Comparison of Two Intravenous Fluid Management Strategies in COVID-19 Patients in Hubei, China: A Retrospective Multicenter Study

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Research

Keywords: SARS-Cov-2, COVID-19, Intravenous Fluid Management Strategies

Posted Date: August 12th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-55580/v1>

Abstract

Background

Optimal fluid management in patients with COVID-19 has not been reported. This retrospective, multicenter study investigated the impact of intravenous infusion volume in the early stage of COVID-19 on clinical outcomes.

Methods

127 patients from two tertiary hospitals were separated into the “conservative” and “liberal” groups based on average daily intravenous infusion volume within the first seven days after admission. Basic information, demographic and epidemiological characteristics, laboratory findings, treatments, and outcome measures were retrieved from medical records. The disease progression and prognosis were analyzed and compared.

Results

The average daily intravenous infusion volume within 7 days was 500 (150–700) ml/day in the conservative-strategy group ($n = 87$), and 1100 (1000–1288) ml/day in the liberal-strategy group ($n = 40$) ($p < 0.001$). There were no statistical differences in median age, male-to-female ratio, epidemiology, laboratory findings on admission, comorbidities, and average daily urine output within the seven days ($p > 0.05$). The final K^+ in the liberal group was slightly higher than that at admission, and the final hematocrit level in the conservative group had a significant difference than that at admission ($p < 0.05$). The mean ($\pm$ SD) duration of hospitalization was 22.41 ± 11.99 days in the conservative group and 25.28 ± 12.08 days in the liberal group ($p = 0.120$). However, compared to the liberal group, conservative group had statistically lower rates of disease progression (9.3% vs 37.5%, $p < 0.001$), mechanical ventilation (2.3% vs 27.5%, $p < 0.001$) and in-hospital mortality (2.3% vs 15.0%, $p = 0.012$).

Conclusions

Although there appeared to be no significant difference in the duration of hospitalization between using conservative and liberal fluid management strategies, the former was associated with lower rates of disease progression, mechanical ventilation and in-hospital mortality without increased nonpulmonary-organ dysfunction. These results support the importance of implementing conservative intravenous fluid infusion in the early stage of COVID-19.

Background

Since its outbreak in Wuhan, COVID-19 has spread globally, causing over 11 million infections and 537,000 deaths as of July 6, 2020.^{1,2} The World Health Organization (WHO) had declared COVID-19 a pandemic in March, 2020.³ Despite the gradual decrease in cases in some countries, the pandemic has not yet been brought under control in many other regions of the world.

Studies on its clinical presentation, laboratory and pathological findings along with its clinical outcome have shown that a large proportion of patients died of SARS-CoV-2 associated acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).^{4,5} Yet, the optimal fluid management for ALI/ARDS has not been determined.⁶⁻⁹ Most practitioners believed that appropriate restriction of fluid input is beneficial to a good prognosis of ARDS, and previous studies have supported that a conservative fluid-management strategy for patients with ALI or ARDS may alleviate lung edema, improve lung function, shorten Intensive Care Unit (ICU) stay, decrease duration of mechanical ventilation, and improve prognosis.¹⁰⁻¹² However, some scholars believed that possible risks of this approach are the decrease of cardiac output and deterioration of nonpulmonary-organ function.¹³⁻¹⁶

The incidence of advanced ARDS in patients with COVID-19 pneumonia has been reported to be over 20%.¹⁷ Nevertheless, the impact of fluid restriction in the early stages of COVID-19 on clinical outcomes is unclear.¹⁸ Current evidence is insufficient to support the use of either a liberal or conservative intravenous fluid strategy in the early stages. In this study, we enrolled patients with confirmed COVID-19 from two hospitals in the epicenter province of Hubei (with Wuhan as its capital) and investigated the impact of the two strategies on the outcomes in COVID-19 patients.

Methods

Study design and participants

We conducted a retrospective, cross-sectional, multicenter study focusing on intravenous fluid management in patients diagnosed with COVID-19 from January 1 to April 1, 2020, recruited from the Affiliated Hospital of Wuhan University of Science and Technology and Huanggang Central Hospital, two tertiary hospitals in Hubei, China. This study was approved by the ethics committees of the two hospitals. A total of 236 patients with unexplained pneumonia on general wards in the two hospitals were randomly selected as the initial study population. They would then be further checked with the following inclusion and exclusion criteria.

Based on the clinical diagnostic standards in the New Diagnosis and Treatment Scheme for Novel Coronavirus Infected Pneumonia (Trial Edition 7)¹⁹ issued by the National Health Commission of the People's Republic of China, the inclusion criteria were as follows: 1, their COVID-19 infection was confirmed by SARS-CoV-2 positive finding by real-time polymerase chain reaction (RT-PCR) according to WHO interim guidance using nasal and/or throat swabs. 2, their COVID-19 pneumonia was further confirmed by typical chest computerized tomography (CT) findings.

Those patients who met the following criteria were excluded from the study: 1, without complete laboratory data, including blood counts, blood biochemistry and coagulation parameters. 2, without complete physician's orders sheet. 3, with fewer than seven days' in-hospital stay. 4, having developed shock within seven days since hospitalization. 5, with severe cardiovascular diseases on admission, such as acute myocardial infarction or congestive heart failure. 6, with severe renal impairment, such as acute kidney injury. 7, respiratory failure on admission or requiring mechanical ventilation. And/or 8, with respiratory infections caused by other viruses, including influenza A virus, influenza B virus and respiratory syncytial virus.

Study Procedures

Demographic characteristics, epidemiological history, clinical manifestation, daily intravenous fluid administration and urine output within seven days after admission, admission assessment (curb-65 score), laboratory data, treatment programs and outcome measures were extracted from qualified patients' medical records. Clinical outcomes were followed up to May 1, 2020. Patients were divided into two groups according to the average daily intravenous infusion volume within seven days after admission. Those with an average daily intravenous infusion volume of < 1000 ml were assigned to the conservative-strategy group whereas those with the volume of ≥ 1000 ml to the liberal-strategy group. All data were separately obtained by two authors, and when necessary, missing data were re-collected through communications with attending physicians and other medical personnel. Through comparative analyses of the laboratory data and outcomes of the two groups, the impact of intravenous infusion volume on progression and prognosis was observed. Progression of the disease was assessed in terms of an changed curb-65 score.

Outcomes

In this study, we calculated average daily intravenous fluid administration and urine output of seven days after admission, and collected the epidemiological data (i.e., clear or unclear contact history and illness onset to admission), admission assessment (curb-65 Score), coexisting illnesses, laboratory data, medical treatments and clinical outcomes. Our main observed outcomes included duration of hospitalization, organ functional changes, the rate of disease progression and the necessity for mechanical ventilation. The secondary outcome was in-hospital mortality.

Statistical Analysis

For continuous variables, such as age and average daily urine volume within seven days, mean ($\pm$ SD) was used for normally distributed data and median with interquartile range for non-normally distributed data, followed by t-test and non-parametric tests when appropriate. Categorical variables such as chronic medical illness and in-hospital mortality were expressed as number (%) and compared using the χ^2 test. For laboratory results, we also assessed whether the measurements were outside the normal range. All analyses were performed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA). A two-tailed value of $p < 0.05$ was considered statistically significant.

Results

Enrollment and Exclusions

A total of 236 patients with unexplained pneumonia were initially enrolled during screening. Figure 1 shows the reasons for subsequent exclusion of 109 patients. First excluded were 46 patients for having no RT-PCR test or negative test results. Sixty-three patients were excluded for other reasons such as lacking laboratory data or complete physician's orders sheet and duration of hospitalization fewer than seven days. Some of the patients had more than one reason for exclusion. Of 127 patients eventually included, 87 patients received conservative fluid administration while 40 liberal fluid administration.

Baseline characteristics

The baseline characteristics of the 127 patients with COVID-19 are provided in Table 1. The two groups were similar with respect to demographic characteristics, epidemiological history, time from onset of illness to admission, disease severity on admission, organ dysfunction, coexisting illnesses and treatment programs (all $p > 0.05$). There were no significant statistical differences in the results of laboratory data on admission between the two groups (all $p > 0.05$).

Main outcome measures

The average daily intravenous infusion volume over seven days was 500 (150-700) ml/day in the conservative group, as compared to 1100 (1000-1288) ml/day in the liberal group ($p < 0.001$). There was no significant difference between the two groups in the average daily urinary output during 7 days after admission (1514.93 ± 137.79 ml/day vs. 1511.23 ± 243.28 ml/day, $p = 0.751$) (Table 2).

In the final laboratory examination after seven days of fluid management and before discharge, the lymphocyte count and albumin in the conservative group were higher than those in the liberal group (all $p < 0.05$). In addition, we found that urea nitrogen value and ESR were lower in the conservative group (all $p < 0.05$). No significant differences were found in hematocrit, bilirubin, aminotransferases, creatinine, CRP, NT-pro BNP, ESR and other laboratory results between the two groups (all $p > 0.05$) (Table 2). In the intra-group comparison of laboratory tests, the mean final K^+ in the liberal group was higher than that at admission, and the mean final hematocrit level in the conservative group was lower than that at admission (all $p < 0.05$), but within the normal range. In addition, the hematocrit, Na^+ in the liberal group and K^+ , Na^+ in the conservative group showed no difference (all $p > 0.05$).

The duration of hospitalization was 22.41 ± 11.99 days in the conservative strategy group and 25.28 ± 12.08 days in the liberal group ($p = 0.120$). However, when compared to the liberal group, the conservative group was found to have statistically lower rates of disease progression (9.3% vs 37.5%, $p < 0.001$), mechanical ventilation (2.3% vs 27.5%, $p < 0.001$) and in-hospital mortality (2.3% vs 15.0%, $p = 0.012$) (Table 2).

Discussion

While knowledge regarding epidemiologic features and diagnostic tools of COVID-19 is rapidly evolving, uncertainties surrounding various aspects of optimal management strategies persist. Front-line multidisciplinary experts are deeply concerned about the irregular use of antimicrobials and adjuvant drugs in the international guidelines, as this has resulted in an excessive amount of intravenous fluids in some patients in the short term.²⁰ Whether fluid management should be introduced early in COVID-19 patients to slow down disease progression has not been studied. Relevant previous research into fluid management has mostly focused on patients with ARDS or in other critical conditions. In a study in 416 patients with COVID-19, Shi et al¹⁷ reported an incidence of ARDS as high as 23.3%. A considerable number of COVID-19 patients died of respiratory failure associated ALI /ARDS.^{4,21}

To the best of our knowledge, this study has been the first to focus on the relationship between early intravenous fluid volume and prognosis of COVID-19. It was conducted by examining the medical records of patients during the initial outbreak of COVID-19 in two hospitals in Hubei Province from January to April 2020. In this retrospective study, we chose the daily intravenous infusion volume as a quantitative measure. Although we did not detect a significant difference between the conservative and liberal strategies of intravenous fluid management on the duration of hospitalization, the conservative strategy was significantly associated with lower rates of disease progression, mechanical ventilation and hospital mortality. Therefore, our data appear to suggest that a conservative intravenous fluid strategy leads to fewer complications and better prognosis than a liberal intravenous fluid strategy when managing COVID-19 patients. We speculate that the worse prognosis in the liberal group might be caused by a side effect of over intravenous fluid infusion, resulting in pulmonary interstitial edema.

No significant differences were found in the WBC, hemoglobin, hematocrit levels and other laboratory results between the two groups. The available data are not sufficient to distinguish among these or offer any other potential explanations.

However, during the period studied, most patients' food and drink oral intake was based on their personal appetite and not quantified. The patients' body weight was not monitored, either. These may affect the accuracy in assessing body water retention and need to be addressed in future study.

Although the mean blood urea nitrogen level was slightly lower in the conservative group than that in the liberal group, there were no significant differences in the creatinine level, cardiac and renal function between the two groups. In addition, the conservative strategy was associated with a slightly higher lymphocyte count and albumin level, which might be related to mild dehydration in the patients. The intra-group comparison of laboratory tests showed that there was no dehydration in the conservative strategy and both groups had anhydrous electrolyte imbalance.

In summary, our initial study suggests that conservative intravenous fluid management may result in a favorable prognosis of COVID-19 within the first seven days after patients' admission. Therefore, clinical

treatment may need considering the total amount of daily intravenous infusion in such patients. This should be investigated in prospective and large-scale studies.

Conclusions

Although there appeared to be no significant difference in the duration of hospitalization between using conservative and liberal fluid management strategies, the former was associated with lower rates of disease progression, mechanical ventilation and in-hospital mortality without increased nonpulmonary-organ dysfunction. These results support the importance of implementing conservative intravenous fluid infusion in the early stage of COVID-19.

Abbreviations

WBC: White blood cell count, PT:Prothrombin time, ALT:Alanine aminotransferase, AST:Aspartate aminotransferase, LDH:Lactic dehydrogenase, CRP:C-reactive protein, hs-CRP:High-sensitivity C-reactive protein, NT-proBNP:N-terminal pro-brain natriuretic peptide, PCT:Procalcitonin, ESR:Erythrocyte sedimentation rate.

Declarations

Ethical approval and consent to participate:

This study (S2020-063-01) was approved by the Ethics Committee of Chinese PLA General Hospital. Patient consent was obtained upon hospitalization according to government policy.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

This study was funded by Beijing Municipal Natural Science Foundation General Program (CN, 7192197).

Authors' Contributions:

HL and GX conceptualized the paper. YY and JW analyzed the data with input from RW, ZW, LP, JC, YQ and JD. The data was collected by ZW, LP, JC, YQ and JD. YY, JW and RW wrote the initial draft with all authors providing critical feedback and edits to subsequent revisions. All authors approved the final draft of the manuscript. CC, HL and GX are the guarantor. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Acknowledgments:

We thank all the patients and their family, and the clinical staff who treated the patients in Xiaogan and Huanggang City.

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Tables

Table 1. Baseline characteristics of patients with COVID-19				
Characteristics	All patients (n=127)	Conservative-strategy group (n=87)	Liberal-strategy group (n=40)	<i>p</i> Value
Age, years (mean [SD])	48.90 ± 13.49	48.20 ± 13.31	50.40 ± 13.91	0.389
Sex (male)	62/127 (48.8%)	38/87 (43.7%)	27/40 (60.0%)	0.087
Epidemiological history				
Clear contact history	63 (49.6%)	44 (50.6%)	19 (47.5%)	0.748
Unclear contact history	64 (50.4%)	43 (49.4%)	21 (52.5%)	0.748
Days from illness onset to admission	7 (5-11)	7 (5-11)	7 (5-13)	0.753
Chronic medical illness				
Respiratory system disease	15 (11.8%)	10 (11.5%)	5 (12.5%)	0.541
Cardiovascular system disease	33 (26.0%)	20 (23.0%)	13 (32.5%)	0.256
Chronic liver disease	9 (7.1%)	7 (8.0%)	2 (5.0%)	0.418
Chronic kidney disease	0	0	0	1.000
Endocrine system disease	7 (5.5%)	4 (4.6%)	3 (7.5%)	0.385
Admission assessment (curb-65 Score)				
0	75 (62.0%)	57 (65.5%)	18 (52.9%)	0.132
1	31 (25.6%)	18 (20.7%)	13 (38.2%)	0.132
2	15 (12.4%)	12 (13.8%)	3 (8.8%)	0.132
Medical treatment after admission				
Antibiotic treatment	106 (84.0%)	73 (83.9%)	33 (82.5%)	0.843
Antiviral treatment	124 (97.7%)	85 (97.7%)	39 (97.5%)	0.682
Glucocorticoids	76 (59.8%)	50 (57.5%)	26 (65.0%)	0.421
Intravenous immunoglobulin	61 (48.0%)	41 (47.1%)	20 (50.0%)	0.763

Laboratory tests				
WBC (x10 ⁹ /L)	4.51 (3.59-6.63)	4.50 (3.51-5.84)	4.61 (3.71-8.49)	0.199
Hemoglobin (g/L)	130.56 ± 20.86	131.68 ± 20.37	128.00 ± 22.03	0.387
Hematocrit (%)	39.81 (37.05-43.23)	39.80 (37.13-44.50)	39.50 (35.98-42.83)	0.377
Platelet count (x10 ⁹ /L)	166 (123-206)	167 (134-201)	149 (114-216)	0.575
Lymphocyte count (x10 ⁹ /L)	1.06 (0.75-1.39)	1.11 (0.79-1.48)	0.89 (0.72-1.30)	0.065
PT (s)	13.07 ± 1.65	12.90 ± 1.70	13.58 ± 1.9	0.068
ALT (U/L)	18 (12-31)	17 (12-31)	19 (13-33)	0.362
AST (U/L)	24 (18-31)	22 (18-28)	28 (23-32)	0.054
Albumin (g/L)	38.3 (35.5-41.0)	38.5 (36.1-41.0)	37.5 (34.8-41.2)	0.268
Bilirubin (umol/L)	11.3 (9.3-15.9)	11.1 (9.0-15.1)	13.2 (9.5-23.5)	0.070
Urea nitrogen (mmol/L)	4.06 (3.30-5.18)	3.90 (3.24-4.80)	4.58 (3.63-5.88)	0.053
Creatinine (umol/L)	71.87 ± 18.87	70.57 ± 17.56	72.53 ± 22.07	0.234
K ⁺ (mmol/L)	4.03 (3.73-4.37)	4.11 (3.79-4.40)	3.95 (3.71-4.20)	0.080
Na ⁺ (mmol/L)	140 (138-142)	140 (138-143)	139 (138-141)	0.096
LDH (U/L)	257.56 ± 61.91	251.61 ± 60.38	275.67 ± 60.41	0.117
CRP (mg/L)	38.04 ± 37.59	34.90 ± 40.72	44.33 ± 32.38	0.601
hs-CRP (mg/L)	16.38 (4.08-33.66)	10.40 (3.71-32.27)	23.73 (6.87-42.63)	0.070
NT-pro BNP (pg/ml)	250.30 ± 243.42	188.61 ± 149.02	324.33 ± 312.58	0.112
PCT (ng/ml)	0.20 (0.11-0.33)	0.22 (0.11-0.33)	0.17 (0.11-0.36)	0.627
ESR (mm/h)	33.19 ± 16.15	31.61 ± 17.57	37.41 ± 11.10	0.294

Table 2. Main Outcome Variables of patients with COVID-19			
Characteristics	Conservative-strategy group (n=87)	Liberal-strategy group (n=40)	<i>p</i> Value
Average daily intravenous fluid volume (ml/day) over 1st 7 days after admission	500 (150-700)	1100 (1000-1288)	<0.001
Average daily urine within 7 days (ml)	1514.93 ± 137.79	1511.23 ± 243.28	0.751
Laboratory tests			
WBC (x10 ⁹ /L)	6.17 (4.42-7.76)	6.29 (4.69-10.08)	0.252
Hemoglobin (g/L)	125.02 ± 21.96	122.41 ± 23.23	0.607
Hematocrit (%)	37.92 ± 6.25	38.13 ± 6.61	0.895
Platelet count (x10 ⁹ /L)	211.08 ± 84.36	206.50 ± 100.29	0.827
Lymphocyte count (x10 ⁹ /L)	1.22 ± 0.58	0.95 ± 0.54	0.025
PT (s)	12.56 ± 1.72	12.97 ± 1.63	0.413
ALT (U/L)	33 (16-43)	34 (21-75)	0.299
AST (U/L)	22 (17-28)	24 (17-39)	0.235
Albumin (g/L)	35.9 (32.5-39.2)	33.7 (30.5-36.8)	0.040
Bilirubin (umol/L)	11.9 (8.5-17.0)	13.0(9.6-21.8)	0.441
Urea nitrogen (mmol/L)	4.11(3.20-5.56)	5.00 (4.09-9.06)	0.034
Creatinine (umol/L)	60.65 (51.35-71.05)	66.70 (51.70-79.70)	0.283
K ⁺ (mmol/L)	4.10 ± 0.63	4.35 ± 0.76	0.145
Na ⁺ (mmol/L)	141 (139-143)	141 (138-142)	0.799
LDH (U/L)	229 (185-292)	211 (187-299)	0.924
CRP (mg/L)	7.20 (5.00-15.98)	10.80 (5.50-57.42)	0.482
hs-CRP (mg/L)	5.00 (0.88-21.23)	5.00 (2.48-33.50)	0.241
NT-proBNP (pg/ml)	433.32 ± 431.04	391.25 ± 557.74	0.628
PCT (ng/ml)	0.19 (0.09-0.46)	0.33 (0.13-0.59)	0.447
ESR (mm/h)	18.50 (15.25-41.75)	44.00 (28.75-	0.031

		78.50)	
Progression of the disease			
Disease progress	8 (9.3%)	15 (37.5%)	<0.001
No progress	78 (90.7%)	25 (62.5%)	<0.001
Mechanical ventilation	2 (2.3%)	11 (27.5%)	<0.001
Cases transferred to ICU	3 (3.4%)	12 (30.0%)	<0.001
Total days in hospital	22.41 ± 11.99	25.28 ± 12.08	0.120
Clinical outcome			
Discharged	85 (97.7%)	34 (85.0%)	0.012
Died	2 (2.3%)	6 (15.0%)	0.012

Table 3. Intra-group differences in laboratory tests of COVID-19 patients				
Groups	Laboratory tests	laboratory tests on admission	Final laboratory tests	p Value
Liberal-strategy group (n=40)	Hematocrit (%)	39.50 (35.98-42.83)	39.10 (32.75-43.05)	0.940
	K ⁺ (mmol/L)	3.98 ± 0.67	4.35 ± 0.76	0.017
	Na ⁺ (mmol/L)	139 (137-141)	141 (138-142)	0.054
Conservative-strategy group (n=87)	Hematocrit (%)	39.80 (37.13-44.50)	37.30 (33.50-41.93)	0.024
	K ⁺ (mmol/L)	4.11 (3.79-4.40)	4.25 (3.47-4.6)	0.420
	Na ⁺ (mmol/L)	140 (138-143)	141 (139-143)	0.841

Figures

Figure 1

Figure 1