Can the prophylactic administration of tranexamic acid reduce the blood loss after robotic assisted radical prostatectomy? RARPEX (Robotic Assisted Radical Prostatectomy with TranEXamic acid): study protocol for a randomized controlled trial (SPIRIT Compliant)

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Study protocol

Keywords: Tranexamic acid, robotic assisted radical prostatectomy, bleeding prophylaxis

DOI: https://doi.org/10.21203/rs.3.rs-350770/v1

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Abstract

Background

The prophylactic administration of tranexamic acid reduces the blood loss during procedures at high risk of perioperative bleeding. Several studies in neurosurgery, cardiac surgery, and orthopedics confirmed this finding. The aim of this prospective, double-blind, randomized study is to evaluate the effect of tranexamic acid on peri-and postoperative blood loss and on the incidence and severity of complications.

Methods / Design

Based on the results of our pilot study, we decided to conduct this prospective, double-blind, randomized trial to confirm preliminary data. The primary end-point is to analyze the effect of tranexamic acid on perioperative and postoperative blood loss (decrease in hemoglobin levels) in robotic-assisted radical prostatectomy. The secondary end-point is to analyze the effect of tranexamic acid on postoperative complications. Additional end-point is to confirm the safety of tranexamic acid in robotic assisted radical prostatectomy.

Discussion

No study to date has tested the prophylactic administration of tranexamic acid in the beginning of robotic assisted radical prostatectomy. This study is designed to answer the question whether it might lower the blood loss after the procedure or increase the rate and severity of complications.

Trial registration

The trial was prospectively registered under title “Can the Prophylactic Administration of Tranexamic Acid Reduce Blood Loss After Robotic-assisted Radical Prostatectomy? (RARPEX)” on 25th March 2020 at ClinicalTrials.gov with the registration number NCT04319614.

Background

Prostate adenocarcinoma is the second most common malignancy in men. The incidence increases over time and with patient age. It is the second most common cause of death due to malignancy in men, after lung cancer. Standard treatment includes radical prostatectomy or radiotherapy in patients with life expectancy more than 10 years (LE1b, GRA) (1–3).

In recent years, there is a general tendency towards minimally invasive surgical procedures. In the treatment of localized prostate cancer, laparoscopic or robotic-assisted radical prostatectomy has become the standard modality of treatment. Despite tremendous development in the technology and technique of robotic-assisted radical prostatectomy over more than 25 years, new ways and methods to improve oncological and functional outcomes are still needed (4–8).
Decreasing peri- and postoperative blood loss may lead to faster recovery after the procedure (9). Concerns have been raised about the possible relationship between the administration of blood derivatives and an increased risk of relapse of malignancy and tumor-specific mortality (10, 11).

Tranexamic acid is an antifibrinolytic agent used to relieve bleeding. The mechanism of action lies in binding to plasma free plasminogen with higher affinity than tissue plasminogen activator. It prevents its conversion to plasmin, which is responsible for the degradation of fibrin polymers. It results in greater stability of the fibrin clot at the site of bleeding and; and therefore lower blood loss (12–14). The use of tranexamic acid during or after the procedure does not improve results, unlike administration prior to surgery. A biological explanation is that tranexamic acid may bind plasminogen in the early phase of the fibrinolytic cascade, after the beginning of the procedure, reducing tissue plasminogen activator activity up to 80 % (15).

In urology, increased conversion of plasminogen to plasmin should occur, both by washing the tissue plasminogen activator from the destroyed tissue and by urokinase present in the urine (16). Only few studies have been published to date on the use of tranexamic acid in transurethral prostate resection, open radical prostatectomy, and open radical cystectomy. Several authors did not confirm the positive effect in terms of reduced perioperative and postoperative blood loss in prostate transurethral resection (17). Increasing evidence of the beneficial use of tranexamic acid in cardiac surgery, neurosurgery, traumatology, and orthopedics has led to the renewal of this idea (18–20). However, newer urological papers continue to produce ambiguous results, from clearly negative (21) to confirmation of the positive effect (22–25), including a recent meta-analysis (26). Therefore, this trial was conducted in order to clarify this issue.

**Methods/design**

**Objectives and hypothesis**

The primary aim of the Robotic Assisted Radical Prostatectomy with EXacyl (RARPEX) trial is to investigate the effect of tranexamic acid on perioperative and postoperative blood loss (decrease in hemoglobin levels) in robotic-assisted radical prostatectomy.

H0: The drop of hemoglobin level after the procedure is similar in both groups.

HA: The drop of hemoglobin level after the procedure in control group is higher than in study group.

The secondary aim of the RARPEX trial is to analyze the effect of tranexamic acid on postoperative complications.

H0: The rate of postoperative complications within 90 days after the procedure is similar in both groups.

HA: The rate of postoperative complications within 90 days after the procedure is different between the groups.
Additional end-point of the RARPEX trial is to confirm the safety of tranexamic acid in robotic assisted radical prostatectomy.

**Study population and eligibility criteria**

All patients who are scheduled for operation due to low or intermediate risk prostate cancer in our institution will be screened and assessed for eligibility.

Only patients who will undergo robotic assisted radical prostatectomy with suturing of dorsal complex vein (DVC) bundle at the beginning of the procedure without pelvic lymph node dissection will be included in the study. Patients with nonstandard procedures or a procedure associated with higher morbidity will be excluded from the study to achieve a homogeneous study group.

Detailed inclusion and exclusion criteria are described below.

**Inclusion criteria**

1. Patient scheduled for robotic assisted radical prostatectomy without pelvic lymph node dissection
2. Signed informed consent provided
3. Body mass index ≤ 35
4. Age of patient ≤ 75 years
5. Operating surgeon with experience of more than 100 cases

**Exclusion criteria**

1. Body mass index > 35
2. Age of the patient > 75 years
3. Coagulation disorder (congenital or iatrogenic due to the chronic use of anticoagulants)
4. Thromboembolic, cerebral, or an acute coronary event within the 6 months prior to prostatectomy
5. Chronic renal insufficiency (arbitrary cut-off level of creatinine 200 µmol/l)
6. Allergic reaction to tranexamic acid
7. Operating surgeon with experience < 100 cases
8. Patient participating in another study

If subjects do not meet the inclusion criteria or withdraw their consent, they will be excluded from the study. The researcher will record the reason for their withdrawal.

**Sample size calculation**

The sample size calculation is based on the data from our pilot study (27). We used a Two-Sample T-Tests Allowing Unequal Variance with respect to the primary endpoint, which is the drop of hemoglobin level. With \( \alpha = 1\% \) and \( \beta = 10\% \), a sample size of 64 patients per group is necessary to detect a clinically
significant difference between the groups. With an expected dropout rate over 33%, we plan to enroll 200 patients into the study.

**Ethics, study registration and consent**

This trial was approved by independent ethics committee at the University Hospital Hradec Kralove (registration number 201903 I90P). The RARPEX trial will be conducted in the context of Good Clinical Practice and in accordance with the Declaration of Helsinki. The trial is registered at ClinicalTrials.gov under the registration number NCT04319614. All patients who are scheduled for robotic assisted radical prostatectomy in our institutions will be screened for eligibility and informed in detail about the RARPEX trial. Informed consent will be obtained from each participant. The study procedures, risks, benefits, and data management will be clarified with the patients before they are asked to give their informed consent to participate. Any participant in this study may withdraw consent or voluntarily cease to participate at any time for any reason.

**Study treatment**

Based on the literature and our pilot study (27), we decided to administer a single dose of tranexamic acid, corresponding to 20 mg/kg in 100 ml saline to all patients in the treatment group 1 at the beginning of procedure. In the control group 2 we administer only 100 ml saline as placebo.

For prophylaxis of venous thromboembolism, the combination of mechanical device (graduated compression stockings) and pharmacologic agents (low-molecular-weight-heparin - LMWH) in both treatment groups will be used. The dose LMWH is administered in the evening before the procedure, next dose at least 8 hours after the procedure and then every evening till postoperative day (POD) 7.

Antibiotic prophylaxis is provided by a single dose of potent aminopenicillin as recommended by the antibiotic center; fluoroquinolone in patients with an allergy to aminopenicillin. During the procedure, the console time, and weight of prostate is monitored.

The surgical technique is standardized and has been described previously (28). Standard robotic-assisted radical prostatectomy without pelvic lymphadenectomy using DaVinci Xi surgical system is performed. The dorsal vein complex (DVC) is sutured in the beginning of the procedure with two rounds of resorbable monofilament suture. To accelerate the return of continence, a modified Rocco stitch is performed in all patients. The anastomosis is performed by two tied V-loc stitches. No additional manipulation, such as fibrin glue or reinforcement with meshes, is allowed. Patients with rectal or bowel injury during the procedure will be excluded from evaluation.

For three hours after the procedure patients of both groups will stay in intermediate care unit, after moving to standard ward, blood samples will be obtained. On POD 1 all the patients will start with mobilization and solid food intake. The volume of the fluids in drain will be measured on postoperative day 1 and if the volume will not exceed 200 ml for 24 hours the drain will be extracted. If the volume is...
higher than 200 ml / 24 hours and the creatinine level in drain fluid exceeds 500 µmol/l, urinary leakage will be confirmed (29).

On POD 2 the patients will be released for home care with indwelling permanent urinary catheter.

On POD 7 the urinary catheter and skin sutures will be extracted and the blood sampling and ultrasound of the lower abdomen will be performed. Three months after the procedure a follow up visit is scheduled. The evidence of complication and level of prostatic specific antigen (PSA) is monitored.

Upon completion in 200 patients the statistical processing will be performed, and patients will be unblinded.

**Safety aspects**

Robotic assisted radical prostatectomy is a highly technically demanding procedure. High-volume surgeons with great experience have better results than low-volume surgeons with less experience (30).

In order to avoid bias based on the learning curve of the surgeons, every surgical procedure will be performed by a senior surgeon who has experience with at least 100 robotic assisted radical prostatectomies. Administration of tranexamic acid at the beginning of the procedure by anesthesiologist is a simple common procedure, performed on a routine basis, and no special training is necessary, and no complications are expected.

**Data collection**

A daily visit of the study patients will be made by clinical investigators or a delegated physician. All protocol-required information collected during the trial will be entered into the patient's record form. Preoperative data gathered include patient age, body mass index, American Society of Anesthesiologists physical status classification system score and comorbidities. Intraoperative data to be collected include surgery duration (skin to skin), console time (console surgeon activity time), and weight of the prostate.

According to data from our pilot study (27), we are not able to measure perioperative blood loss, because of many biases. The volume of suction fluid is affected by urine coming out of open urinary tract, lymphatic secretion from damaged tissue.

Laboratory tests will include blood count and plasmatic creatinine level at the beginning of procedure, 3–6 hours after the procedure, on POD 1, POD 2 and POD 7 in the morning.

The differences between the hemoglobin levels (eventually weighted for the grams of the prostatic tissue) and hemoglobin / creatinine ratios are obtained.

The volume of the fluids in drain is measured on postoperative day 1 and if the volume does not exceed 200 ml for 24 hours the drain is extracted. If the volume is higher than 200 ml / 24 hours and creatinine
level in the drain fluid exceeds 500 µmol/l urinary leakage is confirmed (29). Patient with confirmed urinary leakage or urinoma will be excluded from the evaluation.

Postoperative course assessments will include duration of intermediate / intensive care, hospital stay including readmissions for postoperative complications, reinterventions (reoperations, endoscopy and interventional radiology procedures), the reasons for readmissions and transfusion rates. The patients will be seen by a clinical investigator 3 months after the surgery in the outpatient fashion. The evidence of complication and level of prostatic specific antigen (PSA) is monitored. Upon completion of 200 patients the statistical processing will be performed, and results will be unblinded.

**Primary and secondary endpoints**

The primary endpoint is to analyze the effect of tranexamic acid on perioperative and postoperative blood loss – the decrease in hemoglobin levels after robotic-assisted radical prostatectomy. Clinically significant difference between treatment groups is set at 10 g/l. We assume that the results will be significantly affected by the weight of the prostate. A larger prostate could mean longer operating time and greater blood loss. Therefore, the results are weighted for the grams of the prostatic tissue. Another potential bias could be different hydration of subjects before, during and after the procedure. Therefore, the hemoglobin / creatinine ratio was used.

The secondary aim of the RARPEX trial is to analyze the effect of tranexamic acid on other postoperative complications: wound infection, intraabdominal collections, urinary leakage, delayed gastro-intestinal emptying, postoperative hemorrhage, pneumonia, abdominal rupture (Table 1).

Additional end-point of the RARPEX trial is to confirm the safety of tranexamic acid in robotic assisted radical prostatectomy, especially analyzing the incidence of cardiac events and venous thromboembolism (VTE) after the procedure.

**Table 1 Clinical parameters and postoperative complications for analysis**

| Parameters                  | Definitions                                                                 |
|-----------------------------|------------------------------------------------------------------------------|
| Hospital stay               | Days from initial operation to hospital discharge plus any readmission within 30 days |
| Console time                | Time of console surgeon activity (minutes)                                  |
| Postoperative haemorrhage   | Evidence of blood loss from drains, based on ultrasonography or CT            |
| Transfusion rate            | The number of blood transfusions                                             |
| Urinary leakage output      | Evidence of creatinine level > 500 µmol/l and volume of the drain output exceeds 200ml / 24 hours, confirmed on cystography |
| Lymphorrhea                 | Evidence of creatinine level < 500 µmol/l, hematocrit< 0,2 and volume of the drain output exceeds 200ml / 24 hours, no urinary leakage on cystography |
Intraabdominal fluid  Collection of fluid measuring ≥3 cm associated with clinical or laboratory collection
Symptomatic Fluid in the pleural cavity associated with respiratory distress or a need to fluidothorax evacuate the fluid
Thromboembolism Unilateral limb swelling, acute respiratory insufficiency, based on ultrasonography or CT
Myocardial infarction Increase of serum concentration of CK-MB and troponin and/or the following ECG changes: new Q waves ≥0.04 in duration, new persistent ST elevation and/or depression
Brain stroke Presence of neurological symptoms, findings on CT scan or MRI
Pneumonia Presence of a new infiltrate on chest X-ray, as well as the following: temperature >38°C, abnormal elevation of WBC, or positive sputum, and requiring antibiotic treatment
Acute renal failure Serum creatinine > 300 μmol/l and/or need for dialysis
Wound infection Surgical site infection associated with laparotomy that develops during the initial hospital stay
Urinary tract infection Culture-positive urine, pyuria or bacteriuria on urinalysis requiring antibiotic treatment

aCK-MB, Creatine kinase MB isoenzyme; ECG, Electrocardiogram; WBC, White blood cells; CT, Computer tomography; MRI, Magnetic resonance imaging.
Postoperative complications are graded based on severity according to the Clavien-Dindo definition (Table 2) (31).

| Grade     | Definition                                                                 |
|-----------|----------------------------------------------------------------------------|
| Grade I   | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiologic intervention |
| Grade II  | Requiring pharmacological treatment with drugs other than those allowed for grade I complications |
| Grade III | Requiring surgical, endoscopic or radiological intervention                 |
| Grade IIIa| Intervention not under general anesthesia                                 |
| Grade IIIb| Intervention under general anesthesia                                      |
| Grade IV  | Life-threatening complications requiring intensive care unit management    |
| Grade IVa | Single-organ dysfunction                                                   |
| Grade IVb | Multiorgan dysfunction                                                     |
| Grade V   | Death of the patient                                                       |
Methods for avoiding bias

Minimizing systemic bias

Patients will be randomized to one of groups before the surgical procedure after meeting eligibility criteria. Randomization will be accomplished using balanced permutation blocks by generation of random numbers in order to obtain homogeneity between groups. Opaque, sealed envelopes will be produced, labeled with the randomization number and containing a sheet that states the group allocation for the patient. Randomization envelopes will be used in consecutive order. Basic characteristics of the patient and the day of randomization will be documented on a data sheet so that compliance to the randomization scheme may be checked retrospectively. To maintain the double-blinding, the placebo and active ingredient are identical and cannot be distinguished by appearance by the participants or staff. The code assigned to subjects will be kept sealed and will not be released until the end of the clinical trial. Cases in which the blinding must be unsealed, such as a serious adverse drug reaction, will be managed using a separate envelope created for each subject so that only their randomization is revealed. Randomization and blinding will not be revealed to the researchers until the end of the study. If patients are excluded from the study after randomization, their numbers will not be reused.

Unblinded nurse will prepare an infusion set according to the information in the sealed envelope with the patient's study number on the day of procedure. For patients in the intervention group 1, the dose of tranexamic acid according to target 20mg/kg will be added to 100 ml of physiological saline. For patients in the intervention group 2 she will add no other substance to 100 ml of physiological saline. Infusion will be given into the sealed envelope, sent to the operating theatre and given within 5 minutes after the robotic system is docked.

Operating surgeons, attending physicians, nursing staff and outcome assessors will be blinded. The randomization process will follow the CONSORT guidelines (32) (Fig. 1).

Minimizing treatment bias

Administration of tranexamic acid at the beginning of the procedure by anesthesiologist is a simple common procedure, performed on a routine basis, which eliminates a learning curve.

All patients will undergo robotic-assisted radical prostatectomy without pelvic lymphadenectomy using the same technique. All surgeons participating in the study are familiar with this procedure. The dorsal vein complex (DVC) will be sutured at the beginning of procedure.

Minimizing measurement bias

Measurement of hemoglobin level drop and detection and grading postoperative complications will be based on data in the patient’s record form. Patient and clinical investigators or a delegated physician will be blinded.

Statistical methods
Each patient’s allocation to the analyzed population will be defined prior to the analysis and will be documented. In the full-analysis set, patients will be analyzed as randomized according to the intention-to-treat principle. The intention-to-treat principle implies that the analysis includes all randomized patients. The per-protocol analysis set will include all the patients without major protocol deviation. Deviations from the protocol will be assessed as major or minor. Patients with major deviations from the protocol will be excluded from the protocol analysis. The safety analysis set will analyze patients according to the treatment. The null hypothesis assumes that there is no difference in the hemoglobin level drop after the procedure in both groups. We will use a Two-Sample T-Tests Allowing Unequal Variance with respect to the endpoint, which is the drop of hemoglobin levels. Differences between age and PSA will be assessed by the nonparametric Mann-Whitney U test. BMI and specimen weight will be compared by the Kolmogorov-Smirnov test. A P-value < 0.05 will be considered statistically significant. Statistical analyses will be performed using NCSS statistical software (NCSS, Kaysville, UT, USA).

Discussion

One of the greatest risks of any technical demanding surgical procedure is bleeding. It is similar in radical prostatectomy. The robot-assisted approach leads to a significant reduction of blood loss. Nevertheless, efforts to reduce the blood loss even more are eagerly awaited. Perioperative hemorrhage makes the surgical terrain unclear, makes it difficult to dissect the tissue precisely, increases the risk of complications and worsens functional and oncological results. Excellent experience in orthopedics and other cardio-surgical fields with the prophylactic administration of tranexamic acid after the introduction to anesthesia gives rise to the hope of successful use in urology as well. Based on the results of our pilot study, we demonstrated lower blood loss in the tranexamic acid group compared to the placebo group. The differences were statistically significant evaluating the decrease in hemoglobin, especially when related per gram of prostate removed (27).

The therapeutic concentration of tranexamic acid in plasma ranges from 5 mg/kg to 10 mg/kg. After an intravenous dose of 10 mg/kg, plasma concentration was maintained for 3 hours, but orthopedics proved to be inadequate. Based on the above-mentioned literature, we decided to administer a single dose, corresponding to 20 mg/kg to all patients in the treatment group 1 at the beginning of procedure.

Radical prostatectomy is associated with a higher risk of thromboembolism. Open radical prostatectomy has a considerably higher risk of thromboembolic events (1.0–15.7%) compared to a robotic (0.2–3.7%) and laparoscopic approach (0.4–6.0%) (34). Administration of antifibrinolytics, which potentially increase the risk of thromboembolism in laparoscopic surgery for pelvic malignancy, may seem too risky. According to literature data from a meta-analysis of 11 studies involving 1177 patients with malignancy found no demonstration of an increased risk of thromboembolism following treatment with tranexamic acid (26). Our data from the pilot study correspond with this statement. Despite the enormous development in robot assisted radical prostatectomy over 25 years, improvement is still needed.
One possibility is to implement the ERAS (early recovery after surgery) protocol in everyday practice. Each of the original 22 recommendations (for example, preoperative nutritional examination and nutritional preparation, intestinal preparation, fasting time, prevention of thromboembolism, antibiotic prophylaxis, decolonization of the skin, minimally invasive approach, prevention of hypothermia, intestinal prokinetics, etc.) might significantly improve the postoperative results. The prophylactic use of tranexamic acid in the beginning of robotic-assisted prostatectomy could be another method how to improve the results.

**Trial Status**

The RARPEX trial is recruiting patients under protocol version 1.0 since February 24, 2020. The last patient is expected to be recruited by December 31, 2021.

**Declarations**

**Ethics approval and consent to participate**

This trial was approved by independent ethics committee at the University Hospital Hradec Kralove (registration number 201903 I90P). The RARPEX trial will be conducted in the context of Good Clinical Practice and in accordance with the Declaration of Helsinki. All patients who are scheduled for robotic assisted radical prostatectomy in our institutions will be screened for eligibility and informed in detail about the RARPEX trial. Informed consent will be obtained from each participant. The study procedures, risks, benefits, and data management will be clarified with the patients before they are asked to give their informed consent to participate. Any participant in this study may withdraw consent or voluntarily cease to participate at any time for any reason.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality. The datasets used and analyzed during the current study will be available from the corresponding author on reasonable request.

**Competing interest**

The authors declare that they have no competing interests.

**Funding**
This project was supported by the institutional research project PROGRES Q40/04 of the Charles University, Prague, Czech Republic.

Author's contributions

Balik M wrote most parts of the protocol, he was responsible for study design and revision of the manuscript and he obtained funding. Brodak M, Pacovsky J and Cecka F helped with definition of the primary and secondary endpoints and made revision of the manuscript. Balik M, Kosina J, Husek P and Brodak M performed procedures. All authors read and approved the final manuscript.

Acknowledgements

We thank the teams (especially Bc. Lenka Pasztorova) in the Department of Urology at the University Hospital Hradec Kralove, Czech Republic for their support. We thank Dr Eva Cermakova and Selke – Grulichova of the Department of Medical Biophysics and Biostatistics, Faculty of Medicine, Charles University in Prague, Hradec Kralove, Czech Republic, for planned statistical analyses. We also thank all the patients who are participating in this trial.

Author's contributions

MBa is the Chief Investigator. He conceived the study, led the proposal and protocol development. He wrote most parts of the protocol, he was responsible for study design and revision of the manuscript and he obtained funding. MBr, JP and FC helped with definition of the primary and secondary endpoints and contributed to study design and to development of the proposal. MBa, JK, PH and MBr will perform the procedures. All authors read and approved the final manuscript.

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Abbreviations

VTE: Venous Thromboembolism; DVT: Deep Vein Thrombosis; POD: Postoperative day; PE: Pulmonary Embolism; LMWH: Low Molecular Weight Heparin; RARP: Robot-Assisted Radical Prostatectomy; CT scan: Computed Tomography scan; MRI: Magnetic Resonance Imaging

References
1. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2014;65:124-37.

2. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71:618-29.

3. Nilsson S, Norlen BJ, Widmark A. A systematic overview of radiation therapy effects in prostate cancer. Acta Oncol. 2004;43:316-81.

4. Barry MJ, Gallagher PM, Skinner JS, Fowler FJ, Jr. Adverse effects of robotic-assisted laparoscopic versus open retropubic radical prostatectomy among a nationwide random sample of medicare-age men. J Clin Oncol. 2012;30:513-8.

5. Gandaglia G, Sammon JD, Chang SL, Choueiri TK, Hu JC, Karakiewicz PI, et al. Comparative effectiveness of robot-assisted and open radical prostatectomy in the postdissemination era. J Clin Oncol. 2014;32:1419-26.

6. Kasabwala K, Patel NA, Hu JC. Review of optimal techniques for robotic-assisted radical prostatectomy. Curr Opin Urol. 2018;28:102-7.

7. Montorsi F, Wilson TG, Rosen RC, Ahlering TE, Artibani W, Carroll PR, et al. Best practices in robot-assisted radical prostatectomy: recommendations of the Pasadena Consensus Panel. Eur Urol. 2012;62:368-81.

8. Sammon JD, Karakiewicz PI, Sun M, Sukumar S, Ravi P, Ghani KR, et al. Robot-assisted versus open radical prostatectomy: the differential effect of regionalization, procedure volume and operative approach. J Urol. 2013;189:1289-94.

9. Lee SJ, Seo H, Kim HC, Lim SM, Yoon SJ, Kim HS, et al. Effect of Intraoperative Red Blood Cell Transfusion on Postoperative Complications After Open Radical Cystectomy: Old Versus Fresh Stored Blood. Clin Genitourin Cancer. 2015;13:581-7.

10. Linder BJ, Frank I, Cheville JC, Tollefson MK, Thompson RH, Tarrell RF, et al. The impact of perioperative blood transfusion on cancer recurrence and survival following radical cystectomy. Eur Urol. 2013;63:839-45.

11. Wang YL, Jiang B, Yin FF, Shi HQ, Xu XD, Zheng SS, et al. Perioperative Blood Transfusion Promotes Worse Outcomes of Bladder Cancer after Radical Cystectomy: A Systematic Review and Meta-Analysis. PLoS One. 2015;10:e0130122.

12. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999;57:1005-32.
13. Erstad BL. Systemic hemostatic medications for reducing surgical blood loss. Ann Pharmacother. 2001;35:925-34.

14. McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs. 2012;72:585-617.

15. Benoni G, Lethagen S, Nilsson P, Fredin H. Tranexamic acid, given at the end of the operation, does not reduce postoperative blood loss in hip arthroplasty. Acta Orthop Scand. 2000;71:250-4.

16. Nielsen JD, Gram J, Fabrin K, Holm-Nielsen A, Jespersen J. Lack of correlation between blood fibrinolysis and the immediate or post-operative blood loss in transurethral resection of the prostate. Br J Urol. 1997;80:105-10.

17. Sharifi R, Lee M, Ray P, Millner SN, Dupont PF. Safety and efficacy of intravesical aminocaproic acid for bleeding after transurethral resection of prostate. Urology. 1986;27:214-9.

18. Casati V, Guzzon D, Oppizzi M, Cossolini M, Torri G, Calori G, et al. Hemostatic effects of aprotinin, tranexamic acid and epsilon-aminocaproic acid in primary cardiac surgery. Ann Thorac Surg. 1999;68:2252-6; discussion 6-7.

19. Claeyss MA, Vermeersch N, Haentjens P. Reduction of blood loss with tranexamic acid in primary total hip replacement surgery. Acta Chir Belg. 2007;107:397-401.

20. Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008;358:2319-31.

21. Jendoubi A, Malouch A, Bouzouita A, Riahi Y, Necib H, Ghedira S, et al. [Safety and efficacy of intravenous tranexamic acid in endoscopic transurethral resections in urology: Prospective randomized trial]. Prog Urol. 2017;27:1036-42.

22. Kumsar S, Dirim A, Toksoz S, Saglam HS, Adsan O. Tranexamic acid decreases blood loss during transurethral resection of the prostate (TUR-P). Cent European J Urol. 2011;64:156-8.

23. Pourfakhr P, Gatavi E, Gooran S, Etezadi F, Khajavi MR, Pourroustaei R, et al. Local Administration of Tranexamic Acid During Prostatectomy Surgery: Effects on Reducing the Amount of Bleeding. Nephrourol Mon. 2016;8:e40409.

24. Rannikko A, Petas A, Taari K. Tranexamic acid in control of primary hemorrhage during transurethral prostatectomy. Urology. 2004;64:955-8.

25. Zaid HB, Yang DY, Tollefson MK, Frank I, Winters JL, Thapa P, et al. Efficacy and Safety of Intraoperative Tranexamic Acid Infusion for Reducing Blood Transfusion During Open Radical Cystectomy. Urology. 2016;92:57-62.
26. Montroy J, Fergusson NA, Hutton B, Lavallee LT, Morash C, Cagiannos I, et al. The Safety and Efficacy of Lysine Analogues in Cancer Patients: A Systematic Review and Meta-Analysis. Transfus Med Rev. 2017;31:141-8.

27. Balik M, Kosina J, Husek P, Brodak M, Cecka F. Safety and Efficacy of Using Tranexamic Acid at the Beginning of Robotic-Assisted Radical Prostatectomy in a Double-Blind Prospective Randomized Pilot Study. Acta Med. 2020;64:176-82.

28. Martini A, Tewari AK. Anatomic robotic prostatectomy: current best practice. Ther Adv Urol. 2019;11:1756287218813789.

29. Pacovsky J, Husek P, Balik M, Louda M, Kosina J, Navratil P, et al. Biochemical evidence of the presence of urine in a drain following surgery. Rozhl Chir. 2011;90:478-81.

30. Dias JAN, Dall'oglio MF, Colombo JR, Jr., Coelho RF, Nahas WC. The influence of previous robotic experience in the initial learning curve of laparoscopic radical prostatectomy. Int Braz J Urol. 2017;43:871-9.

31. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.

32. Moher D, Schulz KF, Altman DG, Consort. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol. 2001;1:2.

33. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200–7.

34. Tikkinen KAO, Craigie S, Agarwal A, Violette PD, Novara G, Cartwright R, et al. Procedure-specific Risks of Thrombosis and Bleeding in Urological Cancer Surgery: Systematic Review and Meta-analysis. Eur Urol. 2018;73:242-51.

Figures
Figure 1 Process phases flowchart of randomized trial according to the CONSORT guidelines

Figure 1

See figure for caption. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Checklist was used to improve the quality of the study protocol (33).
| TIMEPOINT                          | Screening | Enrolment | Treatment | Follow-up |
|----------------------------------|-----------|-----------|-----------|-----------|
| ENROLMENT:                        |           |           |           |           |
| History of disease and drug administration | x         |           |           |           |
| Eligibility screen                | x         |           |           |           |
| Subject basic information         | x         |           |           |           |
| Informed consent                  | x         |           |           |           |
| ALLOCATION:                       |           |           |           | x         |
| INTERVENTIONS:                    |           |           |           |           |
| Group 1                           |           |           |           |           |
| Group 2                           |           |           |           |           |
| ASSESSMENTS:                      |           |           |           |           |
| Physical examination              |           |           |           |           |
| Clinical laboratory test          | x         |           |           |           |
| - blood count and creatinine level| x         |           |           |           |
| - PSA level                       | x         |           |           |           |
| The volume of the fluids in drain|           |           |           | x         |
| Ultrasound of lower abdomen       |           |           |           | x         |
| Adverse reaction check            |           |           |           |           |
| Complication check                |           |           |           |           |
| Compliance check                  |           |           |           |           |
| Confirm withdrawal a dropout criteria |         |           |           |           |

**Figure 2** – The schedule of enrolment, interventions and assessments of randomized trial according to the SPIRIT guidelines (\(t_2 = -14 \pm 1\) days; \(t_4 = -1\) day; \(t_6 = \) at the beginning of the procedure; \(t_1 = 3\) hours after the procedure; \(t_2 = \) POD1; \(t_3 = \) POD2; \(t_4 = \) POD7; \(t_5 = 3\) months after the procedure \(\pm 7\) days)

**Figure 2**

See figure for caption.