments and risk assessment in 76% (n=16). Dose of LMWH is determined by anesthesiologist in 53% (n=11), by urologist in 33% (n=7) and according to common decision in 14% (n=3).. Graduated compression stockings was applied by 67% (n=14) of the departments from the 1st preoperative day to the mobilization of the patient. This was performed within 2 postoperative days in 86% of the institutes (n=18).

6. Discussion

Radical prostatectomy (performed in high volume center) is oncologically efficient, safe and provides acceptable changes in life quality parameters. This statement was proven by the results of the 24 followed up patients.

The results of the postoperative laboratory parameters met the expectations of the preliminary results according to the severity of the surgical procedure. Changes in white blood cell counts reveal the acute immunological reaction to the tissue trauma, with an early compensation. Platelet count and conventional clotting tests varied somewhat, but all remained within the reference ranges,

The results of our thrombin generation tests showed remarkable changes following radical prostatectomy. An even more significant difference in

thrombin generation was found between the preoperative patient group and healthy control group. When compared to the controls, baseline thrombin generation and AUC were higher in the cancer patients which finding could be due to a variety of causes such as the presence of tumor cells, of microparticles and tissue factor. Tissue factor and microparticles highly enhance procoagulant activity and thus influence the thrombin generation parameters. The difference of the TGA parameters between the controls and the preoperative values of the study population revealed increased procoagulant activity, which were further stimulated by the surgical intervention. The effect of the operation decreased at the end of the first postoperative month. This supports the findings of other studies that the high-risk period after radical pelvic surgery ends at the first postoperative month. The difference compared to the control group disappeared only by the 10 month check.

According to the correlation analysis of the FNG levels, conventional clotting times and TGA parameters we found that increased procoagulant activity is more readily detected when using the TGA, than by measuring changes in PT, APTT and TT levels. Elevated basic d dimer level was similar to published results. Fibrinogen-levels did show a slower response to tissue trauma, than d dimer and peak thrombin. Since we did not find a correlation between fibrinogen and peak thrombin generation, although fibrinogen

influences thrombin generation, we conclude that in this altered balance of hemostasis as seen in the patients, it has a lesser contributing effect to the rise in peak thrombin levels or other TGA parameters.

A 50% decrease of AT increases thrombin production from 104% to 196%. However, as the decrease of AT in our samples was less than 10% and all levels remained within the reference range (80–120%), this cannot explain the remarkable increase in the thrombin generation seen in our study. Possible LMWH inhibitory actions on procoagulant factors were low as at the moment of blood sampling. The levels in all samples were below the detection limit when measuring inhibition of FXa, consequently LMWH had only minor influence on the result of TGA parameters.

Pathological tumor stage (pT) or additional lymphadenectomy was not significantly linked to TGA results. However, longer narcosis was observed to correlate with increased peak thrombin levels in the first postoperative sample. Baseline peak thrombin levels in plasma of patients with elevated body mass index (BMI>25) were similar to the normal BMI patients, but here a significant difference was seen on the sixth postoperative day.

Besides evaluation of increased hypercoagulability after radical prostatectomy the other main goal of the study was to assess the present practice of thrombosis prophylaxis after urological procedures and to refer it to the guidelines.

The response rate of 59% (including the four Hungarian medical universities) reflects the Hungarian practice to prevent venous thromboembolism.

The number of the reported radical prostatectomies represents the current practice in Hungary. The most experienced centers in the country prefer the laparoscopic approach. Since more than 70% of the procedures were performed by a single surgeon in 93% of the institutes thus we could draw the conclusion, that especially in the high volume centers the surgeons are experienced enough where most of the patients were treated (62%), which is the most important factor regarding the oncological and functional outcome independent from the preferred approach. Proper skill of the surgeon can also decrease blood loss during RP so the departments can better focus on thrombosis prophylaxis.

The first step of the proper thrombosis prophylaxis is the risk assessment. This is performed in 78% before radical prostatectomy, in 77% before transurethral surgery, in 85% before pelvic surgery, in 64% before urological laparoscopy, in 76% before open procedures at the Hungarian departments of urology. So 25% of the patients are not under prophylaxis according to the present Hungarian guidelines.

Regarding laparoscopic procedures it is recommended to use pneumatic compression boots (PCB) at the time of the surgical intervention. In high-risk and very high risk groups (like laparoscopic and open radical prostatectomy)

patients may require the use of low dose unfractionated heparin (LDUH) or LMWH, but clear recommendation cannot be done regarding the use of pharmacological prophylaxis due to the lack of randomized controlled trials in this population. Given the increased risk factors within the patients' population undergoing open urologic procedures, more aggressive regimens combining the use of PCB with pharmacologic prophylaxis may be considered. The recommendation is the following for open urological procedures: high risk patients require UFH 3x or LMWH 1x daily or PCB if bleeding high, in case of very high risk patients UFH 3x and or LMWH 1x daily and PCB are recommended. In case of increased risk of bleeding mechanical prophylaxis is favored against pharmacologic prophylaxis.

The most common method of prevention after radical prostatectomy is pharmacological prophylaxis in the studied Hungarian hospitals, although the timing of LMWH administration is not unified. By almost 20% of the patients the LMWH administration was stopped before the end of the second week.

The PCBs are available in almost 30% of the departments, but they do not use them. The graduated compression stockings were applied by 57% and early mobilization in 86% of the patients.

Early mobilization is the recommended way of thrombosis prophylaxis in cases of transurethral surgeries by low risk patients according to the AUA guidelines.

Early mobilization is suitable for thrombosis prophylaxis in cases of transurethral operations of patients without comorbidities. PCB should be applied or LMWH/UFH administered by patients in high risk group. Early mobilization is preferred in 86% of the Hungarian departments of urology. The intents of the other (14%) institutes is unknown. Application of GCS in the early postoperative period is useful, since it is a cost-efficient and non-invasive way of thrombosis prophylaxis. LMWH should be considered in case of treatment of malignancy (e.g. bladder cancer) or patients with prostate enlargement and comorbidities.

Pelvic (anti-incontinent and reconstructive) surgery requires early mobilization in low risk, additional PCB/LMWH/UFH in moderate risk and combination of the above in high risk groups. Thus early mobilization is essential in this group as well. This is applied in 85% of the departments along with GCS in 70%. LMWH should be considered in moderate risk group, what can be an explanation of the high rate of administration (100%) by the Hungarian urologists.

In case of laparoscopic procedures application of PCB is recommended for the length of the procedure. In high risk and very high risk group

administration of LMWH/UFH is considerable. Guidelines emphasize that clear recommendation cannot be given regarding urological laparoscopic operations due to the lack of randomized studies. PCBs are available in 29% of the Hungarian institutes, but no one use these devices. Mechanic prophylaxis is common in this group, especially early mobilization (85%), the ratio of GCS application is 50 %. LMWH is administered by 79% of the departments, but in some cases this can be over-prophylaxis (laparoscopic varicocele surgery).

The recommendation is the following for open urological procedures: high risk patients require UFH 3x or LMWH 1x daily or PCB if bleeding high, in case of very high risk patients UFH 3x and or LMWH 1x daily and PCB are recommended. In case of increased risk of bleeding mechanical prophylaxis is favored against pharmacologic prophylaxis. According to different studies the risk of thrombotic events are present till at least the end of the first postoperative month, so LMWH administration should be continued to the end of the first postoperative month. This recommendation is considered in 57% of the Hungarian departments of urology. Due to the heterogeneity of these types of intervention risk assessment and dose adjustment is essential.

The PCBs are available in almost 30% of the departments, but they do not use them. The reason of this is yet to be evaluated, since PCB is a noninvasive prophylactic method with moderate costs, and these are highly

recommended by the guidelines. If the reason is only the lack of knowledge, this should be promoted among urologists, since in 25-36% urologists decide the way and length of thrombosis prophylaxis.

The majority of the departments had stopped any other anticoagulant therapy or prophylaxis before surgery, and many of them replaced it with LMWH. The timing was really heterogeneous as the results shows. The acetylsalicylic acid is for prevention and not for anticoagulant therapy, so it is not absolutely necessary to replace. Thienopyridins can lead to excessive bleeding during surgical procedures so it is recommended to replace it with LMWH 8 days before operation (lifetime of the thrombocytes is that long), and to switch back only when risk of bleeding is over. Perioperative antiplatelet drugs may increase the risk of on bleeding complications in urological surgery according to a recent meta-analysis, but still more high-quality trials with larger samples and longer follow-ups are required. These statements suggest that urologist should have a basic knowledge regarding the mechanism and potential effects of these drugs.

6.1. New statements

1. We assessed the extent of hypercoagulability by measuring the plasma thrombin generation capacity in the early and late postoperative period after radical prostatectomy. To the best of our knowledge, this study is the first to evaluate the course of the hypercoagulability in cancer patients undergoing major pelvic surgery.
2. It has been proven, that the conventional clotting tests are less sensitive to hypercoagulability than thrombin generation assay.
3. This is the first trial assessing the applied prophylactic methods of the Hungarian departments of urology. The length and type of thrombosis prophylaxis has been evaluated regarding radical prostatectomy, transurethral operations, pelvic surgeries, laparoscopic procedures and open urological operations. We have stated that pharmacological prophylaxis with LMWH is dominating, but timing is not unique. Risk assessment and dose adjustment should be more common than the present stud reveals. Compression boots are available at some institutes but they are not applied. The most common ways of mechanic prophylaxis are early mobilization and graduated compression stockings.

4. Modification of ongoing antiplatelet and anticoagulant is very heterogeneous.
5. The incidence of thrombotic events after radical prostatectomy is similar to the international findings.

6.2. Conclusions

Assessment of individual thrombotic risk before urological procedures with high risk (especially in cases of radical prostatectomies) is essential. It is considerable to start individual thrombosis prophylaxis in very high risk cases. The conventional clotting test are not sensitive enough in the follow up of hypercoagulability after radical prostatectomy, application of more specific test are considerable.

The present practice of dominating pharmacological prophylaxis should be reconsidered focusing on mechanical methods of thrombosis prevention.

The thrombosis prophylaxis of patients undergoing radical prostatectomy is not unified. Due to the potential mortality of thrombotic complications as urologists it is essential to know the different prophylactic methods, and to evaluate the effectiveness of the known ones. It would be beneficial that urological guidelines would include a chapter of thromboprophylaxis as well.

Register Number: DEENKÉTK/322/2013.

Item Number:

Subject: Ph.D. List of Publications

Candidate: Mátyás Benyó

Neptun ID: LMR1XN

Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. **Benyó, M.**, Hársfalvi, J., Pfliegler, G., Molnár, Z., Murányi, M., Józsa, T., Flaskó, T.: Present practice of thrombosis prophylaxis of radical prostatectomy in a European country - a Hungarian multicenter study.
Urol. Int. "accepted by publisher", 2013.
DOI: <http://dx.doi.org/10.1159/000353918>
IF:1.065 (2012)
2. **Benyó M.**, Hársfalvi J., Pfliegler G., Kiss Z., Murányi M., Berczi C., Varga A., Flaskó T.: Trombózis profilaxis gyakorlat a magyar urológiai osztályokon.
Magyar Urol. "közlésre elfogadva", 2013.
3. **Benyó, M.**, Flaskó, T., Molnár, Z., Kerényi, A., Batta, Z., Józsa, T., Hársfalvi, J.: Follow-Up of Thrombin Generation after Prostate Cancer Surgery:Global Test for Increased Hypercoagulability.
PLoS One. 7 (12), e51299, 2012.
DOI: <http://dx.doi.org/10.1371/journal.pone.0051299>
IF:3.73

List of other publications

4. **Benyó, M.**, Berczi, C., Józsa, T., Csanádi, G., Varga, A., Flaskó, T.: Fertility preservation in cases of laparoscopic treatment of seminal vesicle cysts.
Central Eu. J. Urol. 65 (3), 144-145, 2012.



5. Murányi, M., Salah, M.A., **Benyó, M.**, Flaskó, T.: Serious contracted bladder and vesicoureteral reflux after intravesical Mitomycin-C treatment.
IJCRI.
DOI: <http://dx.doi.org/10.5348/ijcri-2012-03-103-CR-8>
6. Murányi, M., Józsa, T., **Benyó, M.**, Salah, M., Flaskó, T.: Laparoscopic Removal of a Paracaval Air Gun Bullet in a Child.
Urol.Int. 89 (2), 246-248, 2012.
DOI: <http://dx.doi.org/10.1159/000337693>
IF:1.065
7. Murányi, M., Salah, M.A., Tállai, B., **Benyó, M.**, Flaskó, T.: Very Late Relapse of Testicular Tumour in Combination with Renal Cancer and Their Retroperitoneoscopic Removal.
Case Reports in Medicine. 2011, Article ID 164070, 2011.
DOI: <http://dx.doi.org/10.1155/2011/164070>
8. Józsa, T., Telek, A., Kutasy, B., **Benyó, M.**, Csanádi, G., Kovács, I., Balla, G., Flaskó, T., Csernoch, L., Kiss, C.: Effect of hydrocele on appendix testis in children.
Asian J. Androl. 11 (6), 741-745, 2009.
DOI: <http://dx.doi.org/10.1038/aja.2009.54>
IF:1.688
9. Flaskó, T., Tóth, G., **Benyó, M.**, Farkas, A., Berczi, C.: A new technical approach for extraperitoneal laparoscopic bladder diverticulectomy.
J. Laparoendosc. Adv. Surg. Tech. A. 17 (5), 659-661, 2007.
DOI: <http://dx.doi.org/10.1089/lap.2006.0235>
IF:0.606

Total IF: 8.154

Total IF (publications related to the dissertation): 4.795

The Candidate's publication data submitted to the Publication Database of the University of Debrecen have been validated by Kenez Life Sciences Library on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

09 October, 2013

