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Original Article

High dose of furosemide associated with severe acid-base disturbances in treatment of critically ill patients: a retrospective observation analysis

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Abstract: *Objectives:* The aim of this study was to investigate the effects of overusing furosemide on acid-base disturbances (ABD) in the treatment of critically ill patients. *Methods:* Clinical records were collected from 109 critical ill patients (CIPs), hospitalized at the Emergency Intensive Care Unit (EICU) in Yangpu District Central Hospital (Shanghai, China), from January to May of 2010. Based on use or nonuse of diuretics within 24 hours at admission, patients were divided into 4 groups. Arterial blood gas (ABG) analysis, concentration of potassium (K^+), sodium (Na^+), chlorine (Cl^-), lactic acid, and glucose in serum were measured at 6, 12, and 24~48 hours after admission. *Results*: There were no significant differences in incidence of ABD among all groups at 6 hours after admission ($P > 0.05$). Percentages of non-ABD were significantly increased from about 20% at 6 hours to 35% at 24 hours (in groups A and B) and 40.5% or 55 % at 48 hours (groups A and B, respectively) after admission. Percentages of T-ABD type showed no changes at the 3 time points. In group D, percentages of No-ABD were significantly decreased from 20% at 6 hours to 4.2% at 24 hours and 8.3% at 48 hours after admission. Percentages of T-ABD were significantly increased from 12.5% at 6 hours to 33.3% at 24 hours and 58.3% at 48 hours after admission. *Conclusion:* These results demonstrate that high dose usage of furosemide is associated with ABD, especially T-ABD occurrence in CIPs.

Keywords: Acid-base disturbance (ABD), triple acid-base disturbance (TABD), diuretics, iatrogenic factors

Introduction

Acid-base disturbance (ABD) means that plasma pH has deviated out of normal range (7.35 to 7.45). These disturbances are related to water and electrolyte disorders, directly leading to organ dysfunction and endangered lives [1, 2]. ABD can usually be divided into three categories, simple ABD, double ABD, and triple ABD (T-ABD). Considering the impact of respiratory and renal function on production and regulation of ABD, it can be divided into two types: respiratory and metabolic ABD (namely respiratory acidosis/alkalosis or metabolic acidosis/alkalosis) [3]. T-ABD can happen in critically ill patients (CIPs) [4] with a variety of diseases. It is involved with a variety of complex factors. More than two-thirds of patients may merge with multiple organ dysfunction syndrome (multiple outraged disfunction syndrome, MODS). Studies have reported that fatality rates of T-ABD cases are as high as 50% above, while TABD has been positively correlated with severity of MODS. If the MODS condition is heavier, prognosis of TABD is worse. Mortality of CIPs with T-ABD was significantly higher than in patients with single ABD or double ABD. Thus, TABD is an important factor influencing the prognosis of disease [3].

ABD is the formation of internal environment disturbances. It is influenced by many factors, including diuretics [5, 6], and is life-threatening. Therefore, timely correction of ABD has gained much attention. Since CIPs often suffer with cardiac dysfunction, leading to fluid retention, diuretics have been widely used. Moreover, diuretics can help discharge out redundancy liquid ds and metabolic waste caused by medicine intravenous drips in emergency treatment. The pathogenesis of ABD is complex, including primary disease and secondary influencing factors such as hyperventilation caused by using ventilators, electrolyte imbalance (low potassium, low chlorine) caused by high doses of glucocorticoids and diuretics, and loss of gastric

acid caused by gastrointestinal decompression. However, physicians on the first-line have been very cautious in choosing ventilators, doses of glucocorticoids, and gastrointestinal decompression, but somewhat casual about using diuretics in CIPs in China [7].

This study was designed to determine any connection between higher dose diuretics and severe ABD in critically ill patients. If found, attention should be paid to reduce occurrence of iatrogenic ABD and increase success rates of emergency treatment.

Patients and methods

This retrospective study reviewed clinical data of 109 patients (58 males and 51 females) from the Emergency Intensive Care Unit (EICU) at Yangpu District Central Hospital (Shanghai, China), from January 1 to May 31, 2010. Reviewed items included age, sex, primary disease, underlying disease, complications, acute physiology, and chronic health evaluation II (APACHE II score) [8], as well as brand and dosage of diuretics used within 24 hours at admission, hospital days, and outcomes of treatment. APACHE II scores were calculated with computer software based on data within 2 hours after admission. For standardized usage of diuretics, only cefuroxime sammy (furosemide) and spironolactone, as oral diuretics, and furosemide via intravenous drip were allowed.

Inclusion criteria: 1) Critically ill patients that underwent treatment in EICU; and 2) Patients voluntarily participating in this study. Exclusion criteria: 1) Death within 24 hours of admission; 2) Referral to another hospital or left the hospital against medical advice (AMA); 3) Patients refusing to have blood taken; 4) Patients that did not have blood gas analysis or did not have their blood potassium (K^+), sodium (Na^+), and chlorine (Cl^-) levels checked within 48 hours after admission for a variety of reasons; and 5) Patients with a history of ABD or chronic use of loop diuretics. This study was approved by the Institute Ethics Committee and all patients provided written informed consent.

Grouping

Patients were grouped based on whether diuretics were used within 24 hours of admission. Group A: patients not receiving any diuretics; Group B: patients receiving only oral furosemide (20 mg daily) and spironolactone (Huawei Pharmaceuticals, Hengshui, Hebei, China); Group C: patients receiving intravenous administration of furosemide ≤ 20 mg; Group D: patients receiving intravenous administration of furosemide ≥ 40 mg.

Treatment and use of diuretics

All patients underwent routine treatment, including treatment of primary disease, removal of incentives, correction of electrolyte disorders, and life/organ support therapy (invasive or noninvasive ventilation therapy and vasoactive drugs). Use of diuretics was based on patient conditions and physician's preference of medication. Use of diuretics was not deliberately promoted or limited in this study.

Blood indicators and ABD calculation

Blood was drawn from the veins and arteries of each patient at 6 hours, 24 hours, and 48 hours after admission to perform artery blood gas analysis and to check blood K^+, Na^+, Cl^-, and lactic acid levels. Arterial blood gas analysis was performed with Bayer automatic blood gas analyzer (Brea, USA). Biochemical testing was performed using Johnson automatic biochemical analyzer (New Brunswick, USA).

Values of each measured arterial blood gas parameter were put into the ABD expected compensation formula [9]. Anion gap (AG) values were calculated using the formula: $Na^+ - (HCO3^- + Cl^-)$ [10-12]. Potential value of $HCO3^-$ was calculated using the formula: measured $HCO3^- + \Delta AG$ [10, 13].

Statistical analysis

Statistical analysis was performed using software SAS9.3. Countable data are expressed as frequency (%) and were compared with X^2 test or Fisher's exact test among groups. Measurable data are expressed as mean ± standard deviation and were compared with ANOVA with post hoc of SNK test. Comparison of incidence of ABD before and after treatment was performed using paired Chi-squared test. If $P < 0.05$, differences were considered statistically significant.

Results

General characteristics of patients

A total 167 critically ill patients were emergently sent into the EICU from January to May of 2010. A total of 109 medical records of patients

Table 1. Distribution of primary diseases among patients included in the study

Primary diseases	Patient number (%)	Primary diseases	Patient number (%)
Acute heart failure	28 (25.7)	Infectious shock	3 (2.7)
AECOPD	24 (22.0)	Upper GI bleeding	2 (1.8)
Pneumonia	22 (20.2)	Acute kidney failure	2 (1.8)
Stroke	11 (10.1)	Medicine intoxication	2 (1.8)
MODS	5 (4.6)	Hyperosmolar non-ketotic diabetic coma	1 (0.9)
Acute myocardial infarction	4 (3.7)	Hypertension crisis	1 (0.9)
Advanced tumor	4 (3.7)		

Table 2. Basic information of patients at admission among the four groups

	Group A n = 42	Group B n = 20	Group C n = 23	Group D n = 24	*P*
Male, n (%)	22 (52.4)	11 (55.0)	12 (52.7)	13 (54.2)	1.000
Age (years old), mean ± sd.	78.8 ± 13.5	83.1 ± 7.3	80.0 ± 7.4	78.9 ± 9.2	0.468
APACHE score, mean ± sd.	19.7 ± 6.4	19.3 ± 5.0	20.3 ± 6.2	21.0 ± 6.2	0.667

Table 3. Comparison of incidence of ABD at 6, 24, and 48 hours after admission among the four groups

Time	ABD	Group A n = 42	Group B n = 20	Group C n = 23	Group D n = 24	*P*
6 h after admission	No-ABD	8 (19.0)	4 (20.0)	5 (21.7)	5 (20.8)	1.000
	S-ABD	16 (38.1)	8 (40.0)	8 (34.8)	7 (29.2)	
	D-ABD	13 (31.0)	6 (30.0)	7 (30.4)	9 (37.5)	
	T-ABD	5 (11.9)	2 (10.0)	3 (13.0)	3 (12.5)	
24 h after admission	No-ABD	15 (35.7)	7 (35.0)	5 (21.7)	1 (4.2)[a,b,c]	0.142
	S-ABD	11 (26.2)	5 (25.0)	5 (21.7)	7 (29.2)	
	D-ABD	12 (28.6)	6 (30.0)	9 (39.1)	8 (33.3)	
	T-ABD	4 (9.5)	2 (10.0)	4 (17.4)	8 (33.3)[a,b,c]	
48 h after admission	No-ABD	17 (40.5)	11 (55.0)	4 (17.4)[b]	2 (8.3)[a,b,c]	< 0.001
	S-ABD	8 (19.0)	3 (15.0)	2 (8.7)	5 (20.8)	
	D-ABD	12 (28.6)	3 (15.0)	11 (47.8)	3 (12.5)	
	T-ABD	5 (11.9)	3 (15.0)	6 (26.0)	14 (58.3)[a,b,c]	

Note: a: P < 0.05 when compared with that of group A; b: P < 0.05 when compared with that of group B; c: P < 0.05 when compared with that of group C. S-ABD: single ABD; D-ABD: double ABD. Data were shown in n (%).

meeting the inclusion criteria were collected for the study. There were 58 males (53.2%) and 51 females (46.8%), with mean age of 79.5 ± 11.2 years, ranging from 27 to 97 years. Mean APACHE II score was 19.9 ± 6.4 points (range 10-37 points). Primary original diseases included 28 cases of acute heart failure (25.7%), 24 cases of acute exacerbation of chronic obstructive pulmonary disease (22%), 22 cases of pneumonia (20.2%), including severe pneumonia in 8 cases (7.3%), 11 cases of cerebrovascular accident (10.1%), 5 cases of MODS (4.6%), 4 cases of acute myocardial infarction (3.7%), 4 cases of advanced tumor (3.7%), 3 cases of infectious shock (2.7%), 2 cases of upper gastrointestinal hemorrhage (1.8%), 2 cases of acute renal failure (1.8%), 2 cases of drug poisoning (1.8%), 1 case of hyperosmolar nonketotic diabetic coma (0.9%), and 1 case of hypertensive crisis (0.9%) (**Table 1**).

There were no significant differences among the four groups in terms of general characteristics, gender, age, and APACHE II scores (P > 0.05, **Table 2**).

Comparison of incidence of ABD at 6 hours, 24 hours, and 48 hours after admission among the four groups

Significant changes of ABD types at the 3 time points were mainly observed in group A and D. First, at 6 hours after admission, incidence of

each type of ABD among the 4 groups was similar, about 20%, indicating the percentages and types of ABD caused with primary diseases. Second, in groups A and B, percentages of No-ABD were significantly increased from 20% at 6 hours to 35% at 24 hours and 40.5% or 55% at 48 hours after admission. Percentages of TABD type showed no changes at the 3 time points, respectively, indicating an improved ABD situation without or with low dose of furosemide. Third, in group D, percentages of No-ABD were significantly decreased from 20% at 6 hours to 4.2% at 24 hours and 8.3% at 48 hours after admission. Percentages of TABD were significantly increased from 12.5% at 6 hours to 33.3% at 24 hours and 58.3% at 48 hours after admission, suggesting a direct connection between high dose furosemide and TABD (**Table 3**). Briefly, at 24 and 48 hours after admission, percentages of No-ABD were the lowest while percentages of TABD were the highest in group D.

Discussion

Diuretics are effective drugs for alleviation of fluid retention in patients. High dose diuretics, however, can increase urine volume companied with the loss of electrolytes (Na, K, Cl, Ca, Mg, and P), directly leading to ABD and hypokalemia arrhythmias [5]. Furosemide acting on the distal tubules is independent of any inhibitory effects on carbonic anhydrase or aldosterone. It also abolishes the corticomedullary osmotic gradient and negatively blocks free water clearance. Thus, early diagnosis and correction of ABD greatly improves prognoses of CIPs. This present study analyzed ABG and blood electrolytes at 6, 24, and 48 hours after admission and calculated AG and potential $HCO3^-$ to determine patient acid and alkali statuses.

In this study, each type of ABD in each group was similar ($P = 1.000$). Results showed strong evidence that percentages and distribution of ABD types were not been influenced by high dose furosemide at 6 hours after admission. However, decreased No-ABD and increased T-ABD in group D demonstrated that administration of high dose furosemide induced T-ABD occurrence. In the ICU, ABD has high incidence with complex type and rapid change. T-ABD is an extremely severe form of ABD. Incidence of T-ABD is closely related with diagnosis methods and criteria. Timely detection and diagnosis of T-ABD can provide the basis for further correction of T-ABD to prevent deterioration. A common cause of missed diagnosis of T-ABD is inappropriate diagnostic methods and standards. Previous research has shown that if AG values are not calculated, missed diagnosis rate of T-ABD is 83.1%. If potential HCO3 values are not calculated, the missed diagnosis rate of T-ABD is 88.7% [14]. Therefore, it is necessary to calculate AG and potential HCO3 values in combination with the expected value compensation formula for CIPs.

In the present study, corresponding changes of serum potassium and chlorine were not analyzed. Thus, whether the underlying mechanisms of our findings were due to the increase of excretion of potassium and chlorine was not confirmed. Future studies should further analyze changes in electrolyte levels associated with changes in arterial blood gas analysis, especially changes in serum potassium and chlorine, to explore mechanisms in which diuretics affect ABD incidence and type.

In summary, the present results suggest that high dose usage of furosemide is associated with ABD, especially T-ABD occurrence in CIPs. Thus, caution should be taken when diuretics are used in emergent treatment.

Disclosure of conflict of interest

None.

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