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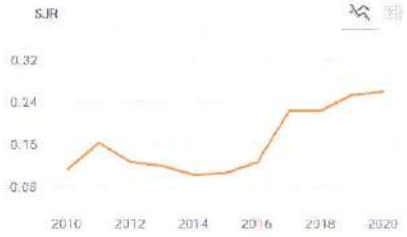

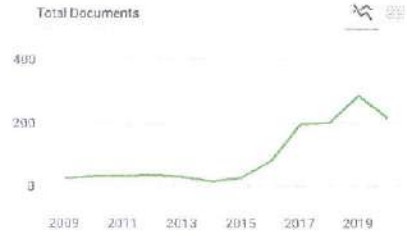

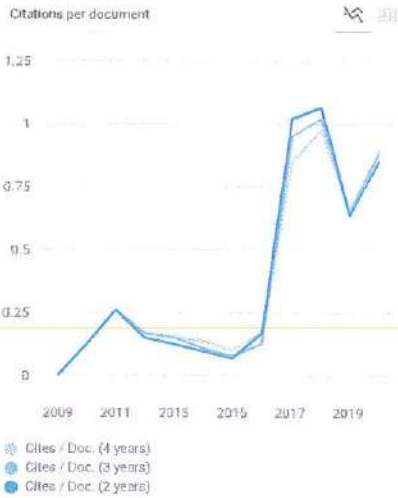

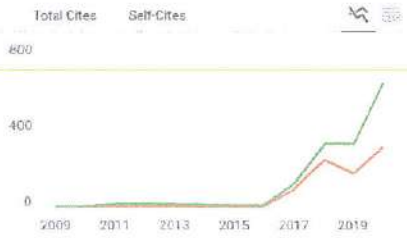

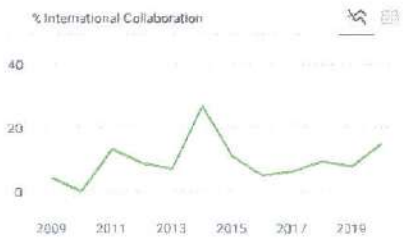

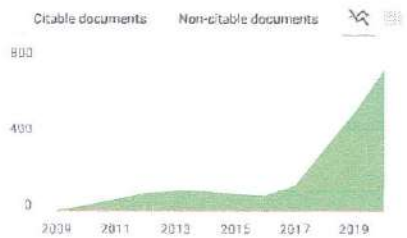

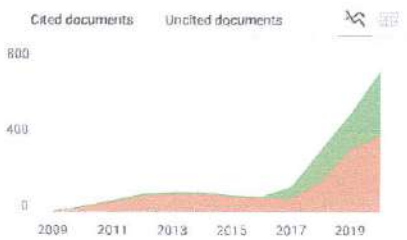

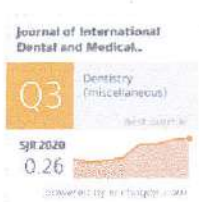

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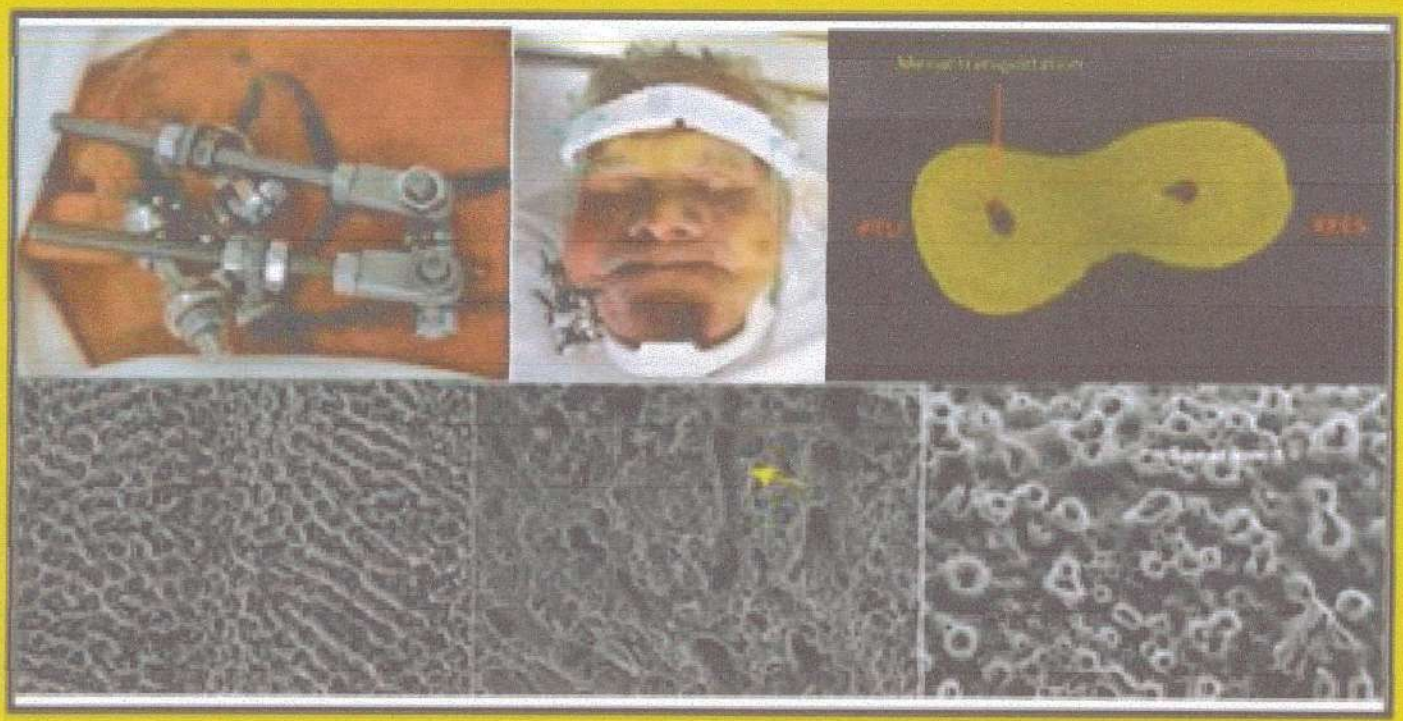

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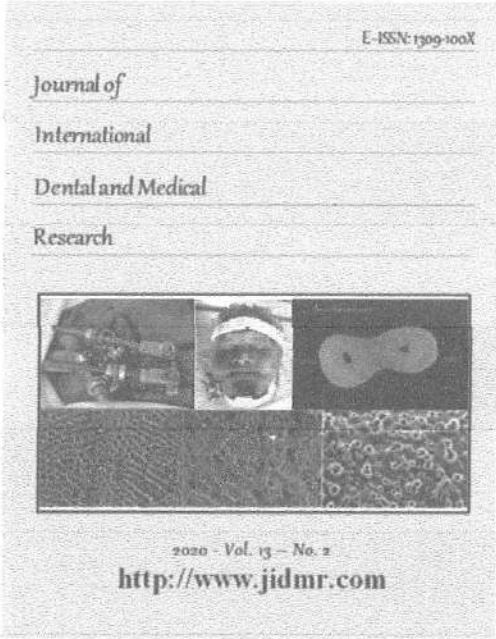

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Corticosteroid Effects and Administration Time Difference on Mice Model of Biliary Atresia

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Abstract

Corticosteroid therapy (steroid) has evolved into a commonly selected therapy after portoenterostomy therapy and is believed to improve clinical outcomes in biliary atresia (BA).

This study aims to evaluate the effects of corticosteroid administration and its administration time on innate immune response, the changes from innate to non-self adaptive immunity, non-self adaptive immunity, and self-adaptive immunity, as well as a biliary obstruction on animal models of biliary atresia.

This study utilized a randomized multiple factorial and posttest-only control group designs on newborn Balb/c mice as the animal models. Forty-four mice were randomly categorized into two groups, i.e., the experimental and control groups. All mice underwent the examination of several liver variables, liver histopathology, as well as bile ducts after the termination process. Univariate T-test and factorial MANOVA were employed for the data analysis. If the data were not normally distributed, the analysis could be carried out using the median and interquartile range, Mann-Whitney U test, and Kruskal-Wallis test.

Dexamethasone administration, Rhesus Rotavirus (RRV) induction, and pain duration after RRV exposure provided interaction effects towards CD68 expression with the significance values as follows: day 7= (0.01), day 14 = (0.001), and day 21 = (0.035); CD39 expression on day 7 (0.01), day 14 (0.001), and day 21 (0.001); CD4 expression on day 7 (0.001), day 14 (0.018), and day 21 (0.018); CD8 expression on day 7 (0.001), day 14 (0.018), and day 21 (0.014); B cell expression on day 7 (0.001), day 14 (0.002), and day 21 (0.018); ANCA expression on day 7 (0.012), day 14 (0.05), and day 21 (0.001).

After RRV induction, the immune response on animal models of biliary atresia increases. Dexamethasone administration on day 7 after RRV induction provides the most effective effects on immune response decrease.

Experimental article (J Int Dent Med Res 2020; 13(2): 553-560)

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Introduction

Biliary Atresia (BA) is a condition or clinical disorder resulting from a progressive inflammatory obstruction and fibro-obliteration on the whole or some parts of the extrahepatic and intrahepatic bile ducts exclusively found in the first few months of infant life [1,2]. The incidence of this disorder range from 1 in 5,000 to 8,000 live births, and it is assumed that there are 400-500 new cases anually, as well as to become the indicator of 50-60% of liver transplants in children worldwide [3].

Generally, when the diagnosis was conducted (1-3 months of age), several parts or the entire extrahepatic bile ducts are obliterated with an inflammatory cell infiltration in the remaining ducts [4,5]. The intrahepatic bile ducts experience a sustained inflammatory response with lymphocytes surrounding and attacking the ducts' epithelial cells [6,7].

BA etiology has not been discovered clearly. Nevertheless, recently, the understanding of its pathogenesis develops rapidly. At first, the recognized pathogenesis mechanism starts from a viral infection in the bile duct epithelium, followed by the secondary immunological and

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autoimmune processes, and ends with the bile duct obliteration [8,9]. Various current researches have demonstrated a lot about how infants' innate immune systems contributed to the damage of bile duct epithelium [8,10,11].

As an effort to cure refractory ascending cholangitis on infants with BA after hepatic portoenterostomy (HPE) [12], Corticosteroid therapy (steroid) has evolved into a commonly used therapy after portoenterostomy and is believed to improve clinical outcomes in BA. The use of steroids came from the theories about its choleretic and anti-inflammatory effects [13]. It aims to reduce bile duct colonization by increasing bile flows and reducing periductal and edema inflammation or hypertrophy in certain injuries [14,15].

Intravenous steroid administration with a short duration and a high dose is believed to reduce bilirubin serum, increase the bilirubin excretion, treat fever, and allow cholangitis resolution during antibiotic administration [16]. In addition, It has also been reported that steroids can control the chemokine expression, such as interleukin-8 and monocyte chemotactic protein-1 [17]. Since the fibrosis from the remnants of extrahepatic and intrahepatic bile ducts in BA are associated with a strong inflammatory response, steroids are expected to reduce the fibrosis and blockage of the bile ducts by suppressing the immune response, so that bile flows will be maintained [12,18].

This study aims to evaluate the impacts of corticosteroid administration and the difference of its administration time on the changes of an innate immune response, the changes from innate to non-self adaptive immunity, non-self adaptive immunity, and self-adaptive immunity, and biliary obstruction on animal models of biliary atresia.

Materials and methods

This study utilized a randomized multiple factorial and posttest-only control group designs on newborn Balb/c mice as the animal models. Infant mice, as the samples, were randomly selected from the population and placed in the control and experimental groups. This study was conducted for two months, starting from February until March 2014 in the BioMolecular and Biomedical Laboratory at the Faculty of Medicine, Universitas Brawijaya. This study was carried out through two stages. The first stage was the precondition stage in which the bile ducts of infant mice had been led to be fibrosis by 50 µl phosphate-buffered saline induction containing 1.5 x 10^6 fluorescence-forming units of Rhesus Rotavirus (RRV) intraperitoneally in the first 24 hours after their birth [19]. In the second stage, the mice received intraperitoneal administration of 0.5 mg/kg of dexamethasone [20] consecutively on day 3, 7, and 14 after RRV induction. Dexamethasone therapy effects were further investigated on day 7, 14, and 21 after the induction.

A total of 44 mice were randomized in each group using the simple random technique with a lottery method. Each group was then distinguished by a color code and each sample was assigned a code number. The mice were randomly divided into two groups, i.e., the experimental group with treatment (KC) and the control group (KK). In the control group, 16 mice were induced with 50 µl phosphate-buffered saline within 24 hours after their birth. Then, the sample animals were randomly terminated to have their variables examined. In the experimental group (KC), 28 mice were induced with 50 µl phosphate-buffered saline in the first 24 hours after their birth. Then, the sample animasl were randomly selected for termination and have their variables examined. Twelve of twenty-eight mice in the experimental group were randomly selected to be administered with an intraperitoneal injection of dexamethasone 0.5 mg/kg of body weight (BW). After termination, the examination of ectonucleoside triphosphate diphosphohydrolase-1 or cluster of differentiation 39 (CD39), cluster of differentiation 68 (CD68), tall like receptor (TLR), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), cluster of differentiation 4 (CD4), cluster of differentiation 8 (CD8), anti-neutrophil cytoplasmic antibody (ANCA) of liver, liver histopathology, and the biliary tract were performed to all mice.

The mean of normally distributed numerical data was analyzed by calculating the mean and the standard deviations (SD) of each variable using the univariate t-test. Afterward, the inferential analysis was carried out using a multivariate ANOVA or MANOVA factorial test. If the data were not normally distributed, the analysis could be carried out using the median and interquartile range, the Mann-Whitney U test,

and subsequently analyzed inferentially with the Kruskal-Wallis test. The PATH analysis was conducted to identify the correlation flow in each variable. This study had received ethical clearance from the health research ethics committees, Faculty of Medicine, Universitas Brawijaya No. 361/EC/KEPK-S3/11/2012.

Results

During the research, an infant mouse from the control group (KK3) died on the second day. Meanwhile, in the experimental group, one infant mouse from each control group died, i.e., KC1 (died on day 2), KC2 (died on day 3), KC3 (died on day 15), and KC4 (died on day 17) after RRV administration and before termination time, therefore, there were only 37 infant mice to be analyzed as samples. Table 2 suggests that there was interaction effects among dexamethasone administration, RRV induction, and the duration of illness after the exposure of RRV towards the NK cell expressions(CD68) in biliary atresia mice on day 7, 14 and 21 with $p < 0.001$.

Based on the result showed in Table 3, there was an interaction effect between the dexamethasone administration, the RRV induction, and the duration of illness after the exposure of RRV towards the CD39 expression in biliary atresia mice on day 7, 14 and 21 with p-value of less than 0.001. In Table 4, the results show that there were the interaction effects of dexamethasone administration, RRV induction, and pain duration after RRV exposure on TLR expression in mice models of biliary atresia on day 7, 14, and 21 with a p-value of less than 0.001.

In Table 5, the RRV induction of the experimental group indicated changes in the NF-kB expression profile compared to the control group. Dexamethasone administration on day 3, 7, and 14 after RRV induction resulted in significant changes in the NF-kB expression compared with RRV induction only. A Significant decrease mainly occurred in the dexamethasone administration on day 3 after RRV induction. Based on the result presented in table 6, there were interaction effects of dexamethasone administration, RRV induction, and pain duration after RRV exposure on CD4 expression in mice models of biliary atresia on day 7, 14, and 21 with a p-value of less than 0.001.

Based on the result showed in Table 7, there were interaction effects of the dexamethasone administration, RRV induction, and pain duration after RRV exposure on CD8 expression on mice models of biliary atresia on day 7, 14, and 21 with a p-value of less than 0.001. In Table 8, the results suggested that there were interaction effects of dexamethasone administration, RRV induction, and pain duration after RRV exposure on B cell expression in mice models of biliary atresia on day 7, 14, and 21 with a p-value of 0.001. Table 9 suggested that there were interaction effects of dexamethasone administration, RRV induction, and pain duration after RRV exposure on ANCA expression in mice models of biliary atresia on day 7, 14, and 21 with a p-value of less than 0.001.

Discussion

In this research, the experimental group had a higher mortality rate, especially before day 7 and between day 14 and day 21. The death was caused by mice mothers that ate their sick infants as their nature. Histopathological examination results found that the process description of the inflammatory on day 3 after RRV induction greatly increased on day 7, and there were biliary tract obstructions found on day 14. All samples experienced total blockage on the terminated group on day 21 after RRV induction. This result was not quite different from the previous research conducted by (Carvalho et al., 2005) that had also obtained the description of the high inflammatory process in the biliary tract on day 3 and 7 after RRV induction. However, in this research, the total blockage already occurred on day 14. The dexamethasone administration after RRV induction inhibited the process of biliary atresia: (BA).

RRV induction on infant mice, performed within 24 hours after their birth, increased the NK cell expression (CD 39). In the final path analysis, the impacts of the activation power of $CD39^{+}$ natural killer cell path triggered by CD8 reached 0.96. The higher CD 8 expression, the higher activation and $CD39^{+}$ expressions will be. This finding is in accordance with the research on BA that found NK cells' the roles in BA pathogenesis both in human and animal models [11,21]. In this research, the RRV induction performed within 24 hours after the models' birth had an impact on the changes of macrophage expression. In the

final path analysis, the activation power impacts of $CD68^+$ macrophage path triggered by CD4 reached 0.8. It indicated that the higher CD 4 expression, the higher activation and expression levels of $CD68^+$ macrophage would be. This research found that the changes in macrophage cell expression, indicated by an increase in its levels and changes in histopathological features of the mice models with BA based on time sequences, showed macrophages' roles in BA pathogenesis.

TLR impacts on Nuclear Factor-κappa B activation (NF-kB) amounted to 0.66. In this research, RRV induction affected the changes of NF-kB expression in mice with biliary atresia compared to the control group. The Rotavirus induction resulted in a significant change in the NF-kB increase. RRV exposure significantly increased the NF-kB expression in two groups, mice group induced with RRV ($p < 0.001$) and the control group ($p < 0.001$) with a higher increase in the experimental group. This result was in line with the previous research stated that the NF-kB expression activation of the mice induced with rotavirus came from different strains with the control group [22]. Compared to the RRV group, NF-kB expression differences in the dexamethasone administration occurred markedly on day 3 to day 21 ($p < 0.001$). There was a decrease in TLR3 expression during the monitoring process after dexamethasone administration. The highest expression decrease was on day 21 with an expression difference ($p = 0.018$). The TLR3 expression decrease was caused by the RRV that could not be recognized by TLR3 on day 14. Besides, the dexamethasone administration on day 14 caused greater expressions to decrease compared to the previous days.

Intraperitoneal RRV induction less than 24 hours after the birth of Balb/c mice provided significant effects on $CD4^+$ expression increase compared to the control group ($p < 0.001$). CD4+ expression increase occurred based on the time sequence, started from day 3 after RRV induction, which became higher and progressive on day 7, and reached the highest expression on day 14. Dexamethasone administration on day 3, 7, and 14 could reduce the $CD4^+$ expression on day 7, 14, and 21. This situation was caused by effector cell infiltration that surrounded and attacked bile ducts. Furthermore, cells producing cytokines could directly damage the epithelial cells or indirectly damage it through the stimulation of other immune cells [7,23].

The dexamethasone administration on day 3, 7, and 14 could reduce $CD8^+$ expression on day 7, 14 and 21 respectively. In the final path analysis, the power activation impacts of the $CD8^+$ path triggered by NF-kB reached 0.2. $CD8^+$ activation through $CD4^+$ (indirect tracts) had the most influence through NF-kB. It showed that CD 8 expression increase was not directly associated with the NF-kB expression increase, but through $CD4^+$ expression increase.

In this research, B cell expression was found to be higher in the experimental group on day 3 after RRV induction compared to the control group, however, it then decreased on day 7. This research also suggested that dexamethasone administration on day 3, 7, and 14 had an effect on B cell expression changes on day 7, 14, and 21 compared to the experimental group that only induced with RRV. The specific autoantibodies on bile duct epithelium were proven by the expression measurement of the anti-neutrophil cytoplasmic antibody (ANCA). The result indicated that RRV induction and pain duration after RRV exposure had significant effects on the changes in the number of ANCA expression in rotavirus-induced mice compared with the control group. Dexamethasone administration had significant effects on ANCA expression decrease compared to those with no dexamethasone intervention. the highest decrease occurred when the dexamethasone was given on day 7 after RRV induction.

This study had several limitations, including clinical assessments that were not performed during the research due to the difficulties encountered in distinguishing mice's clinical states. In addition, the laboratory markers were also not performed to compare the histopathological findings and immune responses. This research used flow cytometry to quantitatively measure the number of cells that express immune response with extrahepatic bile duct samples and mice liver. Furthermore, it could not be distinguished whether the amount of expression originated from the biliary tract or liver. The immunohistochemical examination should be performed to distinguish which cells express an immune response, whether from the liver or biliary tracts.

Conclusions

There is an increase in the innate immune responses in CD39 and CD68; a change from innate to non-self adaptive of TLR3 and NF-kB; non-self adaptive of CD4 and CD8; and self adaptive of B cells and ANCA in the experimental animal models with biliary atresia induced with RRV. The dexamethasone administration, especially on the days after day 7, can reduce the high increase of innate immune response (CD39 and CD68), the change from innate to non-self adaptive immunity (TLR3 and NF-kB), non-self immunity (CD4 and CD8), and self adaptive immunity (B cells and ANCA) immunity, as well as prevent a bile duct obstruction.

Declaration of Interest

The authors report no conflict of interest.

	Control Group				RRV Group				RRV + Dexamethasone Group		
Day	3	7	14	21	3	7	14	21	3	7	14
Total of Each Group	4	4	4	4	4	4	4	4	4	4	4
Mean of initial BW (g)	1.84	1.82	1.80	1.81	1.85	1.83	1.80	1.82	1.83	1.80	1.81
SD	(0.01)	(0.02)	(0.01)	(0.02)	(0.02)	(0.01)	(0.01)	(0.02)	(0.01)	(0.02)	(0.01)
Dropped out of trials	0	0	1	0	1	1	1	1	1	0	1
Final Samples	4	4	3	4	3	3	3	3	3	4	3

Table 1. Research Subjects' Weight.
Assessing the homogeneity using the Kolmogorov-Smirnov test p=0.2

Variable	day	Control Group Median (interquartile)	RRV Group Median (interquartile)	Dexa Group Median (interquartile)	*p** Each variable of All Groups
CD 68	3	8.72(0.05)	9.47(0.08)	-	0.02***
	7	4.34 (0.10)	16.48(0.0)	4.91(0.09)	0.01****
	14	7.60 (1.1)	22.25(0.0)	13.94(0.0)	<0.001**
	21	8.2 (0.54)	55.86(0.0)	46.53(0.0)	0.035****
	P	0.004****	0.01****	0.018****	<0.001****

Table 2. The Changes of CD 68 expression in the control group, RRV induction, and dexamethasone.
* *Significant differences from the T-test on p-value less than 0.05*
** *Significant differences from the ANOVA test on p-value less than 0.05*
*** *Significant differences from the Mann-Whitney test on p-value less than 0.05*
**** *Significant differences from the Kruskal-Wallis test on p-value less than 0.05*

Variable	day	Control Group Median (interquartile)	RRV Group Median (interquartile)	Dexa Group Median (interquartile)	*p** Each Variable of All Groups
CD 39	3	1.9 (0.02)	3.04(0.05)	-	0.001*
	7	16.26(0.07)	16.59(0.0)	2.12(0.15)	0.01****
	14	23.12 (0.18)	65.19(0.0)	44.38(0.0)	<0.001**
	21	15.90 (1.12)	32.65(0.0)	23.19(0.0)	<0.001**
	P	0.004**	<0.001**	0.018****	<0.001****

Table 3. The Changes of CD39 Expression in the Control Group, RRV Induction, and Dexamethasone.
* *The Significant differences from the T-test on p-value less than 0.05*
** *The significant differences from the ANOVA test on p-value less than 0.05*
*** *The significant differences from the Mann-Whitney test on p-value less than 0.05*

Variable	day	Control Group Median (interquartile)	RRV Group Median (interquartile)	Dexa Group Median (interquartile)	*p** Each Variable of All Groups
TLR 3	3	6.08(0.29)	6.95(0.07)	-	0.02***
	7	37.06 (0.18)	16.55(0.0)	10.07(0.13)	0.01****
	14	9.63 (2.66)	64.2(0.0)	45.90(0.0)	0.018****
	21	6.09 (0.1)	54.08(0.0)	15.94(0.0)	0.018****
	P	0.005****	<0.01***	0.018****	<0.001****

Table 4. The Changes of TLR3 Expression in Control Group, RRV Induction, and Dexamethasone.

* *The Significant differences from the T-test on p-value less than 0.05*
** *The Significant differences from the Anova test on p-value less than 0.05*
*** *The significant differences from the Mann-Whitney test on p-value less than 0.05*
**** *The Significant differences from the Kruskal-Wallis test on p-value less than 0.05*

Variable	Day	Control Group Median (interquartile)	RRV Group Median (interquartile)	Dexa group Median (interquartile)	*p** Each variable of all groups
NF-kB	3	2.18 (0.13)	8.07(3.36)	-	0.04*
	7	9.48(1.90)	15.59(0.0)	5.21(1.09)	0.02****
	14	9.12 (0.34)	16.03(0.0)	14.23(0.0)	<0.001**
	21	3.18 (0.04)	10.46(0.0)	4.62(0.0)	0.018****
	P	0.005****	0.006**	0.025****	0.001****

Table 5. The Changes of NFκB Expression in Control Group, RRV Induction, and Dexamethasone.

* *The significant differences from the T-test on p-value less than 0.05*
** *The significant differences from the ANOVA test on p-value less than 0.05*
*** *The significant differences from the Mann-Whitney test on p-value less than 0.05*
**** *The significant differences from the Kruskal-Wallis test on p-value less than 0.05*

Variable	day	Control group Median (interquartile)	RRV Group Median (interquartile)	Dexa Group Median (interquartile)	*p** Each variable of all groups
CD 4	3	2.32(0.39)	2.40(0.45)	-	0.49*
	7	1.94 (0.08)	3.82(0.0)	3.24(0.15)	<0.001**
	14	1.22 (0.07)	8.18(0.0)	7.34(0.0)	0.018****
	21	0.88 (0.22)	6.06(0.0)	5.61(0.0)	0.018****
	P	0.004****	0.015****	<0.001**	<0.001****

Table 6. The Changes of $CD4^+$ expression in Control Group, RRV Induction, and Dexamethasone.

* *The significant differences from the T-test on p-value less than 0.05*
** *The significant differences from the Anova test on p-value less than 0.05*
*** *The significant differences from the Mann-Whitney test on p-value less than 0.05*
**** *The significant differences from the Kruskal-Wallis test on p-value less than 0.05*

Variable	day	Control Group Median (interquartile)	RRV Group Median (interquartile)	Dexa Group Median (interquartile)	p* Each variable of all groups
CD 8	3	0.99(0.02)	1.36(0.27)	-	0.02***
	7	1.83 (0.08)	2.4(0.0)	2.24(0.09)	<0.001**
	14	4.56 (0.05)	10.55(0.00)	9.06(0.0)	0.018****
	21	5.04 (0.25)	7.30(0.0)	8.23(0.0)	0.014**
	P	0.005****	0.01****	0.035****	<0.001****

Table 7. The Changes of $CD8^+$ Expression in Control Group, RRV Induction, and Dexamethasone.

* *The significant differences from the T-test on p-value less than 0.05*
** *The significant differences from the Anova test on p-value less than 0.05*
*** *The significant differences from the Mann-Whitney test on p-value less than 0.05*
**** *The significant differences from the Kruskal-Wallis test on p-value less than 0.05*

Variable	day	Control Group Median (interquartile)	RRV Group Median (interquartile)	Dexa Group Median (interquartile)	p* Each variable of all groups
B cells	3	6.64(0.29)	12.83(0.09)	-	0.02***
	7	5.06 (0.05)	6.13(0.0)	3.20(0.11)	<0.001**
	14	7.25 (1.51)	16.36(0.0)	13.11(0.0)	0.002**
	21	10.64 (0.59)	41.75(0.0)	17.85(0.0)	0.018****
	P	0.003****	0.018****	0.018****	<0.001****

Table 8. The Changes of B cells Expression in Control Group, RRV Induction, and Dexamethasone.

* *The significant differences from the T-test on p-value less than 0.05*
** *The significant differences from the Anova test on p-value less than 0.05*
*** *The significant differences from the Mann-Whitney test on p-value less than 0.05*
**** *The significant differences from the Kruskal-Wallis test on p-value less than 0.05*

Variable	day	Control Group Median (interquartile)	RRV Group Median (interquartile)	Dexa Group Median (interquartile)	p* Each variable of all groups
ANCA	3	6.16(0.07)	6.25(0.05)	-	0.003*
	7	0.14 (0.04)	3.15(0.0)	0.34(0.07)	0.012****
	14	4.44 (0.61)	24.82(0.0)	4.48(0.0)	0.05****
	21	0.86 (0.08)	6(0.0)	4.27(0.0)	<0.001**
	P	0.003****	0.018****	0.03****	0.001****

Table 9. The Changes of ANCA Expression in Control Group, RRV induction, and Dexamethasone.

* *The significant differences from the T-test on p-value less than 0.05*
** *The significant differences from the Anova test on p-value less than 0.05*
*** *The significant differences from the Mann-Whitney test on p-value less than 0.05*
**** *The significant differences from the Kruskal-Wallis test on p-value less than 0.05*

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