Original article

Effect of Fluid Therapy on Coagulation in COVID-19 Patients in the Intensive Care Unit

Didem Onk[1], Onur Işik[1], Fethi Akyol[1], Nurcan Kutluer Karaca[1], Yusuf Kemal Arslan[2], Ufuk Kuyrukluyildiz[1]

[1]Department of Anesthesiology and Reanimation, Faculty of Medicine, Erzincan Binali Yıldırım University, Erzincan, Turkey; [2]Department of Biostatistics, Faculty of Medicine, Cukurova University, Adana, Turkey.

Abstract. *Study Objectives*: Several studies have evaluated CT pulmonary angiography of COVID-19 patients and reported a 7%–30% increase in the incidence of pulmonary embolism. In this study, it was aimed to investigate the effect of fluid therapy on coagulation in COVID-19 patients in the intensive care unit. *Methods:* This retrospective study included 120 patients hospitalized in the COVID-19 Intensive Care Unit for more than one week, between August 2020 and February 2021. Blood prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, troponin, D-dimer levels, platelet count measured at the time of admission (T1, baseline) and one week after admission (T2), and the fluid treatments administered during this period were recorded. Patients were divided into the saline solution (SS) group (n=75), 0.45% saline solution group (0.45%, n=30), and combined fluid therapy group (SS+0.45%, n=15). *Results:* The change in PT was statistically significant for the SS group (p = 0.005), but not for the 0.45% and SS+0.45% groups (p = 0.625, p = 0.262, respectively). In the SS group, the aPTT levels increased posttreatment (p = 0.005). INR levels were significantly different between SS and SS+0.45% groups (p = 0.008). In the SS group, the INR levels increased between T1 and T2 (p = 0.014). In the SS group, the D-dimer levels significantly increased posttreatment. *Conclusion:* The D-dimer levels were prominent in the follow-up of the COVID-19 patients. Accordingly, using SS for fluid therapy may increase hypercoagulation and the risk of an embolism when compared to the SS, 0.45%, and combined (SS+0.45%) treatment.

Key words: COVID 19, coagulation, fluid therapy, intensive care unit

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization (WHO) in March 2020. A growing body of evidence has suggested that coagulopathy is common in patients with COVID-19 (1–3). In addition, thromboembolic events are prevalent in the setting of COVID-19. Several studies have evaluated the computed tomography (CT) pulmonary angiographies of COVID-19 patients who did or did not receive anticoagulant therapy and reported a 7%–30% increase in the incidence of pulmonary embolism (4,5). A systematic review of lower extremity ultrasounds of COVID-19 patients in the intensive care unit (ICU) demonstrated deep vein thrombosis in 69%–85% of the patients, despite anticoagulant therapy (6–8).

A better understanding of the characteristics of the SARS-CoV-2 virus and the pathophysiological mechanisms associated with coagulopathy, together with the autopsy findings of COVID-19 patients, have shown that the pulmonary vascular occlusions

consisted of both immunothrombosis and pulmonary thromboembolism in this population (9–12). To the best of our knowledge, there are no studies on the impact of fluid therapy on coagulation in COVID-19 patients. In this study, it was aimed to investigate the effects of fluid therapy on coagulation in COVID 19 patients in the ICU of Anesthesiology and Reanimation Department of Erzincan Binali Yıldırım University.

Material and Method

Participants

The study included 120 patients hospitalized in the COVID-19 Intensive Care Unit of Anesthesiology and Reanimation Department for more than one week, between August 2020 and February 2021. Blood prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, troponin, D-dimer levels, and platelet count measured at the time of admission (T1, baseline) and 1 week after admission (T2), and the fluid treatments administered during this period were recorded. After reviewing the file records, patients were divided into 3 groups; as saline solution group (SS group, n=75), 0.45% saline solution group (0.45% SS group, n=30), and combined fluid therapy group (SS+0.45% group, n=15). All of the patients were given enoxaparin sodium for anticoagulation. Patients with sepsis or septic shock were excluded.

This retrospective study was done in the COVID-19 Intensive Care Unit of Anesthesiology and Reanimation Department of Erzincan Binali Yıldırım University. This study was approved by the Ethics Committee of Erzincan Binali Yıldırım University Faculty of Medicine (approval number: E-21142744-804.99-70874).

Data Collection

All data were collected in the Intensive Care Unit of Anesthesiology and Reanimation Department of Erzincan Binali Yıldırım University.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows 22 (IBM Corp, Armonk, NY, USA). Descriptive statistics were presented as the mean±standard deviation or median (minimum-maximum). Normality of distribution was tested with the Shapiro-Wilks test. Normally distributed data were compared with one-way ANOVA. The Bonferroni test was used as a post hoc test to determine the source of any resulting significant difference. Non-normally distributed data were compared with the Kruskal-Wallis test, and the Dunn test was used as a post hoc test to determine the source of the resulting significant differences. Pre-post changes were analyzed with dependent samples t-test or Wilcoxon signed-rank test depending on the distribution. A p-value <0.05 was accepted as statistically significant.

Results

There were 120 patients, comprising 75 in the SS group, 30 in the 0.45% group, and 15 in the SS+0.45% group. All of the patients, 76 were male (63.3%) and 44 were female (36.7%). The mean age was 72.7±11.1 years (range: 22–92).

When the blood parameters were examined, the baseline (T1, p = 0.816) and posttreatment (T2, p = 0.255) PT levels were statistically similar for the 3groups. In Figure 1 the change in the PT was statistically significant for the SS group (p = 0.005), but not for the 0.45% and SS+0.45% groups (p = 0.625, p = 0.262, respectively).

In Figure 2 the baseline (p = 0.144) and T2 (p = 0.357) aPTT levels of the 3groups were not statistically different. In the SS group, the aPTT levels increased posttreatment (p = 0.005). There was no significant change in the 0.45% and SS+0.45% groups.

In Figure 3 the baseline INR measurements were similar between the 3 groups (p = 0.316), whereas the T2 INR levels were significantly different (p = 0.028). The pairwise post hoc comparisons revealed a statistically significant difference between the SS and SS+0.45% groups (p = 0.008). In the SS group, there was a significant increase in the INR levels between T1 and T2 (p = 0.014).

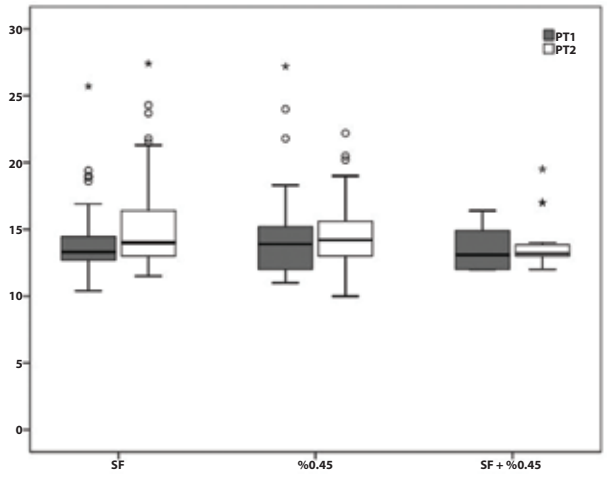

Figure 1. Comparison of PT levels change between three groups

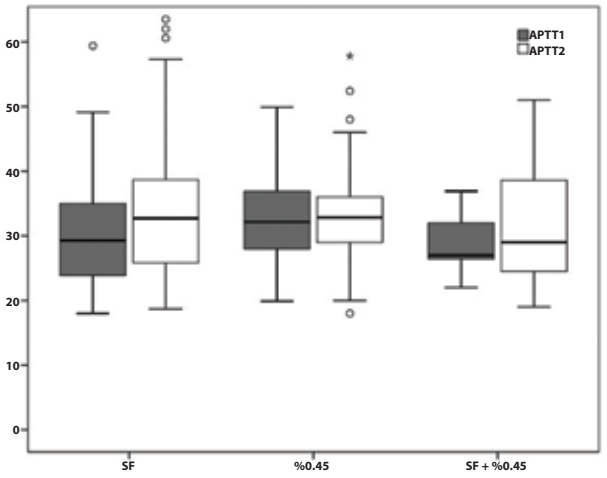

Figure 2. Evaluation of aPTT levels

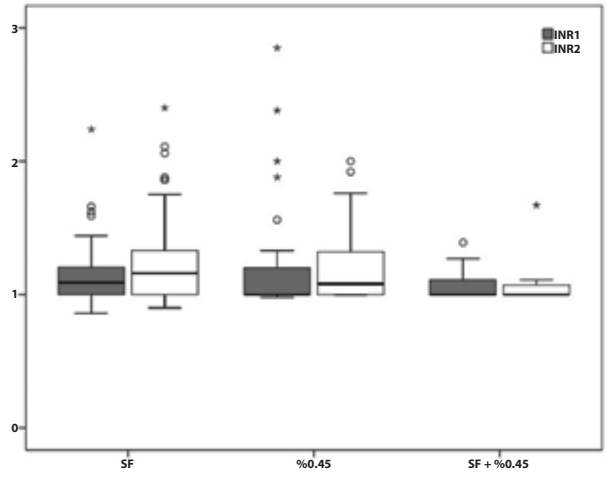

Figure 3. Comparison of INR levels change between three groups

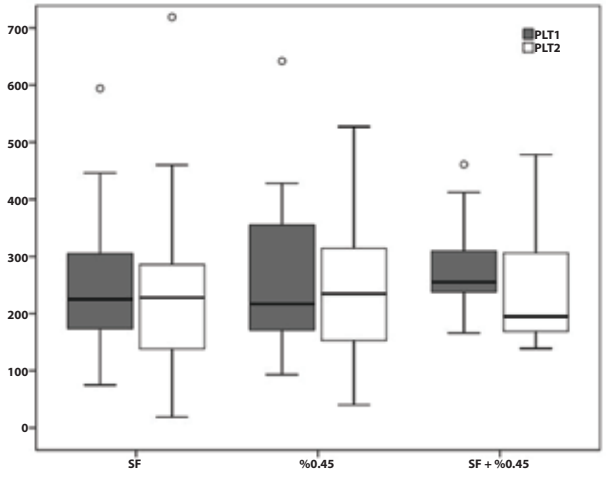

Figure 4. Comparison of platelet count (Plt) change between three groups

In Figure 4 the baseline platelet levels of the 3 groups were similar (p = 0.366). There was no significant change in the platelet levels between T1 and T2. The T1 and T2 fibrinogen and troponin values were not significantly different between the groups. Similarly, there was no significant change between T1 and T2 in any of the groups.

In Figure 5 the baseline and T2 D-dimer measurements of the 3 groups were not statistically significantly different. In the SS group, the D-dimer levels significantly increased posttreatment (p = 0.010).

Discussion and Conclusion

In the literature, one study found the incidence of venous thrombotic complications to be 23% versus 7.9% among patients who were admitted versus those who were not admitted to the ICU. More importantly, thrombotic complications were associated with mortality in COVID-19 patients (13,14).

Like many ICU patients, COVID-19 patients do not often require the transfusion of blood products, but they do require significant amounts of crystalloids

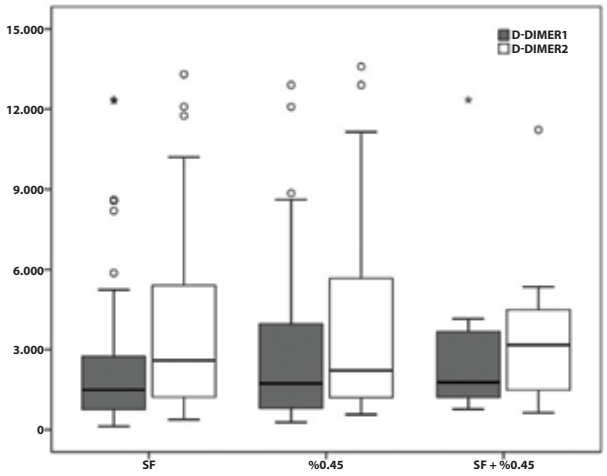

Figure 5. Evaluation of D-dimer levels

over days or weeks in the ICU. Which liquid is the most effective and safe? Since hypercoagulability and complications are increased in this population, we aimed to investigate the answer to the question, which fluid therapy is more frequently associated with hypercoagulability in the ICU?

Surgical guidelines recommend Ringer's lactate (RL) solution due to hyperchloremic metabolic acidosis associated with SS 0.9% (15). However, it is known that this recommendation is based on randomized trials without strong evidence. SS contains 0.9% sodium chloride (9 g/L). The osmolarity of saline is approximately 300 mOsm/L (154mEq/L Na+and Cl–) and is also sometimes referred to as physiological saline or isotonic saline (16).

Recently, the safety of saline solution has come into question due to short-term storage and washing of red blood cells, particularly in patients in critical condition. Although there is no conclusive evidence, it is argued that SS can disrupt kidney function, as well as cause hyperchloremic metabolic acidosis (17–20).

In a sheep model of peritoneal sepsis, animals resuscitated with SS had more severe acidosis and lower cardiac output, lower microcirculatory perfusion, and lower muscle oxygenation when compared to animals receiving similar volumes of lactated Ringer's or Plasma-Lyte. Mortality was lower in the Lactated Ringer group when compared to the normal saline group (21). Similarly, when human saphenous vein grafts were stored in normal saline for 2 hours, the grafts exhibited increased graft injury, decreased viability, and increased endothelial cell dysfunction (22).

In the current study, the PT, aPTT, and INR values increased statistically between T1 and T2 in the SS group. This difference was not statistically significant in the 0.45% and SS+0.45% (0.675%) groups. Smith et al. stated that SS administration may indirectly impair the coagulation mechanism and cause coagulopathy in trauma patients. In addition, this coagulopathy may be a result of hyperchloremic acidosis caused by SS administration (23). This finding was consistent with the results herein.

The D-dimer values significantly changed between T1 and T2 only in the SS group. In the SS group, the T2 measurements were prominently higher when compared to T1. Ramesh et al. stated that the mortality rate was associated with D-dimer levels in COVID-19 patients and that D-dimer levels increased inversely with decreasing eGFR levels, especially in patients with severe disease. This finding was ascribed to the reduced renal clearance of products of the coagulation cascade, resulting in increased D-dimer levels (24).

Due to the coagulopathy associated with hyperchloremic acidosis induced by SS administration and the decreased renal function in severe COVID-19 patients, the PT, aPTT, INR, and D-dimer levels were significantly increased between T1 and T2 in the SS group.

In conclusion, due to hypercoagulation and the associated complications, D-dimer levels are prominent in the follow-up of COVID-19 patients. Accordingly, using SS for fluid therapy may increase hypercoagulation and the risk of an embolism compared to SS 0.45% and combined (SS+0.45%) treatment.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients

with novel coronavirus pneumonia. J Thromb Haemost 2020;18(4):844-847. doi: 10.1111/jth.14768.
2. Levi M, Thachil J, Iba T, Levy H J. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 2020;7(6):e438-e440.doi: 10.1016/S2352-3026(20)30145-9.
3. Cannegieter SC, Klok FA. COVID-19 associated coagulopathy and thromboembolic disease: Commentary on an interim expert guidance. Res Pract Thromb Haemost. 2020;4(4):439-445. doi: 10.1002/rth2.12350.
4. Leonard-Lorant I, Delabranche X, Severac F, et al. Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels. Radiology 2020;296(3):E189–E191. doi: 10.1148/radiol.2020201561.
5. Mestre-Gómez B, Lorente-Ramos RM, Rogado J, et al. Incidence of pulmonary embolism in non-criticallyill COVID-19 patients. Predicting factors for a challenging diagnosis. J Thromb Thrombolysis. 2021;51(1):40-46. doi: 10.1007/s11239-020-02190-9.
6. Ren B, Yan F, Deng Z, et al. Extremely high incidence of lower extremity deep venous thrombosis in 48 patients with severe COVID-19 in Wuhan. Circulation. 2020;142(2):181-183. doi:10.1161/CIRCULATIONAHA.120.047407.
7. Nahum J, Morichau-Beauchant T, Daviaud F, et al. Venous thrombosis among critically ill patients with coronavirus disease 2019 (COVID-19). JAMA Netw Open. 2020;3(5):e2010478-e2010478. doi: 10.1001/jamanetworkopen.2020.10478.
8. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020;18(7):1743-1746. doi: 10.1111/jth.14869.
9. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, andangiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-128. doi: 10.1056/NEJMoa2015432.
10. Ren B, Yan F, Deng Z, et al. Extremely high incidence of lower extremity deep venous thrombosis in 48 patientswith severe COVID-19 in Wuhan. Circulation. 2020;142(2):181-183. doi:10.1161/CIRCULATIONAHA.120.047407.
11. Van Dam LF, Kroft LJ, Dronker CE, et al. Magnetic resonance direc thrombus imaging (MRDTI) can distinguish between old and new thrombosis in the abdominal aorta: a case report. Eur J Case Rep Intern Med. 2020;7(1). doi: 10.12890/2020_001351. eCollection2020.
12. Van Dam L F, Kroft L J M, van der Wal L I, et al. Clinical and computed tomography characteristics of COVID-19 associated acute pulmonary embolism: a different phenotype of thrombotic disease? Thromb Res. 2020;193:86-89. doi: 10.1016/j.thromres.2020.06.010.
13. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-1424. doi: 10.1111/jth.14830.
14. Klok F A, Kruip M J H A, van der Meer N J M, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res. 2020;191:148-150. doi: 10.1016/j.thromres.2020.04.041. doi: 10.1016/j.thromres.2020.04.041.
15. Dyer RA, Reed AR, James MF. Obstetric anaesthesia in low-resource settings. Best Prac Res Clin Obstet Gynaecol. 2010;24(3):401-412. doi: 10.1016/j.bpobgyn.2009.11.005.
16. Prough DS, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology. 1999;90(5):1247-1249. doi: 10.1097/00000542-199905000-00003.
17. Lobo DN. Intravenous 0.9% saline and general surgical patients: a problem, not a solution. Ann Surg. 2012;255:830–2. doi: 10.1097/SLA.0b013e318250766c.
18. Hahn R G. Should anaesthetists stop infusing isotonic saline? Br J Anaesth. 2014;112(1):4-6. doi: 10.1093/bja/aet292.
19. Pfortmueller C A, Fleischmann E. Acetate-buffered crystalloid fluids: current knowledge, a systematic review. J Crit Care. 2016;35:96-104. doi: 10.1016/j.jcrc.2016.05.006.
20. Moritz M L, Ayus J C. Maintenance intravenous fluids in acutely ill patients. N Engl J Med. 2015;373(14):1350-1360. doi: 10.1056/NEJMra1412877.
21. Orbegozo D, Su F, Santacruz C, et al. Effects of different crystalloid solutions on hemodynamics, peripheral perfusion, and the microcirculation in experimental abdominal sepsis. Anesthesiology. 2016;125(4):744-754. doi: 10.1097/ALN.0000000000001273
22. Wise E S, Hocking K M, Eagle S, et al. Preservation solution impacts physiologic function and cellular viability of human saphenous vein graft. Surgery. 2015;158(2):537-546. doi: 10.1016/j.surg.2015.03.036.
23. Smith C A, Gosselin R C, Utter G H, et al. Does saline resuscitation affect mechanisms of coagulopathy in critically ill traumapatients? An exploratory analysis. Blood Coagul Fibrinolysis. 2015;26(3):250-254. doi: 10.1097/MBC.0000000000000154.
24. Ramesh J, Rajesh M, Varghese J, Reddy S L S. Calculated plasma osmolality at hospital admission correlates well with eGFR and D-Dimer, a simple outcome predictor and guiding tool for the management of severe COVID-19 patients. Diabetes Metab Syndr. 2021;15(5):102240. doi: 10.1016/j.dsx.2021.102240.

Correspondence:
Didem Onk
Faculty of Medicine,
Erzincan Binali Yıldırım University, Erzincan, Turkey
Mobil phone: +90 505 385 63 22
E-mail: d.hesapdar@gmail.com