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ORIGINAL ARTICLE

Efficacy of a short prophylaxis with tranexamic acid on hemostasis during transrectal prostate biopsy in patients taking oral anti-platelet treatment

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Summary

Purpose: *To assess the efficacy of a short prophylaxis with tranexamic acid in reducing blood loss during transrectal ultrasound-guided prostate biopsy (TRUSBx) in patients taking oral anti-platelet therapy and to prospectively compare this approach with patients without oral prophylaxis.*

Methods: *A total of 359 consecutive patients taking chronic low dose aspirin were enrolled in this prospective study. Before TRUSBx all patients were randomly assigned into two groups; a short oral prophylaxis with tranexamic acid 500 mg orally, taken one hour before the procedure (group A, N:178) and those without oral prophylaxis (group B, N:181). Patients were asked about complications, their frequency, severity of bleeding (hematuria, hematospermia, rectal bleeding) on a 0-5 scale, with 0 representing absence of bleeding and 5 very severe bleeding.*

Results: *No significant differences were noted between the two groups in radiation to age, preoperative PSA level, prostate volume, biopsy numbers, and Gleason score. There were no severe bleeding complications (grade 5) recorded in both groups. The study revealed significant differences in the incidence of hematuria ($p<0.001$) and rectal bleeding ($p<0.002$) between the groups. Patients in group A (16.9%) experienced fewer hematuria and rectal bleeding episodes than did the group B patients (31.5%). The number of sexually active men still reporting hematospermia was 16.6% in group A and 19.4% in group B, with no statistical difference ($p=0.32$).*

Conclusion: *The continued use of anti-platelet agents in patient undergoing TRUSBx does not increase the incidence of mild bleeding complications, if these are associated with a short-term tranexamic acid treatment.*

Key words: *anti-platelet, aspirin, biopsy, bleeding, prostate, tranexamic acid*

Introduction

TRUSBx is one of the most common urological procedures, with approximately 1 million prostate biopsies performed annually in Europe and United States with this method [1]. TRUSBx is generally a safe procedure with minimal haemorrhagic complications such as hematuria (21-43%) [2], hematospermia (17-28%) [3], and rectal bleeding (13-19%) [4]. During the last decade there has been a marked increase in the number of core prostate biopsies with a greater postprocedural number of complications. The urologist is often dealing with patients with cardiovascular comorbidities managed by oral antiplatelet agents. The risk and severity of thromboembolic complications with the discontinuation of these drugs may be markedly higher than bleeding associated with elective procedures [5]. Not stopping aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) is controversial, but it is not an absolute contraindication to TRUSBx [6]. In this study we assessed the efficacy of a short prophylaxis with tranexamic acid in reducing blood loss during TRUSBx in patients taking oral anti-platelet low-dose aspirin and to compare this prospectively with patients

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without oral prophylaxis.

Methods

A single-centre prospective study of 359 consecutive patients referred for TRUSBx to our Department was performed between October 2009 to December 2014.

All patients underwent an initial TRUSBx for abnormal digital rectal examination (DRE), high prostate-specific antigen (PSA) levels (≥ 4 ng/mL), or both. Patients with a history of biopsy, surgical treatment of prostatic disease, neoadjuvant therapy or incomplete clinical data were excluded from study. Before the biopsy, all patients with regular low-dose aspirin use were randomly assigned into two groups: a short oral prophylaxis with tranexamic acid (UGUROL®, Rottapharm, MB, Italy) 500 mg (250 mg tabs x 2 taken one hr before the procedure (group A, N:178) and no oral prophylaxis (group B, N:181). Patients were instructed to take antibiotics, usually levofloxacin 500 mg orally, for 5 days starting the evening before the procedure and a small evacuative enema administered two hrs before the procedure. All procedures were performed in order to empty the bladder, since we believe that even the state of bladder repletion may be an element of discomfort during the performance of mapping biopsy. TRUSBx was performed with the patient in left lateral decubitus position using a General Electric Logiq 7 machine (GE Healthcare, Milwaukee, WI, USA) equipped with a 5-9MHz multi-frequency convex probe "end-fire". Each transrectal ultrasound performed included an assessment of the prostatic diameter, the volume of the whole prostate, the transition zone, capsular and seminal vesicle characteristics, as well as morphological description of potential pathologic features. After the prostate imaging, sampling was carried out with a 18-Gauge Tru-Cut needle (Bard Biopsy Systems, Tempe, AZ, USA) powered by an automatic spring-loaded biopsy disposable gun. Three experienced urologists of our Department performed a 14-core biopsy as first intention, including 2 basal samples (lateral and medial), 2 parasagittal samples (lateral and medial), 2 apical samples (lateral and medial) and 1 transitional zone sample on each side. Each patient was subjected to local anesthesia with Lidocaine Spray 10g/100ml (ECOCAIN®, Molteni Dental, FI, Italy) applied 2 min before the procedure [7]. The transrectal ultrasound-derived prostate volume was invariably calculated using the prostate ellipse formula (0.52 x length x width x height). All patients read a detailed informational guide before the procedure and filled-in a questionnaire with information of the participant's age, PSA, prostate volume (PV), DRE findings, use of anticoagulants/antiplatelets, and the number of core biopsies taken. The patients were called 14-18 days after the procedure to inform them about the results. This time we gave to the patients a questionnaire to obtain data on post-biopsy experience. Patients were asked about complications that occurred (yes/no), how long for (hours/ days), kind and severity of bleeding (hematuria, hematospermia, rectal bleeding) on a 0-5 scale, with 0 representing absence of bleeding and 5 very severe bleeding. The presence or absence of each bleeding episode and its duration and severity was reported but the blood loss amount was not quantified. Values of 1-2 were classified as low severity and values of 3-5 as high severity.

Statistics

Comparisons between the two groups were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Univariate logistic regression analysis was used to identify the individual clinical factors predictive of hemorrhagic complications. All statistical analyses were conducted on Microsoft Excel 2010 platform version 10.1. A p value < 0.05 was considered to indicate statistical significance.

Results

The mean age of the enrolled patients was 64.2 ± 6.7 years, with a PV of 38.5±19.6 mL, and initial PSA of 10.3 ± 8.7 ng/mL. Two hundred and seventy-five patients (76.6%) were biopsied for the first time. The number of biopsy cores was 10.8 ± 5.1. No significant difference was noted between the two groups when comparing age, preoperative PSA level, PV, DRE, number of biopsies, and Gleason score (Table 1). In group A, 2 patients (1%) were subjected to 6 core biopsies, 11 patients (6.7%) to 8, 24 patients (13.4%) to 10, 41 patients (23%) to 12, 56 patients (31.4%) to 14, and 44 patients (24.5%) to 16 core biopsies. In group B, 3 patients (1.6%) were subjected to 6 core biopsies, 10 patients (5.5%) to 8, 27 patients (14.9%) to 10, 39 patients (21.5%) to 12, 53 patients (29.3%) to 14, and 49 patients (27.2%) to 16 core biopsies. Prostate cancer was detected in 115 patients (32%) and their Gleason score was ≤6 (63 patients, 54.8%), 7 (37 patients, 32.2%), and ≥8 (15 patients, 13%). There were no significant differences in the clinical variables among the patients in the two groups, except for DRE findings. In group B more frequent abnormal DRE findings were observed (p<0.002). Post-biopsy results of the 359 patients included in group A revealed that hematuria was present in 10.7% (19/178) of the patients, while in group B it was present in 18.8% (34/181) of the patients. In group A patients 6.2% (11/178) and in group B 12.8% (23/181) experienced rectal bleeding. In group A patients 38.2% (68/178) and in group B patients 40.3% (73/181) experienced hematospermia (Figure 1).

Table 1. Demographic and clinicopathologic characteristics of patients undergoing transrectal prostate biopsy

Characteristics	*Group A (N:178)*	*Group B (N:181)*	*p value*
Age (years), mean ± SD	63.8±6.2	64.9±7.5	NS
PSA (ng/mL), mean ± SD	10.1±8.9	10.6±7.8	NS
PV (mL), mean ± SD	38.1±19.2	37.7±20.1	NS
Abnormal DRE, N (%)	32 (17.9)	69 (38.1)	<0.002
N° biopsy cores, mean ± SD	10.7±5.4	10.3±6.1	NS
Gleason score, N (%)			NS
≤6	29 (16.3)	34 (18.8)	
7	19 (10.7)	18 (10)	
≥8	9 (5)	6 (3.3)	

SD: standard deviation, PSA: prostate-specific antigen, DRE:digital rectal examination, PV:prostate volume, NS: not significant

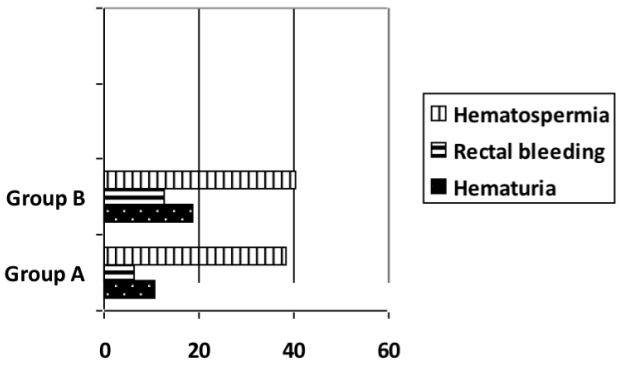

Figure 1. Incidence of hematuria, rectal bleeding, and hematospermia in the groups. Numbers represent the percentage of patients with hematospermia, rectal bleeding and hematuria.

Table 2 shows the incidence and severity of complications among the two groups. Grade 1, 2, 3 and 4 complications occurred in 107 (29.8%), 76 (21.1%), 34 (9.5%), and 9 (2.5%) patients, respectively. There were no severe bleeding complications (Grade 5) recorded in the two groups and patients did not require intervention for bleeding. Two patients in group B were admitted to the hospital having developed urinary retention. The study revealed that there were significant differences in the incidence of hematuria (p<0.001) and rectal bleeding (p<0.002) between the groups. Moreover, a statistically significant difference was found in the duration of hematuria and rectal bleeding between the two groups. The duration was longer in group B (4.8 days) than in group A patients (2.8 days;p<0.002). The number of sexually active men still reporting hematospermia 4 weeks after TRUSBx was 18 (16.6%) in group A, and 22 (19.4%) in group B (p=0.32). All complications, except hematospermia, resolved within 14 days after TRUSBx.

Discussion

Anti-platelet agents are members of a class of pharmaceuticals that decrease platelet aggregation and inhibit thrombus formation. Low-dose aspirin is prescribed largely for primary and secondary prevention of coronary artery and cerebrovascular disease in patients with myocardial infarction, transient ischemic attacks, peripheral vascular disease and carotid artery stenosis [8,9].

Approximately 10% of the patients on oral anti-platelet drugs will require an invasive procedure each year [10].

Severe hemorrhagic complications after TRUSBx are rare, but mild hemorrhagic complications, such as hematuria, hematospermia and rectal bleeding, are very common in patients taking anti-platelet medications [11]. However, the risk of thromboembolic complications with the discontinuation of anti-platelet drugs may be markedly higher than bleeding associated with elective procedures [12]. TRUSBx complications for patients on continuing low-dose aspirin were studied in prospective, controlled trials and meta-analyses (total more than 3.000 patients) [4,6,8,13-15]. Uninterrupted use of low-dose aspirin does not increase the risk of moderate/severe hematospermia and rectal bleeding after TRUSBx. However, Halliwell et al. [14] compared 387 patients on as-

Table 2. Incidence of complications between in the two groups

Complications	*Group A (N: 178)*				*Group B (N: 181)*				*Total*
Complication grade	G1	G2	G3	G4	G1	G2	G3	G4	
Hematuria	8	7	3	1	12	13	8	1	53
Rectal bleeding	5	3	2	1	9	7	5	2	34
Hematospermia	34	21	10	3	39	25	7	2	141

p: non significant in any category

pirin vs 731 patients not on antiplatelet therapy control. In this study the incidence of hematuria and rectal bleeding was higher in the aspirin users than in the control group (72 vs 61%, p<0.001, and 21 vs 13%, p<0.001, respectively), but there were no significant differences in hematospermia. The findings of Kariotis et al. [6] showed that younger patients with lower (<21kg/m^2) body mass index taking aspirin were at higher risk of developing hematuria after TRUSBx. Another comparative study by Giannarini et al. [15] reported that the overall bleeding rate in the aspirin group was not significantly higher at 78.5% than the 81.5% in the group of non aspirin users.

In our study, hemorrhagic complications graded as low and high severity occurred in 63.5% of the patients and most were self-remitting. There was no statistically significant difference in the occurrence of hematospermia in both groups (38.2% in group A vs 40.3% in group B). However, a limitation of our analysis is attributed to the non-homogeneity in the method of enrollment of bleeding complications. The rate of hematospermia had to be calculated from the number of sexually active patients who pledged in sexual activity after TRUSBx and not from the overall number of patients included in the study.

In addition, 16.9% of group A patients experienced fewer hematuria and rectal bleeding episodes than did those in group B (31.5%). It could be deduced that patients not receiving a short prophylaxis with tranexamic acid had a tendency to bleed easily.

Univariate analysis shows that hemorrhagic complications are linked with anti-platelet medications and are not uncommon after TRUSBx.

Tranexamic acid is a synthetic antifibrinolytic drug that acts by competitively inhibiting the activation of plasminogen to plasmin used to prevent bleeding [16]. There are various methods of administering tranexamic acid to reduce blood loss in urological practice: intramuscular, oral and intravenous [17]. The time to reach maximum plasma levels of tranexamic acid ranges from 1 hr for oral to 10 min for intravenous administration. However, there is no consensus regarding the timing and dose of tranexamic acid. Also, there are no studies that speak of its use as a prophylaxis in urological surgery [18]. There have been studies related to tranexamic acid usage pre and postoperatively via intravenous infusion [18,19]. We used tranexamic acid taken orally one hr before the procedure.

Several studies have demonstrated that tranexamic acid does not predispose a patient to thromboembolic complications [20,21]. Similarly, we did not observe any thromboembolic complications.

The present results suggest that the continued use of anti-platelet agents in patient undergoing TRUSBx does not increase the incidence of mild bleeding complications, if these are associated with a short-term tranexamic acid treatment. Its effect, however, on bleeding remains to be determined.

Conflict of interests

The authors declare no confict of interests.

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