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Skrining ultrasonograficzny w kierunku zakrzepicy żył głębokich u krytycznie chorych pacjentów neurologicznych: prospektywne badanie obserwacyjne

Ultrasound screening for deep vein thrombosis in critically ill neurological patients: a prospective observational case series

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Streszczenie

Wstęp. Krytycznie chorzy pacjenci neurologiczni są szczególnie zagrożeni zakrzepicą żył głębokich (ZŻG) z powodu unieruchomienia, zabiegu operacyjnego, urazu, jak również wielu indywidualnych czynników ryzyka. ***Cel pracy.*** Celem pracy była ocena częstości występowania ZŻG wykrytej ultrasonograficznie u pacjentów u których stosowano różne metody profilaktyki przeciwzakrzepowej. ***Materiał i metody.*** Grupę badaną stanowiło 13 krytycznie chorych pacjentów neurologicznych, którzy byli poddawani skriningowi w kierunku ZŻG za pomocą wykonywanego codziennie, kompleksowemu badaniu ultrasonograficznemu typu Duplex od momentu przyjęcia pacjenta do Oddziału Intensywnej Terapii (OIT) do maksymalnie 10 dób. Odnotowywano metody zastosowanej profilaktyki przeciwzakrzepowej. ***Wyniki.*** Pięciu (38,5%) pacjentów rozwinęło ZŻG. Wszystkie przypadki ZŻG wykryto u pacjentów niechirurgicznych. U 4 z tych 5 pacjentów (80%), ZŻG pojawiła się w naczyniu żylnym, w którym znajdował się cewnik centralny. Brak było różnic pomiędzy pacjentami którzy rozwinęli i nie rozwinęli ZŻG w odniesieniu do parametrów krzepnięcia przy przyjęciu do OIT (aPTT, PT, FDP, liczba płytek krwi), liczby płytek krwi w trakcie badania oraz metod profilaktyki przeciwzakrzepowej. ***Wnioski.*** Pomimo stosowania profilaktyki przeciwzakrzepowej, ZŻG występuje często u krytycznie chorych pacjentów neurologicznych. Istotnym czynnikiem ryzyka jest tutaj kaniulacja żył centralnych. Przyłóżkowy skrining ultrasonograficzny jest wskazany w celu szybkiego wykrycia zakrzepicy żył głębokich, wdrożenia odpowiedniego leczenia, i zapobiegnięcia zatorowości płucnej w tej grupie pacjentów. *Anestezjologia i Ratownictwo 2021; 15: 157-163. doi:10.53139/AIR.20211516*

Słowa kluczowe: zakrzepica żył głębokich, ultrasonografia typu Duplex, oddział intensywnej terapii, neurochirurgia, czynniki ryzyka, skrining

Abstract

Introduction. Critically ill neurological patients are at high risk for deep vein thrombosis (DVT) due to immobility, surgery, trauma, as well as numerous individual risk factors. ***The aim of the study.*** We aimed to evaluate the exact incidence of ultrasound-detected DVT in patients receiving different methods of thromboprophylaxis. ***Material and methods.*** A study group comprised 13 critically ill neurological patients who were prospectively

screened for DVT by performing daily comprehensive duplex ultrasound of all deep venous circulation from the time of ICU admission up to 10 days. Methods of thromboprophylaxis employed in individual patients were recorded. ***Results.*** Five (38.5%) patients developed DVT. All cases of DVT occurred in non-surgical patients (62.5%). In 4 out of 5 (80%) of patients with DVT, it was detected in a cannulated vein. There were no significant differences in coagulation parameters on admission, including aPTT, PT, FDP and platelet count throughout the study period, method of thromboprophylaxis (mechanical or pharmacological) between patients with and without DVT. ***Conclusions.*** Despite thromboprophylaxis, DVT occurs frequently in critically ill neurological patients. Central venous cannulation plays an important role in risk generation. Bedside ultrasound screening for DVT should be advised to implement prompt treatment and prevent pulmonary embolism. *Anestezjologia i Ratownictwo 2021; 15: 157-163. doi:10.53139/AIR.20211516*

Keywords: deep vein thrombosis, duplex ultrasound, intensive care unit, neurosurgery, risk factors, screening

Introduction

Deep vein thrombosis (DVT), potentially leading to life-threatening pulmonary embolism (PE), may complicate the course of neurological patients admitted to the intensive care unit (ICU). Asymptomatic DVT is present in 15.9% of patients with non-traumatic intracranial haemorrhage in whom elastic stockings are used [1]. Depending on the method of detection and thromboprophylaxis applied, the risk of venous thromboembolism (VTE) following elective brain tumour surgery ranges from 0.5 to 42.6% [2, 3]. Due to disease itself (i.e. consequences of neurological injury) or its management (i.e. sedation with or without muscle paralysis), patients with neurological disorders hospitalised in the ICU are frequently immobilised. Another risk factor for DVT in this patient population is a surgical procedure or trauma. There may also be individual risk factors for DVT present. On the other hand, these patients may be at increased risk of intracranial bleeding, leading to delayed commencement of pharmacological thromboprophylaxis. There is no consensus as to the exact timing of introduction of pharmacologic thromboprophylaxis in these patients. In recent guidelines on perioperative venous thromboembolism prophylaxis, in high DVT risk craniotomy patients and non-traumatic intracranial haemorrhage patients with low risk of bleeding, the European Society of Anaesthesiology suggests adding low molecular weight heparin (LMWH) to intermittent pneumatic compression (IPC) when 'the risk of bleeding is presumed to be low' [4].

The aim of our study was to analyse the exact incidence of ultrasound-detected DVT under mechanical or combined mechanical/chemical thromboprophylaxis in the population of medical-surgical neurological patients admitted to the ICU. By performing daily ultrasound examinations we tried to find temporal incidence of DVT in this patient population.

Material and methods

Consecutive medical neurological and post-craniotomy patients admitted to a mixed medical-surgical ICU between October 2019 and February 2020 were prospectively screened for DVT. Demographic, clinical and laboratory data were recorded. To estimate the risk of DVT we used Padua Prediction Score, Wells' Score and Caprini Score for Venous Thromboembolism [5-7]. We assessed methods of thromboprophylaxis used in the study group, including mechanical (IPC device – Flowtron ACS900, Arjo, Malmo, Sweden), pharmacological (LMWH), or both (IPC+LMWH). The method of thromboprophylaxis was ordered by an attending physician taking into account individual bleeding risk. Standard laboratory tests of coagulation were determined at the ICU admission, including fibrinogen concentration (Clauss method), prothrombin time (PT), international normalised ratio (INR), prothrombin activity, activated partial thromboplastin time (aPTT), D-dimers and platelet count. Reference ranges were as follows: fibrinogen (200-393 mg dL-1), PT (9.4-12.5 s), INR (0.8-1.2), prothrombin activity (80-120 %), aPTT (25.4-36.9 s), D-dimers (<500 ng mL^{-1}), PLT (130-400x 10^3 μL^{-1}). Re-evaluation of haemostasis was performed when necessary.

For detection of DVT we performed daily duplex ultrasound (US) examination (M5, Mindray, Shenzhen, People's Republic of China) of all acces-

sible veins in upper and lower extremities bilaterally: jugular, subclavian, axillary, brachial, femoral, and popliteal. Daily examinations were performed up to day 10 of ICU hospitalisation 10 (n=6), discharge (n=5) or death (n=2), whatever came first. US examination was randomly performed by one of the four researchers, following an introductory training aiming at minimum 90% intra-individual and inter-individual reproducibility. If there was any uncertainty about the results obtained, a radiology consultation was requested. If there was thrombosis detected, we recorded the name of the thrombosed vein and if thrombosed vein was cannulated with central venous catheter (CVC), the time of DVT detection.

The Bioethics Committee of the Medical University of Silesia in Katowice waived the approval of written informed consent (PCN/0022/KB/256/I/19). However, participants provided informed verbal consent when possible, otherwise a next of kin was approached.

For statistical analysis we used licensed Statistica® (version 13, StatSoft, Krakow, Poland) statistical software. Quantitative variables were expressed as medians and interquartile ranges (IQR). Qualitative variables were presented as numbers and percentages. Between-group differences were assessed using the U Mann-Whitney test for quantitative variables, or the Fisher's exact test or Chi-squared test for qualitative data. Statistical significance was set at $p < 0.05$.

Results

The study group comprised 13 patients. The demographic and clinical characteristics of the study group are presented in Table I. Our patients were categorised as high risk for DVT according to Padua Prediction Score (5, IQR 4-5 points), Caprini Score for Venous Thromboembolism (8, IQR 7-10 points), and moderate risk according to Wells' Score (1, IQR 1-2 points).

Table I. Study group characteristics

Variable	Value
Sex (male/female) [n, %]	5(38.5)/8(61.5)
Age (median, IQR) [years]	63, 53-67
Non-surgical status [n, %]: - non-traumatic subarachnoid haemorrhage [n] - neuroinfection [n] - arterio-venous malformation (endovascular treatment)[n] - intracranial hypertension due to brain tumour [n] - post-cardiac arrest syndrome [n] Surgical status [n, %]: - haematoma evacuation [n] - brain tumour removal [n]	8(61.5) 3 2 1 1 1 5(38.5) 3 2
Risk of deep vein thrombosis	
Padua Prediction Score (median, IQR) [points] [5] Wells' Score (median, IQR) [points] [6] Caprini Score for Venous Thromboembolism [7]	5, 4-5 1, 1-2 8, 7-10
Thromboprophylaxis (post-admission) [n, %]	
IPC LMWH LMWH+IPC None	4(30.8) 5(38.5) 2(15.4) 2(15.4)
Standard laboratory tests of coagulation (post-admission)	
Fibrinogen (median, IQR)[mg dL^{-1}] PT (median, IQR)[s] INR (median, IQR) prothrombin activity (median/IQR)[%] aPTT (median, IQR)[s] D-dimers (median, IQR)[ng mL^{-1}] Platelets (median, IQR)[x 10^3 μL^{-1}]	344, 293-463 13.2, 11.9-14.5 1.2, 1.1-1.3 80, 71-93 29.6, 27.0-30.4 3290, 1057-19425 279, 200-289

aPTT – activated partial thromboplastin time, INR – international normalised ratio, IPC – intermittent pneumatic compression, IQR – interquartile range, LMWH – low molecular weight heparin, PT – prothrombin time

Table II. Incidence of deep vein thrombosis during the study period

Day of observation	Patients under observation [n]	Patients with DVT [n]	Frequency of DVT [%]	Patients with new DVT [n]
1.	13	2	15.4	2
2.	13	3	23.1	1
3.	13	3	23.1	0
4.	12	4	33.3	1
5.	9	5	55.5	1
6.	9	5	55.5	0
7.	8	3	37.5	0
8.	8	3	37.5	0
9.	8	2	25.0	0
10.	8	2	25.0	0

DVT – deep vein thrombosis

Table III. Thromboprophylaxis up to the moment of DVT diagnosis in individual patients

Patient	1	2	3	4	5
DVT location	IJV(R), FV(R)	IJV(R+L)	IJV(L)	IJV(R)	IJV(R)
CVC location	IJV(R)	none	IJV(R+L), FV(R)	IJV(R)	IJV(R)
Day of observation	Thromboprophylaxis				
1.	IPC	IPC+LMWH	IPC	LMWH	IPC
2.			IPC	LMWH	IPC+LMWH
3.				LMWH	LMWH
4.				LMWH	LMWH
5.					LMWH

CVC – central venous catheter, DVT – deep vein thrombosis, FV – femoral vein, IJV – internal jugular vein,
IPC – intermittent pneumatic compression, L – left, LMWH – low molecular weight heparin, R – right

Table IV. Standard laboratory tests of coagulation on the first day of observation in patients with and without DVT

Parameter (median, IQR)	Patients with DVT	Patients without DVT	p-value
Fibrinogen [mg dL^{-1}]	463, 357-576	296, 264-345	0.08
PT [s]	13.2, 12.5-16.6	13.0, 11.9-14.9	0.77
INR	1.2, 1.1-1.5	1.1, 1.0-1.3	0.78
prothrombin activity [%]	80, 63-87	82, 69-94	0.76
aPTT [s]	28.7, 26.0-34.3	29.8, 27.5- 31.2	0.66
D-dimers [ng mL^{-1}]	2209, 800-22136	11206, 2174-20648	0.71

aPTT – activated partial thromboplastin time, INR – international normalised ratio,
IQR – interquartile range, PT – prothrombin time

During the study period 5 out of 13 (38.5%) patients developed DVT. The temporal incidence of DVT is presented in Table II. Two patients developed DVT on day 1 of observation and additional 1 patient developed DVT on day 2, 4, and 5 of observation. Five out of 8 (62.5%) non-surgical vs. none out of 5 surgical patients developed DVT during the study period (OR 0.036; 95%CI 0.002-0.746; p=0.04). All patients had central venous catheter (CVC) implanted. Four out of 5 (80%) patients with developed DVT in a vein in which a CVC was placed (Table III). DVT in a cannulated vein was always in the form of mural catheter-related thrombosis (CRT). Thromboprophylaxis up to the moment of DVT diagnosis in individual patients is presented in Table III. There were was no differences between patients who developed and not developed DVT in terms of the use

of mechanical thromboprophylaxis, pharmacological thromboprophylaxis, combined thromboprophylaxis, or no prophylaxis from the first day of observation (ICU admission) up to the moment of DVT occurrence (p=0.22).

There were no differences in SLTs of coagulation determined on the first day of observation between patients who developed or not developed DVT (Table IV).

Discussion

In our case series we reported high prevalence of US-detected DVT (80%) in non-surgical patients admitted to the ICU with heterogeneous neurological diagnoses. The risk of DVT in our study population was moderate to high according to three established predictive instruments. The incidence of DVT may depend on several factors: method of detection (clinical, US, venography), neurological diagnosis (acute ischaemic stroke, AIS; intracerebral haemorrhage, ICH; subarachnoid haemorrhage, SAH; traumatic brain injury, TBI; urgent vs elective craniotomy), thromboprophylaxis employed (none, mechanical, pharmacological), time of observation. Symptomatic in-hospital DVT was present after AIS, ICH and SAH in 1.9%, 5.7% and 7.9% of patients, respectively. Majority of these patients received pharmacological thromboprophylaxis [8]. Although DVT is rare in non-surgical AIS patients, the incidence of US-detected DVT may reach 35% in patients scheduled for decompressive craniectomy despite pharmacological thromboprophylaxis [9]. In the study by Ogata et al., the reported incidence of US-detected DVT in ICH patients was 40.4% in those with mechanical thromboprophylaxis [10]. The incidence of US-detected lower extremity (LE) DVT without prophylaxis was reported in no patients with ischemic stroke, in 53.3% of patients with traumatic brain injury (TBI), and in 66.7% of patients with intracerebral haemorrhage [11]. Based on the National Surgical Quality Improvement Program database, the incidence of symptomatic DVT in general neurosurgical patients (cranial + spinal procedures) was 1.3% [12], in craniotomy patients alone 2.6% [13]. The patients undergoing craniotomy for tumours are particularly high-risk group as far as risk of VTE is concerned [14]. The incidence of symptomatic DVT in tumour craniotomy patients in a single regional institution was 3.9% despite thromboprophylaxis [15]. The incidence of venous thromboembolism (VTE) following elective craniotomy for brain tumour ranged from 0.5 to 42.6%, depending on method of detection and thromboprophylaxis used [2,3]. The incidence of US-detected LEDVT in general neurosurgical patients receiving dual modality thromboprophylaxis was 9.7%.

The question whether to perform US screening remains unanswered. Dickerson and al. showed no improvement in outcome with a weekly LEUS screening in neurosurgical patients [16].

Ogata et al. showed increased risk of DVT in ICH patients with elevated D-dimers [10]. Multivariate analysis in aneurysmal SAH patients revealed the following risk factors: increasing age, black race, male sex, teaching hospital, congestive heart failure, coagulopathy, neurologic disorders, paralysis, fluid and electrolyte disorders, obesity, weight loss [17]. Rolston et al. identified several clinical risk factors for VTE in neurosurgical patients: ventilator dependence, immobility , chronic steroid use, sepsis, cranial procedure [12]. According to Virchow, interplay of three factors lead to DVT: disturbed blood flow, coagulation factors and vessel wall injury. In our study majority of thrombosis occurred in a cannulated vein and could be caused by vessel wall injury during cannulation exposing sub-endothelial tissue factor and thereafter by ongoing movement of a CVC within a vessel. Presence of a CVC leads to blood flow disruption. Blood flow in a cannulated vein can be reduced by up to 60% [18]. Presence of a CVC is the most frequent cause of upper extremity (UE) DVT [19]. Asymptomatic CRT may be present in 19% and 41% of patients with CVC screened with DUS and venography, respectively [20]. To our knowledge, our study was the first to perform UE and LE US for DVT screening in critically ill neurological patients.

A recent meta-analysis in elective cranial and spinal surgery favours pharmacological thromboprophylaxis with no extra bleeding [21]. Combination of mechanical and pharmacological prophylaxis might be even better [22,23]. Because almost all DVT in our study subjects occurred in the upper body (4 cases of DVT only in the upper body, 1 case of DVT in upper and lower body), by using mechanical thromboprophylaxis DVT could not be prevented. Even use of pharmacological prophylaxis did not prevent DVT – 3 patients out 5 with DVT were on LMWH.

Study limitations

The study group was relatively small due to the epidemiological situation at the time (novel coronavirus pandemic). Full coagulation panel was determined only on the first day of hospitalisation and as required, so we could not check associations between coagulation tests and the risk of DVT. We could not give an accurate answer to the clinical question if central venous cannulation is a risk factor for DVT because we lacked a control group. Nevertheless the association between CVC and DVT was present.

The results of our study showed that majority of critically ill neurological patients admitted to the ICU developed early, mostly central catheter-related thrombosis. It seems that central venous cannulation is one of the most important DVT risk factors in critically ill neurological patients. As there is no consensus as to when to start pharmacological thromboprophylaxis in these patients, the results of our study show that these patients may benefit from early pharmacological prophylaxis. To draw firm conclusions studies in larger populations should be performed.

Conclusions

Despite different methods of thromboprophylaxis, DVT occurs frequently in high-risk critically ill neurological patients. Central venous cannulation plays an important role in risk generation. Bedside ultrasound screening for DVT should be advised to implement prompt treatment and prevent pulmonary embolism.

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