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RESEARCH ARTICLE

The use of a low dose hydrocortisone to prevent pulmonary embolism in patients with multiple trauma

Anis Chaari · Hatem Ghadhoune · Olfa Chakroune · Hanen Abid · Olfa Turki · Mabrouk Bahloul · Mounir Bouaziz

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Abstract *Background* Venous thromboembolism events are common in trauma patients. Immediate acute inflammation following injury triggers coagulation cascade and may increase the risk of pulmonary embolism (PE) in this population. *Objective* We aimed to evaluate whether early low-dose steroids prevent symptomatic PE onset in multiple trauma patients. *Setting* The medical surgical intensive care unit of Habib Bourguiba University Hospital (Sfax—Tunisia). *Methods* Comparative study of two cohorts: a retrospective cohort of patients who didn't receive early low-dose steroids (steroid (−) group) and a prospective cohort of patients who received hydrocortisone with a dose of 100 mg/8 h for a scheduled period of 7 days (steroid (+) group). All adult patients admitted in our intensive care unit (ICU) for multiple trauma with predicted duration of mechanical ventilation over 48 h were included. *Main outcome measure* Evaluation of the impact of low-dose steroids on the incidence of symptomatic PE. *Results* We included 175 patients: 92 in the steroids (−) group and 83 in the steroids (+) group. PE was diagnosed in 15 patients (8.5 %). The incidence of PE was significantly lower in steroid (+) group (3.6 vs 13 %; $p = 0.013$). In multivariate analysis, independent factors predicting PE onset were meningeal hemorrhage [OR = 14.7; 95 % CI (2.2–96.3); $p = 0.013$] and pelvic ring trauma [OR = 8; 95 % CI (1.8–36.4); $p = 0.007$] whereas low-dose steroids were significantly associated with a protective effect [OR = 0.2; 95 % CI (0.05–0.77); $p = 0.019$]. There was no significant difference between steroids (+) and steroids (−) groups neither in terms of mean ICU length of stay (LOS) (respectively 11 ± 9.7 and 12.3 ± 10.7 days; $p = 0.372$) nor in terms of ICU mortality (respectively 29.3 and 24.1 %; $p = 0.434$). *Conclusion* Steroids are effective in reducing the incidence of PE in multiple trauma patients. However, no significant benefice was found on ICU mortality.

Keywords Hydrocortisone · Multiple trauma · Pulmonary embolism

A. Chaari · H. Ghadhoune · O. Turki · M. Bahloul · M. Bouaziz
Intensive Care Unit Department, Faculté de médecine de Sfax, Sfax, Tunisia

A. Chaari (✉)
Service de Réanimation médicale, Hôpital Habib Bourguiba, Route el Ain Km 1, 3029 Sfax, Tunisia
e-mail: anischaari2004@yahoo.fr

O. Chakroune
Emergency Department, Faculté de médecine de Sfax, Sfax, Tunisia

H. Abid
Radiology Department, Faculté de médecine de Sfax, Sfax, Tunisia

Impacts on Practice

- Preventing pulmonary embolism is challenging in trauma patients.
- Low dose hydrocortisone therapy (100 mg/8 h given during 7 consecutive days) prevents symptomatic pulmonary embolism in critically-ill trauma patients.

Introduction

Severe trauma is one of the leading causes of death and morbidity in the world [1]. Venous thromboembolism (VTE) remains a major challenge in high-risk trauma

patients. In fact, rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) in this population might be as high as 40 and 20 % respectively [2, 3]. Moreover PE was reported as the third major cause of death after trauma in patients who survive longer than 24 h after injury [4]. Thrombosis in the veins is triggered by venostasis, hypercoagulability, and vessel wall inflammation. These three underlying causes are known as the Virchow triad [5]. Several studies highlighted that traumatic injury is followed by a profound increase in systemic levels of proinflammatory and anti-inflammatory cytokines [6, 7]. Recent structural and functional studies have demonstrated that inflammation triggers clotting, decreases the activity of anticoagulant mechanisms and impairs the fibrinolytic system [8]. Thus, early modulation of post-traumatic overwhelming inflammation via stress-dose hydrocortisone therapy may contribute to prevent PE in patients with multiple injuries. The efficacy of this therapy in dampening induced-trauma inflammation was previously demonstrated [9]. This may be particularly helpful in critically-ill trauma patients as pharmacologic thromboprophylaxis is usually delayed because of high risk of bleeding events. Moreover, using mechanical prophylaxis device could be hampered in patients with lower limb injuries.

Aim of the study

In our study we tested the hypothesis whether low dose hydrocortisone therapy reduces the prevalence of symptomatic PE in critically-ill multiple trauma patients.

Methods

All patients admitted to the medical surgical ICU of Habib Bourguiba University Hospital (Sfax—Tunisia) within 24 h after non-penetrating blunt trauma were eligible for the study. The study was conducted over a period of 19 months (01/06/2010–31/12/2011). Inclusion criteria were an age >15 years, need for mechanical ventilation within the few hours following trauma and predicted duration of mechanical ventilation >48 h. Patients needing long course corticosteroid treatment and those who received steroids within the last 3 months were excluded. We also excluded patients with contraindication for iodinated contrast media and those who are receiving anticoagulation because of any medical disease.

We considered as multiple trauma patients all victims with 2 or more traumatic injuries and an injury severity score (ISS) higher than 15. Severe trauma brain injury was defined as a Glasgow Coma Scale score of less than or equal to 8 after initial care [10].

The diagnosis of PE was considered when spiral computed tomography (CT) scan showed one or more filling defects or obstructions in the pulmonary artery or its branches [11]. Massive PE was defined by the presence of sustained hypotension (systolic blood pressure (SBP) <90 mmHg for at least 15 min or requiring inotropic support, not due to a cause other than PE such as arrhythmia, hypovolemia, sepsis or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (heart rate < 40 bpm with symptoms of shock) [12].

Design of the study

In our ICU, stress-dose steroids became routinely prescribed in patients with multiple trauma since June 2011. This strategy was triggered by the results of the "HYPOLYTE study" and aimed to prevent ventilator-associated pneumonia [9]. As we considered that depriving patients from this therapy was not ethic, we decided to compare two different cohorts of patients admitted during two different periods:

- A retrospective cohort (from 01/06/2010 to 31/05/2011): Patients were managed without low-dose steroids (steroid (−) group). In our institution, steroids are not used to treat intracranial hypertension.
- A prospective cohort (01/06/2011–31/12/2011): Steroids were used in trauma patients for preventing VAP (steroid (+) group). Included patients received hydrocortisone 100 mg/8 h daily during 7 consecutive days and then immediately stopped.

In our ICU, most of the severe trauma patients have required sedation and mechanical ventilation and the diagnosis of symptomatic PE is usually suspected in patients with unexplained hypoxemia and/or arterial hypotension. A medical committee of six ICU physicians daily examined all available data in order to classify patients according to the importance of the clinical suspicion of PE. The diagnosis was confirmed by a spiral computed tomography (CT) scan showing one or more filling defects or obstructions in the pulmonary artery or its branches [11]. Except patients with head injury, all our patients received pharmacological thromboprophylaxis (enoxaparin 40 mg once a day or dalteparin 5,000 IU, each administrated by subcutaneous injection.) within the first 48 h. In our hospital, only enoxaparin and dalteparin were available for pharmacological thromboprophylaxis. Patients with severe renal failure (creatinine clearance < 30 ml/min) received unfractionated heparin 5,000 U bid. In patients with head injury, preventive anticoagulation was administrated if the initial injuries did not worsen on a control brain CT-scan performed within 24 to 48 h. In all cases, anticoagulation was not given in patients with uncontrolled hemorrhage or persistent coagulopathy (thrombocytopenia < 100 G/l, activated partial

trhomboplastin time (APTT) > 1.5 and/or prothrombine time (PT) > 1.5). Mechanical preventive devices were used in patients with contraindication of pharmacological thromboprophylaxis if the lower limb were not injured.

Data collection

For each patient, we recorded demographic parameters (age, sex, comorbidities). Clinical severity was assessed by SAPSII score and SOFA score whereas trauma severity was assessed by ISS score [13–15]. We also recorded biological finding and therapeutic measures on admission, delay of pharmacological thromboprophylaxis and delay of PE onset regarding trauma. For each patient, we mentioned the length of mechanical ventilation, ICU length of stay (LOS) and ICU mortality.

Our study was conducted with an "intention to treat" basis. In fact, we also included in our prospective cohort the patients who didn't receive steroids for the whole scheduled period.

The study primary outcome was occurrence of symptomatic PE during ICU stay.

Our study was approved by our hospital's committee (SPHB105). For the prospective cohort, a signed consent was obtained from patients' surrogates.

Statistical analysis

Qualitative variables were expressed as percentages whereas quantitative variables were expressed as mean ± standard deviation. The normal distribution of quantitative variables was checked by using the Kolmogorov–Smirnov test. Baseline characteristics of the two studied groups (steroid (+) and steroid (−)) were compared by the χ^2 test or Fisher exact test for qualitative variables and Student test or Mann–Whitney test for quantitative variables as appropriate. All tests were two-sided. The level of significance was set at $p < 0.05$. Multivariate analysis was then performed using a stepwise logistic regression model in order to identify independent factor predicting PE. Included explanatory variables in the logistic regression were variables which are known by the scientific community as quietly linked to PE onset. Odds ratios were calculated with 95 % confidence intervals. SPSS version 18 was used for statistical analyses.

Results

Population characteristics

During the study period, 231 trauma patients were admitted in the ICU department of Habib Bourguiba University Hospital. Only 175 patients (75.8 %) were included: 92 in the retrospective cohort (steroid (−) group) and 83 in the prospective cohort (steroid (+) group) (Fig. 1). Mean age was 38 ± 18 years. Sex-ratio (M/F) was 6.6. All our patients were intubated in the scene of the accident. Etomidate was used for anesthesia induction in all cases. Mean SAPSII was 33 ± 8 whereas mean SOFA score was 8 ± 2. Eighty patients (45.7 %) were hypotensive and needed vasopressor support. Mean Glasgow coma scale (GCS) was 9 ± 4 points. Identified traumatic injuries were head trauma in 175 patients (100 %), chest trauma in 78 patients (44.6 %) and abdominal trauma in 26 patients (14.9 %). Mean ISS score was 37 ± 6. There was no significant difference between the two studied cohorts in terms of baseline characteristics (Tables 1, 2, 3). Pharmacological thromboprophylaxis was indicated for 169 patients within 2.6 ± 0.7 days. Only 2 patients (1.1 %) received mechanical preventive devices. Among patients included in the prospective cohort, 53 received steroids for the whole scheduled period. Mean duration of steroid treatment was 6.47 ± 4.4 days. Urgent surgery was performed within the first 24 h for 60 patients (34.3 %). Mean duration of mechanical ventilation was 8.2 ± 7 days. There was no significant difference found between the two studied cohorts in terms of therapeutic measures (Table 4). During their ICU stay, 59 patients developed nosocomial infections (33/92 in the steroid (−) group vs 26/83 in the steroid (+) group; $p = 0.525$). Forty-nine patients developed ventilator-associated pneumonia (27/92 in the steroid (−) group vs 22/83 in the steroid (+) group; $p = 0.676$). Only three patients needed to go back to surgery during their ICU stay.

Main outcome

PE was suspected in 101 patients (57.7 %). As a result, a spiral computed tomography (CT) was performed for 52 patients in the steroids (+) group and 49 patients for the steroids (−) group ($p = 0.702$). The diagnosis was confirmed in 15 patients (8.5 %). Mean delay of PE onset regarding trauma was 6.3 ± 2.7 days (ranging from 3 to 12 days). None of our patients had a contraindication of iodinated contrast media. PE was proximal (main branch of the pulmonary artery, lobar or segmental thrombi) in 12 patients (6.9 %) and distal (sub-segmental defect) in 3 patients (1.7 %). Eleven of these patients (6.3 %) developed cardiogenic shock and PE was considered as massive. The proportion of patients who received pharmacological thromboprophylaxis was similar between steroid (−) and steroid (+) groups (respectively 89/92 and 80/83; $p = 1$) within a similar delay regarding trauma onset (respectively 2.6 ± 0.6 and 2.6 ± 0.7 days; $p = 0{,}689$). However, the incidence of PE was significantly higher in patients who

Fig. 1 The study flow chart

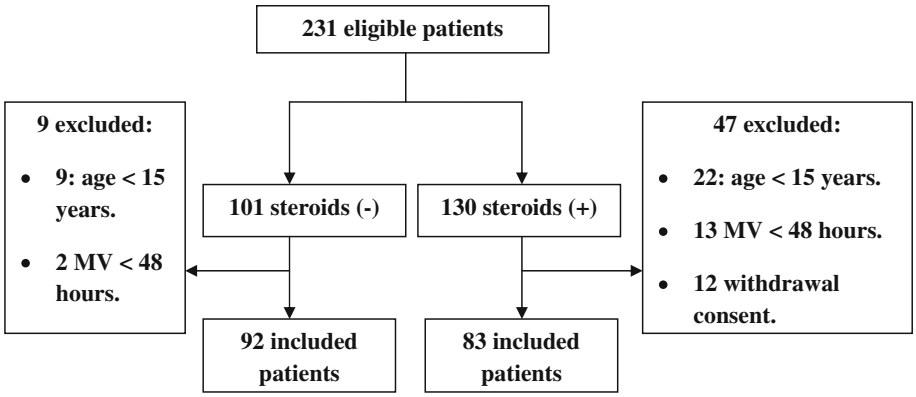

Table 1 Comparison of steroid (+) and steroid (−) patients according to demographic characteristics

	Steroid (−) (n = 92)	Steroid (+) (N = 83)	*p*
Age (years ± SD)	36 ± 16	41 ± 18	0.06
Sex-ratio (M/F)	5.6	8.2	0.39
Comorbidities (N/%)	6/6.5	12/10	0.21
Arterial hypertension	3/3.3	4/4.8	0.71
Diabetes	2/2.2	3/3.6	0.67
CHF	2/2.2	0/0	0.5
COPD			
SAPSII (±SD)	34 ± 9	32 ± 7	0.13
SOFA (±SD)	8 ± 2	7 ± 2	0.49
ISS (±SD)	37 ± 7	36 ± 6	0.69
GCS (±SD)	9 ± 4	10 ± 3	0.5
Shock (n/%)	34/37	37/44.6	0.31

CHF congestive heart failure, *COPD* chronic obstructive pulmonary disease

Table 2 Biological findings on admission

Parameter	Steroids (−) (N = 92)	Steroids (+) (N = 83)	*p*
pH (±SD)	7.37 ± 0.09	7.38 ± 0.09	0.404
$PaCO_2$ (mmHg ± SD)	36 ± 9	35 ± 8	0.339
PaO_2 (mmHg ± SD)	126 ± 66	133 ± 69	0.537
Bicarbonates (mmol/l ± SD)	22 ± 13.6	20.3 ± 3	0.257
SaO_2 (% ± SD)	98 ± 14	98 ± 12	0.374
PaO_2/FiO_2 (mmHg ± SD)	272 ± 117	287 ± 110	0.443
Leucocytes (/mm^3 ± SD)	13329 ± 5014	14662 ± 6876	0.150
Hemoglobin (g/dl ± SD)	11.1 ± 2.4	10.9 ± 2.4	0.628
Platelets (G/l ± SD)	162.7 ± 61.6	153.7 ± 79.6	0.410
Sodium (mmol/l ± SD)	138 ± 4.9	139 ± 5	0.606
Potassium (mmol/l ± SD)	3.8 ± 0.7	3.7 ± 0.7	0.510
BUN (mmol/l ± SD)	5.8 ± 3.7	6.1 ± 2.8	0.604
Creatinin (μmol/l ± SD)	98 ± 107	92 ± 46	0.654

BUN blood urea nitrogen

didn't receive steroids according to the scheduled regimen (12/92 (13 %) vs 3/83 (3.6 %); $p = 0.013$). All our patients received effective anticoagulation. Fibrinolysis was considered as contraindicated for all our patients.

In the multivariate analysis, stress-dose steroid therapy was identified as an independent factor protecting against PE [OR = 0.2, 95 % CI (0.05–0.77); $p = 0.019$]. Independent factors increasing the risk of PE were meningeal hemorrhage [OR = 14.7; 95 % CI (2.2–96.3); $p = 0.03$) and pelvic trauma (OR = 8; 95 % CI [1.8–36.4]; $p = 0.007$) (Table 5).

Secondary outcomes

When we compared steroid (+) and steroid (−) groups, we didn't find any difference about neither duration of mechanical ventilation (respectively 7.7 ± 6.5 days and 8.6 ± 7.5 days; $p = 0.372$) nor duration of ICU LOS (respectively 11 ± 9.7 days and 12.3 ± 10.7 days; $p = 0.417$). We also found that stress-dose steroid therapy was not associated to a significant survival improvement as mortality was 29.3 % in steroid (+) group vs 24.1 % in steroid (−) group ($p = 0.434$).

Discussion

Our study shows that low-dose hydrocortisone therapy given early after trauma is effective to prevent symptomatic PE in trauma patients. To the best of our knowledge, this finding was not previously reported in the literature. Prevention of PE in critically-ill trauma patients is challenging. In fact, venous thromboembolism (VTE) events are common complications that are associated with high rates of morbidity and mortality in this population [16]. The rate of symptomatic PE in injured patients has been reported previously to range from 2 to 6 % [2, 17–19].

Table 3 Comparison of steroid (+)/steroid (−) patients according to elementary injuries

	Steroid (−) (N = 92)	Steroid (+) (N = 83)	*p*
Head trauma (N/%)	92	83	1
Extradural hematoma (N/%)	15/16.3	13/15.7	0.906
Subdural hematoma (N/%)	41/44.6	33/39.8	0.52
Meningeal hemorrhage (N/%)	52/56.5	52/62.7	0.410
Parenchymal contusion(s) (N/%)	33/35.9	26/31.3	0.525
Chest trauma (N/%)	44/47.8	34/41	0.544
Pulmonary contusions (N/%)	33/55.9	26/44.1	0.525
Hemothorax (N/%)	7/53.8	6/46.2	0.924
Rib fracture (N/%)	16/44.4	20/55.6	0.273
Abdominal trauma (N/%)	13/14.1	13/15.7	0.776
Pelvic ring trauma (N/%)	9/9.8	8/9.6	0.974
Lower limb trauma (N/%)	24/28.9	26/28.3	0.924

Table 4 Comparison of steroid (+) and steroid (−) groups according to therapeutic measures during ICU stay

	Steroid (−) (N = 92)	Steroid (+) (N = 83)	*p*
Mechanical ventilation (N per group/%)	89/96.7	81/97.6	1
Transfusion (N per group /%)	47/51.6	36/44.4	0.345
Vasopressors (N per group/%)	40/43.5	40/48.2	0.532
Urgent surgery (N per group/%)	36/39.1	24/28.6	0.155

MV mechanical ventilation

Moreover, PE was reported as the third most common cause of death in patients who survive after the first 24 h of trauma [4, 18]. Till now, the prevention of this serious complication is axed on pharmacological thromboprophylaxis and mechanical devices. However, many trauma patients cannot wear bilateral compression devices because of the presence of lower extremity injuries and others have contraindications to receiving an anticoagulant even in prophylactic doses. Classically, VTE has been attributed to the Virchow triad: venous stasis, venous injury, and a hypercoagulable state which may be triggered and then enhanced by an overwhelming inflammatory reaction [8]. In fact, the acute phase following trauma is associated with an inflammatory immune response aiming to improve wound healing and antimicrobial defense [20]. This inflammatory response is mediated by pro—(Tumor Necrosis Factor (TNF)-α, interleukin (IL)-1β, IL6)—and anti-inflammatory (IL10) cytokines, which are polypeptide, normally barely detectable in healthy tissue but rapidly up-regulated in response to pathological or stressful challenges, such as multiple trauma [21]. Furthermore, the highest levels of pro-inflammatory cytokines were measured within 2 h of injury, suggesting that the inflammatory

Table 5 Multivariate analysis of factors predicting pulmonary embolism onset

Factors	*p*	OR	CI (95 %)	
			Minimum	Maximum
Age > 50 years	0.217	2.7	0.6	12.9
Preventive anticoagulation	0.894	0.83	0.05	13.1
ISS > 25	0.119	1.2	0.04	1.4
Low-dose steroids	0.019	0.2	0.05	0.77
Meningeal hemorrhage	0.013	14.7	2.2	96.3
Pelvic ring trauma	0.007	8	1.8	36.4
Lower limb fracture	0.789	1.2	0.3	4.8
Urgent surgery	0.228	2.47	0.6	10.7

cascade is activated on injury [22, 23]. This overwhelming inflammation seems to play a central role in the pathogenesis of VTE by inducing a procoagulant state through the action of cytokines and chemokines on monocytes and endothelial cells. In fact, Van Aken et al. reported that plasma concentrations of interleukin 6 (IL-6), interleukin 8 (IL-8) and monocyte chemotactic protein 1(MCP-1) were significantly higher in patients with recurrent thrombosis than in healthy subjects [24]. Moreover, the risk of venous thrombosis was shown to be significantly correlated with elevated IL-8 plasmatic levels [25]. Recently, Roquilly et al. reported in the HYPOLYTE study, that the use of intravenous stress-dose of hydrocortisone during 7 consecutive days, compared with placebo, resulted in a significantly decreased risk of hospital acquired pneumonia [9]. The authors hypothesized that low-dose steroids were effective through the attenuation of the overwhelming inflammatory response following trauma. Our results shows that stress-dose hydrocortisone was an independent factor protecting from PE which may support the hypothesis that modulating the inflammatory reaction reduces the risk of PE via its effects on coagulation. Interestingly, most of PE developed by our patients occurred during the early phase following trauma. This finding was previously reported and may be related to the early effects of inflammation on coagulation cascade [19, 25]. Moreover, it could explain the efficacy of early administration of low-dose steroids.

On the other hand, we found that steroids had no significant effect neither on ICU LOS nor on ICU mortality. In fact, crude mortality in this population depends on multiple factors such as injury severity, comorbidities, nosocomial events…

Several limitations must be mentioned: First, our study was conducted with an "intention to treat" basis. As a consequence, we also included in our prospective cohort the patients who didn't receive steroids for the whole scheduled period. Second, all our patients received

etomidate for endotracheal intubation. Malerba et al. reported that a single dose of this anaesthetic agent may blunt the adrenal function for 4–24 h [26]. Vinclair et al. reported that 12 h after etomidate administration, 80 % of patients had etomidate-related adrenal insufficiency which resolved within 48 h [27]. In our study, hormonal investigations were not performed in order to identify patients with hypothalamic–pituitary–adrenal (HPA) axis impairment. In fact, low-dose steroids may be more effective in patients with corticosteroid insufficiency. Thus, the effectiveness of steroids that we reported may be explained by the fact that hydrocortisone counterbalances the effects of etomidate on adrenal cortisol. Third, specific investigations for diagnosing PE were not systematically performed for all patients: only those with high suspicion of PE underwent spiral-CT scan. Thus, further studies are required to support our results.

Conclusion

An early low-dose steroid therapy is effective for preventing symptomatic PE in patients with multiple trauma. Usual preventive measures must be instituted as soon as possible, when feasible. Further studies are needed to support this finding.

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Conflicts of interest None.

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