Aspirin as added prophylaxis for deep vein thrombosis in trauma: A retrospective case-control study

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BACKGROUND: Current prophylaxis does not completely prevent deep vein thrombosis (DVT) in trauma patients. Recent data suggest that platelets may be a major contributor to hypercoagulability after trauma, indicating a potential role for antiplatelet medications in prophylaxis for DVT. We sought to determine if preinjury aspirin use was associated with a reduced incidence of lower extremity DVT in trauma patients.

METHODS: Using a retrospective case-control design, we matched 110 cases of posttrauma lower extremity DVT one-to-one with controls using seven covariates: age, admission date, probability of death, number of DVT risk factors, sex, mechanism of injury, and presence of head injury. Data collected included 26 risk factors for DVT, prehospital medications, and in-hospital prophylaxis. Logistic regression models were created to examine the relationship between prehospital aspirin use and posttrauma DVT.

RESULTS: Preinjury aspirin was used by 7.3% of cases (patients diagnosed with in-hospital DVT) compared with 13.6% of controls ($p = 0.1$). Aspirin was associated with a significant protective effect in multivariate analysis, with an odds ratio of 0.17 (95% confidence interval, 0.04–0.68; $p = 0.012$) in the most complete model. When stratified by other antithrombotic use, aspirin showed a significant effect only when used in combination with heparinoid prophylaxis (odds ratio, 0.35; 95% confidence interval, 0.13–0.93; $p = 0.036$).

CONCLUSION: Preinjury aspirin use seems to significantly lower DVT rate following injury. This association is strongest when heparinoid prophylaxis is prescribed after patients on preinjury aspirin therapy are admitted. Aspirin as added prophylaxis for DVT in trauma patients needs to be further evaluated. (*J Trauma Acute Care Surg.* 2016;80: 625–630. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic and epidemiologic study, level III.

KEY WORDS: Aspirin; deep vein thrombosis; prehospital therapy; prophylaxis; trauma.

Venous thromboembolism (VTE) occurs in up to 58% of trauma patients in the absence of prophylaxis[1] and is associated with increased mortality.[2,3] VTE continues to be a significant source of morbidity despite better recognition, increased screening, and widespread thromboprophylaxis. Patients who receive thromboprophylaxis experience lower rates of deep vein thrombosis (DVT).[4] However, even with combined heparinoid and mechanical prophylaxis, the VTE rate can reach 28%.[5] In addition, 80% of severely injured patients with a VTE event are receiving thromboprophylaxis at the time of diagnosis.[6]

Trauma patients are hypercoagulable following injury, and platelets are thought to play a major role.[7–9] Because platelet function is not directly affected by standard heparin-based prophylaxis, antiplatelet agents might be useful in reducing the DVT rate in this population. Aspirin is used for VTE prophylaxis for elective orthopedic surgery and certain medical indications[10–12] but has not been as thoroughly studied in trauma.

We hypothesized that adult trauma patients admitted on aspirin therapy would have a lower rate of in-hospital lower extremity DVT compared with patients not on aspirin therapy.

PATIENTS AND METHODS

Following approval by the Scripps Office for the Protection of Research Subjects, matched case-control study methodology was used to evaluate the association between prehospital aspirin use and lower extremity DVT in adult trauma patients. Cases and controls were obtained from the VTE surveillance registry, which includes all patients admitted to the Scripps Mercy Hospital Level I trauma center between June 2006 and December 2011. Cases were defined as patients diagnosed with a lower extremity DVT identified by venous duplex ultrasound surveillance. Controls were selected from a population who received at least one venous duplex ultrasound as part of the Scripps Mercy Hospital trauma service DVT surveillance program[13] but showed no evidence of lower extremity DVT. Cases were matched to controls at a one-to-one ratio based on age (±5 years), admission date (±270 days), Trauma Mortality Prediction Model (TMPM) probability of death (±5%),[14] total number of DVT risk factors (±1), sex, mechanism of injury (blunt or penetrating), and presence of head injury. Patients were excluded for the following: (1) admission with a preexisting DVT based on inpatient or outpatient records; (2) in-hospital death, on the basis that deaths constituted a more severely injured population without adequate matches for a case-control study; (3) an inability to be matched to an eligible control; and (4) diagnosis of a pulmonary embolism (PE) owing to the potential for de novo events unrelated to lower extremity DVT.[15–17]

Risk factors for VTE were those previously published by multiple investigators (Table 1).[1,13,18–20] Prophylactic measures included mechanical (foot and/or leg compression pumps) and pharmacologic prophylaxis: unfractionated heparin 5,000 U subcutaneously three times daily (UFH) or low-molecular-weight heparin 30 mg twice daily (LMWH), according to group practice guideline.

Medical records of eligible patients were examined in a blinded fashion for prehospital medications. The primary exposure of interest was defined as prehospital daily aspirin use. Sources included the admission history and physical, medication reconciliation, medical consultations, emergency department record, and outpatient visit notes, which were reviewed to determine antiplatelet therapy use at the time of admission to the trauma service.

Data were managed and analyzed using Stata MP version 13.0 (StataCorp LP, College Station, TX). McNemar's χ^2 test and paired *t* tests were used to evaluate demographic characteristics, risk factors, and all outcomes between cases and controls. Conditional logistic regression was used to evaluate the relationship between each risk factor and case status. Adjusted conditional logistic regression models were iteratively constructed to assess the relationship between aspirin and DVT after sequential addition of relevant risk factors based on $p < 0.1$. Standard logistic regression was used for subanalyses on aspirin use stratified by other prehospital or prophylactic antithrombotic agents. For these analyses, the grouping structure was removed owing to reductions in sample size after stratification. Data were presented as mean (SD), median (25th and 75th interquartile range [IQR]), or proportions, as appropriate. Hospital length of stay

TABLE 1. Patient Characteristics and VTE Risk Factors by Case Status

	Cases	Controls	mOR	95% CI	*p*
Characteristics					
Age at admission, mean (SD), y	51.8 (21.0)	51.5 (21.4)	1.07	0.95–1.20	0.255
Body mass index, median (IQR)	26.0 (22.5–30.0)	25.4 (22.0–28.9)	1.01	0.97–1.04	0.635
ISS, median (IQR)	14 (9–21)	13 (9–21)	1.03	0.99–1.07	0.190
Ventilator time, median (IQR), d	0 (0–3)	0 (0–1)	1.07	1.00–1.14	0.040
TMPM death probability, mean (SD), %	4.8 (5.6)	4.9 (5.6)	0.98	0.85–1.13	0.802
Total risk factor count, mean (SD)	2.7 (1.4)	2.3 (1.4)	3.00	1.76–5.11	<0.001
Hospital length of stay, mean (SD),* h	259.5 (2.7)	169.0 (2.3)	2.32	1.50–3.57	<0.001
Male sex, %	72	72	—	—	1.000
Blunt mechanism of injury, %	91	91	—	—	1.000
Prehospital antithrombotics, %					
Aspirin	7.3	13.6	0.42	0.15–1.18	0.100
Warfarin	7.3	5.5	1.40	0.44–1.41	0.566
Clopidogrel	3.6	0.9	4.00	0.45–35.79	0.215
Risk factors, %					
Total GCS score < 8	7.3	10.9	0.67	0.27–1.63	0.374
Ventilated > 4 d	28.2	11.8	4.60	1.75–12.10	0.002
Required extrication	2.7	2.7	1.00	0.20–4.95	1.000
Lower extremity fracture	24.6	27.3	0.83	0.42–1.65	0.602
Active cancer	4.6	0.9	—	—	1.000
History of cancer	7.3	6.4	1.14	0.41–3.15	0.796
Thrombocytopenia	0.9	0.0	—	—	1.000
History of DVT/PE	10.0	4.6	7.00	0.86–56.89	0.069
PRBC administration > 4 U	9.1	6.4	2.50	0.49–12.89	0.273
Operative time > 2 h	50.9	44.6	1.50	0.76–2.95	0.240
Venous repair	2.7	1.8	2.00	0.18–22.06	0.571
Spine fracture	18.2	20.0	0.88	0.44–1.77	0.724
Pelvic fracture	12.7	10.0	1.30	0.57–2.96	0.533
Spinal cord injury	5.5	5.5	1.00	0.32–3.10	1.000
Presentation in shock	9.1	4.6	3.50	0.73–16.85	0.118
History of congestive heart failure	2.7	6.4	0.43	0.11–1.66	0.220
History of COPD	5.5	6.4	0.80	0.21–2.98	0.739
History of myocardial infarction	2.7	2.7	1.00	0.20–4.95	1.000
Smoking behavior	17.3	22.7	0.68	0.34–1.39	0.292
Obesity	25.5	20.9	1.33	0.68–2.60	0.400
IVC filter placement	24.6	0.9	—	—	<0.001
Central line placement	13.6	5.5	2.80	1.01–7.77	0.048
Prophylaxis measures, %					
LMWH	71.8	57.3	2.00	1.10–3.64	0.024
UFH	17.3	5.5	3.17	1.26–7.93	0.014
Foot compression pumps	16.4	9.1	2.00	0.86–4.67	0.109
Leg compression pumps	91.8	83.6	2.29	0.94–5.56	0.068

*Reported as geometric mean with geometric SD.
COPD, chronic obstructive pulmonary disease; IVC, inferior vena cava; mOR, matched odds ratio; PRBC, packed red blood cells.

was log transformed because of skew and displayed as geometric mean (geometric SD). Associations between exposures and outcomes are shown as matched odds ratios. Statistical significance was attributed to $p < 0.05$ or with 95% confidence intervals (CIs) that do not include a null value (1.00).

RESULTS

We identified 172 cases of patients with posttrauma lower extremity DVT and 1,901 control patients who met the inclusion criteria. Of these, 62 cases (36%) were excluded because a comparable control was nonexistent. In all, 110 matched pairs met all criteria for the study, for a total of 220 patients. Of the 24 patients taking prehospital aspirin, 17 patients were on 81 mg daily, 3 patients were on 325 mg daily, and 4 dosages were unknown.

The characteristics of cases and controls are shown in Table 1. There were no significant differences between cases and controls in age at admission, body mass index, Injury Severity Score (ISS), or Trauma Mortality Prediction Model (TMPM) probability of death. There were differences in total

TABLE 2. Estimates of Association for Prehospital Aspirin Use Adjusted for Relevant Covariates

	Adjusting Risk Factor			Aspirin		
Risk factor	**mOR**	**95% CI**	***p***	**mOR**	**95% CI**	***p***
Total risk factor count	3.15	1.82–5.43	<0.001	0.34	0.11–1.04	0.059
Hospital length of stay	2.35	1.52–3.64	<0.001	0.38	0.12–1.13	0.082
Ventilated > 4 d	5.30	1.95–14.43	0.001	0.31	0.10–0.96	0.043
Central line placement	2.85	1.02–7.99	0.046	0.41	0.14–1.17	0.096
History of DVT/PE	6.36	0.76–53.55	0.089	0.45	0.15–1.36	0.160
IVC filter	—	—	0.992	0.50	0.17–1.46	0.206
Prophylactic LMWH	2.34	1.24–4.43	0.009	0.30	0.10–0.92	0.036
Prophylactic UFH	3.35	1.30–8.60	0.012	0.38	0.13–1.14	0.084
Leg compression pumps	2.05	0.83–5.05	0.121	0.48	0.17–1.40	0.180

IVC, inferior vena cava; mOR, matched odds ratio.

number of risk factors and hospital length of stay. Regarding VTE risk factors, cases had higher rates of mechanical ventilation for more than 4 days, inferior vena cava filter placement, central line placement, LMWH administration, and UFH administration. Cases and controls were largely similar for all 21 other VTE risk factors.

Bivariate associations for prehospital aspirin use and DVT, adjusting for one other relevant factor, revealed that total VTE risk factors, hospital length of stay, mechanical ventilation for more than 4 days, prophylactic LMWH use, prophylactic UFH use, and central line placement were all statistically significantly associated with being a case (Table 2). Adjusted aspirin associations were consistently protective (matched odds ratio < 1.00) in each analysis, although not always statistically significant, with odds ratios ranging between 0.50 (nonsignificant) to 0.30 (significant).

Matched odds ratios for prehospital aspirin use in six iteratively adjusted conditional logistic regression models are shown in Table 3. In Model 1, aspirin use was adjusted for log-transformed hospital length of stay and total count of VTE risk factors and approached significance ($p = 0.051$). In every subsequent model, prehospital aspirin use was significantly associated with being a case and showed protective matched odds ratios of increasing magnitude with the inclusion of each additional and relevant risk factor.

Aspirin use was consistently protective across all strata of other antithrombotic use, although this reached statistical significance only in the subset of patients also receiving heparinoid chemoprophylaxis (Table 4). The magnitude of the protective association for aspirin was stronger in patients given another antithrombotic agent compared with those without the secondary agent. The association between aspirin and DVT could not be estimated for patients on prehospital clopidogrel, owing to low sample size.

DISCUSSION

In this matched case-control study design, we found that aspirin use in trauma patients before injury was associated with lower odds of in-hospital lower extremity DVT. All iterative logistic regression models constructed with relevant risk factors showed aspirin to be a protective factor in matched case-control pairs. This validates our hypothesis that adult trauma patients admitted while taking antiplatelet agents experience lower rates of lower extremity DVT.

Coagulation profile changes in trauma patients have not been shown to predict VTE[21] but do suggest a mechanism for continued hypercoagulable states despite heparin-based prophylaxis. Allen et al.[9] compared thromboelastography (TEG) before and after initiation of thromboprophylaxis in 74 trauma patients, 81% of whom remained hypercoagulable on thromboprophylaxis. Maximum clot formation, as detected by TEG, seemed to be associated with platelet counts. While heparin affects factor Xa primarily, neither LMWH nor UFH directly affects platelet activation, adhesion, or aggregation. Aspirin, by permanently inhibiting prostaglandin H-synthase-1, also known as cyclo-oxygenase-1 (COX-1), decreases aggregation for the lifetime of the platelet.[22] This may represent the gap in current thromboprophylaxis regimens.

Antiplatelet agents as thromboprophylaxis for surgical patients have been well studied in the orthopedic literature. The Anti Platelet Trialists' Collaboration meta-analysis determined that in orthopedic surgery, general surgery, and high-risk medical patients, aspirin monotherapy significantly reduced VTE compared with placebo from 34% to 25%.[23] These results were corroborated in patients undergoing hip operations by a multicenter randomized controlled trial, the Pulmonary Embolism Prevention, which showed a relative reduction in DVT rate of 29% with perioperative aspirin.[24] In comparing aspirin to UFH, LMWH, and warfarin, there seems to be clinical equipoise regarding prophylaxis for orthopedic patients, who can experience DVT rates as high as those of severely injured trauma patients.[12] The current CHEST guidelines for major orthopedic surgery recommend aspirin, heparinoid, direct Xa inhibitor, warfarin, or mechanical prophylaxis over no prophylaxis for a minimum of 10 days to 14 days postoperatively. They include a specific recommendation for LMWH over other medications.[25] Because of the lower bleeding risk seen with aspirin, however, some authors have advocated for aspirin monotherapy in selected patients, such as those undergoing total joint arthroplasty.[26,27] When used in conjunction with heparinoid prophylaxis, aspirin seems to decrease the rate of DVT by

TABLE 3. Association of Aspirin Use and DVT by Model Iteration After Sequential Addition of Covariates

Model	Aspirin mOR	Aspirin 95% CI	*p*
Model 1	0.32	0.10–1.01	0.051
Model 2	0.27	0.08–0.89	0.032
Model 3	0.25	0.07–0.83	0.023
Model 4	0.18	0.05–0.67	0.010
Model 5	0.17	0.05–0.63	0.008
Model 6	0.17	0.04–0.68	0.012

Model 1, aspirin + hospital length of stay + risk factor count.
Model 2, Model 1 + prophylactic LMWH.
Model 3, Model 2 + prophylactic UFH.
Model 4, Model 3 + mechanically ventilated for more than 4 days.
Model 5, Model 4 + central line placement.
Model 6, Model 5 + history of DVT/PE.
mOR, matched odds ratio.

TABLE 4. Aspirin Use and DVT Association Stratified by Other Antithrombotic Use

	Cases, n	Controls, n	Aspirin Use, %	OR	95% CI	*p*
Prehospital medications						
Warfarin	8	6	21.4	0.29	0.02–4.24	0.363
No warfarin	102	104	9.7	0.52	0.20–1.35	0.178
Clopidogrel	4	1	20.0	—	—	—
No clopidogrel	106	109	10.2	0.44	0.17–1.13	0.090
In-hospital prophylaxis						
LMWH or UFH	90	67	12.7	0.35	0.13–0.93	0.036
No LMWH or UFH	20	43	4.8	1.08	0.09–12.65	0.952

approximately 50%, although this figure is compromised by a lack of direct comparison.[23] It should be noted that no pharmacologic prophylaxis is without accompanying risks. Compared with placebo, aspirin is associated with bleeding events requiring transfusion at a rate of three to six events per 1,000 patients.[23,24]

Our study shows an association between aspirin and DVT after trauma. The case-control design was chosen as a consequence of practicality. Few trauma patients are continued on antiplatelet agents in the acute inpatient setting, especially those with head trauma, making a prospective trial problematic. Importantly, the antiplatelet effect of aspirin extends for approximately 4 days after ingestion, well beyond the incident trauma. Bleeding time corrects (although not to baseline) 48 hours after cessation of chronic aspirin use,[28] and platelet aggregometry indicates that global platelet function returns to baseline at 96 hours after the last aspirin dose.[29] While these figures are not the 7 days to 10 days of effect traditionally discussed,[30,31] it is clear that the irreversible inhibition caused by acetylation of platelet COX-1 causes coagulation changes well beyond the time of administration of the most recent dose. This effect would extend the potential protective ability of aspirin through the incident injury and the first days of hospitalization during which hypercoagulability may be at its apex.

The strengths of this study include the number of patients with DVT (110 cases) matched with controls by seven covariates. While the total number of risk factors for DVT formation was predictably higher in cases compared with controls, cases more frequently received both mechanical and chemical prophylaxes. Cases were likely identified correctly by the trauma team as patients at increased risk for DVT, who were therefore more often prescribed prophylaxis. The 26 risk factors collected for analysis represent an inclusive data set for a patient population undergoing surveillance with a standardized venous duplex ultrasound screening protocol to detect in-hospital DVT.[13]

We acknowledge the limitations of our retrospective design, which reduce the generalizability of the results beyond the matched case-control pairs. Removal of the 62 unmatched cases may have minimized the role of some risk factors on DVT risk. The difficulty in matching these patients resulted from the number of criteria used as matched covariates, which increased the quality of the matching at the expense of the quantity of the matches. However, these patients may represent outliers in their total DVT risk, as the included cases and controls were relatively similar after matching. Matching was imperfect given the number of risk factors included in the process. Rather than limit the number of risk factors examined, which would have removed the statistical difference in the risk factor count, we chose to analyze every available recognized risk factor, all of which were then available for multivariate analysis. Reliance on retrospective records review for prehospital medications may have introduced inaccuracies, particularly regarding the use of over-the-counter low-dose aspirin, which some patients may fail to report as a "medication." The most recent dose of aspirin per patient is unknown, but medication lists were cross-referenced among several sources, drawing from both inpatient and outpatient records to achieve the most accurate picture possible. The incidence of aspirin resistance or noncompliance is also unknown in this study, as is the short- and long-term morbidity of the DVTs diagnosed.

While these cases represent a moderately to severely injured population, the risk factors for DVT formation remain incompletely understood. The inclusion of a broad range and number of risk factors serves to better match cases with controls but does not allow for direct translation of the results into clinical practice. Patients with minor injuries or at lower risk for DVT may not significantly benefit from aspirin's effect on DVT formation, although defining any group as low or high risk remains problematic.[32] Nevertheless, aspirin is an inexpensive, oral medication with maximal antiplatelet effect at doses as low as 75 mg and a favorable side effect profile, particularly in short-term use.[33,34] Any protective effect as a prophylactic agent, therefore, would represent a favorable risk-benefit ratio and value. Furthermore, aspirin can readily be continued in the outpatient setting.

Our findings warrant further research into aspirin's effect as a potential thromboprophylactic medication in trauma patients. A prospective trial would allow for more generalizable conclusions. Our findings suggest that such a trial should be designed to compare aspirin in addition to heparinoid and mechanical thromboprophylaxis versus heparinoid and mechanical thromboprophylaxis alone, likely in patients with orthopedic trauma as that population has been studied previously. TEG with platelet mapping would be helpful in determining responsiveness to antiplatelet prophylaxis because it would provide data on platelet mechanics before and after initiation of aspirin. Timing of the initiation of aspirin would ideally fall within 48 hours of injury, as platelets become the dominant contributor to hypercoagulability after this window.[7] Because there are some data suggesting that antiplatelet

medications as a class increase the risk of intracranial hemorrhage progression,[35] initial trials should exclude these patients until aspirin is adequately described in isolation of other anticoagulants and antiplatelet agents.

AUTHORSHIP

J.B.B., R.Y.C., J.D.W., P.R.L., M.J.S., V.B., and S.R.S. designed this study. J.B.B. and R.Y.C. collected and analyzed the data. J.B.B., R.Y.C., J.D.W., P.R.L., M.J.S., V.B., and S.R.S. participated in the data interpretation and manuscript preparation.

DISCLOSURE

The authors declare no conflicts of interest.

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