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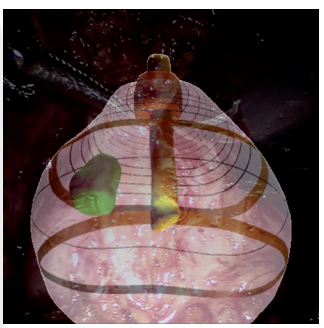

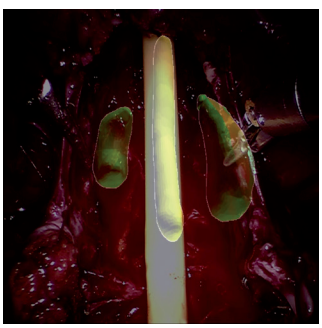

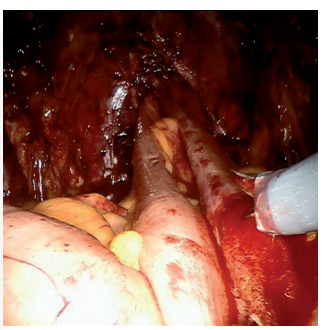

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REVIEW

Perioperative antithrombotic therapy in patients undergoing endoscopic urologic surgery: where do we stand with current literature?

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ABSTRACT

The number of patients on chronic anticoagulant or antiplatelet therapy requiring endoscopic urological surgery is increasing worldwide. Therefore, there is a strong demand to standardize the perioperative treatment of this cohort of patients, both from a surgical and cardiological point of view, balancing the risks of bleeding *versus* thrombosis, and the important possible clinical and medical legal repercussions therein. Although literature is scarce and the quality of evidence quite low, in line with other surgical specialties, guidelines and recommendations for the management of urological patients have begun to emerge. The aim of this review is to analyze current available literature and evidence on the most common endoscopic procedures performed in this high-risk group of patients, focusing on the perioperative management. In particular, to analyze the most frequently performed endoscopic procedures for the treatment of benign prostate enlargement (transurethral resection of the prostate, Thulium, Holmium and greenlight laser prostatectomy), bladder cancer (transurethral resection of the bladder), upper urinary tract urothelial cancer, and nephrolithiasis. Despite the lack of randomized studies, regardless of individual patient considerations, studies would support continuation of acetylsalicylic acid, which is recommended by cardiologists, in patients with intermediate/high risk of coronary thrombosis. In contrast, multiple studies found that bridging with light weight molecular weight heparin can potentially lead to more bleeding than continuation of the anticoagulant(s) and antiplatelet therapy, and caution with bridging is advised. All urologists should familiarize themselves with emerging guidelines and recommendations, and always be prepared to discuss specific cases or scenarios in a dedicated multidisciplinary team.

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The number of patients on chronic oral anticoagulant (AC) and/or antiplatelet (AP) therapy is increasing worldwide, thus increasing the rate of patients on antithrombotic therapy who undergo non-cardiac surgery.[1] Perioperative management of antithrombotic therapy is a matter of debate and there exists wide heterogeneity in perioperative AC and

AP management in urological procedures. The paucity of prospective studies on the subject and concerns regarding difficulties in achieving adequate intraoperative hemostasis are likely to have contributed to these differences.[2, 3] Likely anecdotal experience taints practice, even if urologists are aware of recommendations regarding cessation, as seen in several surveys showing wide variations in practice.[4, 5] Recent data from the literature reveals increasing interest in management guidelines for surgical patients, particularly as regards management of patients on long term AC [2] and dual AP therapy following cardiac stenting.[3, 6]

A search of PubMed and Web of Science (1st June 2017) was performed for the last 20 years using the following terms: "antiplatelet therapy," "anticoagulant therapy," "atrial fibrillation," "bleeding," "endoscopic urologic surgery," "HoLEP," "holmium laser," "GreenLight," "ThuLEP," "thulium laser," "ThuVARP," "upper tract surgery," "monopolar TURP," "bipolar TURP," "TURB," "laser prostate." Cited references from publications were also assessed for additional relevant articles**.** Using a synthesis of the highest level of evidence, the authors produced a narrative of recommendations.

The cardiologist's point of view

The dimension of the problem

It has been estimated that approximately 1 million patients undergo coronary stent implantation in the United States, and about as many in Europe, every year.[1] Approximately 15% of these patients will require an invasive diagnostic or surgical procedure within the first year after stenting, and up to 25% within 5 years.[7] Similarly, 10% of patients on oral AC therapy undergo surgical interventions every year.[2] Perioperative management of AP and AC therapies raises important challenges and safety concerns. On one hand, discontinuation of antithrombotic therapy is associated with an increased risk of ischemic events, including life-threatening stent thrombosis (ST), myocardial infarction (MI) and stroke. On the other hand, perioperative antithrombotic therapy might enhance the risk of bleeding and negatively influence patients' outcomes and prognosis.[8, 9]

Defining the trade-off between cardiac events and bleeding requires not only an understanding of the thrombotic risk of the individual patient, but also a clear understanding of the hemorrhagic risk specific to each surgical procedure, which requires the expertise of the surgeon. Therefore, the urologist's point of view is essential when it comes to issuing recommendations on how to manage antithrombotic therapies in the perioperative period. However, characterization of the perioperative bleeding risk of each surgical procedure is an area not well covered by current guidelines.[10, 11]

Antiplatelet therapy

The use of drug eluting stents (DES) represents the standard-of-care for percutaneous coronary intervention (PCI) of coronary artery disease (CAD).[12] After DES implantation, dual antiplatelet therapy (DAPT) is required to prevent stent thrombosis (ST) while vascular healing and strut endothelialization are ongoing. Discontinuation of DAPT during this period is associated with an increased risk for ischemic events, including ST, especially during the first weeks after DES implantation, while the risk progressively attenuates during the following months.[13] Surgery represents a very common reason for early discontinuation or interruption of DAPT, both of which are associated with pro-inflammatory and pro-thrombotic changes that may amplify the risk of ST.[14] The minimally required DAPT duration after DES implantation is, therefore, a fundamental issue that has to be considered in patients with coronary stents undergoing surgery.

Based on the results of several randomized studies and meta-analyses, the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines have shortened the period of mandatory DAPT duration after second generation DES to 6 months for patients with

stable CAD.[11, 12] DAPT duration <6 months has been demonstrated safe in some randomized trials using a second-generation DES with low anti-proliferative efficacy. However, these are no longer commercially available.[15] While the existing clinical data do not support a routine strategy of DAPT shorter than 6 months, in selected patients treated with specific DES types, and always after a careful balance of ischemic and bleeding risk, DAPT duration shorter than 6 months may be considered. Notably, the prior Class IIb recommendation that elective non-cardiac surgery (NCS) in patients treated with DES may be considered after 180 days has been modified to "after 3 months." [11] Along with the type of stent, procedural complexity (*e.g.*, number of lesion/vessels treated, stent number and total length, and type of lesion) is also an important parameter to consider in defining optimal DAPT duration and the risk of premature discontinuation in each single patient.

Oral anticoagulant therapy

Anticoagulants are also used to reduce the risk of thromboembolic events in patients with atrial fibrillation (AF), mechanical heart valves, deep venous thrombosis, and hypercoagulable conditions.[1, 2] These drugs are increasingly prescribed worldwide, mostly because of the rising prevalence and incidence of AF. About 2% of the population in developed countries receives long-term anticoagulation, reaching 8-10% in elderly patients.[16] After decades during which vitamin K antagonists (VKAs) were the only oral AC option, the spectrum of oral AC has been recently broadened by the introduction of new oral therapies, also named direct oral anticoagulants (DOACs), as they directly inhibit either thrombin (dabigatran, Pradaxa®, Boehringer Ingelheim, Ingelheim, Germany) or the activated coagulation factor X (rivaroxaban, Xarelto®, Bayer AG, Leverkusen, Germany; apixaban, Eliquis®, Bristol-Myers Squibb, New York, NY, USA; edoxaban, Lixiana®, Daiichi- Sankyo, Tokyo, Japan). DOACs offer several benefits over VKAs. Up to 7% of patients undergoing PCI also have AF or other indications for chronic use of OAC.[17] These estimates are expected to increase as the global burden of AF increases, driven in large part by the aging population in industrialized counties.[16]

The surgeon/urologist's point of view

When possible and clinically sound, limiting AC with urologic endoscopy is preferred as surgeons are working in a limited space, with irrigation, and bleeding can obscure visualization.[18, 19] However, endoscopic surgery tends to be less traumatic and tools such as lasers can be used, with their favorable hemostatic properties, and thereby allow for continuation of therapy. Specialized high-volume centers with laser abilities are increasingly treating AC patients, and under pressure to do so.[20-22]

Decisions for therapy can be stratified based on low, intermediate and high risk of thrombosis. Guidelines are clear that whenever possible, defer intermediate and high-risk patients until AC can be held, or limited. But even for elective surgery, patients may suffer consequences from delays, particularly those with indwelling catheters, intermittent symptomatic stones, and/or recurrent UTIs. Legal ramifications from delay, or proceeding, are a matter of risk and sound documentation of proper informed consent is essential. For all patients, a unique and tailored approach is necessary and factors such as the size of the stones/prostate, estimated duration of surgery, and a myriad of other factors should be considered.[6, 23, 24]

Penetration of thermal injury varies between monopolar, bipolar, and different laser energies and can affect both surgical bleeding and the degree of tissue slough that occurs during healing.[25, 26] Monopolar seems to have a more superficial and narrow field of effect, while bipolar has a greater depth thought still reasonable diameter thermal effect.[25, 27] During surgery it would seem bipolar would elicit better coagulation, but this greater degree of thermal effect could lead to more tissue ischemia and potentially delayed bleed. Lasers have better coagulative properties in tissue than either monopolar or bipolar. While there are differ-

ences between wavelengths, in general, lasers have superficial penetration and thermal diffusion depths that lead to concentration of high-density energy in a superficial layer, "sealing" vessels with shallow coagulation zones. Some lasers have deeper effects, such as the Nd:YAG, but these are nowadays rarely used in Urology.[26]

The endpoint of this review is to analyze current available literature and evidence on the most common endoscopic procedures performed on patients taking AC and AP therapy, focusing on the peri-operative management. Unfortunately, the majority of available studies investigating continuation of therapy with many endoscopic procedures are modest and non-randomized, making development of guidelines challenging.

A multidisciplinary approach to patients on antithrombotic therapy undergoing urological surgical procedures

International guidelines recommend postponing elective surgical procedures until completion of the mandatory dual antiplatelet therapy (DAPT) duration regimen and to discontinue aspirin therapy only if surgical hemostasis is expected to be difficult.[23, 24] However, existing guidelines are limited in providing practical guidance regarding the management of AP therapy in the perioperative phase of semi-elective or urgent surgical or endoscopic procedures. Moreover, no clear definition of perioperative bleeding risk is provided, and the advocacy towards a multidisciplinary approach falls short in providing clear guidance on multiple practical issues.

Due to these limitations, an Italian National consensus document was published aimed at providing a standard definition of thrombotic and hemorrhagic risk.[28] The scientific panel was composed of cardiologists, surgeons, and anesthesiologists. The document derived from a multidisciplinary collaboration and provided practical recommendations on the perioperative management of antithrombotic therapy in patients treated with coronary stents. These recommendations could also be accessed through a workable web application (https://itunes.apple.com/us/app/stent-surgery/id551350096?mt=8). According to the SAS document, aspirin can be maintained in the vast majority of surgical procedures. In selected cases, if discontinuation of oral AP therapy is required due to high hemorrhagic risk, a bridge therapy with intravenous AP therapy may be considered. A national registry surveyed the applicability of the recommendations in real-world clinical practice and supported the relative merit of a risk stratification approach for both ischemia and bleeding in patients with coronary stents undergoing cardiac and NCS.[29]

As for AP agents, the perioperative management of OAC should also be based on the ischemic risk of the patient and hemorrhagic risk related to the specific surgical or endoscopic procedure. Given the long and variable half-life of VKAs, guidelines recommend that patients discontinue treatment 5 days before major procedures. In the European Heart Rhythm Association (EHRA) Practical Guide on the Use of Non-Vitamin K Oral Anticoagulants (NOAC), procedural hemorrhagic risk has been defined according to the frequency of bleeding and its impact.[30] The more predictable anticoagulant effect and shorter half-life of NOACs compared with VKA have the potential to simplify the perioperative management of OAC,[30] particularly if a standard hemorrhagic stratification of the types of surgical and endoscopic procedures has been provided.

As already standard practice for different specialties, all urologists should familiarize with emerging recommendations guideline standardizations, if these increasingly complicated patient subgroups are to benefit from optimal perioperative management.[31]

Practical suggestions

In 2014, ICUD and AUA jointly published their recommendations on anticoagulant therapy in urological surgery. Culkin *et al*. provided a series of guidelines about the peri-procedural management of antithrombotic medications for urologists.[23] Very recently, EAU guidelines on Thromboprophylaxis in Urological

Surgery were published for the first time.[32] In addition, a consensus document on the optimal AP regimen in patients with coronary stents undergoing urologic interventions has recently been proposed by a multidisciplinary panel composed of urologists and cardiologists, who contributed equally to its creation.[33] The Italian Society of Urology, Interventional Cardiology, and Cardiology endorsed the document. An ST risk was graded considering procedural features such as stent type, time from PCI to urologic surgery, and clinical aspects such as concomitant diabetes, renal impairment, low cardiac ejection fraction, and age.

The authors divided patients according to surgical bleeding risk related to the procedure (low-risk endoscopy and laser prostatectomy) and intermediate-high risk (transurethral resection of bladder tumors [TURB], transurethral resection of the prostate [TURP]), according to the thrombotic risk (Table I). As expected, it is clear that it is extremely difficult to balance between bleeding and thrombotic risk in patients undergoing urologic surgery in a real-life scenario, especially without clear evidence and guidelines.[6] With regard to AP therapy (especially aspirin), it is important to maintain it whenever possible, especially when the ischemic risk is intermediate or high. In case of withdrawal of the AP therapy in the perioperative phase, it should be restarted as soon as possible after the intervention (ideally, 24-48 hours later). In selected cases, such as patients with high ischemic and hemorrhagic risk who require non-deferrable surgery, "bridge therapy" may be necessary when discontinuation of oral AP is essential.

Interestingly, the initial pioneering report did not consider laser procedures for BPH, bipolar TUR, or any endoscopic prostate-enucleating technique (EEP). Thus, in the absence of solid literature, it would be prudent to consider at baseline all these procedures as intermediate risk for bleeding, like TURP.

TABLE I.—*Perioperative antiplatelet therapy in patients with coronary stents who are undergoing endoscopic urologic surgery (modified from Rossini* et al.*).*[28]

	Low risk of thrombosis	Intermediate risk of thrombosis	High risk of thrombosis
Low hemorrhagic risk Flexible cystoscopy Ureteral catheterization Ureteroscopy	ASA: continue P2Y12 receptor inhibitors: – discontinue 5 days before* – resume within 24-72 h with a loading dose	*Elective surgery* Not contraindicated ASA: continue P2Y12 receptor inhibitors: continue	*Elective surgery* Not contraindicated ASA: continue P2Y12 receptor inhibitors: continue
Intermediate hemorrhagic risk Laser vaporization of prostate?	ASA: discontinue P2Y12 receptor inhibitors: – discontinue 5 days before* – resume within 24-72 h with a loading dose	*Elective surgery* Postpone *Non-deferrable surgery* ASA: continue P2Y12 receptor inhibitors: – discontinue 5 days before* – resume within 24-72 h with a loading dose †	*Elective surgery* Postpone *Non-deferrable surgery* ASA: continue P2Y12 receptor inhibitors: – discontinue 5 days before* – resume within 24-72 hours with a loading dose † Bridge therapy with small molecules †
High hemorrhagic risk Percutaneous nephrostomy Radical cystectomy Radical prostatectomy Endoscopic resection of the prostate Endoscopic treatment of Bladder	ASA: discontinue P2Y12 receptor inhibitors: – discontinue 5 days before* – resume within 24-72 h with a loading dose	*Elective surgery* Postpone *Non-deferrable surgery* ASA: continue (if possible) P2Y12 receptor inhibitors: – discontinue 5 days before* – resume within 24-72 h with a loading dose † Bridge therapy with GPIIb/IIa inhibitors † if ASA is discontinued	*Elective surgery* Postpone *Non-deferrable surgery* ASA: continue P2Y12 receptor inhibitors: – discontinue 5 days before* – resume within 24-72 h with a loading dose † Bridge therapy with GPIIb/IIa inhibitors † if ASA is discontinued

ASA: aspirin.
*Seven days before for prasugrel; † collegial discussion of risk, even with family/patient.

Evidence synthesis of different surgical (urological) endoscopic procedures in patients with anticoagulation/antiplatelet therapy.

TURP and TURBT

The majority of literature recommends discontinuation of all anti-thrombotic medications. However, this evidence is predominantly drawn from observational and retrospective studies in which AP and AC medications are grouped together, with minimal focus on other patient and operative factors that may significantly impact perioperative risk of thromboembolic or bleeding complications.[18] As such, traditional risk stratifications used in the perioperative management of these patients may be sub-optimal.

Several reports reveal an increased need for blood transfusions, higher risk of clot retention and increased re-hospitalization rate after TURP (14.2% *vs.* 5.9%) in patients who continued anti-coagulation compared to those who did not.[34] A retrospective review of 293 higher-risk consecutive elective TURP patients bridged with enoxaparin revealed an increased risk of both perioperative bleeding and thromboembolic complications.[35] Conversely, a retrospective series of 305 patients who had AC therapy stopped before TURP did not have a higher incidence of cardiovascular or cerebrovascular events compared with AC-naïve patients, revealing that cessation did not increase cardiac/stroke risk.[19] The BRIDGE trial similarly revealed that bridging was not associated with a reduction in arterial thromboembolism, but the incidence of major bleeding in non-cardiac surgery was three times higher in the perioperative bridged group.[36]

While cessation of AP therapy prior to TURP/TURBT is supported in the literature and recommended in lower-risk patients by the American College of Chest Physicians,[18, 19, 36] recent evidence suggests that this blanket approach may not be optimal.[6] The greatest cardiovascular risk occurs immediately after abrupt withdrawal of AP therapy, resulting in a dramatic rebound in the inflammatory and prothrombotic state, which promotes platelet aggregation.[37] Additionally, Bell *et al.* also reported that in patients undergoing TURP, it is possible to demonstrate increases of thrombin-antithrombin complexes with a decrease in activated partial thromboplastin time, which results in a hypercoagulable state.[38] While the possibility of problematic intra- and postoperative bleeding is a major deterrent in AP continuation, there is growing evidence to suggest these complications may be overstated. Raj *et al.* (2001) did not note a higher incidence of bleeding related complications in patients undergoing TURP who continued aspirin.[19] This has also been confirmed by other non-randomized studies.[39] For patients undergoing TURBT, Picozzi *et al.* demonstrated that continued use of AP monotherapy did not increase risk of bleeding or re-intervention.[40]

In creating clearer recommendations for TURP, consideration of prostate volume, and pre-treatment with 5-ARIs are important, as well, and have been shown to influence perioperative bleeding.[41] In the case of TURBT, tumour stage and grade may have a greater influence on transfusion requirements than concomitant anticoagulation.[42] While high-powered evidence is necessary to create definitive recommendations, evidence to date seems to support continuation of aspirin therapy in patients undergoing TURP and TURBT.

Holmium laser enucleation of the prostate

There is more robust literature with endoscopic laser prostate surgery, both continuation of therapy, and bridging. Studies of holmium laser prostate surgery with continuation of therapy and heparin bridging have shown no significant bleeding complications as compared to matched controls.[43] Due to the chromophore of water and minimal tissue depth penetration (0.4 mm), the laser achieves rapid vaporization and coagulation of tissue without the disadvantage of deep tissue penetration. Because of these hemostatic properties, use of the holmium laser was adopted early in patients on chronic AC/AP.[44]

In 2006, Elzayad *et al*. published their results in a group of 83 patients who assumed AC therapy, or had bleeding disorders. Four-

teen patients underwent holmium laser enucleation of the prostate (HoLEP) without withdrawal of oral AC, 34 underwent surgery bridging with LMWH, and 33 stopped AC before surgery, including 8 on AP therapy. One patient required intraoperative platelet transfusion, and 7 required blood transfusion early in the postoperative period due to hematuria coinciding with restarting oral AC therapy. Two of 14 patients were on full AC, including 5 of 34 with LMWH substitution and 1 of 33 who stopped AC therapy before surgery. Due to the low rate of blood transfusion (around 14%) the authors concluded that HoLEP is a safer and effective alternative to conventional treatment in patients on AC or with bleeding disorders.[45]

In 2013, an Australian group performed a retrospective review on a series of 125 patients treated with HoLEP. Fifty-two patients were on antithrombotic therapy at the time of surgery and 73 patients were not. Four men (7.7%) in the anti-thrombotic group required a blood transfusion, compared to none in the control group. According to the authors, HOLEP is safe in the anti-thrombotic group, but they underline that these patients should discontinue therapy when possible, prior to surgery.[46]

A similar study was published in 2016 comparing 116 patients who required AC/AP therapy when undergoing HoLEP to 1558 patients who did not. Other than slight increased duration of bladder irrigation and hospital stay, the use of AC/AP therapy did not adversely affect outcomes of HoLEP, confirming that HoLEP is an attractive approach for such patients.[21] A recent meta-analysis of patients on AP/AC undergoing HoLEP further supports that this approach can be performed safely on these patients, but stressed there is limited data surrounding DOACs and HoLEP.[44]

Photoselective vaporization of the prostate

Similar findings have been reported with photoselective vaporization (PVP) throughout its development and increased power (from the 80-W system to the 120-W one, and to the more recent 180-W XPS). Multiple studies have found PVP was safe and effective for patients who continue oral AC/AP therapy, but longer catheterization and irrigation with an increased rate of complications has been reported. Transfusion rate remains negligible, but delayed bleeding is more pronounced in AC patients.[20, 47-49]

Recently Knapp *et al.* confirmed the overall safety of performing greenlight PVP with the 180-W Greenlight lithium triborate laser in a high volume, expert center, in patients on any treatment with heparin, warfarin, clopidogrel, dipyridamol or new oral AC drugs.[50] Patients on AC therapy were older, presented a higher American Society of Anesthesiologists score (ASA) than the control group and, although no patient required blood transfusion, there was a higher incidence of high-grade Clavien-Dindo events in men who continued AC during PVP. Furthermore, the AC group had a significantly longer length of hospital stay and duration of catheterization compared to the controls. These findings could not be confirmed in a large multicentric retrospective study in 941 men since no difference was generally found in safety outcomes of PVP 180-W XPS in high vs low medical risk patients. However, only 14% and 12.7% of these were on AC/AP therapy, respectively.[51]

Although more quality evidence on the safety profile of 180-W PVP is needed in a RCT fashion, current EAU guidelines [22] clearly recommend considering 532-nm laser vaporization in patients receiving anticoagulant medication or with a high cardiovascular risk (level of evidence 3, grade of recommendation B).

Tm:YAG laser enucleation

The Thulium laser has shallow penetration in tissue (0.2 mm), good hemostatic and cutting properties, and has been found to be especially good for patients with high cardiopulmonary risk. The thulium laser operates in continuous-wave mode and permits small and precise cutting, consequently reducing the risk of bleeding.[26]

Netsch *et al*. evaluated the safety of thulium enucleation of the prostate (ThuVEP) in 56 patients with high cardiopulmonary risk on AC

at time of surgery: 32 on aspirin; 8 on clopidogrel, or clopidogrel + aspirin; and 16 on phenprocoumon. Although four patients needed blood transfusions and four patients required immediate re-operation, they concluded that vapo-enucleation could be safely performed in this high-risk group.[52]

Two papers have described the feasibility of Thulium laser vapo-resection of the prostate (ThuVARP) in patients on OAP/OAC therapy. Macchione *et al*. compared results of ThuVARP in patients on AC/AP therapy during surgery, to those who were bridged with LMWH. There were no statistically significant variations in hemoglobin between the two groups.[53] A similar, more recent, study by Sener *et al*. of 103 patients revealed the drop in hemoglobin levels in the pre- and postoperative periods were significantly higher in the LMWH bridged group than those who remained on AC/AP during surgery. Given no cardiopulmonary adverse events occurred and bleeding was not problematic, the authors recommend abandoning LMWH bridging and continuing AP/AC therapy during ThuVARP.[54]

Treatment of stones and urothelial tumor of the upper urinary tract

In general, it would seem that ureteroscopy without interruption of AC therapy does not lead to significant complications. It is expected that patients on AC have greater drops in hemoglobin than controls, but this generally does not result in transfusion. Of three published reviews, only one retroperitoneal bleed occurred.[3, 23, 55]

Upper tract, urolithiasis

The number of patients suffering from urolithiasis requiring active treatment and at the same time on chronic antithrombotic therapy is currently increasing.[56] Flexible retrograde ureteroscopy (fURS) for renal stone treatment is a procedure typically considered low-risk for bleeding. It has been shown to be a safe and efficient treatment modality, even in patients with uncorrected bleeding diathesis.[3, 23] A comparable safety profile has been reported with fURS and holmium laser lithotripsy between patients not using AC, and those that continued their antithrombotic therapies.[55] Others have described minor degrees of bleeding complications associated with the retrograde ureteroscopic treatment of AC patients.[23] It would appear that AP agents do not pose an increased risk of bleeding-related complications, but long-term AC does.[57, 58] The concern with AC therapy is that persistent intraoperative bleeding may cause relevant visual impairment and thus worsening of the stone-free rate, as well as premature termination of the procedure, in spite of the use of small caliber endoscopes and low-pressure procedures.[59] While not studied extensively, stone size, number of stones, and stone location likely have an impact on bleeding risk in patients on AP/AC therapy, and each situation should be evaluated independently. Percutaneous nephrolithotomy (PNL) carries a recognized high risk of bleeding due to the direct traumatic effects of the percutaneous puncture and dilation of the renal parenchyma. There is wide variation on need for transfusions (<1-55%), but without a doubt AP and AC therapies will only increase such risk.[60] All known guidelines recommend discontinuing AC prior to PNL, with or without heparin bridging. Recently, the consensus within the literature is shifting towards continuation of low dose aspirin therapy in high-cardiovascular risk patients, as reported at the 2017 American Urological Association's Annual meeting. In one retrospective study, tubeless PNL was found to be safe in a few patients maintained on aspirin therapy.[61] In contrast, other authors reported an increased hemorrhagic risk and a 5.8-fold increased risk of prolonged macroscopic hematuria, despite the cessation of the AP agents prior to PNL, and a careful perioperative management.[62] Therefore, there remains unclear direction with PNL and AP therapy.

Upper tract, urothelial carcinoma

Conservative management of upper tract urothelial carcinoma (UTUC) is nowadays con-

sidered an accepted option by the EAU guidelines,[63] thanks to advancements in endoscope engineering and laser technologies. However, the issue of concomitant antithrombotic therapies is not specifically debated. Additionally, no results could be obtained using UTUC and related terms combined with ureteroscopy, percutaneous, antiplatelet, anticoagulation, antithrombotic therapy for a MEDLINE search on PubMed. Only two papers on AP and AC agents in routine ureteroscopy [57, 58] explicitly included UTUC cases, although they were not examined separately from the stone procedures.

Reasonably, we can infer that percutaneous UTUC treatment in patients on antithrombotic therapy implies the same high hemorrhagic risks of PNL. Similar to stones, diagnostic fURS might also be a low-bleeding risk procedure, but the need for lesion biopsies and laser cancer ablation clearly increases the hemorrhagic risk. Despite the optimal hemostatic ability of the lasers, this kind of ureteroscopy likely belongs in a higher risk bleeding category.[64]

Conclusions

Management of anticoagulant therapy is an area of significant concern and variation amongst specialties, and providers. The creation of guidelines is challenging, but essential. The consensus of many reviews is that despite the lack of randomized studies, regardless of individual patient considerations, most would support continuation of ASA, which is recommended by cardiologists, in patients with intermediate/high risk of thrombosis. In contrast, bridging with LMWH seems to cause more bleeding than continuation of AC/AP therapy, a finding agreed upon by the authors, and caution with bridging is advised. Alternative approaches that are associated with less bleeding and/or improved hemostasis, such as laser therapy, should be utilized whenever possible. Finally, all urologists should be familiar with emerging recommendations and guidelines and be prepared to discuss specific cases or scenarios in a dedicated multidisciplinary team to recognize when surgery can, or should, be deferred or not.

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