

Research Article

What is the Appropriate Time for Initiation of Thromboprophylaxis Therapy in Visceral Injury Secondary to Blunt Abdominal Trauma: A Systematic Review

Gala T¹, Shahzad N², Mathur P³ and Zafar H^{4*}¹Specialist Registrar, Aga Khan University Hospital, Pakistan and Royal Free London NHS Foundation Trust, UK²Instructor General Surgery, Aga Khan University Hospital, Pakistan³Consultant Surgeon, Royal Free London NHS Foundation Trust, UK⁴Consultant Trauma Surgeon, Aga Khan University Hospital, Pakistan***Corresponding author:** Hasnain Zafar, Department of Surgery, Link Building, Aga Khan University Hospital, Stadium Road, Karachi, Pakistan**Received:** September 05, 2017; **Accepted:** September 28, 2017; **Published:** October 05, 2017**Abstract**

Background: Abdominal solid organ (splenic, renal and hepatic) injuries are the most common injury patterns in patients with blunt trauma. Non-operative management (NOM) is the current standard of care for managing hemodynamically stable patients with blunt visceral injuries. Management of such patients is challenging due to the fear of failure of NOM and reluctance to start Venous Thromboembolism (VTE) prophylaxis early in the course of management.

Objective: To determine the ideal timing of thromboprophylaxis initiation and its effects on NOM of patients with blunt visceral trauma.

Materials and Methods: We searched Pubmed, CINAHL and Cochrane databases from January 2001- July 2017.

- Inclusion Criteria: Studies conducted on adult patients (age > 18 years) with blunt abdominal visceral injury (hepatic, splenic and/orrenal) managed non-operatively who received thromboprophylaxis with timing of initiation mentioned.
- Exclusion Criteria: Studies reported in languages other than English and Unpublished literature.

Data was collected by two independent reviewers. In case of discrepancy, a third reviewer was involved.

Results: From the available literature thromboprophylaxis has not shown to increase failure of NOM when given within 48 hours. However it was also observed that delay in initiation of thromboembolic prophylaxis can potentially lead to increased thromboembolic complications.

Conclusion: We recommend that venous thromboprophylaxis should be started within 48 hours post admission in trauma patients with blunt visceral injuries.

Keywords: Systematic review; Thromboprophylaxis; Non-operative management (NOM); Visceral injuries; Blunt trauma

Introduction

Blunt traumatic injuries account for more than 80% of all trauma-related hospital admissions. Abdominal solid organs (i.e. splenic, renal and hepatic) injuries are the most common injury patterns in patients with blunt trauma [1]. Non-operative management (NOM) is the current standard of care for managing hemodynamically stable patients with blunt visceral injuries [2-4]. Patients sustaining multisystem trauma are at increased risk of venous thromboembolism (VTE). The reported incidence of thromboembolism in trauma patients has increased in recent years; with incidence rising from 0.4% upto 50% [5]. Although Deep Vein Thrombosis (DVT) itself is not life threatening, its association with pulmonary embolism carries a high mortality with rates reported as high as 50% [6].

The American College of Chest Physicians recommends early

initiation of venous thromboembolic prophylaxis to reduce the incidence of thromboembolic complications in patients with multisystem trauma [7]. This has also been supported by the Eastern Association for Surgery of Trauma for solid visceral injury [8]. Managing these patients is quite a challenge. The fear of failure of non-operative management which can have dreadful consequences due to hemorrhage, has on many instances resulted in withholding early thromboprophylaxis. This failure of NOM may require multiple blood transfusions and interventions in the form of angio-embolization and surgery. On the other hand withholding early initiation of thromboprophylaxis can lead to thromboembolic complications. In trauma patients there is Level I evidence to support initiation of DVT prophylaxis with low molecular weight Heparin as soon as resuscitation is completed and the bleeding risk is acceptable [1]. However, the ideal timing of thrombo-prophylaxis

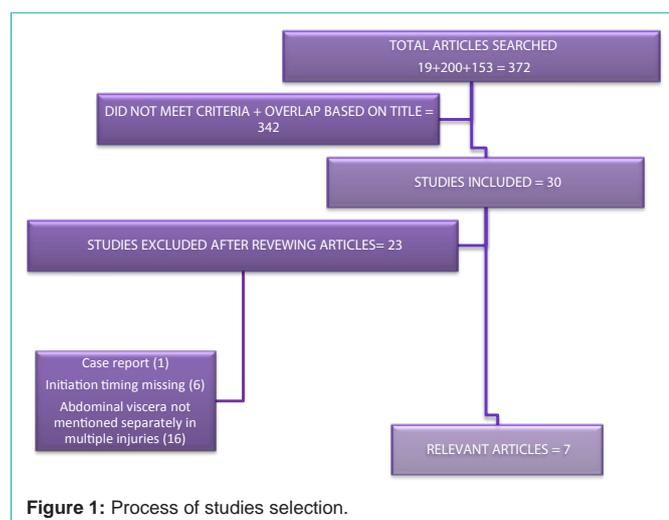


Figure 1: Process of studies selection.

administration in patients sustaining solid abdominal organ injuries remains highly controversial. Little data exists regarding the failure rates of the non-operative management (NOM) in patients with solid abdominal organ injuries who receive thrombo-prophylaxis.

Objective

To determine the appropriate time for initiation of thromboprophylaxis in adult patients with visceral injuries secondary to blunt abdominal trauma.

Materials and Methods

This systematic review was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9].

Eligibility criteria

- Inclusion Criteria: Studies conducted on adult patients (age > 18 years) with blunt abdominal visceral injury (hepatic, splenic and/or renal) managed non-operatively who received thromboprophylaxis with timing of initiation mentioned. Studies between January 2001 and July 2017 were included.
- Of Exclusion Criteria: Studies reported in languages other than English and Unpublished literature.

Information sources

PubMed, CINAHL and Cochrane databases were used.

Outcomes of interest

Search strategy and study eligibility: The search strategy was developed by an iterative process in consultation with a medical librarian. Studies were eligible to be included in the review if they were reviews, Systematic reviews, Randomized controlled trials, case control and cohort studies.

Two reviewers (TG and NS) carried out independent comprehensive systematic literature searches in the above mentioned data-bases. Search terms were selected to identify patient population, intervention and outcomes of interest which were as follows.

Patient population of interest was those patients who had solid visceral injury after blunt abdominal trauma. We identified “blunt”,

“non-penetrating”, “trauma”, “abdom*”, “viscera”, “splenic”, “splenic”, “hepatic”, “renal”, “renal”, “urogenital”, “urolog*”, “Wounds”, “Nonpenetrating”, “abdominal injuries”, “laceration” and “injure*” as terms to look for studies of our interest.

To identify articles that looked into thromboprophylaxis and time to start the therapy, terms “Heparin”, “fondaparinux”, “Enoxaparin”, “LMWH” were used.

And for outcomes of interest, we identified terms “emboli*”, “hemorrhag*”, “bleeding”, “operation”, “operative”, “surgical”, “surgery”, “failure”, “conservative” to look for relevant articles.

These three groups of terms were used to search for articles related to patient population, intervention outcome of interest. All the articles that came out after combined search of terms in included data bases were considered for inclusion in meta-analysis. Duplicates in identified articles through different database searches were identified and excluded. Relevant articles were identified through initial screening of titles. Further scrutiny was done by reading abstracts and final inclusion was decided after full manuscript reviews. References of included articles were also searched to identify further relevant articles. Final inclusion into systematic review was done by consensus of both reviewers. In case of conflict, opinion of third reviewer (HZ) was sought.

Study Selection, Data Extraction and Quality Assessment

The search strategy generated 200 articles. Upon screening of titles, those that did not meet the criteria or had overlap between electronic searches left us with 30 potentially relevant articles. These were further independently reviewed by two reviewers in either abstract or full text as needed to assess eligibility for inclusion. In case of discrepancy, a third reviewer was involved. Disagreements were resolved by discussion and consensus amongst the three reviewers. Seven articles were selected for inclusion in the systematic review. The process of selection can be seen in Figure 1. A specifically designed data extraction form was used to extract data. Extracted data included study characteristics, characteristics of the patient population, severity of visceral injury, drug used and time of initiation, outcomes reported such as need for angioembolization or surgery and thrombo-embolic events.

Characteristics of the studies examined included comparability of the study groups, method used to select study participants, type of drug and its dose used, time of initiation of the drug, ascertainment of outcome variables, follow-up, and analysis and control for potential confounding factors. Each reviewer independently categorized each study as “low risk of bias” (no criterion was judged as poor); “medium risk of bias” (no more than one criterion was judged as poor or unclear); and “high risk of bias” (if two or more criteria were judged as poor or unclear). Disagreements regarding the data extracted were resolved by discussion and with input from a third reviewer.

Results

Studies selected

Table 1 provides the details of the seven studies included. All were observational cohort studies including 6 retrospective and 1 prospective studies. Sample size in these studies varied from 114 to

Table 1: Details of studies included.

Author	Journal	Study design	Country	Target population	Definition of early administration of thromboprophylaxis
Joseph et al. 2015	The American Journal of Surgery	Matched retrospective cohort	Arizona, Usa	Blunt solid abdominal injury (spleen, liver, kidney)	<48 hours
Rostas et al. 2015	The American Journal of Surgery	Retrospective chart review	Alabama, Usa	Blunt liver and/or spleen injury	<48 hours
Eberle et al. 2011	Journal of Trauma	Retrospective study	Los Angeles, Usa	Blunt solid abdominal injury (spleen, liver, kidney)	<72 hours
Norwood et al. 2001	Journal of American College of Surgeons	Prospective single cohort observational study	Texas, Usa	Blunt trauma patients (abdominal along with orthopaedic and neurosurgical injuries)	<24 hours
Khatsilouskaya et al. 2016	World Journal of Surgery	Retrospective study	Switzerland	Blunt trauma patients (abdominal along with orthopaedic and hollow viscus injuries)	<72 hours
Alejandro et al. 2003	American Surgeon	Retrospective study	Puertorico, Usa	Blunt splenic injuries	<48 hours
Murphy et al. 2015	Canadian Journal of Surgery	Retrospective study	Canada	Blunt solid abdominal injury (spleen, liver, kidney)	<48 hours

Table 2: Shows definition of failure of Non-Operative Management for each study.

Author	Definition of early group
Joseph et al. (2015)	Surgical Intervention
Rostas et al. (2015)	Surgical or Radiological (Angioembolization) Intervention
Eberle et al. (2011)	Surgical Intervention
Norwood et al. (2001)	Surgical Intervention
Khatsilouskaya et al. (2016)	Surgical or Radiological (Angioembolization) Intervention
Alejandro et al. (2003)	Surgical Intervention

328 patients. All studies were conducted at dedicated trauma centers.

Quality of included studies

The methodological quality of the studies was variable, with all rated as medium to high risk of bias, primarily because the time of initiation of thromboprophylaxis was at the discretion of surgeon and could have been dictated by severity of injury. None of the studies had a protocol. Potential confounding factors were consistently addressed in the studies, with exception of one study that matched the population to control for confounding factors.

Study characteristics

Population and timing of initiation of thromboprophylaxis:

Table 1 shows the heterogeneity in population studied in all seven studies. Most of them studied patients with blunt hepatic and splenic injuries, however the slight differences between studies are shown in the table. Except Norwood et al all studies had an early and a late group with respect to initiation of thromboprophylaxis. However, for each study the definition of early was different which is also shown in Table 1.

Failure of NOM (Non-operative Management)

There was again heterogeneity found amongst studies regarding what qualified for failure of Non-operative management. Table 2 shows the differences of criteria for failure of non-operative management for each one of them; however, surgical intervention seemed to be the most popular criteria.

Except for *Norwood et al.* [1] which did not have a comparison group, the rest of the studies reported failure in early and late groups each. The results for failure of NOM were again variable in studies; however, this could be attributed to the different definitions of failure for each one of them. These results are shown in Table 3. Some of

the studies also looked at failure rates according to solid organ injury and this is showed in Table 4. It can be seen that patients with splenic injury failed NOM more than those with hepatic and renal injuries. Failure of NOM is feared greater in high grade visceral injuries. To address that, a few studies also looked at failure rates according to grade of organ injury. This is shown in Table 5. It is not surprising that failure rates were found to be higher in early group in most of the studies; however this was not statistically significant.

Thromboembolic events

With holding thromboprophylaxis due to fear of failure of NOM can lead to dreadful consequences like deep venous thrombosis or pulmonary embolism. Table 3 shows thromboembolic events occurring in either group across various studies. Statistically insignificant but a trend of increase incidence is observed in groups who were initiated on thromboprophylaxis late.

Mortality

Mortalities reported by Khatsilouskaya et al. [15], Norwood et al. [1] and Murphy et al. [12] were unrelated to hemorrhagic complications. While *Joseph et al.* [11] reported no mortality in any of the groups and Alejandro et al. [14] reported 2% mortality in early and 1.5% in late group. According to Eberle et al. [10] the mortality rate for patients who underwent NOM was 3.2% however, it was 5.9% amongst those who failed NOM.

To summarise the findings from all the above studies with relevance to our outcomes of interest

Joseph et al. [11] (<48 hours): Early Enoxaparin based anticoagulation is a safe option in trauma patients with blunt solid organ injury. This also was a retrospective review but had a matched cohort to control for confounding factors. However, the sample size was small to address the question and study had no protocol about initiation of thromboprophylaxis. There was no routine screening for VTE.

Rostas et al. [13] (<48 hours): Early use of prophylactic low molecular weight Heparin does not appear to increase non-operative management failure rates. This study has similar limitations of any retrospective analysis. The guidelines for VTE prophylaxis changed during the period of study and therefore the dose of LMWH was variable. Initiation timing was at discretion of the attending physician which was likely to be influenced by the grade of injury. Also routine screening for VTE was not performed.

Table 3: Failure of Non Operative Management and Occurrence of Venous Thromboembolic Complications.

Authors	Failure of Non-Operative Management			p-value	Venous Thromboembolism		No thromboprophylaxis group n(%)	p-value
	Early n(%)	Late n(%)	Failure before starting Thromboprophylaxis n(%)		Early n(%)	Late n(%)		
Joseph et al.	0	0	-	-	0	2 (3.4)		0.3
Rostas et al.	0.0 (0.0)	0.0 (0.0)	13 (3.7)	-	1 (0.6)	5 (2.8)		-
Eberle et al.	3.0 (7.3)	5.0 (7.1)	9 (4.5)	0.621	0	2 (1.3)		-
Norwood et al.	2.0 (9)	-	-	-	2 (2)	-		-
Murphy et al.	0	0	3(4)	0.6	2 (1.9)	0		0.2
alejandros et al.	2(4)	2(3.2)	2(3.2)	0.59	-	-		-
khatsilous et al.	1(3.2)	2(1.3)	4(10.8)	0.043	1(1.3)	3(4.8)	4(10.8)	0.066

Table 4: Failure of non operative management based on different solid viscera.

Authors	Organ	Failure of Non-Operative Management		
		Early n(%)	Late n(%)	Failure before starting Thromboprophylaxis n(%)
	Spleen			
Joseph et al.		0	0	
Rostas et al.		0	0	
Eberle et al.		9.1	8.6	7.2
Norwood et al.		16.7		
Murphy et al.		0	0	
Alejandro et al.		4	3.1	
Khatsilous et al.		3.2	1.3	10.8
	Liver			
Joseph et al.		0	0	
Rostas et al.		0	0	
Eberle et al.		5.6	2.8	1.1
Norwood et al.		0	0	
Murphy et al.		0	0	
Alejandro et al.		0	0	
Khatsilous et al.		0	0	
	Kidney			
Eberle et al.		0	5.9	2.4

Eberle et al. [10] (<72 hours): Early use of thromboprophylaxis does not seem to increase failure rates or blood transfusion requirements. This was a retrospective review.

In blunt trauma patients undergoing non-operative management, the severity of the solid abdominal organ injuries alone seemed to play a secondary role in timing of initiation of low molecular weight Heparin administration as this was at the discretion of the surgeon. In these patients, the early use of thromboprophylaxis does not seem to increase failure rates or blood transfusion requirements.

Norwood et al. [1] (<24 hours): Enoxaparin is a practical and effective method for reducing the incidence of venous thromboembolic complications in high risk, seriously injured patients. The number of patients with hepatic and splenic injuries studied is too small to draw any meaningful conclusions.

Table 5: Failure of non operative management based on grade of injury of solid viscera.

Authors	Organ	Grade	Failure of Non-Operative Management		
			Early n(%)	Late n(%)	Failure before starting Thromboprophylaxis n(%)
Joseph et al.	-	-	-	-	
Rostas et al.	-	-	-	-	
Eberle et al.	Spleen	High	18.2	14.3	15.2
	Liver	High	10	4.8	0
	Renal	High	0	14.3	4.2
Norwood et al.			16.7		
Murphy et al.	-	-	-	-	
Alejandro et al.	-	-	-	-	
Khatsilous et al.	Spleen	High	16	29	50

Alejandro et al. [14] (< 48 hours): Early use of low molecular weight Heparin does not increase failure rate of non-operative management in patients with blunt splenic injuries. The patients in either group were demographically not different and the population was uniform as it only studied patients with splenic injuries. The retrospective nature of this study poses some limitation along with selection bias by the attending physicians when determining the time for administration of LMWH.

Khatsilouskaya et al. [15] (<72 hours): Early chemical VTE prophylaxis with LMWH in patients with blunt solid abdominal visceral injury in the absence of significant head injury showed no difference in NOM failure. This study included a relatively large sample size and homogenous patient population, namely patients with blunt abdominal injury but without significant head injuries. However, the limitations were that it was a retrospective study and lacked controlled protocol for administration of thromboprophylaxis. While patients were similar in age, sex and injury scores there was a significant difference in the percentage of high grade splenic injuries, which could be a confounding factor leading to reluctance to initiate chemical VTE prophylaxis in that particular subset of patients leading to a selection bias that was unlikely to be overcome by using a large sample size.

The event rate for failure of NOM and VTE was low and represents an important limitation. Also patients were not routinely screened for

VTE which possibly could be under reported as only symptomatic patients were scanned.

The strengths of our study is that it is the first systematic review addressing this important topic.

However the limitation is that meta-analysis was not possible as the studies did not have a uniform study design. Also the numbers were small and quality of literature was low.

Discussion

Hypercoagulable state of hospitalized post trauma patients is known to result in thromboembolic complications including mortality due to massive pulmonary embolism [16,17]. Despite this known risk, fear of bleeding in patients having solid visceral injury being managed non-operatively frequently stops the treating physician from giving any form of anticoagulant prophylaxis to reduce this inherent risk at least early in the course of their management. Present systematic review has demonstrated that early start of chemical thromboprophylaxis in these patients is not associated with increased risk of bleeding and thromboembolic complications risk is also reduced. However, many questions such as dose and agent to be used, how early is early and does organ and grade of injury matter remain unanswered.

Literature suggests low molecular weight heparin to be superior to unfractionated heparin so far as therapeutic effect is concerned [18,19]. But in case of trauma patients at high risk of bleeding unfractionated heparin is preferred due to short half-life and reversibility of effect with protamine as antidote [20,21].

Initial 48 hours after blunt trauma are crucial for patients with solid visceral injury as it has been seen that risk of bleeding after that time is reduced significantly [22], but at the same time, this is the time when hypercoagulability can be problem [23]. In order to gain maximum benefit from starting chemical thromboprophylaxis this time window is probably the appropriate point to start it.

Though there is scant literature for grade of injury to various solid organs, caution is advised for high grade injury patients especially splenic lacerations where failure of non-operative management is higher than hepatic and renal lacerations [24,25].

Though this is the best evidence available to date, retrospective nature of most of studies along with non-uniform definitions of intervention and outcome warrant further research in this field.

Conclusion

From the available literature, thromboprophylaxis has not shown to increase failure of non-operative management when given within 48 hours. However it was also observed that delay in initiation of thromboembolic prophylaxis can potentially lead to increased thromboembolic complications. Common limitation of these studies has been that delayed initiation of thromboprophylaxis was common in patients with more severe injuries, particularly high grade visceral trauma (Grade 3 and above) which itself is a known risk factor for thromboembolic events.

Recommendations

Due to consistency of early thromboembolic prophylaxis being

safe, it can be suggested that it can safely be started early (up to 48 hours) in trauma patients with blunt visceral injuries.

References

- Norwood SH, Mc Auley CE, Berne JD, Vallina VL, Kerns DB, Graham TW, et al. A potentially expanded role for enoxaparin in preventing venous thromboembolism in high risk blunt trauma patients. *Journal of the American College of Surgeons*. 2001; 192: 161-167.
- Stassen NA, Bhullar I, Cheng JD, Crandall M, Friese R, Guillaumondegui O, et al. Nonoperative management of blunt hepatic injury: an Eastern Association for the Surgery of Trauma practice management guideline. *Journal of Trauma and Acute Care Surgery*. 2012; 73: S288-S293.
- Stassen NA, Bhullar I, Cheng JD, Crandall ML, Friese RS, Guillaumondegui OD, et al. Selective nonoperative management of blunt splenic injury: an Eastern Association for the Surgery of Trauma practice management guideline. *Journal of Trauma and Acute Care Surgery*. 2012; 73: S294-S300.
- Holevar M, Ebert J, Luchette F, Nagy K, Sheridan R, Spinak J, et al. Practice management guidelines for the management of genitourinary trauma. Eastern Association for the Surgery of Trauma (EAST), Winston-Salem (NC). 2004.
- Knudson MM, Ikossi DG. Venous thromboembolism after trauma. *Current opinion in critical care*. 2004; 10: 539-548.
- Barrera LM, Perel P, Ker K, Cirocchi R, Farinella E, Morales Uribe CH. Thromboprophylaxis for trauma patients. *The Cochrane Library*. 2013.
- Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2008; 133: 110S-112S.
- Rogers FB, Cipolle MD, Velmahos G, Rozycki G, Luchette FA. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group. *Journal of Trauma and Acute Care Surgery*. 2002; 53: 142-164.
- Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery*. 2010; 8: 336-341.
- Eberle BM, Schnüriger B, Inaba K, Cestero R, Kobayashi L, Barmparas G, et al. Thromboembolic prophylaxis with low-molecular-weight heparin in patients with blunt solid abdominal organ injuries undergoing nonoperative management: current practice and outcomes. *Journal of Trauma and Acute Care Surgery*. 2011; 70: 141-147.
- Joseph B, Pandit V, Harrison C, Lubin D, Kulvatunyou N, Zangbar B, et al. Early thromboembolic prophylaxis in patients with blunt solid abdominal organ injuries undergoing nonoperative management: is it safe? *The American Journal of Surgery*. 2015; 209: 194-198.
- Murphy PB, Sothilingam N, Stewart TC, Batey B, Moffat B, Gray DK, et al. Very early initiation of chemical venous thromboembolism prophylaxis after blunt solid organ injury is safe. *Canadian Journal of Surgery*. 2016; 59: 118-122.
- Rostas JW, Manley J, Gonzalez RP, Brevard SB, Ahmed N, Froitan MA, et al. The safety of low molecular-weight heparin after blunt hepatic and splenic injuries. *The American Journal of Surgery*. 2015; 210: 31-34.
- Alejandro KV, Acosta JA, Rodriguez PA. Bleeding manifestations after early use of low-molecular-weight heparins in blunt splenic injuries. *The American surgeon*. 2003; 69: 1006-1009.
- Khatsilouskaya T, Haltmeier T, Cathomas M, Eberle B, Candinas D, Schnüriger B. Thromboembolic Prophylaxis with Heparin in Patients with Blunt Solid Organ Injuries Undergoing Non-operative Treatment. *World journal of surgery*. 2017; 41: 1193-1200.
- Park MS, Owen BA, Ballinger BA, Sarr MG, Schiller HJ, Zietlow SP, et al. Quantification of hypercoagulable state after blunt trauma: microparticle and thrombin generation are increased relative to injury severity, while standard markers are not. *Surgery*. 2012; 151: 831-836.
- Knudson MM, Collins JA, Goodman SB, McCrory DW. Thromboembolism following multiple trauma. *Journal of Trauma and Acute Care Surgery*. 1992; 32: 2-11.

18. Jacobs BN, Cain-Nielsen AH, Jakubus JL, Mikhail JN, Fath JJ, Regenbogen SE, et al. Unfractionated heparin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in trauma. *Journal of Trauma and Acute Care Surgery*. 2017; 83: 151-158.
19. Benjamin E, Recinos G, Aiolfi A, Inaba K, Demetriades D. Pharmacological Thromboembolic Prophylaxis in Traumatic Brain Injuries: Low Molecular Weight Heparin Is Superior to Unfractionated Heparin. *Annals of Surgery*. 2017; 266: 463-469.
20. Olson EJ, Bandle J, Calvo RY, Shackford SR, Dunne CE, Van Gent J-M, et al. Heparin versus enoxaparin for prevention of venous thromboembolism after trauma: A randomized noninferiority trial. *Journal of Trauma and Acute Care Surgery*. 2015; 79: 961-969.
21. Baglin T, Barrowcliffe T, Cohen A, Greaves M. Guidelines on the use and monitoring of heparin. *British journal of haematology*. 2006; 133: 19-34.
22. Wallis A, Kelly MD, Jones L. Angiography and embolisation for solid abdominal organ injury in adults-a current perspective. *World Journal of Emergency Surgery*. 2010; 5: 18.
23. Schreiber MA, Differding J, Thorborg P, Mayberry JC, Mullins RJ. Hypercoagulability is most prevalent early after injury and in female patients. *Journal of Trauma and Acute Care Surgery*. 2005; 58: 475-481.
24. Linnaus ME, Langlais CS, Garcia NM, Alder AC, Eubanks III JW, Maxson RT, et al. Failure of nonoperative management of pediatric blunt hepatic and splenic injuries: A prospective Arizona-Texas-Oklahoma-Memphis-Arkansas Consortium study. *Journal of Trauma and Acute Care Surgery*. 2017; 82: 672-679.
25. Tugnoli G, Bianchi E, Biscardi A, Coniglio C, Iseri S, Simonetti L, et al. Nonoperative management of blunt splenic injury in adults: there is (still) a long way to go. The results of the Bologna-Maggiore Hospital trauma center experience and development of a clinical algorithm. *Surgery today*. 2015; 45: 1210-1217.