Continuous low-dose aspirin therapy in robotic-assisted laparoscopic radical prostatectomy does not increase risk of surgical hemorrhage

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Abstract: Abstract Background: Withdrawal of oral antiplatelet therapy (OAT) is a major risk factor for stent thrombosis, myocardial infarction, and cerebral strokes. In order to minimize the risk of thrombotic complications, since 2007 robotic-assisted laparoscopic radical prostatectomy (RARP) has taken place under continuous OAT with aspirin at our institution. In this retrospective study we analyzed the risk for perioperative bleeding and surgical outcome after RARP with OAT. Patients and Methods: All patients who underwent RARP with aspirin OAT at our institution since 2007 were included in this analysis. The OAT group was compared with a group that underwent RARP without OAT, which contained twice the number of patients. Matching of the two groups was performed with regard to the tumor stage and whether a lymph node dissection or nerve-sparing was performed. Results: Thirty-eight patients were assigned to the OAT group and 76 to the control group. A difference in the decrease of postoperative hemoglobin concentration was not detectable between the two groups (mean drop of 2.9±1.4 g/dL and 2.9±1.1 g/dL, respectively; P=.93). RARP was completed in all OAT patients without conversion to open surgery. Two of the 38 patients (5.3%) in the OAT group and none in the control group required blood transfusions (P=.11). Equivalent rates of positive surgical margins for pT2 tumors were detected (16% OAT versus 14% control group; P=1.0). No adverse cardiovascular events occurred in either group during the hospitalization. Conclusions: Continued perioperative OAT with aspirin in RARP is safe, feasible, and not associated with increased blood loss.

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Continuous anti-platelet therapy in robotic-assisted laparoscopic radical prostatectomy does not increase risk of surgical haemorrhage
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Abstract

**Objective:** To analyze the risk of intra- and postoperative bleeding and the surgical outcome after robotic-assisted laparoscopic radical prostatectomy (RARP) performed with continued oral antiplatelet therapy (OAT).

**Methods:** All patients who underwent RARP with ongoing OAT in our institution from January 2007 to May 2012 were included in this analysis. The OAT group was compared to a double-sized group of patients who underwent RARP without OAT (control group). Matching of the two groups was performed with regards to tumor stage (pT) and whether or not a lymph node dissection or nerve-sparing were performed.

**Results:** A total of 78 patients were included in this study. A difference in the decrease of postoperative hemoglobin concentration was not detectable between the two groups (mean drop of 2.9 +/-1.6 g/dL in the OAT and 3.1 +/-1.1 g/dL in the control group, p=0.52). RARP was completed in all OAT patients without conversion to open surgery. Two of 26 patients (8%) in the OAT group and none in the control group required postoperative blood transfusions (p=0.11). Equal rates of positive surgical margins for pT2 tumors were detected (18% vs. 18%, p=1.0). No major adverse cardiovascular events occurred in both groups during the hospitalization.

**Conclusion:** Continued perioperative OAT with ASS in RARP is safe, feasible and is not associated with increased blood loss. Furthermore, a higher rate of surgical margins and anastomotic leaks was not detectable in the OAT group. RARP offers the possibility to continue the
oral antiplatelet therapy perioperatively in order to prevent cardiovascular complications.
1. Introduction

The number of patients with cerebrovascular or coronary heart disease is growing and the use of coronary stents and antiplatelet drugs is increasing \(^1\). Accordingly, an increasing number of patients presenting for surgery are under antiplatelet medication. Further 5\% of patients receiving an intracoronary stent will undergo non-cardiac surgery within the first year after intervention \(^2\). Depending on the type of stent, the patients require mono or dual oral antiplatelet therapy (OAT) for a certain time period; acetylsalicylic acid (ASS) alone (mono) or in combination with a second antiplatelet agent, mostly an ADP receptor antagonist like clopidogrel (dual). The current guidelines recommend one month of dual antiplatelet therapy if a bare-metal coronary stent and one year of dual antiplatelet therapy if a drug-eluting coronary stent is placed \(^3\). A lifelong continuation of ASS after this time period is highly recommended \(^4\). Other indications for a life-long secondary prophylaxis (preventing recurrence of disease) with ASS are stroke, angina pectoris, myocardial infarction or endovascular/open revascularization \(^4\). Interruption of OAT for invasive, non-cardiac procedures in patients with coronary stents is associated with a high risk of cardiovascular complications \(^5\)\(^-\)\(^7\). Despite this fact, the perioperative withdrawal of anti-platelet therapy is still widely practiced. Urologists often tend to discontinue anti-platelet therapy due to concerns of increased intraoperative or postoperative bleeding complications \(^8\). Nevertheless, thromboembolic complications such as myocardial infarction and cerebral strokes are often irreversible and have a significant morbidity and mortality \(^5\).
Radical prostatectomy is an elective surgical procedure with the possibility of significant blood loss. Therefore current recommendations suggest to postpone RP whenever possible and perform later without any OAT or choose non-invasive therapy options. Increased blood loss due OAT with ASS may be minimized by a minimal invasive (laparoscopic), meticulous surgical technique and compensated by intense postoperative monitoring and transfusions if necessary. Robotic-assisted laparoscopic radical prostatectomy (RARP) is performed under continuous OAT with ASS for secondary prevention at our institution since 2007 to minimize the risk of fatal thromboembolic complications. In this retrospective investigation we analysed the risk for perioperative bleeding and the surgical outcome after RARP performed with continued OAT.

2. Patients and Methods

Patient selection and matching

A retrospective electronic chart review of patients at our institution from March 2007 to May 2012 identified all patients who underwent RARP under continuous mono oral antiplatelet therapy with ASS (OAT group). Documentation of continued OAT before admission and intake of ASS on day of surgery were required criterions for inclusion into the OAT group. Patients on other antiplatelet agents were excluded. This group was compared with a double-sized randomly matched sample of RARP-patients without OAT (control group). Matching of the two groups was performed with regards to tumour stage (pT) and whether or not a
lymph node dissection or nerve-sparing were performed. Approval for this retrospective study was given by the Internal Review Board (USZ-917).

**Surgical technique**

RARPs were performed using the three-arm daVinci System® (Intuitive Surgical Inc., Sunnyvale, USA) by transperitoneal approach. Indications for bilateral extended pelvic lymph node dissection (PLND) were either a PSA ≥10 ng/ml or a preoperative Gleason score ≥7\(^1\). After completion of the PLND the extraperitoneal space was entered through lateral mobilisation of the bladder and an incision of the endopelvic fascia was done in order to gain access to the lateral surface of the prostate. After preparation of the ventral part of the prostate, ligation of the plexus Santorini was performed. Following dissection of the bladder neck in a straight line down to the pillars (antegrade approach), the seminal vesicles were removed completely and the dorsal surface of the prostate was released. In the case of a nerve sparing procedure, preparation of the neurovascular bundle was performed with clips and without coagulation in order to avoid thermal damage of the nerve fibres. After careful preparation of the apex, the prostate was removed. A posterior musculofascial plate reconstruction according to Rocco\(^1\) was completed and finally the vesicourethral anastomosis was performed with running or interrupted sutures. On the fourth postoperative day cystography was performed and the urinary catheter removed if no vesicourethral leak was detected.
Data collection

A retrospective analysis of electronic patient charts was performed. The following data were collected: age, body mass index (BMI), preoperative prostate specific antigen (PSA), clinical stage (pTc), biopsy Gleason score, operation time, lymph node dissection, nerve-sparing, pathologic Gleason score, tumour stage (pT), nodal and margin status, lymph node yield, weight of prostate, anastomotic leakage, day of catheter removal, hospital stay and postoperative complications. To assess bleeding, we recorded the estimated blood loss, haemoglobin / thrombocyte levels before and after surgery and need for blood transfusions (red blood cells, fresh frozen plasma, thrombocytes) with number of administered units. Postoperative complications were graded according to the Clavien-Dindo classification.

Blood count and pathological evaluation

Total blood count including haemoglobin and thrombocytes was routinely performed pre-operatively and on the first day after surgery. For further analysis of the haemoglobin and thrombocyte course the median drop was chosen as cut-off value (2.9 g/dl and 54 x10^3/µl). Pathological tumour stage, Gleason score, surgical margin and lymph node status were retrieved from the pathology report of the Institute of Clinical Pathology of the University Hospital Zürich. Detailed comprehensive pathologic analysis was performed using standardized
whole-mount sections. If tumour cells were detectable at the inked surface, the surgical margins were considered positive \(^{14}\).

**Statistical analysis**

PASW version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. For categorical variables contingency table analysis and two-sided Fisher's exact test were used to assess statistical associations between clinic-pathological data. For comparison of continuous variables the Mann-Whitney-U-Test was performed. All p-values \(\leq 0.05\) are considered significant.

**3. Results**

**Descriptive Analysis**

A total of 78 patients were included in this analysis. Twenty-six patients received a RARP with maintained OAT with 100mg ASS per day. All but two patients received ASS for secondary prophylaxis after cardiac or cerebrovascular events. The other two patients received ASS for idiopathic thrombocythaemia or for primary prophylaxis. Matching of the two groups resulted in comparable preoperative baseline parameters as shown in Table 1. Intraoperative parameters are presented in Table 2. Extended pelvic lymph node dissection was performed in 81\%, nerve-sparing in 46\% of the cases (matched variables). The mean operation time in the OAT group was significantly shorter than in the control group (224 \(\pm\)62 min vs. 259 \(\pm\)61 min, \(p= 0.04\)). RARP was completed in all
OAT patients without conversion to open surgery. In one patient of the control group the operation had to be converted to open prostatectomy due to extensive intraabdominal adhesions after previous abdominal surgery. Neither a significant difference in the decrease of haemoglobin levels (-2.9 ±1.6 g/dL vs. -3.1 ±1.1 g/dL, p=0.52) nor thrombocyte levels (-43 ±111 x10³/μL vs. -54 ±31 x10³/μL; p=0.93) could be noticed. The mean estimated blood loss was significantly higher in the control group (256 ±184 ml vs. 405 ±268 ml, p=0.005).

The postoperative results are displayed in Table 3. No significant differences were detectable between the two groups. Two patients in the OAT group, both on ASS because of coronary heart disease and coronary stenting, received blood transfusions postoperatively. Patient number one received two units of packed red blood cells on the first postoperative day at a haemoglobin level of 6.4 g/dL in a haemodynamically stable condition. Clinically no source of bleeding could be detected, but due to a postoperative INR of 2.0 (preoperatively 1.0) one unit of fresh frozen plasma and intravenous Vitamin K were administered. A sufficient rise of the haemoglobin level could be achieved (9.5 g/dL on the second postoperative day) and no further transfusion was necessary. Patient number two received one unit of packed red blood cells on the first postoperative day at a haemoglobin level of 8.0 g/dL due to dizziness (preoperatively 13.6 g/dL). A second unit was applied on the second postoperative day because of further decrease of the haemoglobin level to 7.5 g/dL. The dizziness improved quickly and the haemoglobin level increased to 9.5 g/dL. Again clinically no source of bleeding could be detected. In the control group no patient
received blood transfusions. No further bleeding complications occurred in the entire cohort. No patient developed adverse cardiovascular events intra- or postoperatively during hospitalization.

Only minor complications (Clavien-Dindo grade I-II) occurred (Table 4). The anastomotic leakage rate was without a significant difference between the groups (4% vs. 8%, p=0.66). The only patient in the OAT Group with an anastomotic leakage also received blood transfusions and was therefore graded for a grade II complication. The mean hospitalization time was 8 days in both groups (8 ±3 days and 8 ±5 days, p=0.76).

Pathologic Evaluation

Evaluation of the specimen revealed, that 65% of the patients had a pT2 tumour (matched variable, see Table 3). No significant difference in the distribution of the Gleason score could be observed, although the percentage of Gleason 8-10 tumours in the ASS group was higher (35% vs. 19%, p=0.32). The rate of positive surgical margins for localized tumours (pT2) was equal in the two groups (18% vs. 18%, p=1.0). For pT3 tumours the rate for positive surgical margins was 67% in the OAT and 50% in the control group (p=0.68).

4. Comment

In the present investigation we could show, that RARP under OAT is feasible and safe. No major bleeding complication intraoperatively requiring conversion to open surgery or postoperatively requiring any
kind of invasive intervention (Clavien-Dindo Classification Grade III or higher) occurred. Two patients (8%) received blood Transfusions, while both were haemodynamically stable. Furthermore, no limitation for tumour control (surgical margins, lymph node yield) or early surgical outcome (anastomotic leakage) could be observed. Most importantly, no cardiovascular events occurred during the postoperative period.

For a long time it has been an accepted policy to withdraw antiplatelet medication 7-10 days before surgery in order to avoid bleeding complications. Nowadays, it is known that this policy puts patients at an increased risk for thromboembolic events compared to patients operated with on-going OAT. Withdrawal of anti-platelet drugs generally bears a very high risk of major cerebro- and cardiovascular complications such as myocardial infarction, stent thrombosis and cerebral strokes with a mortality rate up to 45% . The American Heart Association recommends dual antiplatelet therapy for the first 12 months following drug eluting stent insertion . Afterwards, a life-long continuation of ASS for secondary prevention is recommended. In a meta-analysis performed by the Antithrombotic Trialists’ collaboration, secondary prevention with ASS resulted in a decrease of the myocardial re-infarction rate of 30 % and of the stroke rate of 25% . OAT withdrawal not only results in a restitution of thrombocyte function but also induces a rebound hypercoagulability with pro-thrombotic effects overcoming the physiological balance. In a meta-analysis of 50279 patients with OAT for secondary prevention of coronary heart disease the average delay between stopping aspirin and thrombotic events was 8.5 days . This mostly falls into the time frame of surgery and thereby further increases
the risk of intra- or perioperative cardiovascular events. It is well known, that surgical interventions promote thrombosis by increased synthesis of pro-coagulant clotting factors \(^4\). In a recently performed observational multicentre study with 1134 patients preoperative discontinuation of OAT for more than 5 days was an independent prognostic factor for major adverse cardiac and cerebrovascular events (OR 2.11, 95% CI 1.23 – 3.63; \(p=0.007\)). Continuation of OAT was not identified as a risk factor for major bleeding \(^5\).

Several investigations have reported an increased blood loss in noncardiac surgery by 2.5% to 20% for patients who receive ASS during the perioperative period \(^4\). Notably, except during intracranial surgery, no increase in surgical mortality and morbidity could be observed. This is a key fact for weighting the consequences of ASS continuation or withdraw. Therefore on the basis of the present evidence, although most of the trials are observational and retrospective, perioperative continuation of ASS is more and more supported throughout different medical fields \(^4,20\).

Historically, a retrospective analysis of patients undergoing open radical retropubic prostatectomy (RRP) in 1990 detected a higher risk for bleeding in 52 aspirin treated patients. Due to equivocal data for safety concerning transurethral resection of the prostate (conventional electroresection) the recommendations for prostate surgery have been reluctant regarding definite advice, although no data for minimal invasive approaches under OAT were available \(^10,21,22\). Considering the reports on blood loss in non-OAT patients, laparoscopic radical prostatectomy (LRP) and RARP seemed promising techniques concerning reduction of haemorrhagic complications. While blood loss
for RRP ranged from 750 to 1284 ml, LRP allowed a significant reduction, ranging between 200 to 390 ml \(^9\). RARP led again to a slight, but further decrease of blood loss ranging between 50 ml to 273 ml \(^9,23\). Along with this development also significant lower transfusion rates were reported \(^9\). Possible explanations are mainly the increased intraabdominal pressure in minimal invasive approaches and particularly in RARP a combination with improved visualization and a more intuitive handling of surgical instruments leading to a more precise preparation.

Just recently Parikh et al. \(^24\) and Binhas et al. \(^25\) presented first data regarding implementation of LRP/RARP under continuous OAT showing no significant differences in transfusion rates and postoperative haemorrhagic complications. Both studies showed significant differences in the preoperative parameters due to lack of randomization or matching. Furthermore, no data on oncological and early surgical outcome \(^24\) or only on oncological outcome \(^25\) were presented.

In order to achieve comparable groups we performed a matching of patients in regard of tumour stage, nerve-sparing and lymphadenectomy, while each may have an independent influence on surgical margins or blood loss. Due to this matching the preoperative parameters in this investigation were equal or comparable.

The limitation of this analysis is its retrospective nature and therefore the lack of randomization. The awareness of the surgeon of the maintained OAT might have influenced him on the dissection and on the estimation of blood loss. However, we could demonstrate comparable outcome without loss of clinical safety in RARP under continued OAT.
5. Conclusion

In general the high risk and consequences of cardiovascular events after withdrawal of anti-platelet drugs for secondary prevention outweighs the risk of intra- and postoperative bleeding due to continued anti-platelet treatment. Patients requiring anti-platelet therapy should therefore be evaluated individually and discussed with cardiologists and anaesthesiologists before withdrawing this vital prophylaxis for surgery.

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Figures and Tables
Table 1. Preoperative data
Table 2. Intraoperative data
Table 3. Postoperative data
Table 4: Complications according to the Clavien-Dindo classification

References


