Spinal Cord (2019) 57:890–896
https://doi.org/10.1038/s41393-019-0293-1

ARTICLE

Comparison of two pharmacological prophylaxis strategies for venous thromboembolism in spinal cord injury patients: a retrospective study

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Received: 10 February 2019 / Revised: 1 May 2019 / Accepted: 3 May 2019 / Published online: 17 May 2019

Abstract

Study design Retrospective cohort study.

Objective To compare the cost and incidence of venous thromboembolism (VTE) and bleeding between two different VTE pharmacological prophylaxis strategies in individuals with spinal cord injury: one based on motor impairment (Protocol 1) and the other based on time from the lesion and presence of associated risk factors for VTE (Protocol 2).

Setting A tertiary rehabilitation hospital in Brazil.

Methods We retrospectively reviewed a total of 1475 charts of individual admissions: 814 individuals received pharmacological prophylaxis according to Protocol 1 and 661 according to protocol 2. These cohorts were compared with respect to age, time and level of injury, length of stay, AIS classification, type of injury, and occurrence of VTE and major bleeding. The number of prescribed doses of enoxaparin and expenditures associated with enoxaparin during each period were evaluated.

Results The median lesion time was 3 years. The risk-based strategy drastically reduced the average monthly use of enoxaparin by 75% and the 12-month enoxaparin expenditure by $119,930.33, without increasing the risk of VTE. The incidence density of thromboembolic events was 0.55/10,000 patient-days, and all events occurred in individuals receiving prophylaxis according to Protocol 1.

Conclusions Time from injury and risk of VTE-based protocol for indication of pharmacological prophylaxis drastically reduced costs. No difference in occurrence of VTE was observed.

Introduction

Spinal cord injury (SCI) is associated with both motor and sensory neurological dysfunctions. Motor impairment may lead to mobility restriction, especially during its acute phase and prior to a multidisciplinary rehabilitation program [1, 2].

Previous observational studies have identified an increased risk of venous thromboembolism (VTE) following acute SCI [3–5]. This may not only be associated with movement restriction but also with the acute inflammatory response to trauma, the presence of malignant diseases in non-traumatic cases, or flaccid paralysis associated with spinal cord shock syndrome [6, 7]. As a result of the dysregulation of the autonomic nervous system, there may be alterations in the hemostatic and fibrinolytic systems [8], elevated platelet responsiveness to collagen, and changes in ratios of coagulation factors (such as factor VIII) [6].

Current evidence agrees that VTE prophylaxis should be initiated as soon as possible in acute SCI, if feasible, with pharmacological strategies. The duration of prophylaxis has not yet been established. Suggested strategies vary from pharmacological prophylaxis for 12 weeks up to 6 months to screening for asymptomatic lower limb thrombosis with compression ultrasonography for internal patients [9, 10]. The risk of developing VTE decreases after the acute phase but may still be higher than in the general population

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Table 1 Pharmacological prophylaxis indication criteria

Acute lesion[a]	Indicated for all individuals without active bleeding or other contraindications
Chronic lesion	Indicated for all individuals without active bleeding or other contraindications AND at least one of the following risk factors: - 65 years-old or older - Active cancer - Any previous VTE history - Active systemic infection[b] - BMI > 30 kg m^{-2} - Surgery requiring immobilization for 3 or more days

BMI body mass index

[a]Less than 12 weeks in paraplegia patients OR less than 14 weeks in individuals with tetraplegia

[b]Based on clinical signs of systemic inflammatory response syndrome

[11, 12]. Guidelines for thromboprophylaxis during rehabilitation of the subacute (3 to 6 months) and chronic (more than 6 months) phases of SCI remain unclear and decision making may rely solely on clinical expertise and local service experience [9, 13].

In 2014, the SCI rehabilitation unit in the Rehabilitation Hospital of Brasília (SARAH) promoted a review of its VTE prophylaxis protocol for SCI patients. Here, we report a comparison between the historical cohort and a cohort of patients submitted to this new protocol based on time from lesion and risk factors for VTE.

Methods

VTE protocols

Patients admitted to the SCI rehabilitation unit at SARAH until May 2014 had their VTE risk defined based upon motor impairment. All patients who could not perform any sort of functional gait, regardless of the date of injury and in the absence of clinical contraindications, received a subcutaneous prophylactic dose of 40 mg enoxaparin daily (Protocol 1). Following a critical appraisal of the current guidelines, a new protocol was developed and implemented (Protocol 2) in which risk stratification was based on temporal interval, level of injury, and risk factors for VTE. The rationale for this new protocol was the impression that Protocol 1 overestimated the risk of VTE, leading to an overtreatment of patients with pharmacological prophylaxis, therefore exposing them to an unnecessary elevated risk of bleeding. According to Protocol 2, patients with acute injury received pharmacological prophylaxis for up to 12 weeks, and patients with subacute injury (3 to 6 months) or chronic injury (more than 6 months) [14] received prophylaxis in the presence of one or more risk factors (Table 1) for as long as the risk factor was present or until hospital discharge.

This new protocol was implemented in June 2014. Physicians were trained in the evaluation of risk according to the new risk criteria. Nurses were trained on the new protocol, checking each patient's prescription and risk during hospitalization to assure protocol compliance, and inspecting each patient's legs twice daily for clinical signs that may raise suspicions of deep vein thrombosis (DVT). No screening method for VTE was used, since current guidelines advise against this strategy [9, 10] and studies have shown that lower limb thrombi found via screening may not evolve into a clinically relevant situation [15]. A diagnosis of VTE was confirmed based on clinical suspicion in association with imaging results (duplex scan for DVT and computerized tomographic pulmonary angiography for pulmonary embolism [PE]). A 3-month period was granted for staff adaptation to the new standards of care.

Patient selection

Data for all consecutive patients admitted to the SCI unit for inpatient rehabilitation from 1 April 2013 to 31 August 2015 were extracted from the Electronic Chart Database (Prontuário eletrônico Version 5.7.3.6—SARAH Network of Rehabilitation Hospitals). Each individual chart was reviewed and information regarding age, gender, level, date, cause of injury, Asia Impairment Score (AIS) for traumatic lesions [16], date of hospital admission and discharge, weight, height, performance of surgical procedures during hospitalization, and occurrence of major bleeding or VTE was recorded.

Patients without spinal cord or cauda equina injury were excluded from the analysis. When hospitalization during both periods was identified, only the first admission was considered for analysis. There was no case where missing data implied exclusion from the study. Hospital death registries were reviewed and no deaths were reported in this unit during the study period. The registries of all the duplex scans and computed tomography pulmonary angiograms performed during the study period were cross-checked with the SCI patient dataset to search for any cases of DVT or PE that were not identified upon patient electronic chart review, but none were found.

Patients were divided into two groups according to the different VTE prophylaxis protocols to which they were

exposed. The first group received prophylaxis according to Protocol 1 (admissions from 1 April 2013 to 31 May 2014) and the second group according to Protocol 2 (admissions from 1 September 2014 to 31 August 2015). We opted to compare these two periods as there are no marked seasons in central Brazil and to assure that the unit staffing was the same. Both periods include major national holidays and vacation season. The period from 1 June 2014 to 31 August 2014 was used for training and implementing the new protocol; hence, it was not included in the analysis.

Since all data were assessed retrospectively and no intervention was performed, the institution's research ethics committee approved the exemption of informed consent.

Outcomes

The primary outcome, defined a priori, was the occurrence of a new episode of clinical DVT or PE based on clinical signs and symptoms and a positive duplex scan for DVT or a positive computed tomography pulmonary angiogram for PE. The secondary outcome was the occurrence of major bleeding according to the definition of Schulman and colleagues [17]. Incidences were reported as incidence density.

The mean monthly enoxaparin use during the two periods was compared and a cost analysis was performed based on the enoxaparin dose expenditure. Accordingly, the pharmacy registries of the doses that were dispensed for the SCI unit were checked. Since a reduction in the mean enoxaparin administration was estimated, which would naturally lead to a reduction in mean variance, an *F*-test was chosen to analyze the variances of enoxaparin use; a lower variance suggests a more homogenous pattern of enoxaparin prescription.

Statistical analysis

The Shapiro−Wilk test was used to assess the normality of the data. Data that were normally distributed were reported as the mean ± standard deviation, and data with a non-normal distribution are reported as the median and interquartile range. Student's *t*-test and the Mann−Whitney *U*-test were used for central tendency depending on the normality of the variable's distribution. Fisher's exact test was used for comparison of proportions. All tests were performed using the open license software R (R Developing Core Team, version 3.4).

Results

A total of 1763 admissions were identified (Fig. 1) and 288 were excluded (283 second admissions and five non-SCI patients). A total of 1475 individual charts were selected for review: 814 received VTE prophylaxis according to Protocol 1 and 661 according to Protocol 2. Patient characteristics are shown in Table 2.

Most patients were male (74.4%), and most lesions were due to trauma (80.3%). The median time from lesion was 3 years (interquartile range: 1–8), the majority of the patients had a chronic SCI (90% in Protocol 1 and 87% in Protocol 2). No patient had active cancer. One occurrence of DVT and two major bleeding events were identified.

Table 3 shows the characteristics of patients according to the period of admission. Median age, level of injury, cause of the lesion, and AIS category were similar between both groups. The median time from lesion and length of stay differed in both groups. All outcomes (DVT and bleeding) occurred during the first period, but no statistically significant difference between the periods was found. Bleeding occurred in two patients with a chronic traumatic thoracic level of injury, and DVT was found in one individual with subacute traumatic cervical spine injury. The calculated incidence density for DVT and bleeding during the first period were 0.55/10,000 patient-days (95% CI: 0.0–3.0) and 1.10/10,000 patient-days (95% CI: 0–4.0), respectively.

Mean enoxaparin consumption decreased by 73.25%, from 1098 to 293 units per month ($p < 0.0001$). The *F*-test, with 11 degrees of freedom, showed a statistically significant difference between the variances (*F*-statistic 0.352, $p = 0.049$), indicating a more homogenous use of enoxaparin throughout Protocol 2 as compared with Protocol 1. The 12-month expenditure on enoxaparin decreased from $172,137.23 in Protocol 1 to $52,206.90 in Protocol 2.

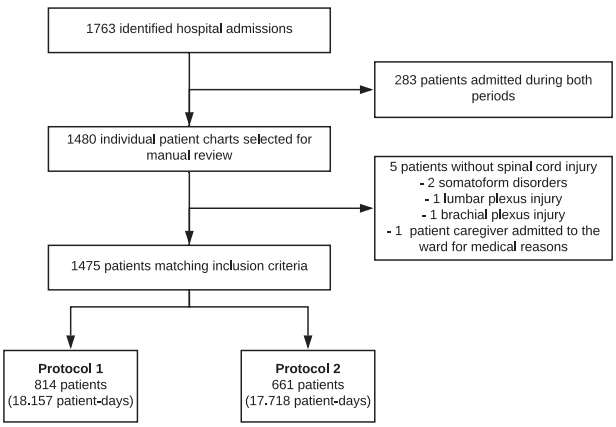

Fig. 1 Patient flow chart

Table 2 Patient characteristics

	Median	Interquartile range
Age (years)	33.9	26.3–44.2
Injury time (years)	3.1	1.0–8.4
Length of hospital stay (days)	18	5–29
Height (cm)	170	163–176
Weight (kg)	65.2	55.5–75.8
Body mass index	22.9	19.8–25.9
Gender	*n*	%
Male	1098	74%
Female	377	26%
Cause of lesion		
Traumatic	1184	80%
Motor complete	741	63%
Incomplete	442	37%
Non-traumatic	291	19,7%
Injury type		
Paraplegia	959	65%
Tetraplegia	516	35%

Discussion

Acute traumatic SCI is considered one of the main risk factors for the development of VTE [11, 18]. There is a general agreement in current guidelines on the importance of pharmacological prophylaxis during the acute phase [9, 10], but its duration has not yet been well established. The American College of Chest Physicians (ACCP) guidelines make no specific recommendation regarding when to stop anticoagulants but suggests that at least 3 months is a reasonable period (GRADE 2C) [10]. The current Paralyzed Veterans of America (PVA) guidelines suggest that the duration should be at least 8 weeks (GRADE 1C) [9] instead of its previous recommendation of up to 14 weeks [19], reflecting uncertainty in this area. The vague recommendations on duration of thromboprophylaxis reflects the fact that, to our knowledge, no trial has compared different treatment durations [9, 10, 20].

Current published data on the incidence of VTE during the subacute (3 to 6 months) and chronic (more than 6 months) phases of SCI are conflicting. But overall, even though the risk diminishes after the first 3 months of SCI, it still remains higher than in the average population [11, 12, 14, 21, 22]. A study including SCI patients admitted for rehabilitation in Italy reported an incidence of 34.3 VTE events/100 patients-year in the first 3 months of follow-up, and after that of 0.3 VTE events/100 patient-years [23]. Chung and colleagues found a DVT incidence of 8.99 cases/10,000 patient-years and a PE incidence of 3.24 cases/10,000 patient-years in a Taiwanese cohort study including both in- and outpatients with SCI. The risk of VTE in patients with SCI remained higher than that in individuals without SCI, even 8 years after the SCI [12]. A systematic review by Alabed and colleagues of seven papers reported a PE incidence ranging from 0.5% to 6.0% and a DVT incidence between 2.0 and 8.0% in the subacute phase; however, the thromboprophylaxis strategies used in those studies were varied and poorly reported [24]. Eichinger and colleagues reported a 2% probability of developing VTE after 6 months of rehabilitation [25]. A cross-sectional study on chronic SCI patients admitted for inpatient rehabilitation in Poland found DVT in 8% of the surveyed patients, one of which had a 4-year cervical injury [13].

The ACCP guidelines make no recommendation in favor or against prophylaxis for individuals with subacute or chronic SCI [10]. The PVA guidelines suggest that either low-molecular weight heparin (LMWH), vitamin K antagonists, or direct oral anticoagulants could be used for prophylaxis following the acute phase (GRADE 2C) and recommends that individuals with chronic SCI who are readmitted for clinical or surgical reasons receive thromboprophylaxis during the period of increased risk (GRADE 1C), without making any recommendation regarding how this risk should be estimated [9]. Published data suggest that risk factors for VTE in individuals with SCI may include

Table 3 Patient characteristics according to the study period

	Protocol type		*p*-value
	1	2	
Age (years)[a]	33.6 (26–43.6)	43 (26.4–45)	0.653
Injury time (years)[a]	3.4 (1.1–8.5)	2.6 (0.9–8.2)	0.035
Acute	19	24	
Subacute	65	61	0.219
Chronic	730	576	
Length of stay (days)[a]	17 (4–30)	20 (8–29)	0.046
Height (cm)[a]	170 (163–176)	170 (162–176)	0.567
Weight (kg)[a]	65.2 (55.4–75.2)	65.1 (55.7–76.3)	0.503
Body mass index ($kg\,m^{-2}$)[a]	22.8 (19.6–25.7)	22.9 (20.0–26.3)	0.182
BMI < 30 $kg\,m^{-2}$	747	598	0.334
BMI > 30 $kg\,m^{-2}$	67	64	
Gender			
Male	606	492	1.000
Female	208	169	
Lesion type			
Paraplegia	511	446	0.062
Tetraplegia	303	215	
Cause of lesion			
Traumatic	652	532	1.000
Non-traumatic	162	129	
AIS classification			
Motor complete	396	345	0.173
Incomplete	255	187	
VTE			
	0.55/10,000 patient-days	0.0/10,000 patient-days	RR 0.0
	(95% CI: 0.0–3.0)	(95% CI: 0.0–2.0)	(95% CI: 0.0–40.0)
Major bleeding			
	1.1/10,000 patient-days	0.0/10,000 patient-days	RR 0.0
	(95% CI: 0.0–4.0)	(95% CI: 0.0–2.0)	(95% CI: 0.0–5.5)

[a]Data are shown as the median and interquartile range

previous VTE [23], elevated D-dimer upon admission [25], completeness of motor paralysis [20, 26], cervical or thoracic spine injury [11, 12], and increasing age [12]. Clements and colleagues also reported an association between VTE and increased weight, length of stay, and delayed admission to the spinal cord service [26], situations that may be more frequent in patients treated in poor resource settings [27]. The absence of specific recommendations and standardization leads to heterogeneous strategies in different centers, which are mainly based on local experience and routines [13, 25]. Furthermore, clinical prediction rules, such as the PADUA and GENEVA scores, have not been validated for SCI individuals [28]. In this scenario, it is of major importance that units involved in the care of SCI patients develop clear thromboprophylaxis strategies and audit its results to continually improve the quality of care [9, 29].

The adoption of protocols with adequate training of multidisciplinary teams appears to improve healthcare outcomes, as demonstrated in a study performed in acute stroke units in Australia [30]. In the present study, the adoption of a thromboprophylaxis protocol drastically reduced the prescription and consequently the costs related to LMWH without increasing the occurrence of VTE. The cost reduction evaluation was based only on the expenditure reductions for enoxaparin, but it is possible that a greater reduction exists when considering costs for storage, dispensing, and disposal of biomedical waste. Administration of enoxaparin doses may also be time-consuming for nursing staff, especially considering a large rehabilitation ward.

The average monthly prescribed doses became less variant, suggesting that patients were receiving a more homogenous treatment, which may be related to the involvement of nursing staff and training of both medical personnel and paramedics. Stronger adherence to evidence-based treatment protocols may be related to better and safer patient care. In comparison with other published papers, a lower incidence density of DVT and no PE or death events were found in the present study. It is reasonable to suggest that this low event rate is related to the chronicity of the SCI lesion in our cohort patients, which may be related to delayed access to rehabilitation services in a poor resource setting as well as the continental dimensions of Brazil. Due to the retrospective nature of this study, underreporting may also have influenced this low event rate. To avoid this bias, we have also reviewed and cross-checked all the death registries and all the registries from duplex scans and computed tomography pulmonary angiograms performed during the study period. No screening method besides leg inspection was used, which may have led to reduced sensitivity also contributing to the low incidence found. It was also not possible to track every prescribed dose and check adherence from staff to the protocols, and risk factors identified by the medical staff may have been underreported on patients' charts. As both medical and paramedical staff received training on Protocol 2 and a 3- month period was provided for adaption, this risk of bias may have been reduced. Detecting DVT based on clinical signs may be challenging in this population, as individuals with SCI may present with lower limb edema from other etiologies, such as postural edema. Nevertheless, guidelines advise against a screening strategy with imaging methods [9]. This low event rate may have influenced the incidence difference between the two periods; nevertheless, the majority of studies have reported a lower VTE incidence during both subacute and chronic phases in comparison with the acute phase. The reported incidence of bleeding in SCI patients receiving prophylactic doses of LMWH is between 2.6 and 4.1% [22, 31]; therefore, a lenient pharmacological prophylaxis prescription strategy may expose patients to unnecessary or even harmful treatment based on overestimation of VTE risk [32]. Moreover, individuals with SCI are frequently exposed to polypharmacy, which may interact with anticoagulants, further enhancing the risk of adverse events [33].

To the best of our knowledge, this is the largest cohort study comparing different strategies of pharmacological

prophylaxis for thromboembolism in individuals with subacute and chronic SCI. There were statistical differences in patient characteristics between the two groups, which may have imbalanced the VTE risk during the studied periods. Such imbalance may occur in a cohort study and be influenced by the fact that some admissions were excluded from the analysis, since the patient was admitted during both periods. In our service, the first admission usually lasts longer than the subsequent admissions, and individuals with tetraplegia are more prone to the need for readmission as compared with individuals with paraplegia. Therefore, there was a trend toward a higher rate of individuals with paraplegia, but a longer length of stay and more recent lesions during the second period. Even though paraplegia may lead to a lower VTE risk, both the length of stay and a more acute lesion are related to a higher risk [11, 26]. As a result, we believe that there was no specific direction of risk imbalance in the present study.

Conclusion

The adoption of a thromboprophylaxis protocol based on time from lesion and risk factors for VTE reduced costs without increasing the risk of VTE. Further studies comparing multiple lengths of pharmacological prophylaxis are necessary to establish the best treatment strategy.

Data archiving

The datasets generated and/or analyzed during the present study are available in the Synapse repository (Synapse ID: syn18199519).

Acknowledgements The authors gratefully acknowledge Mr. Alexandre Vasconcelos Lima, Ms. Lore Martins Bueno, and Mr. Mauro Cardoso for their valuable statistical consulting.

Author contributions RLA was responsible for designing the study protocol, writing the protocol, conducting the chart search, extracting and analyzing data, interpreting results, updating reference lists, and drafting the final report. CCR was responsible for conducting the chart search, extracting and analyzing data, reviewing datasets, and writing the report. PSSB was responsible for designing the study protocol, reviewing the protocol, analyzing data, interpreting results, and providing feedback on the final report. CAMS was responsible for analyzing data, providing feedback on statistical methods, interpreting results, and providing feedback on the final report. VMA was responsible for reviewing the study protocol, analyzing data, interpreting results, updating reference lists, and reviewing the final report.

Compliance with ethical standards

Statement of ethics The present study was approved by the Associação das Pioneiras Sociais Ethics Committee (process number 1.581.383). We certify that all applicable institutional and governmental regulations concerning the ethical use of human health data were followed during the course of this research.

Conflict of interest The authors declare that they have no conflict of interest.

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