

EFFECT OF TACROLIMUS ON GLOMERULAR FILTRATION RATE AND LIPID PEROXIDATION IN RED BLOOD CELLS IN KIDNEY TRANSPLANT PATIENTS

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In many cases, kidney transplant patients have tacrolimus in their immunosuppressive protocol, meaning to control the natural rejection reaction to the presence of foreign tissue. However, it can show chronic nephrotoxicity and lead to chronic allograft nephropathy, which results in a decrease of allograft function, and a decrease in glomerular filtration rate (eGFR). Also, these patients are usually hemodialyzed for a longer period of time, which is known to be a promoter of oxidative stress (1). Oxidative stress itself, a natural process necessary for numerous defense events in the body, when intensified, leads to tissue damage through the oxidation of macromolecules. Lipids are subject to peroxidation, and one of the markers of this process, thiobarbiturate reactive species (TBARS), can be measured in blood samples. Red blood cells (RBC), as the most numerous blood cells, pass through all tissues, are especially exposed to the free radicals. Also, tacrolimus binds extensively to RBC, so its concentrations in RBC are up to 15 times higher than the concentrations in plasma (2). These facts prompted us to examine the possible association of the effects of tacrolimus in the patient treatment and the parameters of renal function and lipid peroxidation of RBC. The study involved 72 transplanted patients and 62 healthy subjects (control group). The pharmacokinetic data used for the study were the daily dose of tacrolimus divided by the patient's body weight, the tacrolimus whole blood concentration measured immediately before the morning dose (C_0) and the C_0 and daily dose ratio (C_0/D). C_0 concentration was measured in whole blood using a chemiluminescent based method (CMIA, applied to Architect, Abbott, Abbott Park, IL, USA.) To determine the content of TBARS in RBC we used the Jain et al method (3). The results of the study showed significantly increased values of TBARS in RBC of patients compared to controls ($p = 0.023$). Correlation analysis showed that TBARS in RBC of patients has a significant negative correlation with eGFR, while correlation between daily dose, C_0 concentration and C_0/D ratio of tacrolimus with TBARS in patients' RBC did not show a significant correlation of these parameters. Nevertheless, the daily dose and C_0/D ratio of tacrolimus show a statistically significant negative correlation with eGFR. We can conclude that the dose of tacrolimus does not affect the extent of lipid peroxidation in patients' erythrocytes, which is definitely enhanced in patients compared to controls.

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EFEKAT TAKROLIMUSA NA JAČINU GLOMERULARNE FILTRACIJE I LIPIDNU PEROKSIDACIJU ERITROCITA KOD PACIJENATA SA TRANSPLANTIRANIM BUBREGOM

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Pacijenti sa transplantiranim bubregom u velikom broju slučajeva u svojoj terapiji imaju takrolimus kao imunosupresivni agens, čiji je cilj da kontroliše prirodnu reakciju organizma na prisustvo stranog tkiva. Ovaj lek, međutim, može da pokaže hroničnu nefrotoksičnost i dovede do hronične nefropatije alografta, što za posledicu ima smanjenje funkcije transplantiranog organa, koje se ogleda u smanjenju veličine glomerulske filtracije (eGFR). Takođe, u pitanju su pacijenti koji su u velikom broju slučajeva dosta vremena proveli na hemodijalizi, koja je pak poznata kao jak promotor oksidativnog stresa (1). Sam oksidativni stres, iako prirodan proces neophodan za brojne odbrambene događaje u organizmu, kada je pojačan, dovodi do oštećenja tkiva putem oksidacije makromolekula. Lipidi podležu peroksidaciji dejstvom slobodnih radikala, i jedan od markera ovog procesa, tiobarbituratne reaktivne vrste (TBARS), mogu se meriti u uzorcima krvi. Eritrociti, kao najbrojnije ćelije krvi, koje prolaze kroz sva tkiva, naročito su izloženi dejstvu slobodnih radikala. Takođe, takrolimus ima svojstvo da se pojačano vezuje za eritrocite, pa su njegove koncentracije u eritrocitima i do 15 puta veće u odnosu na koncentracije u plazmi (2). Ove činjenice podstakle su nas da ispitamo moguću povezanost dejstva takrolimusa u terapiji pacijenata i parametara bubrežne funkcije i lipidne peroksidacije eritrocita. U istraživanju su učestvovala 72 transplantirana pacijenta i 62 zdrava ispitanika, koja su činila kontrolnu grupu. Farmakokinetički podaci korišćeni u svrhu istraživanja bili su dnevna doza takrolimusa, podeljena sa telesnom težinom pacijenta, koncentracija takrolimusa u punoj krvi izmerena neposredno pred primenu jutarnje doze leka (C_0) i odnos koncentracije C_0 i dnevne doze leka (C_0/D), koji predstavlja indeks biorasploživosti leka. Koncentracija C_0 je bila izmerena u punoj krvi pomoću metode u čijoj je osnovi hemiluminiscentno imunoodređivanje na mikročesticama (CMIA metoda, aplikovana na Architect, Abbott, Abbott Park, IL, USA). Za određivanje sadržaja TBARS, markera lipidne peroksidacije, u eritrocitima korišćena je metoda Jain i sar (3). Rezultati istraživanja pokazali su značajno povećane vrednosti TBARS u eritrocitima pacijenata u odnosu na kontrole ($p=0,023$). Korelaciona analiza je pokazala da TBARS u eritrocitima pacijenata pokazuje značajnu negativnu povezanost sa vrednostima eGFR, dok korelaciona analiza između dnevne doze, koncentracije C_0 i odnosa C_0/D takrolimusa sa TBARS u eritrocitima pacijenata sa transplantiranim bubregom nije pokazala značajnu povezanost ovih parametara. Ipak, dnevna doza i C_0/D odnos takrolimusa pacijenata pokazuju statistički značajnu negativnu korelaciju sa eGFR. Možemo zaključiti da doza takrolimusa ne utiče na obim lipidne peroksidacije u eritrocitima pacijenata, koja je definitivno pojačana kod pacijenata u odnosu na kontrole.

Literatura:

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