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Research Article

Continuation versus Discontinuation of High and Low Dose Aspirin Prior to Transrectal Ultrasound-Guided Prostate Biopsy: A Comparison of Cardiovascular Morbidity and Duration of Bleeding

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Abstract

Transrectal Ultrasound (TRUS)-guided 12-core prostate biopsy sampling remains the most common utilized technique for diagnosing prostate cancer. There are limited randomized controlled studies assessing the effect of continuing aspirin on bleeding complications post prostate biopsy and none that assess cardiovascular morbidity following prostate biopsy. Our goal is to conduct a randomized controlled trial comparing the severity and duration of bleeding complications between patients continuing or discontinuing low or high dose aspirin therapy, and to assess post-biopsy cardiovascular morbidity in these patients. 65 veterans undergoing TRUS-guided prostate biopsy and on daily aspirin of 81 mg or 325 mg were randomized to continue or hold their aspirin regimen prior to biopsy. There was no significant difference in the mean duration of minor bleeding events in patients who continued their aspirin regimen compared to patients who discontinued their aspirin regimen or in patients who continued low dose aspirin compared to patients who continued high dose aspirin. No short term or long-term cardiovascular events were identified in the groups that discontinued low and high dose aspirin. It is likely prudent to continue 81 mg of aspirin as the risk of post TRUS prostate biopsy bleeding does not outweigh the benefit of cardiovascular protection. It is difficult to strongly conclude that there is no increased risk of bleeding with continuation of 325 mg of aspirin prior to biopsy due to our sample size and exclusion criteria, however this study's recruitment implies that there is only a small subgroup of the general population who are taking 325mg of aspirin.

Keywords: Aspirin; Prostate biopsy; Haematuria; Cardiovascular; High dose; Low dose

Introduction

Transrectal ultrasound (TRUS)-guided 12-core prostate biopsy sampling remains the most common utilized technique for diagnosing prostate cancer [1]. While prostate biopsy is typically well-tolerated, minor complications including pain and bleeding are common [2,3]. A systematic review on prior studies assessing post TRUS-guided prostate biopsy complications showed that the most common complications related to bleeding included haematuria, haematochezia, and hematospermia. It was also found that these bleeding complications are generally considered minor complications and bleeding rates vary based on factors such as prostate volume, number of biopsy cores, biopsy technique, and the use of anticoagulant medication [3,4]. Due to risk of bleeding complications, it has been common practice to discontinue anticoagulant medications, including aspirin, prior to biopsy.

Co-morbid cardiovascular disease is common in the demographic that is at risk for prostate cancer [5]. Anti-platelet medications such as aspirin are widely used as effective agents for secondary prevention of cardiovascular events, reducing the risk of stroke and myocardial infarction by about one-third and the risk of cardiovascular death by one-sixth. Aspirin is also taken widely for primary prevention of myocardial infarction and stroke, despite conflicting evidence on the benefit/risk ratio present in the literature [6]. Thus, a large cohort of males undergoing prostate biopsy utilize aspirin therapy to prevent cardiovascular events.

The literature shows that 52% of radiologists and 27% of urologists instruct their patients to hold aspirin prior to prostate biopsy which supports conflicting data on which patients can safely continue their aspirin in preparation for prostate biopsy [7]. Previous studies have assessed the effect of low-dose aspirin on severity of TRUS-guided prostate biopsy bleeding complications. A meta-analysis of five prospective studies showed that aspirin use only increased the incidence of mild haematuria after TRUS prostate biopsy, but had no significant effect on rectal bleeding, hematospermia, or the incidence of severe haemorrhaging. However, the studies included in the analysis either limited the aspirin-taking cohort to doses of 75 to 150 mg or were not randomized controlled trials [8].

Our goal is to conduct a randomized controlled trial comparing the duration and severity of bleeding complications between patients continuing or discontinuing aspirin therapy of 81 mg or 325 mg as well as looking at post-biopsy cardiovascular morbidity in patients who are on aspirin therapy.

Materials and Methods

Veterans presenting to a single institution that were deemed candidates for TRUS prostate biopsy were screened for study inclusion. Inclusion criteria consisted of males between the ages of 18 to 69 who were scheduled for TRUS prostate biopsy and on daily antiplatelet therapy consisting of either 81mg (low dose) or 325 mg (high dose) of aspirin. All patients received a cardiovascular risk assessment via cardiology electronic consult to ensure that aspirin cessation would not be harmful. Patients were excluded if they were recommended for a saturation prostate biopsy, had concomitant use of other anticoagulant or antiplatelet drugs, or had pre-existing urological or colorectal conditions that increased their risk of haematuria or rectal bleeding. Patients that were excluded from the study underwent standard of care therapy for our institution which is defined as discontinuing aspirin 7 days prior to prostate biopsy.

Patients who met inclusion criteria were consented and randomized in a 1:1 ratio of continuation of current aspirin therapy versus cessation of aspirin therapy. Patients were instructed to either continue or discontinue their aspirin regimen 7 days prior to their prostate biopsy by telephone. They were asked to maintain a medication log to document adherence to the assigned group and instructed to return the medication log to the study coordinator on the day of prostate biopsy. TRUS biopsy was then performed by usual standard of care and patients were sent home with a post procedure survey asking patients to record the dates they experienced haematuria, haematochezia, and hematospermia and to record biopsy associated bleeding leading to hospitalization. Patients returned for follow up approximately 2 weeks following prostate biopsy with the questionnaire. At this 2-week post-biopsy follow up appointment, they were given a second survey to record bleeding events for the next 2 weeks. A follow up appointment with the study coordinator was conducted via telephone at 30 days from prostate biopsy to assess duration of bleeding events based on answers to their survey.

A total of 89 patients who met inclusion criteria were enrolled and randomized to continue their normal aspirin regimen of 81 mg or 325 mg or discontinue their aspirin regimen 7 days prior to undergoing TRUS prostate biopsy. 24 patients were later excluded from data analysis due to noncompliance with assignment, cancelled biopsy, or lost to follow up. Minor bleeding complications were classified as gross haematuria, haematochezia, and hematospermia, whereas severe bleeding complications were classified as biopsy associated bleeding leading to hospitalization. Statistical analysis was performed using Student's T-test to assess for significant differences between the groups. Cardiovascular events were classified as transient ischemic attack, stroke, or myocardial infarction, with short term events occurring within 30 days of biopsy and long-term events occurring after 30 days post biopsy. Chart review was done to assess the incidence of short term and long-term cardiovascular events following the study

and to collect data on the average length of follow up. Data was analyzed with intention to treat.

Results

Data analysis was performed on 65 patients with a mean follow up of 26 months. The mean duration of gross haematuria, haematochezia, and hematospermia in patients continuing their normal aspirin regimen was 6.9 days, 1.8 days, and 3.8 days, respectively. The mean duration of these same minor bleeding complications when discontinuing aspirin therapy was 5.6 days, 2.8 days, and 3.5 days, respectively. There was no significant difference in duration of gross haematuria ($p=0.17$), haematochezia ($p=0.10$), and hematospermia ($p=0.39$) between continued aspirin therapy verses cessation of aspirin therapy groups.

The mean duration of gross haematuria, haematochezia, and hematospermia in patients continuing low dose aspirin was 7.2 days, 1.8 days, 3.7 days, respectively. The mean duration of these same minor bleeding complications in patients continuing high dose aspirin was 2.3 days, 1.3 days, 5.3 days, respectively. When comparing the low dose aspirin group to the high dose aspirin group, there was no significant difference in duration of gross haematuria ($p=0.16$), haematochezia ($p=0.24$), and hematospermia ($p=0.41$). One patient assigned to continue high dose aspirin was hospitalized for severe bleeding complications. This patient's duration of haematuria is not included in the data analysis due noncompliance in completing the survey while hospitalized.

There were no short-term cardiovascular complications after biopsy in patients who discontinued high or low dose aspirin. There was one long-term cardiovascular complication in a patient who continued high dose aspirin, a stroke leading to death at 5 months post-biopsy. This is the same patient who was excluded in data analysis due to incomplete surveys and lost to follow up secondary to being hospitalized for a severe bleeding complication. It is of note that this patient did not restart his anti-platelet therapy after being hospitalized.

Discussion

Holding aspirin for 7 days prior to biopsy is currently common at many institutions. It is thought that holding aspirin for a short period of time to reduce post biopsy bleeding risk outweighs the cardiovascular risk that withholding aspirin imposes, however there have been no studies that specifically look at the cardiovascular morbidity and mortality when holding aspirin prior to TRUS prostate biopsy [9]. The lack of clinical trials on the bleeding risk and cardiovascular risk of holding aspirin prior to TRUS prostate biopsy has resulted in lack of standardization in practice [7]. Safely continuing aspirin prior to TRUS prostate biopsy is important to implement into practice as the risk of cessation of aspirin may have a higher impact on patient morbidity compared to the risk of bleeding complications due to continued aspirin prior to biopsy.

Among our population, the most common minor bleeding complication was found to be haematuria. This is consistent with findings in prior studies in which 65.8% of men who underwent prostate biopsy as a part of the ProtecT study reported haematuria following biopsy [10]. There was no significant difference in the duration of haematuria in patients who continued aspirin therapy compared to patients who held their aspirin 7 days prior to biopsy as found previously through meta-analysis [5,8]. A prior study has shown that the prevalence of rectal bleeding may be higher when more than 6-core biopsies are taken but that the duration of haematuria, hematospermia, and rectal bleeding is not significantly different based on number of core biopsies taken. This study showed that the prevalence of a minor bleeding complications range anywhere from 1.9-80% for haematuria, 10.2-89% for hematospermia, and 1.8-59% for rectal bleeding [11]. This demonstrates that there is likely a factor other than the number of core biopsies that is influencing the prevalence of bleeding, as they did not control for patient specific factors such as if the patient was on antiplatelet therapy.

Our results demonstrate safety in patients undergoing TRUS prostate biopsy who continue low dose aspirin and that it is not necessary to compromise cardiovascular protection by withholding aspirin therapy. This is consistent with prior prospective studies showing that low dose aspirin does not increase the incidence or duration of minor bleeding complications when compared to patients who do not take aspirin [12]. This is especially important given the increased utilization of vascular stenting which benefits from anti-platelet therapy. Another prospective study and clinical trial show that low dose aspirin may increase the duration of self-limiting mild haematuria but does not increase the incidence of haematuria. It was therefore concluded that low dose aspirin is safe to continue when undergoing TRUS prostate biopsy [10,13].

We also demonstrated safety with high dose aspirin therapy of 325 mg. Although not statistically significant, patients who continued high dose 325 mg aspirin were found to have a lower average duration of haematuria compared to patients who continued low dose aspirin. Patients taking high dose aspirin had similar duration of haematochezia and longer duration of hematospermia when compared to patients continuing low dose aspirin. It is important to note that there are no studies that look at the safety of using 325 mg prior to TRUS prostate biopsy based on our literature review. Conclusions comparing bleeding complications in the low dose aspirin group to the high dose aspirin group are limited due to the number of patients enrolled that were taking 325 mg aspirin. There were few patients undergoing prostate biopsy that were prescribed 325 mg of aspirin and that were also able to safely discontinue aspirin

therapy prior to biopsy based on their cardiac risk assessment. This is likely reflective of the general population, demonstrating that there are notably few people undergoing prostate biopsy that are taking 325 mg of aspirin. This statement is further demonstrated by the limited availability of studies on patients on high doses of antiplatelet medication in which the highest dose identified is 150 mg [14]. It is of note that there is a prospective study on patients who underwent TRUS prostate and continued their prescribed warfarin and aspirin regimen. It was concluded that warfarin did not increase the risk of minor bleeding complications following TRUS prostate biopsy and was safe to continue through prostate biopsy [15]. Although our data showed that taking 325 mg prior to prostate biopsy is safe, it is less important to focus on this small subgroup of people when compared to patients taking 81mg of aspirin and who are more likely to be seen in the clinical setting for prostate biopsy.

Not only can asking patients to hold their aspirin for 7 days prior to biopsy be difficult for patients to remember to do and to comply with, but it can also increase the chance of patients forgetting to restart their aspirin post biopsy. Holding aspirin for longer than needed, if even restarted at all, increases cardiovascular events and related morbidity risk. While there were no cardiovascular complications that occurred within the 30-day post biopsy period in patients who held their aspirin for 7 days in the high and low dose group, it is important to note that one patient in the continued high dose aspirin group experienced severe haematuria following biopsy leading to catheter placement and a 2-day hospitalization period for observation. Although the bleeding stopped 12 days post-biopsy, the patient refused to restart his aspirin therapy or start new anticoagulation therapy recommended by his cardiologist out of fear that he would develop haematuria again. 5 months following biopsy, the patient experienced a stroke leading to his death. This further demonstrates the importance of antiplatelet therapy on reducing cardiovascular morbidity and the impact holding therapy may have on patients in the long term if it not properly restarted. Although objective data from this patient's experience may have changed the results on safety of continuing high dose aspirin, the data had to be excluded due to incomplete surveys secondary to hospitalization and eventual loss of follow up.

When looking at the high dose aspirin group, decisions on continuing versus cessation of 325 mg aspirin should likely be made on an individual basis and involve discussions between urology and cardiology providers. The risk of bleeding in patients continuing specifically 325 mg of aspirin has not been previously studied and there is limited data on this group from this study. Data from this study shows that although minor bleeding complications are not significant, there is a possibility that severe bleeding complications may occur with a bigger sample size. The outcomes also show that continuing 325 mg offers cardiovascular protection and stopping regimen increases patient cardiovascular morbidity, and in this study, may have contributed to mortality. Previous studies show that groups that replaced low dose aspirin with low molecular weight heparin prior to biopsy did not have a significant difference in minor bleeding complications when compared to groups that continued low dose aspirin [17]. The incidence of severe bleeding complications when taking low molecular weight heparin must be further studied and could be a potential alternative to cessation of all antiplatelet and anticoagulation therapy in patients at higher cardiovascular risk that are taking high dose aspirin.

Additional limitations found in this study include the limited number of patients enrolled, as 27% of patients who were initially enrolled did not meet criteria to complete the study. The most common reasons for patients not completing the study are that they did not return for 2 weeks visit after their prostate biopsy and lack of adherence to the regimen for their respective randomized group. Out of the three patients who were unable to follow their regimen one within the discontinued 81 mg aspirin group continued their therapy, and one within the continued 81 mg group and the otherwise the continued 325 mg aspirin group discontinued their therapy. Although these patients were not included in final analysis, there was only one patient with known significant bleeding complication as previously outlined. Data was analyzed with intention to treat, and results were not significantly changed when performing data analysis and excluding these patients.

Conclusion

Continuation of aspirin prior to TRUS-guided prostate biopsy does not significantly increase the duration of bleeding in this study's population and instead, potentially has an increased benefit in populations with more severe cardiovascular disease. In accordance with many surgical guidelines, it is likely prudent to continue at least 81 mg of aspirin in the setting of patient's cardiovascular disease as the risk of post TRUS prostate biopsy bleeding does not outweigh the benefit of cardiovascular protection. It is difficult to strongly conclude that there is no increased risk of bleeding with continuation of 325 mg of aspirin prior to biopsy, however this study's recruitment implies that there is only a small subgroup of the general population who are taking 325 mg of aspirin.

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