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Time is now: venous thromboembolism prophylaxis in blunt splenic injury

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Abstract

BACKGROUND: The safety and timing of venous thromboembolism (VTE) prophylaxis in patients with blunt splenic injuries is not well known. We hypothesized that early initiation of VTE prophylaxis does not increase failure of nonoperative management or transfusion requirements in these patients.

METHODS: A retrospective review of trauma patients with blunt splenic injury was performed. Patients were compared based on initiation and timing of VTE prophylaxis (<24 hours, 24 to 48 hours, 48 to 72 hours, and >72 hours). Patients who received VTE prophylaxis were matched with those who did not. Primary outcomes included were operation or angioembolization.

RESULTS: A total of 497 patients (256 received VTE prophylaxis and 241 did not) were included. There was no difference in the number of interventions based on presence of or time to VTE prophylaxis initiation.

CONCLUSIONS: Early initiation (<48 hours) of VTE prophylaxis is safe in patients with blunt splenic injuries treated nonoperatively, and may be safe as early as 24 hours.

Nonoperative management (NOM) has become the standard of care for treatment of hemodynamically stable patients with blunt splenic injuries.[1–4] However, these trauma patients have an increased risk for developing venous thromboembolism (VTE), including the development of pulmonary embolism (PE), which carries an associated mortality rate approaching 20%.[5–7] The rate of VTE also appears to be increasing.[5] Thus the care of NOM patients presents the challenge of balancing the risk for developing VTE with the increased risk of bleeding and failure of NOM from the splenic injury.

The safety and timing of pharmacologic VTE prophylaxis in this population has not been well established. Guidelines from the American College of Chest Physicians and Eastern Association for the Surgery of Trauma recommended early VTE prophylaxis administration in patients with NOM for blunt solid organ injury but did not reach consensus in addressing the time for initiation.[8,9]

We hypothesized that early initiation (within 48 hours of admission) of VTE prophylaxis does not increase failure of NOM in patients with blunt splenic injuries, including bleeding complications, transfusion requirements, or the need for operative or radiologic interventions.

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Methods

A retrospective study was performed at Community Regional Medical Center in Fresno, California, an ACS-verified level I trauma center. Patients with blunt splenic injury were identified from the trauma registry from July 2007 to December 2015. Exclusion criteria included patients with brain injuries, those less than 13 years of age, undergoing immediate operative intervention, discharged less than 24 hours from arrival, died, or were transferred to another facility within 48 hours of arrival. The trauma registry and medical records were reviewed for demographic data, injury severity score (ISS), grade of splenic injury, ICU, and hospital lengths of stay, splenic interventions (angioembolization, splenectomy, and splenorrhaphy), units of blood transfused, and details of VTE prophylaxis (chemical/mechanical, type/dosage of chemical propylaxis, time initiated and discontinued, and reason for discontinuation). All patients that had angiography underwent embolization of the spleen (with gelfoam, coils or both). The American Association for the Surgery of Trauma organ injury scale was used to classify splenic injury grade. Grades I and II injuries were defined as low grade, grade III as intermediate, and grades IV and V as high-grade splenic injuries.[10] Our trauma service guidelines for management of splenic injuries include immediate operative intervention for patients with hemodynamic instability, angioembolization for extravasation/contrast blush seen on computer tomography scan, and nonoperative management followed with serial hemoglobins for the remaining patients. Decisions regarding immediate intervention vs nonoperative management were made at the discretion of the trauma attending at the time of admission.

Patients were categorized into 2 groups, patients that received VTE prophylaxis and patients that did not. Patients initially managed nonoperatively, and then underwent any intervention including operative or angioembolization, before initiation of VTE prophylaxis, were included in the no VTE prophylaxis group. For sub-analysis of the group receiving VTE prophylaxis, patients were separated into 4 groups by time of initiation of VTE prophylaxis: immediate ($<$24 hours of hospital arrival), early (24 to 28 hours), intermediate (48 to 72 hours), and late ($\geq$72 hours). Enoxaparin 30 mg subcutaneously every 12 hours is used at our institution for VTE prophylaxis in trauma patients and 40 mg subcutaneously daily in general surgery patients. For patients with renal insufficiency, heparin 5000 units subcutaneously every 8 hours was given. The timing of initiation of VTE prophylaxis was left to the attending trauma surgeon's discretion. VTE complications, including PE and deep venous thrombosis (DVT), were identified by computer tomography pulmonary angiography or ultrasound of the extremities. These studies were ordered at the discretion of the attending trauma surgeon in patients with high clinical suspicion for PE and/or DVT.

For those patients who did not receive VTE prophylaxis, failure was defined as the need for splenic angioembolization or any splenic operation, including partial or total splenectomy. Indications for intervention were dropping hemoglobin or hemodynamic instability. In patients receiving VTE prophylaxis, failure of splenic management was broadened to include discontinuation of VTE prophylaxis for dropping hemoglobin, the use of splenic angioembolization, or any splenic operation, including partial or total splenectomy and splenorrhaphy. Patients on VTE prophylaxis after angioembolizaion failed if a splenectomy/splenorrhaphy was subsequently performed for dropping hemoglobin or hemodynamic instability.

Propensity score matching was used to examine treatment failure between patients receiving VTE prophylaxis and those who did not. Age, ISS, and grade of splenic injury were used to match patients 1:1, without replacement, using the nearest neighbor algorithm. Eberley et al[11] reported an NOM failure of 7% in patients with splenic injuries who did not receive VTE prophylaxis. Using this, we conducted a sample size calculation and found that approximately 250 patients in each group would allow us the identification of an 8% difference in failure rates between the 2 groups and 165 patients in each group would allow identification of a 10% difference in failure rates with 80% power.

Continuous variables are reported as mean $\pm$ standard deviation, ordinal data are presented as mean (interquartile range), and categorical data are reported as percentages. Overall continuous data were analyzed using Mann Whitney U and Kruskall-Wallis tests. Matched continuous data were analyzed with Wilcoxon signed-rank tests. Chi-square tests were used to examine categorical data. Significance was attributed to a P value less than .05. Statistics were performed using the Statistical Package for Social Sciences (SPSS version 23.0; IBM Corporation, Armonk, NY). This study was approved by the Institutional Review Board of the University of California San Francisco, Fresno and Community Medical Centers.

Results

During the study period, 21,979 trauma patients were admitted to Community Regional Medical Center, including 18,758 as a result of blunt trauma. Nine hundred thirty-five patients had a splenic injury. Patients were excluded due to brain injury (180), immediate operative intervention (134), death/discharge less than 24 hours (78), transfer in less than 48 hours (7), and age less than 13 (39). Of the remaining 497 patients constituting the study population, 256 received VTE prophylaxis, whereas 241 did not (Fig. 1).

Patients receiving VTE prophylaxis were compared with those who did not. The two groups differed by age, ISS, and spleen grade (Table 1). Reflecting the higher median ISS

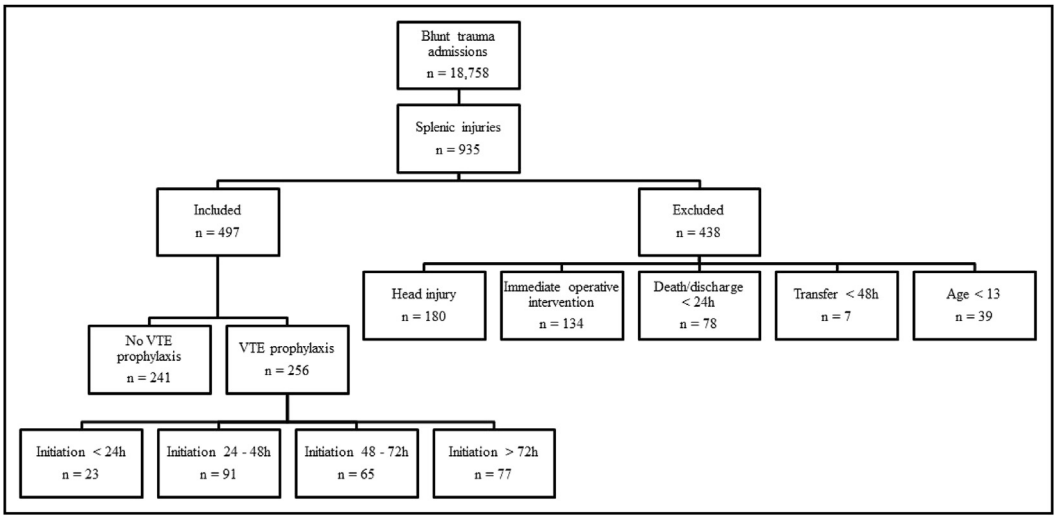

Figure 1 Patient selection. VTE = venous thromboembolism.

(19), patients who received VTE prophylaxis had longer ICU and hospital lengths of stay. Comparison of the failure rate between patients receiving VTE prophylaxis and those receiving none demonstrated that the rate of angioembolization and operative intervention were the same. The failure of nonoperative management was 5% overall.

A total of 7 patients received angioembolizations and 11 required operative interventions in the group with no VTE prophylaxis. All 7 angioembolizations were performed as a result of decreasing hemoglobin. Over half of these (57%, 4/7) failed within 48 hours of admission. Ten patients underwent operative intervention for bleeding and one for splenic infarction. Eight of the patients undergoing intervention were later started on VTE prophylaxis. In the group that did receive VTE prophylaxis, 11 patients had angioembolizations and 15 underwent operative interventions. In all cases, angioembolization was performed for a decrease in hemoglobin with two-thirds (64%, 7/11) failing within 48 hours of admission. In the 15 patients who underwent operative intervention, 7 operations were performed for decreasing hemoglobins and 8 for splenic infarction after angioembolization. The patient with no VTE prophylaxis required a splenectomy, for infarction, 158 days after splenic angioembolization. In the group with VTE prophylaxis, 75% (6/8) underwent splenectomies, for infarction, within 10 days of angioembolizaion. Splenic infarction is not a complication associated with VTE prophylaxis; therefore, these patients were not included in the VTE failure group.

Table 1 Baseline characteristics and outcomes of patients who received VTE prophylaxis vs those who did not

	No prophylaxis	VTE prophylaxis	*P* value
N	241	256	
Age	35 ± 18	40 ± 17	.003
Male sex	164 (68%)	160 (63%)	.20
ISS	14 (9–20)	19 (14–29)	<.001*
Splenic injury grade			
1	52 (22%)	80 (31%)	.015*
2	79 (33%)	93 (36%)	.41
3	66 (27%)	53 (21%)	.081
4	36 (15%)	22 (9%)	.028*
5	8 (3%)	8 (3%)	.90
ICU LOS (days)	0 ± 2	5 ± 11	<.001*
Hospital LOS (days)	4 ± 4	13 ± 14	<.001*
Angioembolization	7 (3%)	11 (4%)	.41
Operative intervention	10 (4%)	7 (3%)	.39
Discontinued VTE prophylaxis	-	3 (1%)	-

ICU = intensive care unit; ISS = injury severity score; LOS = length of stay; VTE = venous thromboembolism.
*Statistical significance attributed to a *P* value less than .05.

Demographics were similar among all groups when compared for time of initiation of VTE prophylaxis; however, grade V splenic injuries were only found in the intermediate and late VTE prophylaxis groups. There were no differences in failure of splenic management between the 4 groups (Table 2). Seventy percent (174/256) of the patients who received VTE prophylaxis were started on enoxaparin 30 mg subcutaneously every 12 hours, 21% (54/256) on enoxaparin 40 mg subcutaneously every 24 hours, and 9% (22/256) on heparin 5000 units subcutaneously every 8 hours.

Overall, the thromboembolic complication rate was 2% in patients receiving chemical VTE prophylaxis. Four patients were diagnosed with a PE and 1 patient with an upper extremity DVT while on VTE prophylaxis. Of the 4 patients with PE, 1 was in the immediate VTE prophylaxis group, 2 in the early group, and 1 in the intermediate group. The patient with the upper extremity DVT had VTE prophylaxis started greater than 72 hours from time of admission.

Table 2 Comparison of outcomes based on time of initiation of VTE prophylaxis

	Immediate (<24h)	Early (24–48h)	Intermediate (48–72h)	Late (>72h)	*P* value
N	23	91	65	77	
Splenic injury grade					
1	8 (35%)	29 (32%)	18 (28%)	25 (32%)	.90
2	12 (52%)	29 (32%)	25 (38%)	27 (35%)	.33
3	3 (13%)	22 (24%)	9 (14%)	19 (25%)	.25
4	0	11 (12%)	7 (11%)	4 (5%)	.17
5	0	0	6 (9%)	2 (3%)	.008*
Blood products received (units)	1 ± 2	0 ± 1	1 ± 1	1 ± 1	.28
Angioembolization	1 (4%)	4 (4%)	2 (3%)	5 (6%)	.81
Operative intervention	1 (4%)	2 (2%)	2 (3%)	2 (3%)	.95
Discontinued VTE prophylaxis	0	2 (2%)	0	1 (1%)	.60
ICU LOS (d)	5 ± 11	2 ± 5	7 ± 13	8 ± 14	.03*
Hospital LOS (d)	13 ± 15	8 ± 6	14 ± 15	17 ± 17	<.001*

ICU = intensive care unit; LOS = length of stay; VTE = venous thromboembolism.
*Statistical significance attributed to a *P* value less than .05.

Case matching of patients for no VTE prophylaxis vs VTE prophylaxis for age, ISS, and splenic injury grade resulted in 165 patients in each group. Patients receiving VTE prophylaxis had longer hospital lengths of stay, but there were no differences in the number of patients requiring embolization or operative intervention (Table 3).

Comments

VTE prophylaxis is an important component of care of the multiply injured trauma patient. Initiation of VTE prophylaxis represents a fine balance between the risk of ongoing bleeding and the prevention of VTE and subsequent PE in patients with blunt solid organ injuries.

Table 3 Propensity-matched comparison of patients who received VTE prophylaxis versus those who received none. Patients were matched on age, ISS, and splenic injury grade

	No prophylaxis	VTE prophylaxis	*P* value
N	165	165	
Age	38 ± 18	39 ± 17	.99
Male sex	112 (68%)	102 (62%)	.25
ISS	17 (10–22)	17 (13–22)	.25
Spleen grade			
1	44 (27%)	49 (30%)	.54
2	58 (35%)	61 (37%)	.73
3	40 (24%)	38 (23%)	.80
4	17 (10%)	12 (7%)	.33
5	6 (4%)	5 (3%)	.76
ICU LOS (d)	1 ± 2	1 ± 2	.094
Hospital LOS (d)	5 ± 5	7 ± 7	<.001*
Angioembolization	4 (2%)	7 (4%)	.54
Operative intervention	8 (5%)	4 (2%)	.24

ICU = intensive care unit; ISS = injury severity score; LOS = length of stay; VTE = venous thromboembolism.
*Statistical significance attributed to a *P* value less than .05.

As NOM in blunt solid organ injuries has become the standard of care, questions regarding safety have arisen including appropriate length of hospitalization, the role of angioembolization, and timing of VTE prophylaxis. There have been only a few studies looking at timing of initiation of VTE prophylaxis in patients with blunt solid organ injuries (including splenic injuries). One of the earliest studies, and the only study to examine the timing of VTE prophylaxis, looked at 188 patients with blunt splenic injuries comparing early administration (≤48 hours) to late administration (>48 hours).[12] The NOM failure rate was comparable between the 2 groups, (4% vs 6%) and the authors recommended initiating VTE prophylaxis within 48 hours of admission. Several more recent studies looking at safety and timing of VTE prophylaxis in all blunt solid organ injuries, including splenic injuries, came to similar conclusions. In a study of patients undergoing NOM of blunt solid organ injury which included only 154 patients with splenic injuries, Eberle et al[11] advocated initiation of VTE prophylaxis within 72 hours while Joseph et al[13] recommended an earlier initiation of less than 48 hours. Both studies were limited by small sample size. The Denver group (2013) looked at 42 patients and determined through the use of thromboelastography that the transition to hypercoagulable state appears to occur at approximately 48 hours in patients with blunt solid organ injuries therefore they recommended initiation of VTE prophylaxis within 48 hours.[14] Our study, which has the largest matched cohort group of any published report, and includes a group with initiation of VTE in less than 24 hours, showed comparable results. In the present study, there was no difference in rates of angioembolization, operative interventions, or blood transfusion requirements between the immediate, early, intermediate, or late groups.

Age greater than 31, ISS greater than 15, and ICU length of stay have been identified as risk factors for VTE complications in trauma patients.[15,16] Although slightly less than 50% of this present study group received

chemoprophylaxis and had variable dosing, the patients that did receive VTE prophylaxis in our study were older (40 years), had a higher median ISS (19), and longer ICU and hospital stay. Despite the fact that those patients receiving immediate VTE prophylaxis had lower grade splenic injuries, we found no difference in rate of angioembolization or operative intervention between the group with VTE prophylaxis compared with the group without VTE prophylaxis. This supports the safety of VTE prophylaxis, even in high-grade splenic lacerations.

Our study is limited by the inherent bias of a retrospective study; however, this is the largest retrospective study and matched cohort population looking at the safety of VTE prophylaxis. Previous studies have examined the timing of initiation of VTE beginning at 48 hours[12–14,17]; our study is thus far the only study that has evaluated the safety of immediate initiation of VTE prophylaxis in patients with blunt splenic injury.

Conclusion

Early initiation of VTE prophylaxis, within 48 hours of hospital arrival, is safe in patients with blunt splenic injuries treated nonoperatively and may be safe as early as 24 hours. In the multiply injured trauma patient with blunt splenic injury, early initiation of VTE prophylaxis should be considered. A prospective, protocol-based study evaluating the early initiation of VTE prophylaxis in high-grade blunt splenic injury would serve to strengthen the findings of the present study.

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Discussion

Discussant

Dr. Justin Regner (Temple, TX): Thank you very much for sending your manuscript in a timely fashion. It was a wonderful paper and a wonderful presentation. I really appreciated it.

Overall, I really want to believe your data, and that's the truth. I do have a few issues and a few questions. I think your goal was to determine that it's equally safe to begin deep venous thrombosis (DVT) prophylaxis in patients at risk of bleeding before 48 hours. In your analysis, you divided your patients up into 4 separate groups. Ultimately, this is a noninferiority study, and we're talking about rates of bleeding somewhere around the 5% range and your venous thromboembolism (VTE) rates, as quoted in your paper, are around the 2% range. Those are fairly small numbers for your data set to conclude. My bias would have been for you to divide your groups up into a less than 48 hours and a greater than 48 hours and then maybe your study would be appropriately powered to come to your conclusion.

Number 2, no VTE prophylaxis group was determined—basically, you all didn't start prophylaxis on that group; is that correct or incorrect?

Dr. Amy Kwok (Fresno, CA): Correct.

Dr. Justin Regner (Temple, TX): Without knowing your system's protocol for how you evaluate grade 3 and grade 4 splenic injury patients, that is, what is your regimen for angiography or CTA to restudy these patients, it inserts

a significant selection bias into that particular patient population that makes them seem like they have worse outcomes than your VTE group.

My third comment is, at this time, I think understanding the etiology of VTE in trauma patients is pretty poor. I think it's fairly aggressive to start anticoagulation within 24 hours. I'm not convinced we have good data unless you're using a TEG to determine if this patient is hypercoagulable to initiate your anticoagulation. Just starting it at 24 hours seems, I don't know, cavalier maybe.

Ultimately, my questions are, number one, do you feel your study is adequately powered to come to the conclusions? And if not, how can we help you achieve that?

Number two, what time frame did your nonoperative failures occur? With that, what was the etiology of the failure? Was it a pseudoaneurysm? Was it an AV fistula? I highly doubt those 2 etiologies would be affected by a DVT prophylaxis.

Finally, is there a test or criteria that we should use to determine who should be initiated on DVT prophylaxis within the first 24 hours?

Dr. Amy Kwok (Fresno, CA): Thank you, Dr. Regner. I really appreciate your thoughtful comments and questions and your courtesy and graciousness for allowing me to review these questions in advance.

In response to your first question, do you feel your study is appropriately powered and how can we improve it, Eberley et al[11] from USC in 2011, reported a nonoperative management failure of 7% in patients with splenic injuries who did not receive VTE prophylaxis. Using this, we conducted a sample size calculation and found that approximately 250 patients would allow us to identify an 8% difference between the 2 groups. And 165 patients would allow us to identify a 10% difference with 80% power. Therefore, our overall analysis and match cohorts were sufficiently powered to identify these differences.

Unfortunately, for the comparison of timing, there were a limited number of patients in the group less than 24 hours, which is a limitation of our retrospective design.

Thank you for your comment regarding comparing groups with initiation greater or less than 48 hours. This would be beneficial in improving the power of the study, but I don't believe it would change our conclusion.

We acknowledge the inherent bias that comes with a retrospective study. To our knowledge, this is the biggest retrospective study looking at VTE prophylaxis safety in blunt splenic injuries. With the strength in numbers of the data, we're looking to support and encourage further prospective trials looking at this issue.

For question 2, what time frame did the nonoperative failures occur, we had a total of 7 angioembolizations and 11 operative interventions in the group with no VTE prophylaxis. All 7 angioembolizations were performed for a drop in hemoglobin. Fifty-seven percent, or 4 of the 7, failed within 48 hours. Nine of the 10 patients' operative interventions were performed for bleeding with one for splenic infarction.

In the group that did receive VTE prophylaxis, 11 angioembolizations and 15 operative interventions were identified. All 11 patients underwent angioembolization for dropping hemoglobin with 64% failing within 48 hours. Fifteen patients underwent operative intervention, 7 for bleeding, and 8 for splenic infarction after embolization.

We appreciate your comments suggesting that not all interventions would be a result of increased bleeding from VTE prophylaxis. Removing those with infarction would lower our operative intervention rate in the group receiving VTE prophylaxis. So our overall conclusion would remain the same. We will reevaluate and address this in our manuscript.

Finally, what test criteria should we use to safely begin early VTE prophylaxis? Although we had no formal protocol for initiation of VTE prophylaxis, we used 3 stable hemoglobin levels drawn every 6 hours from time of admission as criteria for initiating VTE prophylaxis in our trauma patients.

The idea for using TEG to determine timing of VTE prophylaxis is intriguing. The Denver group in 2013 looked at 42 patients and determined that the transition to hypercoagulable state occurs at approximately 48 hours in patients with blunt solid organ injuries, and they recommend initiation of VTE prophylaxis before 48 hours. I believe the use of TEG may be an important tool in determining initiation of VTE prophylaxis, and future prospective studies could help better elucidate the exact timing for VTE prophylaxis.