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ORIGINAL PAPER

BLEEDING DISORDERS IN ACUTE KIDNEY INJURY PATIENTS DEPENDING ON THE CONDITION'S STAGE

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Summary

Among other complications, hemorrhagic disorders occur frequently during the evolution of acute kidney injury lesions. We analyzed two groups of patients with acute kidney injury caused by various factors (sepsis, trauma, surgery, etc.): one group of patients with RIFLE stage III acute kidney injury treated by hemodialysis and another group of patients with mild acute kidney injury (RIFLE stage I and II) that received medical treatment, without hemodialysis. We noticed the fact that most bleeding disorders (over 50% of all cases) occurred in the hemodialysis group, compared with an 8.5% rate found in the second group. The clinical aspects of bleeding disorders were various (gastrointestinal bleeding, airway bleeding, epistaxis, hemorrhagic conjunctivitis, meningo-cerebral bleeding and hematoma). Severe hemorrhagic disorders (gastrointestinal bleeding, hematomas) altered the patient's outcome and prognosis, increasing the protein catabolism. The condition's therapy was complex and difficult.
Key words: acute kidney injury, hemorrhagic disorders, hemodialysis

Résumé

Lésions hémorragiques chez les patients avec insuffisance rénale aiguë en fonction de la phase de la maladie

Au cours de l'insuffisance rénale aiguë, parmi d'autres complications, des lésions hémorragiques se produisent fréquemment. Nous avons analysé deux groupes de patients avec insuffisance rénale aiguë de diverses étiologies (septique, post-traumatique, postopératoire, etc.): un groupe de patients en phase III (failure) de la classification RIFLE traités par hémodialyse, et un autre groupe de patients avec des formes cliniques plus douces (phase I et phase II de la classification RIFLE), qui a reçu un traitement médical, sans l'hémodialyse. Nous avons constaté que la plupart des événements hémorragiques (plus de 50%) est survenue dans le premier groupe de patients traités par hémodialyse, par rapport à 15.31% enregistrés dans le deuxième group. Les formes cliniques de manifestations hémorragiques étaient très diverses (hémorragie digestive, saignements dans les voies aériennes, épistaxis, conjunctivites hémorragiques, hémorragie intra-cérébrale et méningée, hématomes, etc.). Les graves lésions hémorragiques (hémorragie digestive, hématomes) ont influencé le déroulment et l'issue, parce qu'elles ont augmenté le catabolisme des protéines. La thérapie a été complexe et difficile.
Mots clefs: insuffisance rénale aiguë, lésions hémorragiques, hémodialyse

Introduction

Acute kidney injury (AKI) is a polyetiological condition that still has a high mortality rate, of around 50%, especially in RIFLE (risk, injury, failure, loss, end-stage kidney disease) stage III patients. (1,2)

Prognosis is influenced by the condition's etiology and various complications that occur from the acute kidney injury's debut or during its evolution. It depends on the number and gravity of various organ failures. Hemorrhagic lesions that many take different clinical aspects are among the frequent and severe complications.

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Objectives

Our aim is to analyze various aspects of bleeding disorders and their impact on the evolution of a group of acute kidney injury patients admitted to the Intensive Care Unit of Craiova Emergency Hospital. Patients were admitted to different departments (surgery, obstetrics and gynecology, internal medicine, nephrology, infectious diseases). Our purpose was to outline the impact of the acute kidney injury's etiological factor, as well as that of the uremic factor and other renal failure-related disorders, correlated with the condition's stage based on the RIFLE criteria. We also intended to outline the impact of bleeding disorders on the patients' general condition, as well as their evolution and prognosis.

Material and method

Our study included two groups of patients. The first group consisted in RIFLE stage III (failure) acute kidney injury patients that required renal function substitution using hemodialysis for various periods of time (several weeks). The second group consisted in RIFLE stage I (risk) and II (injury) acute kidney injury (3) patients that did not require hemodialysis and received medical treatment only.

Our groups did not include RIFLE stage IV (loss) acute kidney injury patients with the loss of renal function for over 4 weeks and RIFLE stage V (end-stage kidney failure) acute kidney injury patients with a complete loss of the renal function for over 3 months that were included in a long-term hemodialysis program.

Regarding the RIFLE criteria for acute kidney injury, only the first 3 stages include patients with acute renal failure, while the final 2 stages (IV and V) require over 4 weeks or permanent kidney substitution therapy.

All our patients were monitored regarding coagulation parameters (Quick time, Howell time, INR, platelet count, fibrinogen and fibrin monomers blood levels). The acute kidney injury's etiology in the group of patients treated using hemodialysis is shown in table 1 and that of the patients included in the second group in table 2.

Table 1 includes 86 patients who underwent hemodialysis. In most cases (30) the acute kidney injury's etiology was septic, followed by 13 cases of aggravated chronic kidney disease, 12 cases of severe pancreatitis and posttraumatic acute kidney injury and 11 cases of postoperative acute kidney injury. Table 2 includes 111 patients who did not require hemodialysis. In most cases (28) acute kidney injury occurred after water-electrolyte imbalance (digestive loss, insufficient fluid and electrolyte input). This group also included 19 cases of sepsis-induced and postoperative acute kidney injury.

Results

The clinical aspects of bleeding disorders are displayed in table 3 and table 4.

Table 3 displays the clinical aspects of bleeding disorders in patients who required hemodialysis and table 4 the

Table 1 - The acute kidney injury's etiology in the group of patients treated by hemodialysis (RIFLE stage III)

AKI's etiology	Number of cases	%
Severe sepsis and septic shock	30	34.88%
Trauma	12	13.95%
Surgery	11	12.79%
Acute pancreatitis	12	13.95%
Intoxication	7	8.13%
Icterohemorrhagic leptospirosis	1	1.16%
Aggravated chronic kidney disease	13	15.11%
Total cases	86	100%

Table 2 - The acute kidney injury's etiology in the group of patients who did not require hemodialysis

AKI's etiology	Number of cases	%
Sepsis (peritonitis, urosepsis, genital infections, etc.)	19	17.11%
Trauma	11	10%
Surgery	19	17.11%
Pancreatitis	5	4.5%
Intoxication	3	2.7%
Water-electrolyte imbalance	28	25.22%
Viral infections	4	3.6%
Burns	9	8.1%
Aggravated chronic kidney disease	13	11.71
Total cases	111	100%

Table 3 - Clinical aspects of hemorrhagic lesions in acute kidney injury patients treated by hemodialysis

Hemorrhagic lesions	Number of patients	%
Vascular access and surgical wound hemorrhage	12	13.95%
Gastrointestinal bleeding	9	10.46%
Meningo-cerebral bleeding	3	3.48%
Airway bleeding	4	4.65%
Epistaxis	3	3.48%
Hemorrhagic conjunctivitis	4	4.65%
Hematoma	4	4.65%
Multiple hemorrhage	12	13.95%
Total hemorrhagic lesions	51	59.3%
Total AKI patients	86	100%

Table 4 - Clinical aspects of hemorrhagic lesions in acute kidney injury patients who did not require hemodialysis

Hemorrhagic lesions	Number of patients	%
Digestive bleeding (hematemesis, melena, oral bleeding)	3	2.7%
Meningo-cerebral bleeding	1	0.9%
Airway bleeding	1	0.9%
Epistaxis	1	0.9%
Hemorrhagic conjunctivitis	1	0.9%
Hematoma	1	0.9%
Surgical wound hemorrhage	9	8.1%
Multiple bleeding	0	0%
Total hemorrhagic lesions	17	15.31%
Total AKI patients	111	100%

clinical aspects of bleeding disorders in patients who required medical treatment only (RIFLE stage I and II).

When comparing the results from the two groups of patients (hemodialysis vs. non-hemodialysis), we noticed significant differences regarding the rate of hemostasis disorders.

Over 50% of the patients who underwent hemodialysis (RIFLE stage III) presented at least one hemorrhagic lesion, compared to only 15.31% of the patients from the group that did not require hemodilaysis (table 4).

These tables show that the most severe hemorrhagic lesions with vital impact (meningo-cerebral hemorrhage, airway bleeding and multiple bleeding) were not found in acute kidney injury patients who did not require hemodialysis.

Table 5 and Table 6 display the clinical aspects of hemorrhagic lesions correlated with the acute kidney injury's etiology.

An analysis of table 5 and table 6 shows that the highest rate of bleeding disorders (including severe hemorrhage such as gastrointestinal, airway and meningo-cerebral bleeding) occurred in sepsis-induced acute kidney injury (severe sepsis, septic shock). This suggests that a sepsis-induced coagulation imbalance was the main cause of hemorrhagic disorders in our patients.

The presence of hemostasis disorders was also outlined by macroscopic and microscopic hemorrhagic lesions in various organs revealed during autopsy in deceased patients: figs. 1, 2 show hemorrhagic lesions in the kidney, liver and gastrointestinal tract.

A high rate of hemorrhagic lesions was also found in patients with posttraumatic and postoperative acute kidney injury. The single case in which acute kidney injury was caused by icterohemorrhagic leptospirosis presented multiple bleeding lesions in the context of the general syndrome that clinically defines this infectious disease.

The hemorrhagic syndrome's impact on the protein catabolism was outlined by following the blood urea level over the entire duration of acute kidney injury. An increase of the blood levels was more obvious during hemorrhage, compared to the times when the hemorrhage stopped (fig. 4). Urea was used as a parameter that shows the intensity of

Table 5 - Clinical aspects of hemorrhagic lesions depending on the acute kidney injury's etiology in patients treated by hemodialysis

	Clinical aspects of hemorrhagic lesions									
AKI etiology	Vascular access hemorrhage	Gastrointestinal bleeding	Meningo-cerebral bleeding	Airway bleeding	Epistaxis	Hemorrhagic conjunctivitis	Hematoma	Multiple bleeding	Total AKI cases	Total hemorrhagic complications
Severe sepsis	7	4	3	3	2	2	0	9	30	30
Trauma	1	0	0	1	0	0	4	0	12	6
Surgery	1	3	0	0	0	0	0	0	11	4
Pancreatitis	2	2	0	0	0	0	0	0	12	4
Intoxication	0	0	0	0	1	0	0	2	7	3
Leptospirosis	0	0	0	0	0	0	0	1	1	1
Chronic nephropathies	1	0	0	0	0	2	0	0	13	3
Total cases	12	9	3	4	3	4	4	12	86	51

Table 6: Clinical aspects of hemorrhagic lesions depending on the acute kidney injury's etiology in patients who did not require hemodialysis

	Clinical aspects of hemorrhagic lesions									
AKI etiology	Surgery wound hemorrhage	Gastrointestinal bleeding	Meningo-cerebral bleeding	Airway bleeding	Epistaxis	Hemorrhagic conjunctivitis	Hematoma	Multiple bleeding	Total AKI cases	Total hemorrhagic lesions
Sepsis (peritonitis, urosepsis, genital infections)	0	0	0	0	1	0	0	0	19	1
Trauma	0	0	0	0	0	0	1	0	11	1
Surgery	9	1	0	0	0	0	0	0	19	10
Pancreatitis	0	0	1	0	0	0	0	0	5	1
Intoxication	0	0	0	0	0	0	0	0	3	0
Water-electrolyte imbalance	0	0	0	0	0	0	0	0	28	0
Viral infections	0	0	0	0	0	0	0	0	4	0
Burns	0	2	0	1	0	0	0	0	9	3
Aggravated chronic kidney disease	0	0	0	0	0	1	0	0	13	1
Total cases	9	3	1	1	1	1	1	0	111	17

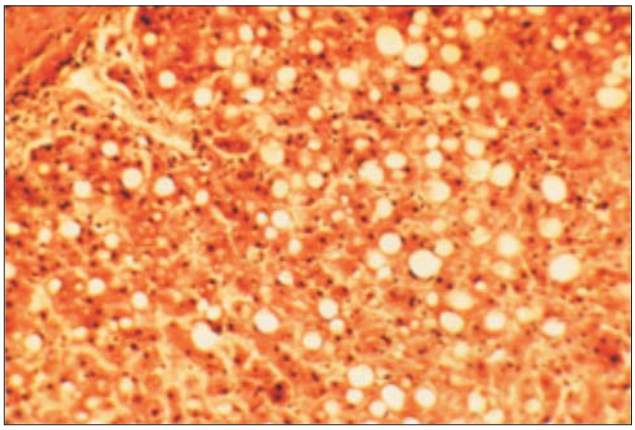

Figure 1 - Liver - Steatosis and hemorrhage

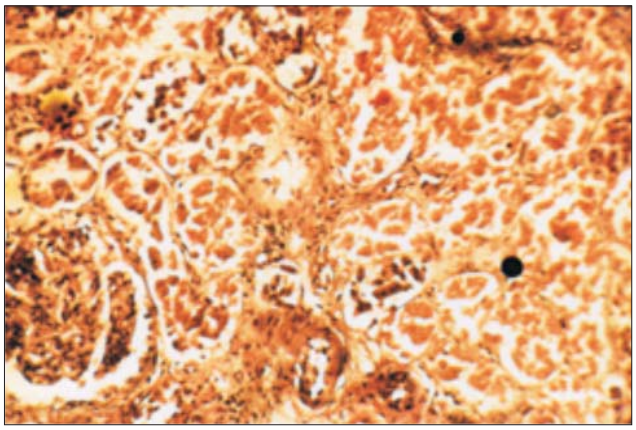

Figure 2 - Kidney – association of hemorrhage and thrombosis

protein catabolism in acute kidney injury patients.

Figure 4 displays a case of posttraumatic acute kidney injury complicated with multiple hematomas. In the first two weeks frequent hemodialysis was necessary because of an increase of the blood urea level and the oligoanuric acute kidney injury stage. After two weeks, when the hematomas diminished, there was an explosive increase of the patient's diuresis, with an improvement of the general condition and a decrease of the blood urea level.

This variation of the blood urea level was also present in patients with other hemorrhagic lesions (melenas).

Discussion

Three issues are discussed based on the clinical results:

1. The causes that disrupt the coagulation balance in acute kidney injury.
2. The variety of clinical aspects of hemorrhagic lesions.
3. The impact of bleeding disorders on the patient's evolution and prognosis.

1. The causes that disrupt the coagulation balance in acute kidney injury are multiple and very complex.

Our clinical analysis has shown that the acute kidney injury's etiological factor has a very important role.

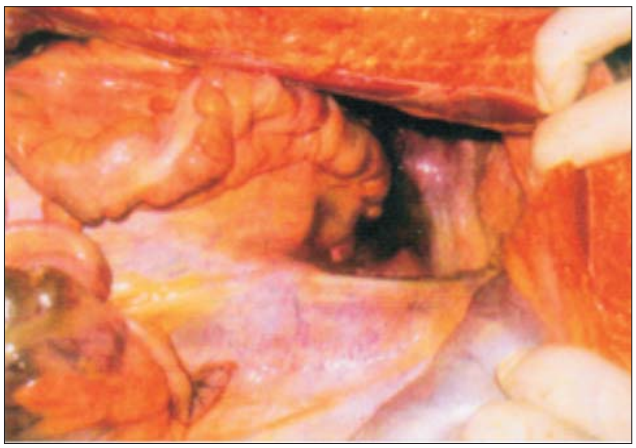

Figure 3 - Intestinal hemorrhage

Septic shock and severe sepsis (that caused most acute kidney injury cases) have the most obvious impact on the coagulation balance. These conditions trigger disseminated intravascular coagulation (DIC) that affects the vascular endothelium and also has a systemic effect because of the released chemical mediators, the acid-base imbalance, the enzyme alterations and the modifications that occur in the protein and lipid balance. (4)

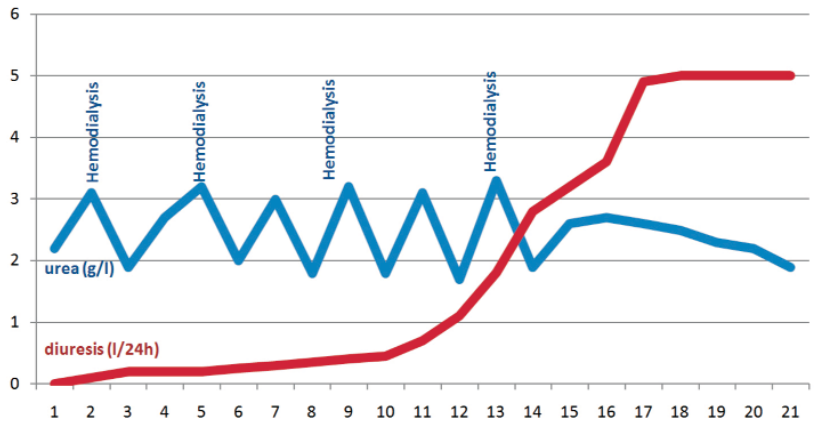

Figure 4 - Evolution of a posttraumatic acute kidney injury patient who presented multiple hematomas

Apart from the consumption of clotting factors, bleeding disorders are caused by thrombocytopenia (5), alterations in fibrin formation, clot lysis caused by plasmin and a difficult synthesis of clotting factors, especially when liver failure is also present. (6)

In acute kidney injury caused by pancreatitis, enzyme-induced capillary and endothelial lesions, mediators that cause the release of acute-phase proteins and granulocyte activation, as well as DIC, are all factors that alter the coagulation balance. (7)

In icterohemorrhagic leptospirosis the hemorrhagic syndrome was usually found, being caused by capillary, hepatic and platelet lesions. In toxic acute kidney injury, the involved chemical substance is important. In our patients the substances involved were carbon tetrachloride and substances used in chemo-therapy that caused tumor lysis. (8)

Postoperative acute kidney injury is caused by postoperative shock, as well as by extended tissue lesions and preserved blood transfusions, especially if patients had a preexisting hematological condition that can affect the coagulation. (9)

In posttraumatic acute kidney injury coagulation disorders are related to the occurrence of the crush syndrome. (1,10) Factors induced by the uremic syndrome affect the coagulation balance during the evolution of acute kidney injury. (11) Many factors are involved: nitrogen retention, anemia, increased nitrous oxide and prostaglandin blood levels, von Willebrand factor alteration, etc.

A series of therapeutic procedures used to treat acute kidney injury is also involved in causing hemorrhagic lesions: hemodialysis, heparin administration, etc. (12,13,14).

2. The variety of clinical aspects of hemorrhagic lesions is displayed in table 3 and table 4. The highest number and the most severe hemorrhagic lesions occurred in the group of patients treated using hemodialysis. The most severe clinical aspects of bleeding disorders were represented by meningo-cerebral hemorrhage, airway bleeding (15) and gastrointestinal bleeding caused by multiple lesions (16), which were very difficult to treat (17). Hematuria and pulmonary hemorrhage also occur in the context of kidney damage (18,19).

Usually, there is an association of multiple causes that affect the coagulation, making it difficult to assess the mechanisms that cause hemorrhagic lesions.

3. The impact of bleeding disorders on the patient's general condition, evolution and prognosis is related to the presence of a hypercatabolic syndrome that requires multiple hemodialysis. Assuring energetic requirements is difficult, regarding the enteral and parenteral nutrition, as well as the inability of cells and tissues to utilize the administered calories. This leads to malnutrition and a difficult recovery.

The hypercatabolic status is also associated with a lack of antibody synthesis that causes immunodeficiency, with an increased risk of septic complications. Severe hemorrhagic lesions can also aggravate anemia.

Conclusions

1. The frequency of bleeding disorders in patients treated using hemodialysis (RIFLE stage III) was higher than in patients who did not require hemodialysis (RIFLE stage I and II). This difference is explained by the many factors that altered the coagulation balance in the first group of patients.
2. There was a large variety of clinical aspects of hemorrhagic lesions: gastrointestinal bleeding, airway bleeding, meningo-cerebral hemorrhage, hematomas, etc.
3. The physiopathological mechanism of bleeding disorders in acute kidney injury is complex, as it involves many factors:
   - etiological factors that triggered the acute kidney injury (shock, trauma, surgery, intoxications, etc.);
   - factors related to the physiopathological changes that occur during acute kidney injury (nitrogen retention, anemia, platelet alterations, etc.);
   - applied therapy that affects the coagulation: hemodialysis, heparin, antiplatelets, preserved blood transfusions, etc;
   - other organ failure associated with the acute kidney injury (liver failure).
4. Severe hemorrhagic lesions have an important impact on the evolution and the prognosis of acute kidney injury patients.

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