Management of blunt hepatic and splenic injuries (grade ≤ III) in patients receiving antithrombotic therapy

Ann. Ital. Chir., 2019 90, 5: 421-426
pii: S0003469X1903046X

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BACKGROUND: *Non-operative management (NOM) may be particularly challenging in patients receiving synchronous antithrombotic therapy (AT). The current study examined the feasibility of NOM in patients under AT who sustained blunt splenic or hepatic injuries.*
METHODS: *We analyzed the results of a 5-year (2010-2014) pre-decided treatment protocol, including 15 patients under AT who were treated for splenic and/or hepatic injuries at our institution. The antithrombotic therapy consisted of acenocoumarol 4 mg, acetylsalicylic acid 100 mg and clopidogrel 75 mg. Vitamin K (Vit K), Fresh frozen plasma (FFP) and Prothrombin Complex Concentrate (PCC) were transfused to patients receiving anticoagulant therapy, while platelets (PLTs) were given to patients under antiplatelet therapy if their level was excessively low. The organ injury grading scale, injury severity score (ISS), the need for blood transfusion and intensive care unit (ICU)/ high dependency unit (HDU) admission, morbidity, mortality and duration of hospital stay were also recorded.*
RESULTS: *Ten patients fulfilled the criteria for NOM and were treated accordingly. No conversion to operative management (OM) was required (success rate 100%). Five patients were managed surgically due to hemodynamic instability and/or signs of peritonitis. Reversal of AT was attempted in all cases.*
CONCLUSIONS: *Hemodynamically stable patients under AT with blunt hepatic or splenic injuries (grade ≤ III) and no signs of peritonitis, may be good candidates for NOM, despite their bleeding tendency. The type of AT does not seem to influence the final outcome. Reversal of AT should be stratified individually.*

KEY WORDS: Antithrombotic therapy, Hemodynamic stability, Non-operative management

Introduction

Trauma is the leading cause of mortality in people under the age of 35 worldwide[1]. Abdominal injuries occur in 31% of poly-trauma patients. Patients with abdominal injuries suffer from more severe trauma compared to patients with injuries of other regions as indicated by the significantly higher average Injury Severity Score (ISS), a significant independent predictor of mortal [2]. The liver and the spleen represent the most commonly injured organs (16% and 13%, respectively)[3]. Over the last decades, a shift has been noted from operative (OM) to non-operative management (NOM), in hemodynamically stable patients with blunt abdominal trauma (BAT), without signs of peritonitis [4].
NOM can be safely applied in trauma centers equipped with newer imaging modalities, HDU/ICU and other supporting services. Focused assessment with sonography for trauma (FAST) and computed tomography (CT) can

Pervenuto in Redazione Febbraio 2019. Accettato per la pubblicazione Aprile 2019
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effectively detect the candidates for NOM, based on the recent guidelines of treatment [5]. Trauma protocols should be meticulously applied in the diagnostic and therapeutic management of such patients targeting better outcomes [6]. Hemodynamically unstable trauma patients with positive FAST undergo emergency laparotomy and are treated according to the recent developments of trauma management for uncontrolled bleeding as recommended by the Damage Control Resuscitation protocols [7] . However, NOM is the first choice for hemodynamically stable patients with no signs of peritonitis. Furthermore, there is evidence that NOM is also successful in 80%–90% of unstable patients with splenic and hepatic injuries, who stabilize rapidly [8].

Nowadays, anticoagulant agents, alone or in combination, are frequently used for the prevention and/or treatment of a wide range of cardiovascular diseases [9]. Traditional anticoagulant treatment includes the use of coumarinic analogues, such as acecoumarol, while newer agents (novel oral anticoagulants - NOACs) are increasingly used. Two classes of NOACs are currently available exerting their effects through inhibition of factor Xa or factor IIa/ thrombin [10]. Antiplatelet therapy is effective in the secondary prevention of athero-thrombotic disease, especially coronary artery disease, cerebrovascular thromboembolism and peripheral arterial disease [11]. In cases of synchronous AT, the treatment of a potentially bleeding trauma patient may be particularly challenging and many trauma surgeons remain reluctant to NOM.

In general, surgical exploration may be conducted with an accepted risk of bleeding if the international ratio (INR) is≤ 1.5 [12]. Available antidotes for restoring INR in patients receiving coumarol-based oral anticoagulants (COAs), are Vitamin K, fresh frozen plasma(FFP) and PCC alone or in combination [12], depending on the severity of bleeding. Antiplatelet medication exhibits short plasma half-life but may have a prolonged biological effect due to the irreversible platelet inhibition. Since there are no specific medical agents for reversal, general measures for preventing severe bleeding should be undertaken, including meticulous hemostasis and transfusion of platelets if their counted level is excessively low [13].

Methods

The present study is a prospective analysis, based on a pre-decided treatment protocol, regarding the application of NOM as the first choice of management in all hemodynamically stable trauma patients under AT, with no signs of peritonitis. Antithrombotic medications included either the use of acecoumarol or the use of agents blocking the aggregation of platelets. Fifteen patients with liver and splenic injuries, receiving AT were reviewed. Data analysis included the type of AT and the administration of any antidotes as well as the final outcome. The demographic data of the patients, the grade of liver or spleen injury, the Injury Severity Score (ISS), the morbidity and mortality rates, the need for blood transfusion or ICU/HDU admission and the length of hospital stay, were also recorded and evaluated.

On admission, all patients were assessed and resuscitated in accordance to the Advanced Trauma Life Support Committee on Trauma (ATLS) protocol. In all cases FAST was conducted at the emergency department. Hemodynamically unstable patients with positive FAST, as well as patients with signs of peritonitis were explored surgically. Stable patients with positive FAST were selected for NOM and they were further evaluated by CT scan with intravenous (IV) contrast, regardless of the type of AT. Patients with minimum systolic arterial blood pressure (SAP) > 90 mmHg without vasopressors and maximum heart rate (HR) < 110 beats/ min were considered as hemodynamically stable [14].

The grade of organ injury was estimated radiologically (CT scan) for NOM patients and intraoperatively for OM patients. The classification of liver and splenic injuries was based on the universal American Association for the Surgery of Trauma (AAST) grading scale [15].

All patients subjected to the NOM group were hemodynamically stable or good responders to the initial resuscitation and were put on close monitoring. Indications for surgical exploration (revision) were the onset of hemodynamic destabilization, the ongoing drop of hemoglobin and any clinical indication of missed hollow organ injuries.

A level of INR ≤ 1.5 was set as goal in all trauma patients who were under anticoagulant therapy with acenocoumarol. Vitamin K alone was administered to patients with grade I injuries and in combination with FFP to patients with higher grades of injury. PCC was administered to patients with life-threatening bleeding who underwent emergency laparotomy [13]. If AT consisted of antiplatelet agents (acetylsalicylic acid and/or clopidogrel), meticulous hemostasis was applied in all cases who were treated surgically. A level of 50.000 count, accompanied with extreme bleeding tendency, was set as the limit for PLTs transfusion.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 20.0 for Windows was used for data analysis. Descriptive statistics were presented as mean and standard deviation (SD). Categorical data were analyzed using the chi-square test. The Significance level was set at $p<0.05$.

Results

Fifteen patients (11 men, 4 women) were included in the study. After initial evaluation and according to the study

TABLE I - *Patient's characteristics*

Patients	Age (years)	Gender	ISS	Injury (organ grade)	Management	Antithombotic therapy	Administration agents (units)	ICU/HDU admision	RBC Transfusion (units)	Morbidity	Mortality	Hospitalazation (days)
1	85	M	9	S,I	NOM	ACEN	1Vit K	N	3	N	N	13
2	80	W	4	S,II	NOM	ACEN	1Vit K,2FFP	N	-	N	N	11
3	83	M	25	S,III	NOM	AC	-	N	-	PE	N	9
4	70	M	4	S,I	NOM	CL	-	N	-	N	N	14
5	86	W	4	S,I	NOM	AC	-	N	-	N	N	6
6	64	M	4	S,I	NOM	AC	-	N	-	N	N	2
7	88	M	4	L,I	NOM	CL	-	N	-	N	N	3
8	81	W	4	L,I	NOM	ACEN	1Vit K	N	-	N	N	3
9	36	M	4	L,I	NOM	AC	-	N	-	N	N	3
10	76	M	12	L,I	NOM	AC	-	N	-	N	N	12
11	86	M	19	S,II	OM	CL	-	Y	3	PF	Y	30
12	84	M	9	S,II	OM	ACEN	PCC	Y	2	PF	Y	19
13	78	M	18	S,III	OM	AC	-	N	2	N	N	8
14	58	W	4	S,II	OM	AC	-	Y	6	N	N	7
15	37	M	26	L,II	OM	AC	-	Y	4	PN	N	22
Mean	**72,80**		**10,00**						**3,33**			**10.80**

Legend: M: Men, W: Women, S: Spleen;L: Liver, NOM: Non operative management;OM: Operative management; ACEN: Acenocoumarol,; CL: Clopidogrel,AC: Acetylsalicylic acid,Vit K: Vitamin K;FFP: Fresh frozen plasma, PCC:Prothrombin complex concentrate, N: No, Y: Yes, PE: Pleural effusion; PN: Pneumonia; PF: Pancreatic fistula; B: Blunt, P: Penetrating

TABLE II - *Comparative data of the two patient groups, regarding the method of treat*

	Operative management(5 pts)	Non-operative management(10 pts)	p
Age (years, mean ± SD)	68.6 ± 20.8	74.9 ± 15.6	0.47
ISS (mean ± SD)	15.2 ± 8.7	7.4 ± 6.8	0.18
ICU/HDU admission (%)	33.3	66.7	**0.001**
Blood transfusion(units, mean ± SD)	3.4 ± 1.7	3.1 ± 1.5	0.49
Morbidity (%)	60	10	**0.05**
Mortality (%)	40	0	**0.03**
Hospital stay (days, mean ± SD)	17.2 ± 9.7	7.6 ± 4.7	**0.02**

protocol, 10 patients (66.6%) were selected for NOM and five patients (33.4%) for OM. There was no concomitant severe traumatic brain injury (TBI) in any case. International ratio (INR) ranged between 2.5 to 3.5 in all patients receiving anticoagulant therapy whereas it was normal in the patients receiving antiplatelet agents. The patients' characteristics are depicted in Table I.

NOM was successful in all patients. Mean ISS in this patient group was 7.4 ± 6.8 and no patient was admitted to ICU/HDU. Vitamin K alone was administered in two patients with grade I splenic and hepatic injury. The combination of vitamin K and two units of FFP were given to one patient with grade II splenic trauma. All these patients were under treatment with acenocoumarol prior to their injury. There was only one minor complication recorded, including a left pleural effusion, which was successfully drained and evacuated, and mortality was null. Mean hospital stay was 7.6 ± 4.7 days. Five patients underwent emergency laparotomy due to grade I-III splenic injuries (four cases) and grade II liver injury (one case). The decision for surgical exploration was based on the presence of hemodynamic instability and positive FAST in all cases. Mean injury severity score (ISS) was 15.2±8.7 and all, but one, patients were admitted to the ICU/HDU. The need for blood transfusion was high in this patient group with a mean rate of 3.4 units/patient. We administered PCC to one patient with life-threatening bleeding and hemodynamic instability due to a grade II injury of the spleen before undergoing emergency laparotomy. Four other cases, who were under antiplatelet therapy, were explored surgically. However, there was no need for administration of platelets and the application of local hemostatic methods sufficed in achieving adequate hemostasis. Two

patients (13.3%), 84 and 86 years old, experienced severe complications and they passed away on the 19th and 30th postoperative day, respectively, due to high-output pancreatic fistulas and non-controlled sepsis, without any evidence of bleeding. The average length of hospital stay in this group was 17.2 ± 7.9 days and it was statistically significantly higher compared to the NOM group (7.6± 4.72 days, p 0.02). However, no statistically significant difference was exhibited regarding the requirement for blood transfusion between the two groups (p 0.49).
The comparative data of the two groups regarding the primary and secondary endpoints of the study are depicted in Table II.

Discussion

Several reports in the literature have validated that NOM is a well-established and accepted management for BAT in hemodynamically stable patients [16,17]. The classification of patients into hemodynamic categories, e.g. responders, transient responders and non-responders, may help to avoid the under-estimation of bleeding [18] and also plays a crucial role regarding the optimal management. However, in cases of synchronous AT, NOM may be particularly challenging.
In the current study, the criteria for NOM were only the absence of hemodynamic instability and any signs of peritonitis, regardless of age, grade and type of injury as well as any type of synchronous AT. The grade of injury is not considered as contra-indication for NOM. In a retrospective study of 732 trauma patients Ruscelli et.al concluded that the AAST Organ Injury Scale was not useful for the therapeutic decision making process and that the only criterion of choice for the therapeutic strategy was hemodynamic stability [19]. Nevertheless, it is well-known that higher grades are associated with a higher rate of failure. Clemente et. al applied NOM in 69.5% of liver trauma patients and reported 24,3% failure rate in IV-V stage as compared to 1.3% and 1.0% in I-II and III respectively [20]. Splenic, as well as hepatic injuries, could benefit form NOM. A retrospective cohort study by Occhionorelli et al. demonstrated low failure rate in 26 splenic trauma patients treated with NOM including 5 patients with oral home anticoagulation or antiplatelet therapy and also highlighted the in-hospital observation and strict monitoring that is needed [21]. Interestingly, the grade of injury of the liver and spleen was similar in both groups although the ISS was higher in the group of patients treated surgically (15.2 vs. 7.4, p0.007).
The mean age of the patients who were included in the current study was 72.8± 17.1 years and all of them had serious cardiovascular comorbidities, necessitating long-term treatment with antithrombotic medication. Several reports have shown that older patients (>65 years old) exhibit a 2-fold increased risk of bleeding [22,23]. The presence of specific morbid conditions such as renal and/or hepatic insufficiency may also increase the risk of bleeding after high or even low-energy injuries significantly. Therefore, in cases of BAT, it is essential that the benefits and risks of reversing the effect of AT as well as the potential strategies to keep the period of reversal as short as possible be assessed. In our study, a stratified administration of antidotes was performed without being aggressive in reversing AT and there was no thrombotic complication as a result of this strategy.
Common indications for the use of vitamin K antagonists, such as acecoumarol, in the community include the prevention of CVAs in patients with atrial fibrillation (AF), the prevention of thrombus formation in patients with mechanical heart valves (MHV) and the treatment of venous thromboembolism (VTE) [12]. The available antidotes to reverse its action are PCC, FFP and Vitamin K.
The advantages of PCC over FFP and Vitamin K include rapid reconstitution into a small volume for infusion over 20-30 minutes, the fast onset of action and that no blood testing is needed [24,25]. In cases where PCC is unavailable and rapid reversal is required, FFP should be used, alone or in combination with vitamin K, in order to sustain the reversal effect [10]. Vitamin K may be administered orally or intravenously; however, the IV route achieves a faster response, with the onset of action to be evident within 6-8 hours. Nonetheless, both routes achieve a similar correction of INR after 24 hours [26].
The use of PCC is associated with an increased risk of both venous and arterial thrombosis during the recovery period [27]. Therefore, it should be applied cautiously and only in cases of severe hemorrhage. In our study, PCC was applied only in one patient who was treated surgically due to life-threatening bleeding. On the contrary, intravenous administration of Vitamin K was applied to all patients who were receiving vitamin K antagonists prior to their injury. Furthermore, since FFP contains 70% of all clotting factors [28], its use may achieve immediate maintenance of PT and APTT <1.5 times, compared to the control values. The administration of two units of FFP in one patient of the NOM group, contributed substantially to INR reversal.
The indications for using antiplatelet agents are most often the presence of coronary artery disease and secondary prevention, after a previous ischemic stroke. The transfusion of platelets (PLTs) should be considered as an additional measure when treating severe cases of bleeding in order to maintain a platelet count above 50 x 10^9/l [24]. Desmopressin has also been recommended for trauma patients with intracerebral bleeding or von Willebrand disease [29]. In the current study, among all patients receiving antiplatelet therapy, no absolute indication for administration of desmopressin was evident and there was no need for transfusing platelets, since the drop of their level was not dangerously low. There was no difference in the final outcome between patients receiving acetylsalicylic acid and clopidogrel.

Furthermore, although the use of acetylsalicylic acid has been associated with increased perioperative blood loss during major procedures, it has not been linked with clinically important endpoints, such as the need for transfusion or the requirement for reoperation [30]. Therefore, meticulous hemostasis intraoperatively is of paramount importance for these patients.

Conclusions

The most recent guidelines regarding the treatment of trauma patients receiving AT were published at 2016 [31,3]. Following this pattern, the current study exhibited that AT is not a contraindication for NOM if other prerequisites are fulfilled. Hemodynamically stable trauma patients with no signs of peritonitis receiving AT with grade ≤ III hepatic or splenic blunt injuries are good candidates for NOM. The type of AT does not seem to influence the final outcome. Morbidity and mortality rates, ICU/HDU admission and the length of total hospital stay are lower compared to the patients undergoing surgical intervention.

Riassunto

La gestione non operatoria (NOM) può essere particolarmente difficile nei pazienti sottoposti a contemporaneo trattamento antitrombotico (AT). Con questo studio è stata esaminata la fattibilità di NOM in pazienti con AT che hanno subito lesioni epatiche o spleniche.
Per questo abbiamo analizzato i risultati a 5 anni (2010-2014) di un protocollo prospettico su 15 pazienti sotto trattamento AT, trattati per lesioni spleniche e / o epatiche presso il nostro istituto.
La terapia antitrombotica consisteva in 4 mg di acenocumarolo, 100 mg di acido acetilsalicilico e 75 mg di clopidogrel. La vitamina K (Vit K), il plasma fresco congelato (FFP) e il concentrato di complesso protrombinico (PCC) sono stati trasfusi nei pazienti sottoposti a terapia anticoagulante, mentre piastrine (PLT) sono state somministrate a pazienti sottoposti a terapia antiaggregante se il loro livello era eccessivamente basso. Sono state inoltre registrate il grado delle lesioni organiche, il punteggio di gravità (ISS), la necessità di trasfusione di sangue e di trattamento in terapia intensiva (HDU) di grado elevato, la morbilità, la mortalità e la durata della degenza ospedaliera.
I pazienti con adeguati criteri per NOM e trattati di conseguenza sono stati dieci. Non è stata necessaria alcuna conversione alla gestione operativa (OM) con un tasso di successo del 100%. Cinque pazienti sono stati gestiti chirurgicamente a causa di instabilità emodinamica e / o segni di peritonite. In tutti i casi è stata tentata la In tutti i casi è stata tentata l'interruzione dell'AT.
Si conclude che i pazienti emodinamicamente stabili sotto AT con lesioni epatiche o spleniche (grado ≤ III) e senza segni di peritonite, possono essere buoni candidati per il NOM, nonostante la loro tendenza al sanguinamento. Il tipo di AT non sembra influenzare il risultato finale. L'interruzione del trattamento AT dovrebbe essere deciso caso per caso.

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