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EFFECT OF FAVIPIRAVIR USE ON INR, PT, APTT TESTS OF COVID-19 PATIENTS

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Abstract

The 2019 coronavirus disease (COVID-19) has caused millions of cases worldwide. As the pandemic progresses, understanding the effects of this disease remains important. We aimed to examine the hematological effects of the disease. The research was carried out as a retrospective study, 50 patients using favipiravir and 50 patients not using favipiravir who had positive COVID-19 RT-PCR test in nasal and throat swabs were included in the study. INR, PTT, aPTT tests were evaluated on all patients. Results of patients using favipiravir; INR 1.3±0.2, PT(s) 16.4±3.4, aPTT(s) 40.7±10.1, while the results of patients who did not use favipiravir were INR 1,2±0.2, PT(s) 14.6±2.5, aPTT(s) was found 38.4±7.8. While PT and INR were found to significantly higher in patients using favipiravir ($p<0.05$), the elevation in aPTT values was not significant. As a consequence, it was obtained that favipiravir prolongs the clotting time. In the light of these results, it is recommended to consider this in anticoagulant therapy used for treatment.

Key Words: COVID-19, INR, PT, aPTT

Özet

2019 koronavirüs hastalığı (COVID-19) dünya çapında milyonlarca vakaya neden oldu. Pandemi ilerledikçe, bu hastalığın etkilerini anlamak önemini korumaktadır. Bu çalışmada hastalığın hematolojik etkilerini incelemeyi amaçladık. Araştırma retrospektif olarak gerçekleştirildi, burun ve boğaz sürüntülerinde COVID-19 RT-PCR testi pozitif çıkan, favipiravir kullanan 50 hasta ve favipiravir kullanmayan 50 hasta çalışmaya alındı. Tüm hastalarda INR, PTT, aPTT testleri değerlendirildi. Favipiravir kullanan hastaların sonuçları; INR 1,3±0,2, PT(s) 16,4±3,4, aPTT(s) 40,7±10,1 iken favipiravir kullanmayan hastalarda INR 1,2±0,2, PT(s) 14,6±2,5, aPTT(s)) 38,4±7,8 bulundu. Favipiravir kullanan hastalarda PT ve INR anlamlı olarak yüksek bulunurken ($p<0,05$), aPTT değerlerindeki artış anlamlı değildi. Sonuç olarak favipiravirin pıhtılaşma süresini uzattığı elde edilmiştir. Bu sonuçlar ışığında tedavi amaçlı kullanılan antikoagülan tedavide bunun dikkate alınması önerilmektedir.

Anahtar Kelimeler: COVID-19, INR, PT, aPTT

1. Introduction

The disease caused by the coronavirus, which first broke out in Wuhan, China in 2019, was named COVID-19, and it was also stated that the causative virus was Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Akbari et al., 2020). The SARS-CoV-2 virus that causes COVID-19 belongs to the Coronaviriadae, a family of single-stranded RNA viruses that can affect many animals, moreover, different corona viruses can infect humans (Le Bert et al., 2020). Its structure includes spike nucleocapsid, membrane, protein and internal proteins (Shang et al., 2020). Biochemical parameters change in early infection, pulmonary and hyperinflammation stages (Yang et al., 2020). Routinely studied clotting factors are analyzed in patients with COVID-19, their clinical significance has not been fully established. The prothrombin time (PT) and international normalized ratio (INR), obtained by dividing a patient's PT result by the laboratory standard, are measured to evaluate the internal and external coagulation pathways. This parameters are helpful in the diagnosis and evaluation of disease and coagulopathy (Zinellu et al., 2021).

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), which is used for the first time against influenza virus resistant to neuraminidase inhibitors and then in the treatment of Ebola

and Norovirus infections, is a new type of RNA polymerase (RdRp) inhibitor that blocks the replication of RNA viruses. Therefore, favipiravir was thought to have potential antiviral effect on SARS-CoV-2, an RNA virüs (De Clercq, 2019; Furuta et al., 2017; Wang et al., 2020).

The aim of the present study was to investigate the tests: INR, PTT and aPTT during treatment with Favipiravir.

2. Material and Methods

The research was carried out as a retrospective study at Amasya University Faculty of Medicine S.Ş.E. Research Hospital. Individuals who applied to the hospital between June 2021 and March 2022 were included.

50 patients who used favipiravir (Favipiravir) and 50 patients who did not use favipiravir,(Non-Favipiravir) whose nasal and throat swabs were positive for COVID-19 RT-PCR were included in the study. Patients who were hospitalized and treated according to the protocol in this process were included in the study. Those under the age of 18, pregnant and those with coagulation disorders were excluded from the study.

Laboratory data of PT, aPTT and calculated INR values measured in Stago Compact Max coagulation analyzer coagulation device were recorded from the system. Coagulation test analyzes were performed on blood samples taken into citrated whole blood tubes.

IBM SPSS 21.0 package program was used for the statistics of the data. The distribution of the data was analyzed using the Kolmogorov-Smirnov test. Student-T test was used for normally distributed data. Data are given as Mean±SD. A value of $p<0.05$ was considered significant.

3. Results

Demographic data of the sample group included in the study are given in Table 1. There was no difference between the two groups in terms of age and gender.

Table 1. Demographic data of the participants

	Favipiravir N:50	**Non- Favipiravir N:50**
Age (years)	56,3 ±19,8	55,2 ±20,4
Gender (Female/Male)	24/26	20/30

While the PT value was 16,4±3,1 seconds in the group using favipiravir, this value was measured as 14,6±2,5 seconds in the group that did not use favipiravir. The PT values of patients using favipiravir were found significantly higher than those who did not (p=0.002, Figure 1).

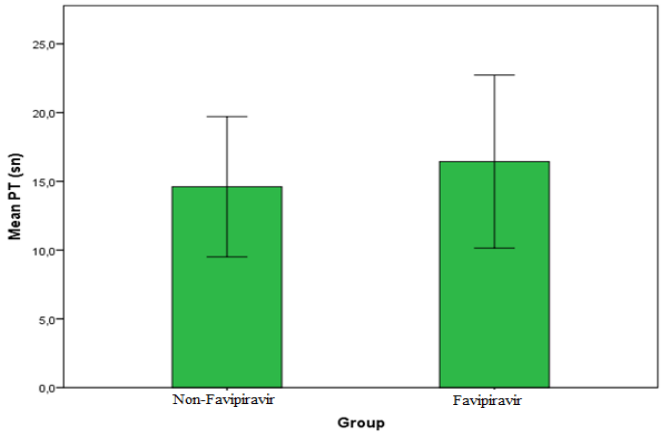

Figure 1. Comparison of PT values of groups using and not using favipiravir.

While the INR value was observed 1,3±0,2 in those using favipiravir, it was found lower as 1,2±0,2 in the group that did not use favipiravir. INR values were significantly higher in the group using favipiravir (p=0.012, Figure 2).

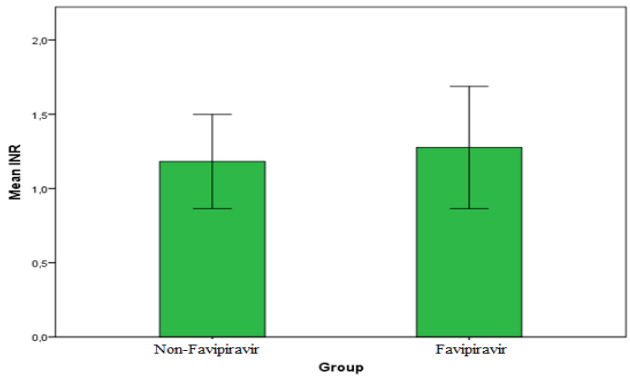

Figure 2. Comparison of INR values of groups using and not using favipiravir.

On the other hand, when aPTT values were taken into account, it was measured as 40,7±10,1h in the group using favipiravir and 38,4±7,8h in the group not using it. aPTT was higher in the group using favipiravir, but no significant difference was detected (p=0.210, Figure 3).

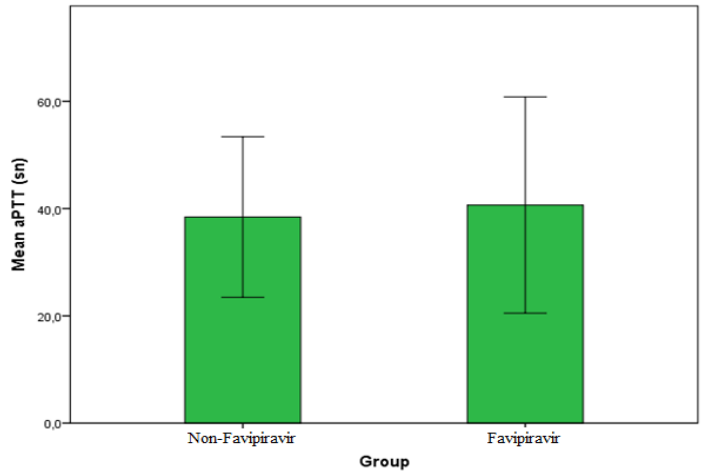

Figure 3. Comparison of aPTT values of groups using and not using favipiravir.

4. Discussion

In this study, the PT and INR values of people with COVID-19 using favipiravir were found statistically significantly higher than those with COVID-19 who did not use favipiravir.

When COVID-19 was divided into three stages, changes were observed in biochemical and hematological parameters. In the first stage, which occurs during the infiltration of the virus, thrombocytopenia, lymphocytopenia formed, D-Dimer, CRP and PT levels increase. In the second stage and in the pulmonary phase which is the most severe stage; ALT and AST levels increase. In the third hyperinflammatory stage, biochemical parameters such as cTn, BNP, cytokines and creatinine increase (Ciaccio & Agnello, 2020; Mir et al., 2022). In COVID-19; coagulation is increased as a result of increased levels of prothrombotic factors. It is thought that increased inflammation, platelet activation, and the effect of stasis in blood flow may cause the development of thrombosis. This situation creates a tendency to thrombosis in both the venous and arterial systems (Connors & Levy, 2020). Coagulation test abnormalities are seen early in infection, but this does not cause clinical bleeding. This picture is called COVID-19-associated coagulopathy

which involves the dysregulation of numerous pathways and culminate in thrombosis (Conway et al., 2022).

In their study, Yaylaci et al. showed that Favipiravir treatment tends to suppress erythrocyte series and increase thrombocyte in COVID-19 (Yaylaci et al., 2020). In parallel with these findings, the animal model study conducted by Atcalı et al. revealed that the use of favipiravir caused a decrease in some hematological parameters including erythrocytes, lymphocytes and monocytes (Atcalı et al., 2021).

Infections initiate a complex systemic inflammatory response as part of innate immunity. It activates coagulation following activation of host defence systems. In studies conducted on COVID-19, prolongation of prothrombin time (PT), INR, and thrombin time (TT) and a shortening of activated partial thromboplastin time (aPTT) have been reported in relation to the severity of the disease (Thachil, 2020; Zhou et al., 2020). In this study regardless of disease severity, in which we examined the effect of favipiravir use on PT and INR values, PT and INR values of people with COVID-19 using favipiravir were found higher than COVID-19 who did not use favipiravir.

5. Conclusion

Prolongation of PT duration and no difference in aPTT duration in patients using favipiravir suggest that favipiravir may have an effect on factors in the extrinsic pathway. As a result, it was observed that favipiravir prolonged the clotting time. In the light of these results, it is recommended to consider this in anticoagulant therapy used as a part of COVID-19 treatment. The possible effects of favipiravir on coagulation in a larger sample group should be investigated and supported in future studies in which patients without anticoagulant use will be included.

Information

This study was presented as an oral presentation at the VII. Turkey In Vitro Diagnostics (IVD) Symposium 2022. We would like to thank the staff and doctors of Sabuncuoğlu Şerefeddin Training and Research Hospital (especially laboratories and clinics related to COVID-19), who worked with great dedication.

Conflicts of interest

The authors declare that there are no potential conflicts of interest relevant to this article.

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