

Management of Acute Clonidine Poisoning in Adults: The Role of Resin Hemoperfusion

Shanshan Fang

Department of Nephrology, 307 Hospital

Bo Han

Department of Nephrology, 307 Hospital

Xiaoling Liu

Department of Nephrology, 307 Hospital

Dan Mao

Department of Nephrology, 307 Hospital

Chengwen Sun

Laboratory of Poisonous Substance Detection, 307 Hospital

Zhi Chen

Department of Nephrology, 307 Hospital

Ruimiao Wang

Department of Nephrology, 307 Hospital

Xishan Xiong (✉ sunghai@163.com)

Affiliated Hengsheng Hospital of the Southern Medical University <https://orcid.org/0000-0002-8557-8025>

Methodology

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Abstract

Clonidine poisoning in adults is rare. An observational retrospective study including 102 adults with clonidine poisoning was conducted. 57 patients with relatively mild conditions were placed in the local emergency departments (EDs) for clinical observation, while the remaining 45 were transferred to the tertiary hospital for intensive treatment, of whom 9 were given supportive care only and 36 were given hemoperfusion (HP), as well as similar supportive treatment. The main symptoms of these cases were: sleepiness, dizziness, fatigue, headache, inarticulacy, tinnitus and dry mouth. Physical examination showed hypotension, bradycardia and shallow and slow breathing. Serum and urine clonidine concentrations were significantly elevated (24.4 ng/ml, 313.2 ng/ml, respectively). All cases slowly returned to their baseline state over 48 to 96 hours, which is co-related with the drawn of serum clonidine level. HP showed more efficient in reducing the serum/urine clonidine level. Clonidine poisoning is a potentially serious condition, which involves multiple system injury, including persistent central nervous system depression, cardiovascular and inhalation inhibition, often requiring intensive treatment. Patients with mild presentations only needed to be monitored and treated with symptomatic support. Of critically ill patients, HP significantly reduced clonidine concentrations, which was effective and had few side effects.

Introduction

Clonidine is a synthetic imidazoline-derived agent, which was initially developed as an antihypertensive agent. Clonidine is also used for several unlabeled indications including ethanol and opioid withdrawal, smoking cessation, muscle spasticity, nicotine dependence, psychosis and mania, and management of attention-deficit/hyperactivity disorder (ADHD) and Tourette syndrome in children. Toxicity from overdose of clonidine has been well described in numerous case series and case reports, mostly in children [1]. Clinical manifestations are characterized by central nervous system (CNS) depression, cardiovascular effects including bradycardia and hypotension, and respiratory depression. The incidence of clonidine poisoning is increasing, and the toxidromic triad of CNS depression, bradycardia and hypotension can often appear serious [2]. Clonidine has been suggested to be a “one-pill can kill” pharmaceutical when children ingest single adult dose unintentionally [3].

Since no specific antidote is available [4], a number of possible nonspecific antidotes have been used for the treatment of clonidine poisoning, including activated carbons, naloxone, multiple vasopressors like dopamine, epinephrine, and norepinephrine, and atropine with variable success [5–7]. Currently, endotracheal intubation (ETI) is performed for somnolence and/or transport in critically ill patients, and approximately 25% were admitted to the intensive care unit (ICU) according to the Florida Poison Center’s data over a period of 15 years, from 2002 to 2016 [8]. However, few case series reported in the literature mentioned the correlation between clonidine concentrations in the blood/urine and clinical presentation, treatment options, and prognosis. There continues to be controversy over monitoring the dosage-dependent severity of clonidine poisoning, adjusting dosage and duration of these antidotes, and further information on the clonidine removal therapy is urgently required [2, 9].

Two small-scale poisonings caused by food contaminated with clonidine powder had occurred in the suburbs around Beijing (Shunyi District in October 2009 and Huairou District in April 2010). About 30–60 minutes thereafter, a total of 102 patients developed altered mental status, sinus bradycardia and hypotension and were referred to 2 nearby EDs. Clonidine was recognized as an etiologic agent within 12 hours after the onset of poisonings, which provided the occasions to examine the manifestations of clonidine poisoning, the dose-response relationships, and the role of HP for clonidine detoxication.

Methods

Summary of the poisoning outbreaks

On October 18th 2009 at about 19:00 p.m, 22 workers were sent to the ED of Shunyi District Hospital after eating noodles at the staff canteen. They showed symptoms of drowsiness, weakness and dizziness. On 23 April 2010 at 12:35 in the afternoon, 80 tourists developed similar symptoms after having lunch in the same restaurant and were taken to the ED of the local hospital. All patients were given gastric perfusion, hydration to promote drainage. Throughout the course of conservative treatment, 45 patients remained bradycardic and hypotensive with a progressively worsening altered mental status, indicating high risk and/or morbidity. After consulting medical toxicologists, these 45 patients were transferred to the Fifth Medical Center of General Hospital of PLA. All ambulances carrying patients were well equipped in case of emergency intubation, tracheotomy and assisted ventilation. After the outbreaks, the local CDC and the public security departments have stepped up efforts to investigate the cause, and specimens from 5 cases were collected randomly and were sent to the Laboratory of Poisonous Substance Detection, The Fifth Medical Center of PLA General Hospital for toxicological testing by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS).

Treatment: supportive care only versus supportive care plus HP

Of all the 102 cases, 57 with relatively mild clinical symptoms were carefully monitored and administered with supportive treatment. After 48–96 hours of treatment, they were discharged from the local EDs. The other 45 cases were transferred to the Fifth Medical Center of General Hospital of PLA, a tertiary general hospital for further management. The vasoactive agents (dopamine and atropine) used since onset were carefully recorded. On arrival to the receiving hospital, these patients remained severely somnolent, bradycardic and hypotensive. After admission, a physical examination, a chest X-ray, abdominal and cardiac ultrasound, electrocardiogram (ECG), electroencephalogram (EEG), magnetic resonance imaging (MRI) of the spine/brain and a full laboratory analysis of blood/urine parameters was performed. After consulting members of the Laboratory of Poisoning Control Center of PLA Academy, the culprit of the poisonings was identified as clonidine. Patient management was at the discretion of the attending physicians and 9 were given supportive care only (SC group) and 36 were given HP, as well as similar supportive treatment modalities (HP group). The main supportive care included carefully monitoring and

intermittent use of dopamine and atropine to maintain hemodynamics stability, and diuresis, supplementation of crystalloids infusion (2500 ml/patient/day), potassium calcium, vitamin B complex, and glutathione were also administered. The clonidine concentrations in serum/urine were tested repeatedly before HP and after HP.

Statistical analysis

Descriptive statistics were used to summarize demographic and practice data. Continuous variables with normal distribution were presents as mean \pm standard deviation (SD); non-normal variables were reported as median (interquartile range, IQR), and number (percentage) as indicated. Normal distribution was determined using Kolmogorov-Smirnov test. Pearson's chi-squared test and Wilcoxon Mann-Whitney U-test were used to compare the clinical findings in the SC group and HP group. Spearman rank correlation analysis was used to analyze the correlation between non-normal variables. A p-value of < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS version 26.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Clinical data from local EDs

All the patients developed drowsiness and fatigue approximately 30–60 minutes after ingestion, which prompted colleagues/restaurant staff to seek immediate medical assistance. Local CDC, police and toxicologist soon arrived at the scene of the poisonings, by sampling and analyzing the results, they concluded that the poisoning was caused by workers eating noodles contaminated with clonidine in the Shunyi District, while tourists in Huairou District have been poisoned by the presence of a powdered form of clonidine in their starches. A report from the Laboratory of Poisonous Substance Detection, The Fifth Medical Center of PLA General Hospital confirmed that the poison was single-drug poisoning of clonidine tested by HPLC-MS/MS. Upon arrival to the referring EDs, all patients underwent gastric lavage, and dopamine, atropine and rehydration support therapy continued without severe inhalation suppression or oxygenation drop beyond normal values requiring intubation. After treatment, 57 patients became awake and their blood pressure and heart rate tended to be stable. After 48–96 hours of carefully monitored and treatment, they were discharged from the local EDs.

Clinical Data from the tertiary hospital

The main symptoms of these cases are: sleepiness, dizziness, fatigue, headache, inarticulacy, tinnitus, dry mouth and blurred vision. Physical examination showed hypotension, bradycardia, low body temperature ($< 36.1^{\circ}\text{C}$), shallow and slow breathing, and normal pulse oximetry on room air. Their peripheral examination was non-significant. A mental status examination was significant for inattention, confusion, delirium and hallucinations. Neurological examination revealed dysesthesia, while deep

tendon and plantar reflexes were normal. A screening laboratory investigation, including full blood count, a chemistry panel including electrolytes, kidney function tests, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and chest X-ray, cranial/spine MRI, were normal. Liver functions in 5 cases including aspartate aminotransferase (AST, 52–68 IU/L (reference: 0–40 IU/l)) and alanine aminotransferase (ALT, 44–78 IU/l (reference: 0–35 IU/l)) and creatine kinase MB isoenzyme (CK-MB, 26–67 IU/l (reference: 0–25 IU/l)) in 6 cases were elevated. The serum clonidine levels ranged from 3.5 to 64.0 (IQR 24.4 (9.2, 38.4)) ng/ml, and urine clonidine concentrations were 52.6 to 590.7 (IQR 313.2 (207.8, 410.0)) ng/ml.

Of the 45 cases, the median age was 19–62 (IQR: 30 (23.0, 40.5)), 22 (48.9%) were female. They were divided into SC group (2 male and 7 female) and HP group (20 male and 16 female). All the 45 patients developed hypotension (< 90/60 mmHg) and dopamine in doses of 6 to 50 ug/kg/minute was used in 42 of them, who developed unbearable headache or dizziness, or the heart rate is less than 40 beats/minute. All of them developed bradycardia, and injections of atropine (dosage: 0.5 to 1.0 mg intravenous (IV) bolus, may repeat every 3 to 5 minutes up to a maximum dose of 3.0 mg/day) are used in 38 of them who developed an extremely low heart rate less than 45 beats/minute or with unbearable headache or dizziness. All the clinical data and the amount of dopamine and atropine were listed in Table 1. The median length of hospital stay was 48–96 hours for both SC group (IQR: 72.0 (72.0, 90.0)) and HP group (IQR: 72.0 (54.0, 72.0)).

Table 1
Demographics, clinical presentations, and treatments-comparing SC to HP group

Main clinical data		SC group (n = 9)	HP group(n = 36)
Median age (IQR)		39.0 (27.5, 45.0)	27.5 (23.0, 39.8)
Sex	male	2 (22.2%)	20 (55.6%)*
	female	7 (77.8%)	16 (44.4%)
Clonidine concentrations	serum (IQR)	13.6 (5.2, 26.0)	26.4 (10.0, 47.1) *
	urine (IQR)	293.8 (201.9, 357.0)	357.5 (216.2, 420.3)
CNS depression	sleepiness	8 (88.9%)	36 (100%)
	dizziness	4 (44.4%)	24 (66.7%)
	fatigue	4 (44.4%)	20 (55.6%)
Cardiovascular inhibition	hypotension	9 (100%)	36 (100%)
	bradycardia	9 (100%)	36 (100%)
Inhalation depression	low respiratory rate	3 (33.3%)	15 (41.7%)
	intermittent apnea	0	12 (33.3%)
Other symptoms	headache	3 (33.3%)	20 (55.6%)
	inarticulacy	2 (22.2%)	12 (33.3%)
	tinnitus	2 (22.2%)	9 (25.0%)
	dry mouth	3 (33.3%)	5 (13.9%)
	blurred vision	2 (22.2%)	6 (16.7%)
	low body temperature	1 (11.1%)	16 (44.4%)
Dopamine (mg)	before admission(IQR)	10.0 (0.0, 15.0)	115.0 (50.0, 225.0) *
	after admission(IQR)	0.0 (0.0, 5.0)	100.0 (0.0, 100.0) *
Atropine (mg)	before admission(IQR)	0.5 (0.25, 1.0)	2.0 (0.5, 3.0) *
	after admission(IQR)	0.0 (0.0, 0.5)	1.0 (0.5, 2.0) *
Other clinical outcome	Hepatic dysfunction	0	5 (88.9%)

There were significant differences between HP group and S C group in the dosage of dopamine/atropine used before/after admission and serum clonidine concentrations; Females were significantly more likely to be admitted to the SC group; Serum clonidine concentration had significant positive correlation with the level in urine. There was no statistical difference in length of hospital stay between the two groups.*P < 0.05

Main clinical data	SC group (n = 9)	HP group(n = 36)
Elevated cardiac enzymes	0	6 (88.9%)
The median length of hospital stay (IQR)	72.0 (72.0, 90.0) h	72.0 (54.0, 72.0) h
There were significant differences between HP group and S C group in the dosage of dopamine/atropine used before/after admission and serum clonidine concentrations; Females were significantly more likely to be admitted to the SC group; Serum clonidine concentration had significant positive correlation with the level in urine. There was no statistical difference in length of hospital stay between the two groups.*P < 0.05		

Effective removal of clonidine by HP

In the HP group, 2-hour HP was administered 1–3 times during the first three days after clonidine poisoning was recognized. The HP was performed through femoral venous catheters at a blood flow rate of 200 ml/min. A single-use HA230 resin HP apparatus (Zhuhai Jianfan Biotechnology Co., Ltd., Guangdong, China) was used which are neutral polymeric adsorbents processed by unique techniques with strong adsorbability to molecules containing lipophilic and hydrophobic groups. Before extracorporeal treatment, the serum clonidine concentration was 26.4 (10.0, 47.1) ng/ml. After HP treatment for 2.0 hours, the serum clonidine concentration had decreased to 8.1 (4.4, 18.3) ng/ml. Resin-based sorbent HP treatment had reduced the clonidine serum concentration by 83.3%, the clonidine removal efficiency of which is a little higher than that of Massimo Bertoli reported in a uremic patient [10]. With the process of treatment, the patients' mental status and cardiovascular inhibition gradually improved, which was consistent with the drawn of serum/urine clonidine level. 19 cases were given the 2nd HP, and 5 cases the 3rd. All cases returned to their baseline state over 48 to 96 hours, which was related with the reduction of serum/urine clonidine level. HP showed more efficient in reducing the serum clonidine level than conventional supportive medical treatment, as shown in Table 2 and Fig. 1.

Table 2
The reduction of serum/urine clonidine concentrations after 1–3 HP

2-hour HP	Serum concentrations		Urine concentrations	
	Before HP	After HP	Before HP	After HP
1st HP (n = 36)	26.4 (10.0, 47.1)	8.1 (4.4, 18.3) *	357.5 (216.2, 420.3)	65.9 (34.5, 229.0) *
2nd HP (n = 19)	4.4(1.2, 15.7)	0.0 (0.0, 4.3) *	158.0 (55.3, 310.6)	17.1 (6.7, 48.5) *
3rd HP (n = 5)	0.5 (0.0, 3.8)	0.0 (0.0, 0.0)	10.1 (5.9, 58.1)	1.5 (0.0, 7.3) *
After 2-hour HP treatment, the clonidine concentrations in serum/urine were significantly decreased. *P < 0.05 ; The concentration of clonidine in urine rebounded slightly the next day before treatment.				

Wakening the patient prevents intubation

The stimulation of alpha-2 adrenoceptors in the locus coeruleus may be responsible for the hypnotic effects of clonidine as this region of the brain helps regulate wakefulness [11]. The somnolence is often accompanied by respiratory depression, decreased oxygen saturation and is frequently treated with ETI, a procedure with significant morbidity [12]. Whether the patient's mental state can keep awake is of great significance in judging the severity, guiding treatment and evaluating prognosis. In our study, by observing the change in level of consciousness from somnolence to wakefulness after treatment and the dynamic change of clonidine concentration in blood and urine accordingly, the relationship between mental state and the concentration in blood and urine could be judged, which was listed in Table 3.

Table 3
Changes of clonidine concentrations in serum/urine following altered mental status

Clonidine level	somnolent			awake		
	max	min	IQR	max	min	IQR
Serum (ng/ml)	35.0	2.4	10.9(4.9, 17.0)	25.0	0.5	4.2(2.8,6.6) *
Urine (ng/ml)	355.0	44.9	154.2(130.1, 222.2)	140.3	72.0	107.5(72.9,140.3)*
Patients tended to be somnolent when the serum concentration exceeded 10.9 ng/ml (urine 154.2 ng/ml), while patients generally remained awake when the serum concentration was less than 4.2 ng / ml (urine 107.5 ng/ml). *P < 0.05						

Favourable prognosis

Throughout the whole process of treatment, variable doses of dopamine, atropine were administered to all the 45 patients, 5 cases awoke following the first HP treatment. Then, the patients in both groups gradually became awake and other clinical manifestations improved. There were no obvious adverse effects in either of the two groups. There were no deaths in the study. All patients were fully recovered before discharge.

Limitation

The major limitation of this study is the retrospective nature and treatments were not randomized, but determined by attending physicians after consulting the toxicologist's opinion. The 45 patients had received variable doses of dopamine, atropine, activated carbons and naloxone before admission to the tertiary hospital, which may have led to changes in the clinical presentation of patients, making scientific

clinical grouping difficult. Naloxone was administered only in a few severely poisoned patients, and did not exceed 10 mg as indicated. So it's hard to tell if naloxone's clinically effective. However, administration of high dose naloxone (10 mg IV bolus) was proved to be effective in reversing the effects of clonidine poisoning [2]. The second major limitation is that HP is more difficult to be applied in children than in adults, while clonidine poisoning mainly occurs in children.

Discussion

Clonidine, an alpha-2 adrenergic agonist that crosses the blood-brain barrier, has been prescribed historically as an antihypertensive agent. Clonidine treats hypertension by stimulating α_2 receptors in the brain, which decreases cardiac output and peripheral vascular resistance, lowering blood pressure [13]. However, with massive overdose, clonidine's peripheral alpha-agonist properties may predominate, resulting in vasoconstriction and marked hypertension [14, 15]. The hypertension is transient because the centrally mediated sympathetic inhibition becomes the predominant effect and BP decreases [16]. Symptoms of clonidine intoxication differ from poisoning with other substances in several reported literature which makes the clinical manifestations of clonidine poisoning more complex. Pomerleau, A. C. et al. reported that a 23-year-old man presented with severe hypertension after rubbing his entire body with compounded medicinal cream containing clonidine and toxicological analysis of initial blood samples revealed a serum clonidine concentration of 5,200 ng/ml [17]. Farooqi, M. et al. reported that a 3.5-year-old male also presented with severe hypertension after a possible accelerated dosing error and the serum clonidine level was 300 ng/ml [6]. Similarly, a 5-year-old boy with clonidine poisoning presented with hypertension and had a serum clonidine concentration of 64 ng/ml [18]. Romano MJ analyzed serial serum samples obtained from a 28 year old man following a 100 mg accidental overdose of clonidine and found that there was a hypertensive response when the serum clonidine concentration was above 50 ng/ml and a hypotensive response when below 50 ng/ml [19]. In our study, the mean median concentrations of Clonidine in blood and urine were 24.4 (ranging from 3.5 to 64.0) ng/ml and 313.2 (ranging from 50.1 to 590.7) ng/ml, respectively and no one was found hypertensive. All above findings were consistent with our patients' presentation, having hypotension with elevated serum clonidine concentrations less than 64.0 ng/ml.

The patterns of clonidine poisoning are changing and there exists great difference between adults and children. Through the literature review, we can find that most cases of clonidine poisoning occur in children, it is related to its wider popularity in pediatric patients for the treatment of ADHD, Tourette syndrome, and sleep disturbances. Clonidine is now used in small amounts in drug withdrawal treatment, in injections, tablets, capsules or patches, and in both children and adults. And its clinical applications as anti-hypertensive agents and nasal decongestants, are very rare. In the past, most clonidine overdoses occurred when a child ingested a grandparent's antihypertensive medications, however, recently case series were involved medication prescribed for children with ADHD or other clinical use in children and occurred in the children's own home [20]. The main poisoning patterns of clonidine in adults include oral overdose, intravenous overdose, excessive use of transdermal patch, for suicide purposes or by mishandling [17, 21, 22]. Our reports have highlighted the emerging new pattern of clonidine poisoning in

adults. It takes about 30–60 minutes from clonidine ingestions to the onset of significant mental disorders, then with toxicological detection technology and other laboratory findings, the diagnosis of clonidine poisoning can be confirmed.

Generally, at therapeutic doses, clonidine has a number of anticholinergic side effects that include dry mouth, constipation, and sedation. While at toxic doses, it can cause hemodynamic instability and depression. However, overdose results in a toxidrome not easily identified, and there is no consensus on how to assess the severity of clinical manifestations. Currently, clinicians assess the degree of intoxication by means of changes in mental status, cardiovascular and respiratory suppression, and then decide on clinical treatment decisions such as the need for ETI and naloxone consumption, application of vasoactive drugs. In theory, studying the correlation between clonidine levels in blood and urine and clinical manifestations and prognosis can help assess severity and guide treatment. Unfortunately, few cases reported on clonidine concentrations, so their relation to clinical manifestations had been seldom analyzed. Our study found a correlation between clonidine concentrations in the blood and urine and clinical presentations including mental disorders, cardiac inhibition. Decreasing the concentrations efficiently and awakening the patients quickly may prevent the high-risk procedure of ETI and duration at ICU. Our study showed that patients could keep awake and relatively safe when clonidine concentrations were less than 4.2 (2.8, 6.6) and 107.5 (72.9, 140.3) in serum and urine respectively. The therapeutic serum clonidine concentrations are variably reported, typically < 4.0 ng/ml [17], or ranging from 0.8 to 2.0 ng/ml [16]. So toxicity can occur frequently with inadvertent double dosing and the narrow therapeutic index suggests that the frequency of severe ingestions will continue in the future.

Clonidine is a fat-soluble compound with a molecular weight of 230 Da, a high distribution volume and a serum drug-protein binding rate of 20–40% [11]. Clonidine is < 50% metabolized in the liver to inactive metabolites, yet the metabolism of clonidine is poorly understood. Approximately 50% of a clonidine dose is excreted in the urine as the unchanged drug and 20% is eliminated in the feces [11, 23]. Clearance of serum clonidine using hemodialysis (HD) is not efficient, and the patient's persistent hemodynamic instability seriously affects the use of HD. However, HP provides advantages compared with HD and has a very small effect on hemodynamics while clearing clonidine from the body [10]. HA230 resin hemoperfusion cartridge is of relatively specific recognition and adsorption capacity to various toxins and drugs. In clinic, the product could be used individually by all kinds of blood purification machines or used in association with other blood purification devices for serum HP treatment. The product is especially applicable in clearing fat-soluble macromolecules, circle-sized micromolecules as well as drugs combined with serum proteins. In the present case, the patient's general condition was improved after starting resin-based sorbent HP.

However, endogenous clearance in patients with normal kidney function also played important role in clonidine's removal. Evaluating clonidine elimination is dependent on creatinine clearance and extracorporeal clearance by HP. Therefore, large amount of crystalloids infusion must be considered and intravenous diuretics for good urine output is functional. Despite these multiple confounders, we feel that HP played prominent a role in the detoxification of clonidine.

Although most of the clonidine poisonings reported in the literature resulted in minimal toxic effects and required only supportive care, clonidine poisoning is a potentially serious problem exhibiting life-threatening symptoms, resulting in significant residual disability and accounting for a significant proportion of ICU admissions. Retrospective study from the American Association of Poison Control Centers National Poison Data System from 2000–2011 showed that clonidine poisoning caused 7 cardiac arrests and 3 deaths [3]. As clonidine ingestions are increasing, intubations will increase and more complications will occur. A lack of reported cases in adults and criteria for assessing the severity of clonidine poisoning has sometimes resulted in aimless treatment or over-treatment, including both level of monitoring and interventions with either antidotes or intubation and ventilation.

Marc Ghannoum et al. suggested that nephrologists and critical care physicians should be commonly involved in the treatment of severely poisoned patients, and various extracorporeal techniques including HP be applied to enhance the elimination of poisons [24]. In HP, blood passes through a charcoal or resin column to which poisons are adsorbed. HP can remove free and protein-bound serum poisons regardless of their molecular size. Our study showed that removal of clonidine efficiently from the body by HP could modify the time course and reduce its severity.

Clonidine has a narrow therapeutic index and clonidine poisoning is a potentially serious condition. Extracorporeal therapy provides the possibility of removing the toxins in the body directly and HP can significantly reduce the serum/urine concentrations of clonidine with few side effects.

Conclusions

Clonidine poisoning is a potentially serious condition, which involves multiple system injury, including persistent central nervous system depression, cardiovascular and inhalation inhibition, often requiring intensive treatment. Elevated clonidine concentrations were closely associated with higher risk of clinical presentations. Patients with mild presentations only needed to be monitored and treated with symptomatic support. Of critically ill patients, HP significantly reduced clonidine concentrations, which was effective and had few side effects.

Declarations

Ethics approval and consent to participate

This was an observational single-center retrospective study, and ethical approval was achieved from the Ethics Committee of the Fifth Medical Center of PLA General Hospital and the study was conducted in accordance with the Declaration of Helsinki for experimental and clinical studies.

Consent for publication

Not applicable.

Availability of supporting data

We agree that the materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors were involved in the development of the views and have approved the final manuscript.

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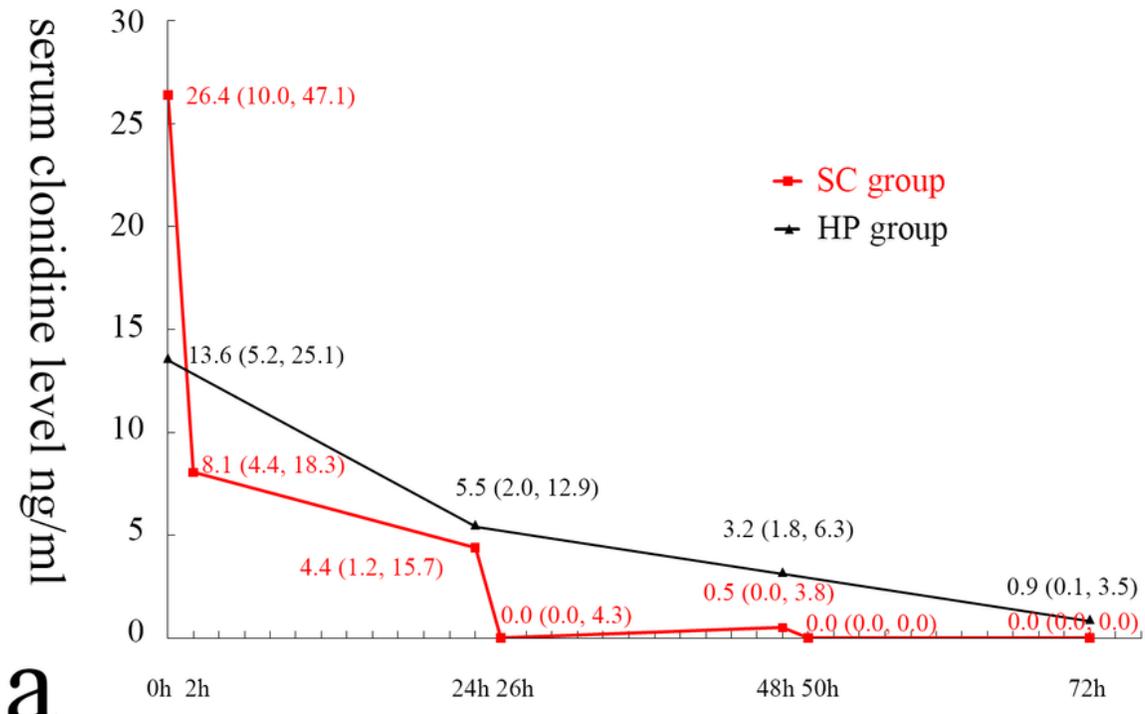
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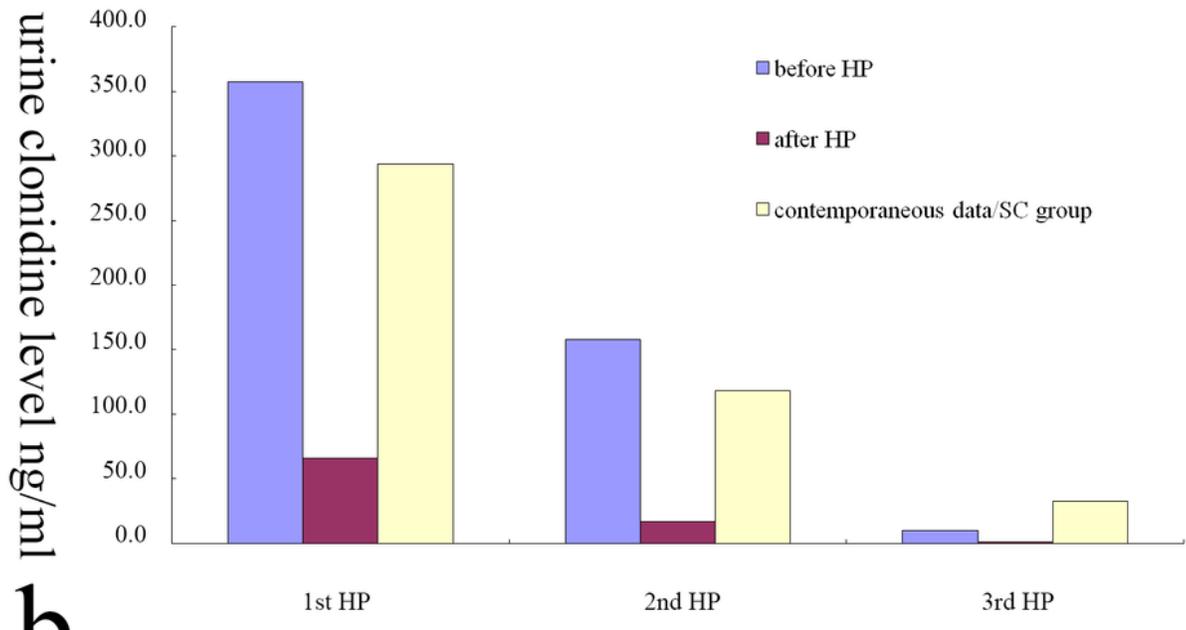
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Figures



a



b

Figure 1

1a, Clonidine elimination was dependent on creatinine clearance with normal kidney function and extracorporeal clearance by HP. HP showed significantly more efficient in reducing the serum clonidine level than conventional supportive medical treatment; $P < 0.05$; 1b The change of urine clonidine level before and after HP was significant and HP showed more efficient in reducing urine clonidine concentrations than treatments in SC group.