Prostate International 7 (2019) 78–81

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Original Article

Is it safe to continue antithrombotic agents before prostate biopsy?

Kuniaki Tanabe [a], Tomotaka Hattori [b, *], Hirohito Kobayashi [b], Kyoko Koike [b], Yasuhiro Maki [b], Takashi Arai [c], Toshiaki Otsuka [d], Yasutomo Suzuki [e], Yukihiro Kondo [a], Naoki Kawamura [b]

[a] Department of Urology, Nippon Medical School, Tokyo, Japan
[b] Department of Urology, Ebina General Hospital, Kanagawa, Japan
[c] Department of Urology Kitakyushu General Hospital, Fukuoka, Japan
[d] Department of Hygiene and Public Health, Nippon Medical School, Tokyo, Japan
[e] Department of Urology, Nippon Medical School Chiba Hokusou Hospital, Chiba, Japan

ARTICLE INFO

Article history:
Received 22 March 2018
Received in revised form
6 June 2018
Accepted 29 June 2018
Available online 5 July 2018

Keywords:
Anticoagulants
Biopsy
Hemorrhage
Platelet aggregation inhibitors
Prostate

ABSTRACT

Background: Whether antithrombotic agents should be stopped before prostate biopsy is unsettled. We investigated the impact of antithrombotic agents on bleeding complications after prostate biopsy.
Materials and methods: Among the patients who underwent transrectal ultrasound-guided prostate biopsy from June 2006 to December 2013 at Ebina General Hospital, Kanagawa, Japan, 1817 cases were retrospectively assessed. Patients were divided into two groups: those not taking antithrombotic agents (control group) and those taking them (experimental group). The frequency and severity of bleeding complications after the procedure were compared. The severity of bleeding events was graded using the Common Terminology Criteria for Advanced Events vol. 4.0.
Results: Hemorrhagic complications were classified into grades 1 to 3. Patients with complications of Grade 2 and above needed treatment. As for the Grade 1 event, there were no differences between two groups. The frequency of more than Grade 2 bleeding events was 1.7% and 3.5% in the control and experimental group, respectively; the odds ratio was 2.18 ($P = 0.039$). Grade 3 events occurred in seven patients of the control group (0.5%) and four patients of the experimental group (1.2%).
Conclusions: The present study showed that continuation of antithrombotic agents increased the frequency of hemorrhagic complications requiring intervention. It suggests that attention should be paid to the patients taking antithrombotic agents before prostate biopsy.

1. Introduction

Antithrombotic agents (AAs) are given to patients at risk of cardiovascular disease. With the rapid aging of society, the number of patients with ischemic diseases is increasing, leading to many patients being prescribed AAs.[1] At the same time, as prostate-specific antigen (PSA) screening becomes more prevalent, the number of patients with suspected prostate cancer is also increasing.[2,3] Transrectal ultrasound (TRUS)–guided prostate biopsy is the standard procedure for making a diagnosis of prostate cancer.[4] Therefore, more prostate biopsies will theoretically be performed in patients treated with AAs. The perioperative management of patients on AAs requiring a prostate biopsy involves the dilemma of whether to continue or discontinue taking these drugs.

Bleeding complications of prostate biopsy are commonly minor in patients not on AAs, but the situation in patients on AAs is not known. According to the American College of Chest Physicians Evidenced-Based Clinical Practice Guidelines,[5] when patients taking a vitamin K antagonist, such as warfarin, or acetylsalicylic acid (ASA) require minor dental or dermatologic procedures or cataract surgery, they should not discontinue using the drugs. In this guideline, there are no suggestions for prostate biopsy. However, it suggests that the assessment of perioperative bleeding risk is important.

Abbreviations & acronyms: AA, antithrombotic agent; PSA, prostate-specific agent; TRUS, transrectal ultrasound; ASA, acetylsalicylic acid; TE, thromboembolism; AP, antiplatelet agent; AC, anticoagulant agent; MAP, major antiplatelet agent; TPV, total prostate volume; SD, standard deviation; OR, odds ratio; RR, relative risk.

* Corresponding author. 1320 Kawaharaguchi, Ebinashi, Kanagawa 243-0433, Japan.
E-mail address: t_hattori@jin-ai.or.jp (T. Hattori).

https://doi.org/10.1016/j.prnil.2018.06.004

If bleeding complications caused by the continuation of AAs use before prostate biopsy can be tolerated, the risk of thromboembolism (TE) may be avoided by not discontinuing AAs. To assess the bleeding risk of TRUS-guided prostate biopsy in patients on AAs, bleeding complication rates and their severity after core needle prostate biopsy were compared in patients with and without concurrent anticoagulation therapy.

2. Materials and methods

2.1. Patients

This was a single-center retrospective study of 1817 consecutive Asian patients who underwent TRUS-guided prostate biopsy from June 2006 to October 2014 at Ebina General Hospital in Kanagawa, Japan. Biopsy indications included an elevated serum PSA level above 4.0 ng/mL, an abnormal digital rectal examination, or both.

The patients were divided into two groups: 1476 patients who were not on AAs were classified as the control group; 341 patients on AAs were classified as the AAs group, and they did not discontinue AAs before the biopsy. The characteristics of these groups are shown in Table 1. There were no significant differences between the two groups.

The patients in the AAs group were on antiplatelet agents (APs) and/or anticoagulant agents (ACs). APs included major APs (MAPs), which are commonly used for treatment or prevention of cardiovascular diseases, such as ASA, clopidogrel, ticlopidine, cilostazol, and other APs such as ethyl icosapentate, sarpogrelate, dipyridamole, and Limaprost alfadex. ACs included warfarin, dabigatran, and rivaroxaban. Overall, 23% of patients were taking several kinds of AAs. Overall, 52% of AAs group patients were using ASA, 15% were using warfarin, and two-thirds of patients did not take either ASA or warfarin.

2.2. Biopsy protocol

A 120-mL glycerin enema was given to all patients before biopsy. They received antibiotic prophylaxis with 500 mg of piperacillin intravenously before prostate biopsy and 6 hours after the procedure. From the day after the biopsy, the patients were given 500 mg of levofloxacin for 3 days.

A 7.0-MHz biplane probe (Aplio SSA-700A; Toshiba Medical Systems Corporation, Tochigi, Japan) and an automatic spring-loaded biopsy gun (BARD MAGNUM; C.R. Bard Inc., Murray Hill, NJ) with an 18-gauge needle (UltraCORE Biopsy Needle; Medical Device Technologies Inc., Plano, TX) were used.

All biopsies were performed under general anesthesia with intravenous injection of propofol performed by anesthesiologists. All biopsies were performed by five urologists with the same protocol that included a systematic 12-core scheme. According to the ultrasound findings, additional targeted biopsies were performed as necessary.

Table 1
Patient characteristics in each group; the control group and the group taking antithrombotic agents.

	Control (n = 1476)	AAs (n = 341)	†*P*-Value
Age (yr/o)	69.6 ± 7.1	72.5 ± 6.7	0.096
PSA (ng/dL)	35.8 ± 404	32.3 ± 19.4	7.419
TPV (mL)	42.8 ± 21.9	43.0 ± 21.7	0.416
Biopsy cores (n)	11.5 ± 1.8	11.6 ± 1.8	0.453

AAs, antithrombotic agents; PSA, prostate-specific antigen; SD, standard deviation; TPV, total prostate volume.
Data presented as mean ± SD. † *P*-value was calculated by Fisher's exact test.

After biopsy, cessation of rectal bleeding was confirmed by digital rectal examination. When bleeding did not stop, we pressed the punctured point until arrest of bleeding was ascertained. If rectal bleeding did not stop after astriction, we observed the bleeding point with a proctoscope and sutured the rectal membrane as necessary.

2.3. Bleeding events

Bleeding events were defined as follows: 1. Some interventions were needed during hospitalization; 2. Emergency consults were needed after leaving hospital; and 3. self-limited events. At follow-up 2–3 weeks after biopsy, patients were asked about bleeding events.

These events were classified using Common Terminology Criteria for Advanced Events version 4.0. Bleeding events that needed mild treatments such as medication and catheterization were classified as Grade 2 events, and those that needed transfusion or rectum suture to stop rectal bleeding were classified as Grade 3 events. These events were defined as major bleeding events. Self-limited bleeding events were classified as Grade 1 and were defined as minor bleeding events.

When Grade 1 bleeding events happened, AAs were continuously taken. Otherwise, when Grade 2 or 3 events happened, we stopped AAs temporarily.

2.4. Analysis

The differences in patient characteristics between the two groups were evaluated using Fisher's exact test. To analyze the relationships of the bleeding events to the patient background factors including the use of AAs, univariate and multivariate logistic regression analyses were performed. The odds ratio (OR) and corresponding 95% confidence interval were calculated using the IBM SPSS 21.0 (IBM Corporation, Armonk, NY).

First, the relationships between age (per 1-year increment), PSA (per1 ug/mL increment), total prostate volume (TPV) (per 1-mL increment), whether prostate carcinoma was detected, and the incidence of bleeding events were investigated by univariate analyses. Then, the impact of AAs on the occurrence of bleeding events was evaluated after adjusting for the patient background factors (Table 2).

Moreover, subanalyses of AAs group were conducted to examine the different effects of each AA. First, AAs group was divided into three groups: MAP group (n = 273), AC group (n = 70), and other AP group (n = 42). The result was shown in Table 3.

Then, to examine the impact of combination of MAPs and ACs, we divided MAP group and AC group into three groups; patients with only MAPs (n = 242), patients with only ACs (n = 39), and patients with both of these agents (MAP+AC) (n = 31). When the effects of these agents were analyzed, adjustment for the effects of other APs were made based on the univariate logistic regression analyses. The ORs for bleeding risks were calculated for these three subgroups (Table 4).

3. Results

There were no significant differences in the frequencies of bleeding events after prostate biopsies for patient background characteristics other than major bleeding complications and TPV increase per 1 mL. The OR of major bleeding events and TPV increase per 1 mL was slightly increased (OR 1.02, 95% confidence interval 1.001–1.017).

Table 2 shows the frequency of major and minor hemorrhagic events. Hematuria, rectal bleeding, and hematospermia as minor

Table 2
Frequencies and ORs of each bleeding complication in the two groups.

	Control (%) n = 1476	AAs (%) n = 341	OR	95% CI	*P*
Grade 1	291 (19.7)	82 (24.0)			
Grade 2	18 (1.2)	8 (2.3)	NA	NA	NA
Grade 3	7 (0.5)	4 (1.2)	NA	NA	NA
Grade 1–3	316 (21.4)	84 (24.6)	1.30	0.98–1.73	0.073
Grade 2 + 3	25 (1.7)	12 (3.5)	2.18	1.04–4.55	0.039

AAs, antithrombotic agents; CI, confidence interval; NA, not available; OR, odds ratio.
OR, 95% CI, and *P* value were calculated by multivariate logistic regression analyses.

bleeding events were seen in both the groups. The incidence of these events was 17.9%, 3.7%, and 1.6% in the control group and 19.6%, 5.6%, and 0.6% in the AAs group, respectively. There was no significant difference between the two groups. Meaningful results were not obtained for hematospermia because the numbers were too small.

The incidence of major hemorrhagic events (Grade 2 + 3) was 1.76% in the control group and 3.81% in the AAs group. The OR was significantly higher in the AAs group (OR = 2.18, $P = 0.039$). All the hemorrhagic events tended to occur in the AAs group, although it was not significantly different (OR = 1.30, $P = 0.073$).

The incidences of bleeding events in subgroups were listed in Tables 3 and 4.

As for Table 3, although there were no significant differences between the three groups, all grades (OR = 1.34, $P = 0.064$) and Grade 2 + 3 bleeding events (OR = 2.09, $P = 0.069$) tended to happen in MAP group.

Table 4 showed that the ORs of the MAPs+ACs group were significantly higher for all bleeding complications (OR = 3.23, $P = 0.002$) and that the Grade 2 + 3 bleeding events were prone to occur in only the MAP group, although the difference was not significant (OR = 2.15, $P = 0.069$).

4. Discussion

There are some reports about prostate biopsy in patients continuing AP or AC.[6–11] Almost all reports showed that although continuation of AAs before prostate biopsy increased the frequency of minor bleeding complications or prolonged the duration of self-limited hematuria or rectal bleeding, it did not increase severe hemorrhagic complications. There is only one case report of a life-threatening rectal bleeding complication in a patient taking ASA. However, that was only one case among 136 patients (0.7%) on ASA, and the causality was not clear.[11]

On the other hand, some reports have investigated the impact of discontinuing AAs.[12–14] Guideline Subcommittee of the American Academy of Neurology[14] showed that temporary ASA discontinuation is probably associated with an increased risk of stroke or transient ischemic attack, and the risk rises in proportion to the duration of interruption. The risk of TE was also probably higher if AC was stopped for more than 7 days.

Hemostasis has two steps. Primary hemostasis is defined as the formation of primary platelet plugs. Platelets stick together to form a temporary seal to cover the break in the vessels. Secondary hemostasis is defined as formation of insoluble cross-linked fibrin by activated coagulation factors, especially thrombin. APs decrease platelet aggregation and inhibit primary hemostasis, whereas ACs prevent secondary hemostasis by inhibiting coagulation cascade such as thrombin, vitamin K, etc. Theoretically, antithrombotic effect must increase by using both APs and ACs. In fact, a considerable number of patients who have chronic atrial fibrillation receive combined APs and ACs therapy. Some randomized trials showed that continuation of antithrombotic therapy consisting of APs and ACs increased the risk for major bleeding events.[15,16] A meta-analysis comparing warfarin and aspirin with warfarin alone showed that the relative risk of major bleeding was 1.58. In our study, the frequency of Grade 2 + 3 bleeding complications was significantly higher in the AAs group, as shown in Table 2. Besides, all hemorrhagic events were more frequently in the MAPs+ACs group, as shown in Table 4. These results may reflect the randomized studies mentioned previously.

Organ biopsies are performed in several organs. There is a guideline regarding discontinuation of AAs before biopsy only in case of gastrointestinal biopsy.[17] According to the guideline, AAs should be discontinued before high-risk procedures except for ASA. MAPs alone other than ASA should be stopped or replaced with ASA, whereas AC should be replaced by heparin in principle. When the patients take several AAs including warfarin or dabigatran, they should put off the procedure if possible. As for prostate, the frequency of major hemorrhagic complication is rare in not using AAs cases. Many reports mentioned previously showed that ASA and some ACs did not increase the frequency of important hemorrhagic events. Because interruption of AAs rises the risk of TE, AAs might not be discontinued before prostate biopsy.

Table 3
Frequency of each hemorrhagic event in patients taking major antiplatelet agents, anticoagulant agents, or other antiplatelet agents.

	MAPs (%) n = 273	ACs (%) n = 70	Other APs (%) n = 42
Grade 1–3	71 (26.0)	20 (28.6)	9 (21.4)
OR	1.34	1.43	0.96
95% CI	0.98–1.83	0.83–2.48	0.45–2.04
P value	0.064	0.197	0.901
Grade 2 + 3	10 (3.7)	2 (2.9)	1 (2.4)
OR	2.09	1.26	1.14
95% CI	0.94–4.64	0.28–5.61	0.14–8.97
P value	0.069	0.766	0.898

AC, anticoagulant agent; CI, confidence interval; OR, odds ratio; MAPs, major antiplatelet agents.

Table 4
Frequency of each hemorrhagic event in patients taking only major antiplatelet agents, only anticoagulant agents, or both agents.

	Only MAP (%) n = 242	Only AC (%) n = 39	MAP+AC (%) n = 31
Grade 1–3	58 (24.0)	7 (17.5)	13 (41.9)
OR	0.83	1.22	3.23
95% CI	0.88–1.69	0.34–1.90	1.52–6.84
P value	0.243	0.243	0.002
Grade 2 + 3	9 (3.7)	1 (2.5)	1 (3.2)
OR	1.49	2.15	2.29
95% CI	0.94–4.89	0.19–11.4	0.29–18.34
P value	0.069	0.704	0.437

AC, anticoagulant agent; CI, confidence interval; MAP, major antiplatelet agent; OR, odds ratio.
MAP and AC here did not include combination therapy.

However, the result of this study showed that the impact of AAs toward hemorrhagic complications after prostate biopsy was not negligible. AAs use significantly increased the risk of bleeding events that required intervention and tended to increase all the hemorrhagic events. Especially MAPs use was prone to increase all and Grade 2 + 3 bleeding events, and the combined use of MAPs and ACs significantly increased all graded events. Accordingly, when we perform prostate biopsy without discontinuation of AAs, we should exercise great caution for hemorrhagic complications. In addition, we probably should consider interrupting MAPs that may mainly have an impact on hemorrhagic complications in this study especially in cases using both MAPs and ACs before prostate biopsy.

There are some limitations about our study. First, its major weakness is that this study was retrospective. Second, the number of patients taking several agents was small. Therefore, the impact of combination therapy was not adequately assessed. Third, because there were several agents in MAPs and ACs and the amount of each agent was not clear, which agent mainly affected the occurrence of hemorrhagic events could not be found. Finally, we did not assess how those agents work in patients, such as prothrombin time, international normalized ratio, and bleeding time, which we should have measured preoperatively.

5. Conclusion

The result of the present study suggests that continuation of AAs may induce major hemorrhagic complications that need interventions after TRUS-guided prostate biopsy. Thus, prostate biopsy is performed without discontinuing AAs, and sufficient attention should be paid to hemorrhagic complications. Besides, we may consider interrupting some antithrombotic agents especially in the cases of concomitant use of both MAPs and ACs.

Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.prnil.2018.06.004.

References

1. Smith NL, Psaty BM, Furberg CD, White R, Lima JA, Newman AB, et al. Temporal trends in the use of anticoagulants among older adults with atrial fibrillation. Arch Intern Med 1999;159:1574–8.
2. Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, Djulbegovic B, et al. Screening for prostate cancer: systematic review and meta-analysis of randomized controlled trials. BMJ 2010;341:c4543.
3. Katanoda K, Hori M, Matsuda T, Shibata A, Nishino Y, Hattori M, et al. An updated report on the trends in cancer incidence and mortality in Japan, 1958–2013. Jpn J Clin Oncol 2015;45(4):390–401.
4. Maan Z, Cutting CW, Patel U, Kerry S, Pietrzak P, Perry MJ, et al. Morbidity of transrectal ultrasonography-guided prostate biopsies in patients after the continued use of low-dose aspirin. BJU Int 2003;91:798–800.
5. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed.: Evidence-based clinical practice guidelines. Chest 2012;141(2 Suppl):e326S–50S.
6. Giannarini G, Mogorovich A, Valent F, Morelli G, De Maria M, Manassero F, et al. Continuing or discontinuing low-dose aspirin before transrectal prostate biopsy: result of a prospective randomized trial. Urology 2007;70:501–5.
7. Carmignani L, Picozzi S, Bozzini G, Negri E, Ricci C, Gaeta M, et al. Transrectal ultrasound-guided prostate biopsies in patients taking aspirin for cardiovascular disease: a meta-analysis. Transfus Apher Sci 2011;45:275–80.
8. Ihezue CU, Smart J, Dewbury KC, Mehta R, Burgess L. Biopsy of prostate guided by transrectal ultrasound: relation between warfarin use and incidence of bleeding complications. Clin Radiol 2005;60:459–63.
9. Raheem OA, Casey RG, Galvin DJ, Manecksha RP, Varadaraj H, McDermott T, et al. Discontinuation of anticoagulant or antiplatelet therapy for transrectal ultrasound-guided prostate biopsies: a single-center experience. Korean J Urol 2012;53:234–9.
10. Culkin DJ, Exaire EJ, Green D, Soloway MS, Gross AJ, Desai MR, et al. Anticoagulation and antiplatelet therapy in urological practice: ICUD/AUA review paper. J Urol 2014;192:1026–34.
11. Ozveren B, Türkeri L. Massive rectal bleeding after prostate biopsy controlled by endoclipping in a patient using acetylsalicylic acid. Can Urol Assoc J 2013;7:E442–4.
12. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol 2005;62:1217–20.
13. Garcia DA, Regan S, Henault LE, Upadhyay A, Baker J, Othman M, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Intern Med 2008;168:63–9.
14. Armstrong MJ, Gronseth G, Anderson DC, Biller J, Cucchiara B, Dafer R, et al. Summary of evidenced-based guideline: periprocedural management of antithrombotic medications in patients with ischemic cerebrovascular disease: report of the guideline development subcommittee of the American Academy of Neurology. Neurology 2013;80(22):2065–9.
15. Gorelick PB. Combining aspirin with oral anticoagulant therapy: is this a safe and effective practice in patients with atrial fibrillation? Stroke 2007;38(5):1652–4.
16. Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. Circulation 2013;127:634–40.
17. Anderson MA, Ben-Menachem T, Gan SI, Appalaneni V, Banerjee S, Cash BD, et al. Guideline: Management of antithrombotic agents for endoscopic procedures. Gastrointest Endosc 2007;70(6):1060–70.