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ORIGINAL ARTICLE

Perioperative management of direct oral anticoagulants in patients undergoing radical prostatectomy: results of a prospective assessment

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Abstract

Introduction and objectives In the perioperative setting, temporary interruption of direct oral anticoagulants (DOACs) is recommended. However, the safety of these recommendations is based on non-urological surgical experiences. Our objective was to verify the safety of these recommendations in patients undergoing radical prostatectomy (RP).

Materials and methods Patients regularly receiving a DOAC and scheduled for RP at our institution were prospectively assessed. DOAC intake was usually stopped 48 h before surgery without any preoperative bridging therapy. Postoperatively, patients received risk-adapted low-molecular weight heparin (LMWH). On the third day after unremarkable RP, DOAC intake was restarted and the administration of LMWH was stopped. We assessed perioperative outcomes and 30-day morbidity.

Results Thirty-two consecutive patients receiving DOAC underwent RP at our institution between 12/2017 and 07/2018. Time of surgery (median, 177 min) and intraoperative blood loss (median, 500 mL) were unremarkable. DOACs were restarted on the third postoperative day in 30 patients (94%). No patient had a significant hemoglobin level reduction after DOAC restart. Overall, 28% of patients experienced complications within 30 days after surgery. Most of which were minor (Clavien ≤ 2), three patients (9%), however, had Clavien ≥ 3 complications.

Conclusion Our report is the first to prospectively assess current guideline recommendations regarding DOAC restarting after major urological surgery. RP can safely be performed, if DOACs are correctly paused before surgery. Moreover, in case of an uneventful postoperative clinical course, DOACs can be safely restarted on the third postoperative day. A 9% Clavien ≥ 3 30-day morbidity warrants attention and should be further explored in future studies.

Keywords Radical prostatectomy · DOAC · Prostate cancer

Introduction

Radical prostatectomy (RP) is a frequently used treatment for localized prostate cancer (PCa) [1]. Due to demographic changes and an overall increasing life expectancy in the Western world, urologists increasingly encounter and treat PCa patients, who have been previously prescribed direct oral anticoagulants (DOACs) by different medical colleagues such as cardiologists. Indications for DOAC treatment are diverse and consist of different medical conditions such as prevention of stroke and systemic embolism in non-valvular atrial fibrillation or treatment and secondary prevention of venous thromboembolism, a composite of deep vein thrombosis and pulmonary embolism [2]. Currently licensed DOACs include the factor Xa inhibitors, apixaban, rivaroxaban and edoxaban, and the thrombin inhibitor, dabigatran, and have largely replaced other anticoagulants such as vitamin K antagonists (VKAs). Advantages of DOACs compared to VKAs are its predictable pharmacokinetics with simplified dosing, the less common interaction with other drugs or food, and that routine monitoring by coagulation tests is not necessary [2]. However, a potential disadvantage of DOACs might be that global coagulation tests, such as

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the prothrombin time or the activated partial thromboplastin time, do not reliably reflect their effective plasma concentration. In consequence, uncertainties might exist regarding the optimal perioperative management of patients receiving DOACs, if minor or major elective surgery is imminent.

Although recommendations for the perioperative handling of DOACs in patients undergoing elective urological surgery are available [3, 4], these recommendations are largely based on pharmacokinetic and dynamic considerations and observations from non-urological surgery. While most guidelines give relatively precise recommendations on when to pause DOACs before surgery (1–3 days), recommendations regarding restarting of DOACs after major surgery are less clear and range from 1 to 5 days, depending on the risk of secondary bleeding. To date, no study has specifically evaluated the safety of recommended perioperative DOAC handling in patients scheduled for major urological surgery, such as RP. This said, it is not downright clear if the aforementioned guideline recommendations of perioperative DOAC handling can safely be applied to such patients, since the risk of secondary bleeding might be different in patients undergoing RP compared to patients undergoing, e.g., orthopedic surgery of the hip or knee. Especially RP patients might harbor a relatively high risk of secondary bleeding, as extensive cauterization of the neurovascular bundles should be avoided to minimize the risk of postoperative erectile dysfunction [5]. So far, only one study examined the efficacy of orally administered dabigatran for prevention of postoperative venous thromboembolism after robotic-assisted laparoscopic prostatectomy (RALP) [6]. After hospital discharge, patients daily received 220 mg dabigatran for 15 days. Only 1 out of 400 (0.25%) studied patients developed venous thromboembolism, thus this therapeutic regime was highly effective for prevention of venous thromboembolism. However, the studied patient population did not receive DOACs before surgery. The aim of the current study was to prospectively evaluate the perioperative clinical course of patients receiving DOACs already preoperatively and undergoing RP at our institution.

Materials and methods

All patients who underwent RP—either open retropubic RP or RALP with the Da Vinci system—at our institution and who were preoperatively receiving a DOAC for various medical conditions were prospectively assessed from December 2017 onwards. DOACs consisted of apixaban, rivaroxaban, edoxaban, and dabigatran. According to guideline recommendations, DOAC intake should be paused 48 h before surgery. No preoperative bridging therapy was regularly recommended. In case of severely impaired kidney function, DOACs had to be stopped earlier before surgery, depending on the estimated glomerular filtration rate (eGFR).

RP was performed as previously described [7, 8.] All RPs were performed by experienced RP surgeons (the number of previously performed RPs ranged from > 100 to > 5000 for each respective surgeon). Postoperatively, patients received subcutaneous (s.c.) risk-adapted low-molecular weight heparin (LMWH) at a dosage of 1 mg/kg body weight daily, divided into two dosages applied in the morning and in the evening (i.e., 2×0.5 mg/kg s.c. per day). However, on the day of RP, only 40 mg of LMWH (Clexane) was given in the evening. In case of uneventful postoperative clinical course, DOACs were restarted at the third postoperative day, and administration of LMWH was ceased. We chose the third postoperative day, since secondary bleeding should reliably be ruled out until then. One day after DOAC restarting, the hemoglobin level of all patients was determined to control for new onset secondary hemorrhage.

We prospectively assessed preoperative clinical features such as the respective indication for DOAC treatment, the type and dosage of DOAC, the day of interruption before surgery, and if any preoperative bridging therapy was performed despite guideline recommendations. Moreover, we assessed typical clinical parameters, which are routinely determined before RP, such as age, BMI, PSA, and biopsy Gleason score. Intraoperatively determined parameters consisted of length of surgery (minutes), intraoperative blood loss (mL), blood transfusions (yes vs. no), and complications (which were specified if present). Postoperatively determined parameters consisted of possible changes of the hemoglobin level after DOAC restart, length of hospital stay, postoperative complications until discharge, and the 30-day morbidity. In consequence, follow-up evaluation for the respective endpoints stopped 30 days after surgery. Complications were reported according to the Clavien-Dindo classification system [9].

Results

Overall, 32 consecutive patients receiving DOACs were assessed from December 2017 until August 2018. Preoperative clinical parameters of those patients are presented in Table 1. The median age was 70 years, and the median PSA was 6.5 ng/mL. Most patients had an American Society of Anesthesiologists (ASA) score of 2 (59.4%). The remaining were ASA 3 (40.6%). Compared to a recent publication of our entire cohort [10], the currently evaluated patients tended to be slightly older (median 70 years vs. 65 years) but were otherwise comparable with respect to preoperatively assessed parameters, such as the PSA value. The majority of patients received rivaroxaban (41%), followed by apixaban (31%), edoxaban (19%), and dabigatran (9%). Indication for

Table 1 Preoperative patient characteristics

Variable	
Age (years)	
Mean (median)	68 (70)
IQR	63–73
ASA score	
1	–
2	19 (59.4%)
3	13 (40.6%)
4	–
5	–
PSA (ng/mL)	
Mean (median)	6.7 (6.5)
IQR	4.0–8.93
Type of DOAC	
Rivaroxaban	13 (40.6%)
Apixaban	10 (31.3%)
Edoxaban	6 (18.8%)
Dabigatran	3 (9.4%)
Indication for DOAC intake	
Atrial fibrillation	26 (81.3%)
State after deep venous thrombosis	4 (12.4%)
State after stroke	1 (3.1%)
Aneurysm of the A. poplitea	1 (3.1%)
Time point of DOAC stopping before surgery	
48 h	26 (81.3%)
> 48 h	6 19.1%)
Preoperative bridging	
Yes	5 (15.6%)
No	27 (84.4%)

Table 2 Intraoperative patient characteristics

Variable	
Open retropubic prostatectomy	23 (71.9%)
Da Vinci prostatectomy	9 (28.1%)
Length of surgery (min)	
Mean (median)	182 (178)
IQR	165–195
Intraoperative blood loss (mL)	
Mean (median)	591 (500)
IQR	350–700
pT stage	
pT2	18 (56.3%)
pT3a	10 (31.3%)
pT3b	4 (12.5%)
Lymph node status	
pN1	4 (12.5%)
pN0	27 (84.4%)
pNx	1 (3.1%)
Prostatectomy Gleason score	
3 + 3	1 (3.1%)
3 + 4	22 (68.8%)
4 + 3	5 (15.6%)
≥ 8	4 (12.5%)
Surgical margin status	
Positive	6 (18.8%)
Negative	26 (81.3%)

DOAC intake was predominantly non-valvular atrial fibrillation (81%) followed by a history of VTE or stroke and an aneurysm of the popliteal artery in 12%, 3% and 3% of cases, respectively. Most patients (81%) stopped DOAC intake 48 h before surgery, while 19% of patients stopped DOACs 72 or more hours before surgery. Reasons for earlier DOAC stopping consisted of an impaired renal function or due to the discretion of the treating outdoor physician. Five patients (16%) received preoperative LMWH bridging therapy until RP. All of those patients with LMWH bridging therapy stopped DOAC 3 or more days before surgery. The last LMWH injection was administered 24 h before surgery.

Table 2 shows intraoperative clinical and histopathological findings. The majority (72%) of patients were treated by open retropubic RP, while the remaining 28% underwent RALP. One of the open retropubic RPs was a salvage RP after failed radiation therapy. The median length of surgery was 178 min, and the median intraoperative blood loss was 500 mL. None of the patients received an intraoperative or postoperative blood transfusion. No intraoperative complications other than an increased blood loss (> 1000 mL in three patients) occurred. However, in one patient ureteral stents had to be inserted bilaterally due to extreme proximity of the ureteral orifices to the prostate resection margins. Further histopathological parameters, such as Gleason score, pT stage distribution, nodal stage, and surgical margin status were within the expected ranges of typical current RP series [10] and are thus not further discussed at this point. When comparing patients treated with open RP vs. RALP, a statistically significant difference between groups was only observed with respect to the mean intraoperative blood loss (715 mL vs. 272 mL; $p = 0.004$). Conversely, the preoperative PSA value, age at surgery, length of surgery, pT stage, pN stage, RP Gleason score, and surgical margin status failed to show statistically significant differences between groups (all $p > 0.05$).

Table 3 shows the post-interventional clinical course. DOACs could be restarted as planned on the third postoperative day in the vast majority of patients (94%). In the remaining two patients, DOACs were restarted on the fourth and sixth postoperative day, respectively. Both patients initially showed a slight decrease of the hemoglobin level over the first 3 days after RP, which eventually stabilized spontaneously. None of the patients who showed a decrease in the

Table 3 Postoperative clinical course

Variable	
Restart of DOAC (days after surgery)	
3	30 (93.8%)
4	1 (3.1%)
6	1 (3.1%)
Removal of surgical drainage (days)	
Mean (median)	2.8 (3.0)
IQR	2.0–3.0
Hospital discharge after surgery (days)	
Mean (median)	5.3 (5.0)
IQR	4.0–5.8
Complications during hospital stay	
None	31 (96.9%)
Urinary tract infection	1 (3.1%)
30-day morbidity	
None	23 (71.9%)
Clavien I	–
Clavien II	6 (18.8%)
Clavien III	1 (3.1%)
Clavien IV	1 (3.1%)
Clavien V	1 (3.1%)

hemoglobin level after DOACs were restarted. Removal of the surgical drainage (after a median of 3 days) as well as the time until hospital discharge (after a median of 5 days) was within the expected range. Until hospital discharge, only one patient (3%) had a complication, which was a urinary tract infection that was effectively treated with antibiotics (Clavien II).

Assessment of the 30-day morbidity (Table 3) revealed an overall complication rate of 28% (9/32). Most were minor complications (Clavien II) such as urinary tract infections. However, three patients had Clavien ≥ 3 complications. Those consisted of a persisting lymphocele requiring surgical marsupialisation (Clavien III) in one patient. Another patient suffered from an embolic stroke (Clavien IV). And unfortunately, one patient died within 30 days (Clavien V), probably due to an arterial embolism of the a. mesenterica superior with severe intestine infarction.

Discussion

To the best of our knowledge, this is the first study in which the perioperative and postoperative clinical course of patients receiving DOACs and scheduled for RP has been prospectively assessed. Our findings show that in case of an uneventful intra- and postoperative clinical course, DOACs can be safely restarted on the third postoperative instead of continuing LMWH injections. Moreover, pausing DOACs 48 h before RP does not appear to be associated with an increased risk of intraoperative bleeding. These findings are of clinical importance, since it is crucial that DOACs should optimally be paused as short as possible to minimize the risk of adverse events attributed to the clinical condition responsible for DOAC prescription. On the other hand, too early restarting of DOAC intake after surgery might lead to unwanted complications such as secondary bleeding. This said, a standardized pre-, intra- and postoperative prescription plan is desirable to avoid both under- and over-anticoagulation with its specific respective risks.

So far, there is only one study in which DOACs were used after RP. Säily et al. [6] assessed the efficacy of dabigatran in preventing VTE after RALP. The authors found that orally administered dabigatran was safe for VTE prophylaxis after RALP. However, the evaluated patient population did not routinely receive any DOACs before surgery, and dabigatran was prescribed not before hospital discharge. In consequence, the observed patient population, the study endpoints, and the DOAC prescription plan are not completely comparable to our study.

Due to the lack of studies in the field of urology, guideline recommendations are somewhat vague. The EAU guidelines for thromboprophylaxis (http://uroweb.org/guideline/thromboprophylaxis/) states that DOACs should be stopped 1–3 days before surgery [11]. However, regarding restarting after surgery, the guidelines are less precise. It is stated that DOACs can be given 1 day after surgery in half the dosage used for, e.g., prevention of arterial embolism caused by non-valvular atrial fibrillation. Patients already receiving DOACs before surgery due to different medical conditions are not explicitly considered. The guidelines of the European Society of Cardiology [4] state that DOACs should be paused for 4–5 times the half-lives of the respective DOAC. Given a half-life of 7–11 h for e.g., rivaroxaban, this results in 2–3 days. Concerning restarting of DOAC therapy after surgery, the guidelines state that DOACs should be restarted after 1–5 days under consideration of the respective risk of secondary bleeding. Our proposed regime is thus in accordance with current guideline recommendations but more precise.

There are some points, which need to be considered for interpretation of our findings. First, one might criticize that this is not a randomized controlled trial in which different anticoagulation regimes have been compared. However, as stated above, guidelines for the perioperative management of DOACs already exist [4, 11]. In consequence, it would have been critical to question those recommendations and to establish a control group with a different anticoagulation regimen, which does not comply with the current guideline recommendations for comparison reasons. Instead, the goal of our prospective data collection was to assess if the existing recommendations can be safely applied to patients

scheduled for RP. Second, we did not compare our findings with RP patients without regular DOAC intake. We decided against such a comparison as any possibly observed difference regarding the intra- and postoperative clinical course would probably not have adjustable clinical consequences. Patients receiving DOACs for different clinical conditions invariably need higher postoperative dosages of LMWH and have thus automatically a slightly increased risk of postoperative secondary bleeding. It must be emphasized that patients receiving DOAC for, e.g., atrial fibrillation should usually not receive standard dosages of LMWH postoperatively, as an increased risk of adverse events such as arterial embolism would be the consequence. Moreover, a larger sample size as we present in our study would be required for statistical comparisons between DOAC patients and counterparts without any standard anticoagulation medication. Again, only two of our patients (6%) had a postoperative higher decrease of the hemoglobin level, which continued for some days and eventually stabilized spontaneously. In consequence, the required postoperative increased, but not therapeutic dosage of LMWH in DOAC patients does not appear to explicitly increase the risk of postoperative secondary bleeding. Furthermore, we do not know whether our presented algorithm for perioperative DOAC handling cannot be further ameliorated. It is possible that in case of an unremarkable intraoperative course, DOACs could be restarted on the second or even first postoperative day without increasing the risk of secondary bleeding. However, we believe that the proposed algorithm is eligible as the observed postoperative clinical course until hospital discharge was uneventful in the vast majority of patients and none showed complications attributed to secondary bleeding. However, three patients (9%) experienced Clavien ≥ 3 complications within 30 days after surgery. Two of which (6.3%) were of severe nature and without much doubt attributed to arterial embolism due to non-valvular atrial fibrillation. This severe complication rate of 6.3% is a lot higher when compared to our overall patient population, where a severe (Clavien IV or V) complication rate was observed in < 1% of patients [10]. Whether this relatively high rate of severe 30-day morbidity would remain stable in larger sample size studies is not known. It underlines the importance, however, of an optimally standardized prescription plan and a critical appraisal of the surgical indication, which should optimally be in collaboration with the cardiologists. Finally we cannot fully rule out the possibility that some form of selection bias influenced our results. Urologists in private outdoor practice refer the vast majority of all our patients to us. It is thus conceivable that patients receiving DOACs and suffering from further medical conditions, which might negatively affect the intra- and postoperative clinical course, such as severe obesity, preferably opt for less invasive treatment options, such as radiation therapy.

In summary, our data show the intraoperative clinical course does not seem to be significantly altered, if DOACs are preoperatively stopped according to current guideline recommendations. Especially the intraoperative blood loss was not higher when compared to our overall patient cohort [10]. Moreover, DOACs can be safely restarted on the third postoperative day after uneventful RP without increasing the risk of secondary bleeding. However, we observed a relatively high rate of severe complications (9% Clavien ≥ 3) within 30 days after surgery. Therefore, an extremely careful patient selection is advised if RP is considered for patients who routinely receive DOACs preoperatively. If those findings are transferable to other major urological surgeries such as radical cystectomy or nephrectomy is not known. As RP is in general a surgical procedure with a rather increased risk of intraoperative bleeding, it is conceivable that DOACs can likewise be safely restarted after other major urological surgeries as well. We would like to encourage the urological community to report on their findings of perioperative DOAC handling to corroborate or question our findings and to especially report on severe 30-day complications after surgery.

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Compliance with ethical standards

Research involving human participants and/or animals Human participants: yes. Animals: no.

Informed consent Provided by all patients.

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