

Relationship between saline infusion and blood pressure variability in non-critically patients with hypertension

A retrospective study

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Abstract

Saline is a commonly used intravenous solvent, however, its excessive infusion may increase drug-induced sodium intake. To investigate the effects of saline infusion on blood pressure variability (BPV) in patients with hypertension, a retrospective study was performed in 1010 patients with hypertension. The patients who received saline infusion before surgery for continuous 3 to 5 days were divided into 2 groups according to the saline infusion volume during the hospitalization, which are >500 mL per day group and <500 mL per day group. The overall incidence of abnormal BPV was 11.58%. As for the incidence of abnormal BPV in the <500 mL per day group with 698 patients was 9.17%, while that in the >500 mL per day group with 312 patients was as high as 16.99%. Additionally, >500 mL of daily saline infusion for continuous 3 to 5 days (P for trend = .004, odds ratio [OR] = 1.911, 95% confidence interval [CI] for OR 1.226–2.977), medical history of diabetes mellitus ($P < .001$, OR = 4.856, 95% CI for OR 3.118–7.563) and cardiovascular diseases ($P < .001$, OR = 2.498, 95% CI for OR 1.549–4.029) may be risk factors of abnormal BPV; while anti-hypertensive therapy with diuretics ($P < .001$, OR = 0.055, 95% CI for OR 0.024–0.125) may be the protective factor. Our study suggests that >500 mL of daily saline infusion for continuous 3 to 5 days may have disadvantages in the blood pressure control for hypertensive patients, especially for the patients with diabetes mellitus and cardiovascular diseases.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = blood pressure, BPV = blood pressure variability, CVD = cardiovascular diseases, DM = diabetes mellitus, V = volume.

Keywords: blood pressure variability, hypertension, saline

1. Introduction

Hypertension is one of the high-risk chronic cardiovascular diseases in China, which affected by multiple factors, such as genetics, environment, lifestyle, and psychologic condition.^[1–3] It has been estimated that there are 270 million patients with

hypertension in China, but the prevention situation remains grim now.^[4] In the 1980s, a multicenter research project called Intersalt showed that individual sodium excretion was significantly positively correlated with blood pressure.^[5] The guidelines for prevention and treatment of hypertension in Europe and the United States indicated that limiting the intake of sodium salt (including salt, sauce, pickled foods, etc) is one of the key measures of lifestyle interventions for patients with hypertension.^[6,7] There are some differences in water and sodium excretion after high-salt intake in population. Some of them have difficulty in excreting too much salt, leading to a significant increase in blood pressure, which is called salt sensitivity.^[8] And high blood pressure associated with salt sensitivity is called salt sensitive hypertension.^[9] It is widely believed that blood pressure related to salt sensitivity is an intermediate genetic phenotype of essential hypertension.^[10–12] In China, 28% to 74% of hypertensive patients are salt-sensitive, of which the elderly people make up a higher proportion.^[13]

Although sodium salt restriction from diet has been noticed by patients and doctors, sodium intake from drugs may be ignored. As we found, solvent of intravenous infusion to patients in orthopedics department of Zhongnan Hospital was almost saline due to doctors' medication experience for several years, which increased the drug-induced sodium salt intake. It may become a potential risk factor for blood pressure variability (BPV) of hypertensive patients, especially those who are salt sensitive. Therefore, the use of saline in patients with hypertension, especially in patients with salt-sensitive hypertension, has been a controversial issue. Meanwhile, it is unclear whether there is

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correlation between the infusion volume of saline and abnormal BPV in hypertensive patients. Based on the background and cases above, in this retrospective study we collected cases of patients with hypertension in department of orthopedics from March 2014 to January 2018 to investigate the effect of saline infusion volume on BPV and to provide the evidence for rational selection of intravenous solvent in hypertensive patients.

2. Methods

2.1. Participants and data source

In our study, patients with essential hypertension (including stage 1, stage 2, and stage 3 hypertension) who used 0.9% sodium chloride solution as an intravenous solvent before surgery for continuous 3 to 5 days and were served with low-salt diet at the same time in the department of orthopedics of Zhongnan Hospital from March 2014 to January 2018 were involved. Meanwhile, patients with all kinds of tumor, renal dysfunction, hyperthyroidism, hypothyroidism, hyponatremia, various types of water loss, or more than 5 kinds of severe combined diseases were excluded. Finally, 1010 patients were selected to meet the criterion. Then age, sex, blood pressure (BP), anti-hypertensive medication, and medical history were retrospectively collected. This study was approved by the ethics committee of Zhongnan Hospital of Wuhan University.

2.2. Design and group classification

The relevant information of 1010 patients were collected, and multivariate regression analysis of the abnormal BPV was conducted later. Chi-square test was used to clarify the relationship between average daily infusion volume (V , mL) of normal saline and BPV (mm Hg) in total participants. The patients were classified into elderly and non-elderly subgroups according to the Chinese standard for whether they are <60 years old.^[14] As for the anti-hypertensive medication in hospitalization, it was divided into 2 types: anti-hypertensive therapy with diuretics, and anti-hypertensive therapy without diuretics. Diuretics includes hydrochlorothiazide, spironolactone, and anti-hypertensive compounds containing hydrochlorothiazide. Whether the patients have diabetes mellitus (DM), involving type 1 and type 2 diabetes, or have history of cardiovascular diseases (CVD), including coronary heart diseases, arrhythmia, heart failure, stroke, and so on, was confirmed and classified as well. Chi-square test was also used in these subgroups above. Classification criterion of BPV was as follows: according to existing studies on BPV, both systolic blood pressure and diastolic pressure compare to themselves within 24 hours.^[15] The BPV was calculated as following formulas: $(|BP_2-BP_1| + |BP_3-BP_2| + |BP_4-BP_3|)/3$ or $(|BP_2-BP_1| + |BP_3-BP_2| + |BP_4-BP_3| + |BP_5-BP_4|)/4$.^[16]

BPV ≤ 20 mm Hg indicates a physiological phenomenon, while abnormal BPV was conformed when BPV > 20 mm Hg, and it would get severe abnormal when the BPV > 30 mm Hg.^[17]

2.3. Statistical analysis

SPSS20.0 (SPSS Software, IBM, USA) statistical software was applied and chi-square test was used for counting data. $P < .05$ is considered as statistically significant. Binary logistic regression was chosen as multiple factors regression analysis with BPV abnormality as the dependent variable, and sex, age, mean daily

saline infusion volume, diuretic medication, history of diabetes, and history of cardiovascular disease as independent variables. If the independent variable satisfies both $P < .05$ and the 95% confidence intervals for odds ratio (95% CI for OR) > 1 , it may be a risk factor for abnormal BPV. The other way around, if independent variable satisfies both $P < .05$ and the 95% CI for OR < 1 , it may be a protective factor for abnormal BPV.

3. Results

3.1. Basic characteristics

Table 1 showed the basic characteristics and number proportion of patients of all ages, and Table 2 showed the number proportion of patients in all ages.

3.2. Result of multiple factors regression analysis

The influencing factors mentioned above were introduced into the logistic model for analysis, as showed in the binary logistic regression result. After screening the variables, the independent variables of the potential risk factors in the model were presented, which included daily average saline infusion > 500 mL during continuous 3 to 5 days (P for trend = .004, OR = 1.911, 95% CI for OR 1.226–2.977), history of diabetes ($P < .001$, OR = 4.856, 95% CI for OR 3.118–7.563) and history of cardiovascular diseases ($P < .001$, OR = 2.498, 95% CI for OR 1.549–4.029). However, anti-hypertensive medication ($P < .001$), especially diuretics medication ($P < .001$, OR = 0.055, 95% CI for OR 0.024–0.125), showed statistically significant, which may be the protective factor. Whereas, the age of elder ($P < .001$, OR = 0.076, 95% CI for OR 0.661–2.029), sex (P for trend = .682, OR = 1.102, 95% CI for OR 0.693–1.751), and anti-hypertensive therapy without diuretics (P for trend = .698, OR = 0.887, 95% CI for OR 0.485–1.624) seemed to had no significant effect.

3.3. Correlation between daily mean infusion volume of saline and BPV

The incidence of abnormal BPV was 9.17% in the group of daily average volume < 500 mL, while in the group of daily average volume > 500 mL, the incidence of abnormal BPV was 16.99%

Table 1
Basic characteristics.

Items	Number (%)
Total	1010
Female	630 (62.38%)
Male	380 (37.62%)
Non-elder (<60 y)	232 (22.97%)
Elder (≥ 60 y)	778 (77.03%)
History of diabetes mellitus (DM)	302 (29.90%)
History of cardiovascular diseases (CVD)	244 (24.16%)
Anti-hypertensive medication in hospitalization	926 (91.69%)
Therapy with diuretics	488 (48.32%)
Therapy without diuretics	438 (43.37%)
Dyslipidemia*	41 (4.06%)
Hepatic dysfunction [†]	28 (2.77%)

Note: Data are given by n (%).

* Dyslipidemia refers to abnormal laboratory value of total cholesterol, serum triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

[†] Hepatic dysfunction refers to abnormal laboratory value of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and ALT/AST.

Table 2
Number proportion of patients of all ages.

Age range	Gender		Number (n)	Proportion (%)
	Male	Female		
Under 40	16	2	18	1.78
40–59	111	103	214	21.19
60–79	200	368	568	56.24
80 and above	53	157	210	20.79
Total	380	630	1010	100

Data are given by number (n) or proportion (%).

(Table 3). The overall incidence rate was 11.58%. Chi-square test result showed that the incidence of abnormal BPV was significantly lower in the group of daily average volume <500 mL, compared with the group of daily average volume >500 mL ($P = .00033$; Table 3). No significant difference was detected between men and women.

3.4. Correlation between age and abnormal BPV

Chi-square test result showed that the incidence of abnormal BPV in elderly patients was not significantly different from that of non-aged patients ($P = .2548$; Table 4). However, as for the incidence of abnormal BPV, the incidence of non-elderly patients is 2.73%, lower than that of elderly patients.

3.5. Correlation between daily mean infusion volume of saline and abnormal BPV in DM and CVD groups

Table 5 showed that among the 1010 patients involved in the data extraction, 302 of them suffered diabetes, and the proportion of abnormal BPV was 22.18%. During continuous 3 to 5 days saline infusion, the proportion of abnormal BPV in the patients who received daily average volume <500 mL was 18.41%; while the proportion of abnormal BPV in the patients who received daily average volume >500 mL was 29.70%. A total of 244 patients with a history of cardiovascular events, the proportion of abnormal BPV was 18.44%. During continuous 3 to 5 days saline infusion, the proportion of abnormal BPV was 15.06% in the group of daily average volume <500 mL; while the proportion of abnormal BPV was 25.64% in the group of daily average volume >500 mL.

Chi-square test indicated that in patients with diabetes mellitus, the incidence of abnormal BPV in the group of daily average volume <500 mL was significantly lower than that in the group of daily average volume >500 mL during continuous 3 to 5 days saline infusion ($P_1 = .02583$, Table 5). Among patients with

Table 3
Relationship between daily mean infusion volume (V) of saline and BPV.

Number (%)	V ≤ 500 mL	V > 500 mL	Gender	Total
BPV ≤ 20 mm Hg	634 (90.83%)	259 (83.01%)	M:338;F:555	893 (88.42%)
BPV > 20 mm Hg	64 (9.17%)	53 (16.99%)	M:42; F:75	117 (11.58%)

Daily average saline infusion V ≤ 500 mL during continuous 3 to 5 days versus daily average saline infusion V > 500 mL during continuous 3 to 5 days.

Data are given by number (n) or n (%).

BPV = blood pressure variability.

$P = .00033$.

Table 4
Incidence of abnormal BPV in elderly and non-elderly patients.

Number (%)	Elder	Non-elder	P value
BPV ≤ 20 mm Hg	683 (87.79%)	210 (90.52%)	.25448
BPV > 20 mm Hg	95 (12.21%)	22 (9.48%)	

Data are given by n (%). BPV = blood pressure variability.

other cardiovascular diseases except for hypertension, the incidence of abnormal BPV in the group of daily average volume <500 mL was significantly lower than that in the group of daily average volume >500 mL during continuous 3 to 5 days saline infusion ($P_2 = .04688$, Table 5).

3.6. Correlation between daily mean infusion volume of saline and severe abnormal BPV

As for the incidence of severe abnormal BPV, there was no statistically significant correlation between the 2 different volume of saline infusion groups ($P = .25554$; Table 6). However, we consulted the medical records of the inpatients with severe abnormal BPV later and found that 4 of them had the record of delaying surgical operation date. It is worth noting that all the 4 patients had received >500 mL volume of saline infusion per day during 3 to 5 days before the original operation.

4. Discussion

4.1. Negative influence of BPV

The patients included and enrolled in this study were almost with mid-term BPV, which implied an adverse factor for both underlying disease control and postoperative recovery indicated by an increasing number of high-level evidence studies at present. A systematic review pointed out that long-term BPV (blood pressure monitoring time was longer than 72 hours) was associated with cardiovascular mortality, even higher than that of the mean blood pressure, while the intermediate variability (blood pressure monitoring time was within 72 hours) and short-term variability (blood pressure monitoring time was within 24 hours) also showed similar correlation.^[18] A recent study also showed that high systolic BPV was related with severe hemorrhagic transformation.^[19] Moreover, according to another study, the amount of salt intake may play a role in the pathogenesis of BPV.^[20] The studies above indicated that BPV caused by salt intake may had the negative influences in cardiovascular system.

4.2. Risk factors and possible mechanisms of abnormal BPV

In our study, logistic regression analysis indicated that when daily average saline infusion volume was >500 mL during continuous for 3 to 5 days, diabetes history, and cardiovascular events history might be the risk factors for abnormal BPV, while diuretics medication might be the protective factor. It is indicated that for patients with underlying hypertension, the daily average saline infusion >500 mL during continuous for 3 to 5 days had disadvantage for blood pressure control. The mechanisms of high salt intake leading to elevated blood pressure is complicated by the following aspects: excessive intake of sodium ions exceeds the

Table 5
Relationship between daily mean infusion volume (V) of saline and BPV in hypertensive patients with diabetes mellitus and a history of cardiovascular diseases.

Number (%)	V ≤ 500 mL		V > 500 mL		Total
	BPV ≤ 20 mm Hg	BPV > 20 mm Hg	BPV ≤ 20 mm Hg	BPV > 20 mm Hg	
DM*	164 (81.59%)	37 (18.41%)	71 (70.30%)	30 (29.70%)	302
CVD†	141 (84.94%)	25 (15.06%)	58 (74.36%)	20 (25.64%)	244

Data are given by number (n) or n (%). BPV = blood pressure variability; CVD = cardiovascular diseases; DM = diabetes mellitus.

* $P_1 = .02583$ daily average saline infusion V ≤ 500 mL during continuous 3 to 5 days versus daily average saline infusion V > 500 mL during continuous 3 to 5 days in patients with DM.

† $P_2 = .04688$ daily average saline infusion V ≤ 500 mL during continuous 3 to 5 days versus daily average saline infusion V > 500 mL during continuous 3 to 5 days in patients with CVD.

maximum excretion of the kidney, which lead to retention of water and sodium and increasing extracellular fluid volume, then salt loading activates renal sympathetic nervous system activity and renal sympathetic over-activity may contribute to salt-induced blood pressure, and eventually cause increased cardiac output and high blood pressure.^[21,22]

Due to long-term high blood glucose status, blood viscosity and hemodynamics of diabetic patients were different from the healthy ones, along with the superimposed effect of hyperglycemia on the kidneys, thus resulting in decreased renal sodium excretion.^[23] Recent studies have shown that diabetes was closely related to hypertension. A number of studies have shown that persistent diabetes could induce cardiovascular neurological disorder, which in turn caused hemodynamic changes that ultimately lead to abnormalities in the structure and function of the heart and blood vessels.^[24–26] Clinical studies have shown that there was a significant difference in the dynamic blood pressure and circadian rhythm between normal people and middle-aged patients with diabetes and hypertension, which was consistent with the results in Table 5, suggesting that patients with diabetes should pay more attention to their BPV. In particular, daily BPV are more valuable and clinically meaningful than BPV during hospitalization.^[27–30] Also, many studies have shown that high salt intake had obvious cardiac damage effect in patients with hypertension and diabetes, which decreased the ventricular septal thickness, left ventricular mass index, and other indicators, and resulted in left ventricular compensatory hypertrophy. The hazard is independent of blood pressure levels.^[31] While the drug-induced intake such as infusion of saline that used to be ignored for a long time before, much more attention should be paid by doctors and patients.

Patients with a history of cardiovascular events had pathological changes in their heart and blood vessels, and the cardiac load and vascular elasticity were not as well as physiological status. Under the condition of high salt intake, due to hemodynamic changes and the activation of renin-angiotensin-aldosterone

system, the patients were prone to water and sodium retention and larger BPV.^[32–34]

As for the hydrochlorothiazide and spironolactone, they can help excrete the over-dose intake of sodium, thus relieving sodium retention caused by infusion, but other antihypertensive drugs, such as calcium channel blockers and β -blockers, cannot contribute to the excretion of sodium.^[35] Angiotensin converting enzyme inhibitors and angiotensin receptor blockers can help keep the sodium balanced, but they usually take several months to show the effect of natriuresis,^[36] so that the hypertensive patients may benefit from the anti-hypertensive medication which contains diuretics in the blood pressure rhythm control.

We found that the proportion of patients with abnormal BPV in the group of daily average saline infusion > 500 mL was 7.46%, higher than that of < 500 mL per day group during continuous for 3 to 5 days (Table 3). Compared with normal people's renal sodium excretion, the salt-sensitive have a low sodium ion excretion function, and they are prone to sodium and water retention in the same amount of normal saline intake. Conservative data show that the population of salt sensitivity hypertensive makes up 28% of the hypertensive, which is still higher than the proportion in Table 3. All these data above suggest that for patients with hypertension, normal saline should be used carefully for intravenous infusion in the treatment of other diseases. It is obviously not a wise choice that > 500 mL of daily average infusion longer than 3 days was performed.

It is believed that the proportion of salt-sensitive patients in the elder is higher,^[37] so that the elder ought to show more tendency of abnormal BPV, which is inconsistent with the results of Table 4 in this study. The elderly population is generally with low bone density, making it more prone to fractures events. Therefore, there are more elder patients in the orthopedics department, which cannot represent the age distribution of patients with hypertension. Nevertheless, in this study, the incidence of abnormal BPV in non-elderly patients was 2.73% (Table 4), lower than that in elderly patients. Even if amplified to the whole population, the absolute number of abnormal BPV is still severe.

Even through the blood pressure below 180/110 mm Hg does not affect the orthopedic operation, there is still the best control range of blood pressure during the perioperative period: for patients younger than 60 years or patients with diabetes or chronic kidney disease, the aim blood pressure is below 140/90 mm Hg; for patients older than 60 years, the aim blood pressure is below 150/90 mm Hg.^[38] Even so, we still found that 4 of the inpatients with severe abnormal BPV had to receive the delayed surgery because of the poor control of blood pressure before the scheduled time for surgery. It will not only increase the suffering

Table 6
Relationship between daily mean infusion volume (V) of saline and severe abnormal BPV.

Number (%)	V ≤ 500 mL	V > 500 mL	P value
BPV ≤ 30 mmHg	671 (96.13%)	295 (94.55%)	.25554
BPV > 30 mm Hg	27 (3.87%)	17 (5.45%)	

Data are given by n (%).

V ≤ 500 mL or infusion for continuous 3 days versus V > 500 mL in all and infusion for continuous 3 days. BPV = blood pressure variability.

of patients but also aggravate their economic burden, resulting in waste of medical resources, which were not what expected.^[39,40]

4.3. Study limitations

There are several limitations in this study. Firstly, ambulatory blood pressure monitoring (ABPM) is not a regular monitoring indicator for the non-critically in the department of orthopedics, however, in somehow, the formula of calculating BPV in this study can also suggest the tendency. Secondly, the urinary sodium excretion is not a routine inspection index in the department of orthopedics, so that the renal dysfunctional are excluded in this study to eliminate the effects of blood pressure variability caused by renal excretion disfunction.

5. Conclusion

Our study suggests that it would have an adverse effect for blood pressure control if the saline infusion was >500 mL per day during continuous for 3 to 5 days. Furthermore, patients with diabetes and cardiovascular events are supposed to limit the volume of saline infusion per day, or receipt other solvents such as glucose or xylitol solution in case of organ damage caused by abnormal BPV. Except for the diet control, the drug-induced salt intake such as saline, sodium bicarbonate tablets, and injection should be taken enough attention by doctors and the hypertensive.

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