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EFFECT OF IONIZING RADIATION (X-RAYS) ON PERIPHERAL BLOOD T-CELL SUBSETS IN INTERVENTIONAL ANGIOPLASTY PROCEDURE WORKERS

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ABSTRACT

Angioplasty is a procedure using x-ray imaging equipment to open stenosed or occluded blood vessels. Ionizing radiation can be considered as a 'two-edged sword' in that it may lead to immune suppression or overreaction. The specific response of the immune system is based on the action of T-cells which are the lymphocytes developed in the thymus. The present study included forty five workers divided into 3 groups fifteen each. Group 1 is control and the other two are members in catheter lab and vascular surgery departments. Groups 2 and 3 were provided with personal dosimeters (TLD-100) to collect and estimate their exposure doses to x-ray for three months duration. Percentage of CD4 in groups 2 and 3 (workers with occupational period < 5 years and those with occupational period > 5 years respectively) increased highly significantly in compared to control group at (P-value <0.001). On the other hand, there is no statistically significant difference between the means of $CD8^+$ groups' percentage at p-value of 0.340. So, there is no influence of the occupational periods on $CD8^+$ counts of workers. The same description is on CD4/CD8 ratio where there is no effect of the occupational period at P-value of 0.08. This indicates that increasing in occupational period may induce changes in the immune system gradually and more investigations are needed to prove that.

KEYWORDS: Ionizing radiation, Immune system, occupational period.

INTRODUCTION

Angioplasty is a procedure during which a balloon-tipped catheter is used to open a stenosed or occluded blood vessel. Imaging guidance is used to position the catheter across the area of narrowing or blockage within the blood vessel and the balloon is inflated to open the narrowing and improve blood flow. It may be done with vascular stenting, which is the placement of a small wire mesh tube within the blood vessel to help keep it open. The procedure is much less invasive than other surgical interventions and usually does not require general anesthesia.[1]

In these procedures, x-ray imaging equipment, a balloon catheter, sheath, stent and guide wire are used (fig.1). This procedure is used for atherosclerotic large arteries, peripheral artery disease, renal vascular hypertension causing narrowing of the kidney arteries, carotid artery stenosis, coronary artery disease, and Venous narrowing involving the central veins (in the chest, abdomen or pelvis).[2]

The highest doses registered among medical staff using X-rays are the occupational doses of radiation in interventional procedures guided by fluoroscopy.[3] Ionizing radiation (IR) is known to cause harm, and high radiation doses tend to kill cells, while low doses tend to damage or alter the genetic code of irradiated cells. The effect of IR on the immune response has become one of the chief research fields in radiation biology and radiation protection.[4] The relationship between IR and the immune system is multifactorial and highly depends on the radiation dose, quality and immune cell types.[5] However it results in changes in morphology and functional activity both at the cellular and system levels causing disturbance of immune reactivity whose final result is modulation of the immune system.[6]

Effects of chronic low-dose radiation on changes in immunological parameters and state of subclinical inflammation require careful examination of the immune status of occupationally exposed persons. Some authors found that doses in the range of 10 to 100 mGy lead to prevalence of T1 helper subpopulation (Th1), while doses above 200 mGy switch the prevalence of T2 immune response which determines an increased risk of

infectious diseases, allergies, and autoimmune diseases. At the same time, experimental data established that low doses stimulate antitumor immunity manifested by increased activity of T, natural killer (NK) cells, and B cells and higher production of interleukin 2 (IL-2), IL-12, interferon g (IFN-g) cytokines, and induced T helper 1 immune response.[7,8]

In addition, there is growing body of evidence regarding immunological changes induced by low dose radiation. Several studies about the effect of occupational exposure to low level of ionizing radiation on cellular and humoral immunities in radiology workers are documented. In some studies, levels of CD4 (+) T lymphocytes and humoral response were found to be weaker in exposed workers compared to controls, indicating the importance of taking appropriate measures to protect workers in radiation field from exposure to ionizing radiation.[9]

Ionizing radiation accounts for both risk-dose-dependent stochastic effects (no threshold dose) and dose-dependent deterministic effects having a threshold dose below which the biological response is not observed.[10] Some interventional procedures with long screening times and multiple image acquisition may give rise to deterministic effects in both staff and patients.[11] Stochastic effects which are probabilistic events such as induction of cancer and genetic defects may differ among individuals. The linear no threshold hypothesis emphasizes the stochastic nature of DNA damage caused by ionizing radiation.[10] Ionizing radiation can induce various forms of DNA damage, including the possibility of increasing the incidence of chromosomal aberrations (CAs) and micronuclei (MN). CAs are the most fully developed biological indicator of ionizing radiation exposure. The analysis of dicentric and centric ring CAs has for many years been the most sensitive biological method for radiation dose assessment. Recently, the results of a cohort study provide support for the hypothesis that the occurrence of CAs in peripheral blood lymphocytes (PBLs) represents relevant events in carcinogenesis and may serve as a surrogate end point for cancer risk.[12] Cytotoxic effects of X-rays in occupationally exposed workers were recorded in several earlier studies. High incidence of dicentrics, rings and acentric fragments were observed in the PBLs of medical staff that were occupationally exposed to X-rays.[13] Depression or dysfunction of the highly radiosensitive cellular components of the immune system, such as the $CD4^+$ T cells, can lead to serious consequences, including increased risk for cancer. However, there are reports that low dose of radiation (LDR) exposure can result in radio adaptation that can be beneficial. There is much controversy about the effects of chronic low-dose exposure to ionizing radiation and the possible consequences particularly in occupational exposure. The reports specifically concerning the immune status of occupationally exposed persons are quite limited and not uniform. It is difficult to identify whether the observed effects are associated only with the received dose, which often does not exceed the natural background level, or other occupational and environmental factors are also involved.[14] Liu has reported that the stimulation of immunity by LDR concerns most anticancer parameters, including antibody formation, natural killer (NK) and macrophage activity, secretion of cytokines as well as other cellular changes. Although proposed mechanisms include more efficient DNA repair and stimulated immunity, the underlying mechanisms remain unclear.[15]

Fig. 1: Angioplasty procedure using x-ray imaging equipment.

SUBJECTS AND METHOD

The present study included forty five workers working at Mataria Teaching Hospital. Their occupational exposures to ionizing radiation due to angioplasty procedures were routinely monitored by TLD-100 card for each worker that read every three months. TLD-100 (Thermoluminescent dosimeter *LiF:Ti,Mg)* is consisting of Lithium Fluoride having characteristics suitable for dosimetry investigations in nuclear medicine because the density of this kind is suitable for the human tissues. It is sensitive and has been used for integrated dose measurements either x-ray or γ-ray. Ambient radiation (in this work x-ray) was monitored and the doses were measured by averaging the values. These values were used to evaluate the effective dose. It is used because of their energy independence and low fading. It has high sensitivity, low leak, good resistance against heat, moisture, and other environmental factors, and un-sensitive to light.

It has filters for protection of radiation disturbance. The individual relative sensitive factors and repeatability for all dosimeters used in this work were investigated for gamma radiation, 1 cGy, 137Cs source. The TLD calibration factors have been determined, in air, for different X-ray beam kVp (Peak kilo voltage). It refers to the maximum high voltage applied across an X-ray tube during the creation of x-rays. The energies of x-ray used were of 63, 66, 70, 73, 77, 81, 85, 90 and 96 kV. The energy dependence curve for the response of the TLDs used was determined using the above-mentioned qualities in terms of effective energy. This procedure allowed the correction of the TLD response with respect to each beam quality considered. This method is quite

effective for TLD-100. The cards were annealed by using (TLD-4000) reader, which is also used in measuring doses in TLD cards after the exposure to x-ray. The effective dose to the angioplastic workers was less than 0.45 mSv per 3 months. The International Commission on Radiological Protection (ICRP) recommends an effective dose of 20 mSv/year for application in occupational exposure, averaged over 5 years (100 mSv in 5 years), with the further provision that the effective dose should not exceed 50 mSv in any single year.[16]

Thirty of the forty five workers were members in catheter lab and vascular surgery departments. The other fifteen were workers in other hospital department who do not have any work related to ionizing radiation and suggested as control group. All the workers were male with a range age of 30-60 years. The average working time at angioplasty department was 6-7hours/week/ personnel. Personal history with special habit especially smoking was taken from all workers. The 45 workers were divided into three groups, 15 for each. The first group was control that is not exposed to x-ray radiation. The second group had 15 workers with an occupational period less than 5 years in vascular surgery department with interventional angioplastic field. The third group was with an occupational period more than 5 years in the same department.

Blood samples were collected from each participant by venipuncture into Vacutainer EDTA Tubes. Twenty microliters of each blood sample were stained for 15 min at room temperature in dark with 20 µL CD4 antihuman monoclonal antibody (Partec, Germany). Then 400 µL of buffer 1 and then 400 µL of buffer 2 were added to each sample and were analyzed with flowcytometer (Patrec PAS, Germany).

According to the CD8 easy count kit (Partec, Germany) instruction, 20 µL of each sample were stained for 15 min at room temperature in dark with 10 µL CD8 antihuman monoclonal antibody (Partec, Germany). In addition, 400 µL of buffer 1 and then 400 µL of buffer 2 were added to each sample and the samples were analyzed with a flowcytometer (Partec PAS, Germany).

Statistical Analysis

Data was statistically described in term of mean ± standard error (SE). As well as, lower and upper bounds at 95% confidence Interval for mean. Statistically significant differences between group's means were determined by one-way ANOVA and Tukey's HSD Post Hoc tests.

In this work one-way analysis of variance (one-way ANOVA) is used to determine whether there are any significant differences between the means of two or more independent groups (Statistics.laerd.com 2015).[17] For $\alpha = 0.05$ and since p-value $\leq \alpha$, the null hypothesis of equal sample means is rejected and concludes that there is a significant difference among the sample means. The one-way ANOVA is an omnibus test statistic and cannot determine which specific groups were significantly different from each other. To determine which specific groups differed from each other, a post hoc test should be use (Statistics. laerd.com 2015). Tukey's HSD (Honest Significant Difference) test is used in conjunction with an ANOVA to find means that are significantly different from each other. Either difference between the groups studied is considered statistically significant at p-value $\leq \alpha$ (0.05).

Data analysis is conducted using the Statistical Package for Social Sciences (SPSS) statistics version 23.

RESULTS

Table (1): The percentage and average count of $CD4^+$ in the different worker groups.

Group 1 ($CD4^+$)		Group 2 ($CD4^+$)		Group 3 ($CD4^+$)	
Control		Occupational period < 5 years		Occupational period > 5 years	
Absolute counts / µL	%	Absolute counts / µL	%	Absolute counts / µL	%
1349	55	847	35	#1587	41
1147	41	848	42	#1508	45
551	33	1110	50	1058	43
916	43	935	44	1395	44
1200	50	1058	47	1054	46
805	29	1264	40	#1514	43
1002	41	1085	43	#1421	43
600	24	1338	44	1214	50
678	31	#1435	50	616	46
784	32	1286	46	1083	45
1075	42	1301	47	1284	43
1126	35	1092	39	915	45
703	27	979	46	1364	44
871	32	1237	44	#1469	42
934	29	#1407	48	#1510	47

Normal range of count: 350-1391 and reference range of %: 26-61.

Table (2): Description of CD4 resulted data.

Group	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	P-value
					Lower Bound	Upper Bound			
1	15	36.27	8.787	2.269	31.40	41.13	24	55	0.001
2	15	44.33	4.135	1.068	42.04	46.62	35	50	
3	15	44.47	2.232	0.576	43.23	45.70	41	50	
Total	45	41.69	6.829	1.018	39.64	43.74	24	55	

Table 1,2 show that there is a highly statistically significant difference (P-value <0.001) between the means of $CD4^+$ groups percentage (control, occupational period < 5 years and occupational period > 5 years). This means that percentage of CD4 in groups 2 and 3 increased highly significantly in compared to control group at(P-value <0.001). To determine which specific group was differed from each other, Tukey's HSD test is used and the results are presented with the mean and SE in Table 3. Tukey's HSD test illustrate that there are highly statistically significant difference between control and each of occupational period < 5 years and occupational period > 5 years ($p \leq 0.001$). Therefore, the occupational period had been impacted on $CD4^+$ percentage of worker.

Table (3): Effect of occupational period on percentage of $CD4^+$.

Groups of $CD4^+$	Average of percentage ± SE	P-value
1 (Control)	36.27± 2.269	
2 (Occupational period < 5 years)	44.33± 1.068 [(a)]	0.001**
3 (Occupational period > 5 years)	44.47± 0.576 [(a)]	0.001**

*$p \leq 0.05$ (statistically significantly difference between groups),
**$p \leq 0.001$ (highly statistically significantly difference between groups)

a Statistically different from control $CD4^+$ measured and worker groups.

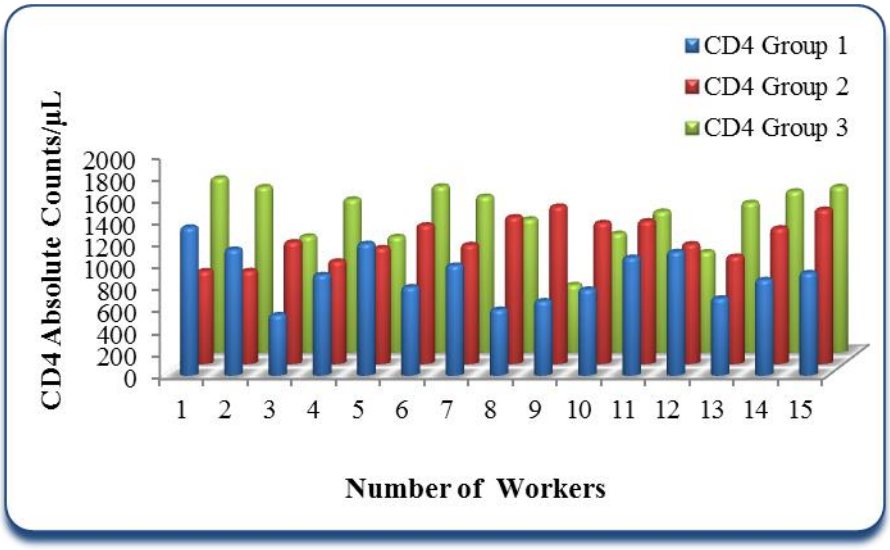

Fig. 2: Comparison between CD4 counts in different worker groups.

Figure (2) illustrates the difference of CD4 counts between the three groups. It is obvious that there is a significant increase in CD4 count with increasing in occupational period compared to control group with a little bit of standard error.

Table (4): The percentage and average count of $CD8^+$ in the different worker groups.

Group 1 ($CD8^+$)		Group 2 ($CD8^+$)		Group 3 ($CD8^+$)	
Control		Occupational period < 5 years		Occupational period > 5 years	
Absolute counts / µL	%	Absolute counts / µL	%	Absolute counts / µL	%
438	14	559	24	#858	22
681	21	414	19	373	11
426	23	563	25	441	19
515	17	512	22	558	21
601	18	385	18	#764	28
635	29	#986	32	#914	24
545	19	678	28	607	21
478	24	#722	24	693	29
609	17	538	19	409	28
519	25	#795	29	#738	25
618	23	#854	28	551	27
656	26	630	21	#775	25
533	18	550	22	615	16
519	22	#729	23	566	18
601	21	570	19	652	23

Normal range count: 59-699 and reference range of %: 10-31

Table (5): Description of CD8 resulted data.

Group	N.	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	P-value
					Lower Bound	Upper Bound			
1	15	21.13	4.015	1.037	18.91	23.36	14	29	0.340
2	15	23.53	4.207	1.086	21.20	25.86	18	32	
3	15	22.47	4.998	1.291	19.70	25.23	11	29	
Total	45	22.38	4.438	0.662	21.04	23.71	11	32	

Table 4,5 show that there is no statistically significant difference between the means of $CD8^+$ groups' percentages (p-value > 0.05). So, there is no influence of the occupational periods on $CD8^+$ counts of workers.

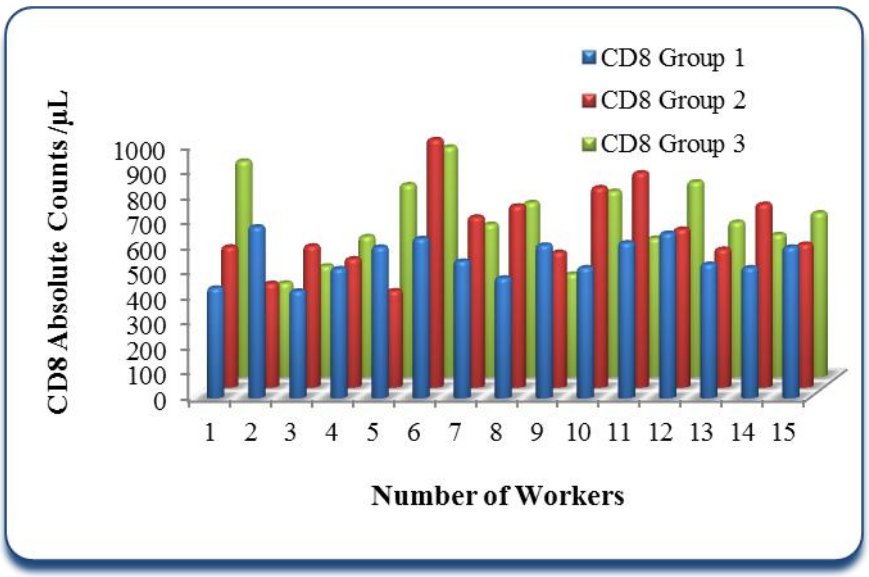

Fig. 3: Comparison between CD8 counts in different worker groups.

In figure (3), in spite of increasing in count with increasing in occupational period, the difference between groups is not significant.

Table (6): Ratio of CD4/CD8 in the different worker groups.

Group 1 (CD4/CD8)	Group 2 (CD4/CD8)	Group 3 (CD4/CD8)
Control	Occupational period < 5 years	Occupational period > 5 years
3.08	1.52	1.85
1.68	2.05	4.04
1.29	1.97	2.40
1.78	1.83	2.50
2.00	2.75	1.38
1.27	1.28	1.66
1.84	1.60	2.34
1.26	1.85	1.75
1.11	2.67	1.51
1.51	1.62	1.47
1.74	1.52	2.33
1.72	1.73	1.18
1.07	1.78	2.22
1.63	1.70	2.60
1.55	2.47	2.32

Table (7): Description of CD4/CD8 resulted data.

Group	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	P-value
					Lower Bound	Upper Bound			
1	15	1.64	0.487	0.126	1.366	1.905	1.07	3.08	0.08
2	15	1.89	0.431	0.111	1.651	2.128	1.28	2.75	
3	15	2.10	0.703	0.182	1.714	2.493	1.18	4.04	
Total	45	1.88	0.574	0.086	1.704	2.048	1.07	4.04	

From Table 7, it is obvious that there is no statistically significant difference between the means of $CD4^+$/ $CD8^+$ groups (p-value > 0.08). That means, there is no effect of the occupational periods on the ratio of $CD4^+$ and $CD8^+$ counts of workers.

DISCUSSION

The responsibility of the immune system for maintaining the integrity of higher organisms is by responding to external agents. The specific response of the immune system is based on the action of T-cells which are the lymphocytes developed in the thymus. T lymphocytes include at least the following subtypes: cytotoxic T-cells, which respond to cells infected by viruses or tumor cells; T helper cells, which secrete mediators to activate lymphocytes; B cells; macrophages; natural killer cells and the T-cells themselves. Certain phases of the activation process of T lymphocytes in response to recognition of an antigen are known. The binding of the antigen transported by the major histocompatibility complex (MHC) molecules with the TCR/CD3 complex triggers a chain of bio-chemical processes leading to the creation of protein phosphorylation as a final common pathway.[18] These raise the intracellular Ca++ concentration and active protein kinases, which in turn leads to the early expression of fas gene and later to the expression c-myc, gamma interferon, and interleukins 1 and 2 and transferring, which are essential for T-cell proliferation.[19] Similar mechanisms appear to operate as a consequence of the action of low doses of radiation. Experimental studies characterizing immune response to radiation implicate intracellular calcium and protein kinases C, which cause transcription of the c-fos gene and production of interleukin-2 to activate T-cells.[20,21] Low doses can be defined as those less than 0.35 Sv to the whole body. Donald provided useful risk estimated for dose as low as 0.05-0.1 Sv, which are not overestimated by linear risk cancer estimates computed from the wider dose ranges 0.2 or 0.4 Sv.[22] The effects of radiation on the immune system generally intensify with the amount of dose received. Researchers know less about the effects of low dose radiation on the immune system than about the effects of high-dose radiation. Liu and colleagues discussed immunological changes in mice exposed to single doses of X-ray in the range of 0.025 to 0.075 Gy and by continuous exposure to gamma rays with a cumulative dose of 0.065 Gy.[23,24]

It has been reported that subgroups of T-lymphocytes are affected at different levels and different cell groups of immune system give different responses in individuals exposed to long-term ionizing radiation. Which is in contrast to the previous study showing levels of CD4(+) T lymphocytes was found to be weaker in exposed workers compared with controls, indicating the importance of taking appropriate measures to protect radiology workers from exposure to IR ionizing radiation.[25] Another report on individuals occupationally exposed to IR showing no change for T-cell and B-cell total counts and for the T cell subset percentages of CD4+, CD8+.[26] These discrepancies might be due to the source and dose of radiation.

Because, the interrelationship between ionizing radiation and the immune system is multifactorial and highly depends on the radiation dose/ quality and immune cell types.[15,30] Ethnic and some differences are factors that may influence the levels of lymphocyte subsets.[27,28,29]

In the present study there is significant increase in CD4 percentage and counts with increasing of occupational period compared to control at P-value 0.001 (table 3). That means there are some changes in the immune system gradually by increasing in CD4 cell percentages over years of working in occupational x-ray field. On the other hand, the effect of the occupational period is non-significant on CD8 in groups 2 and 3 compared to control at p-value 0.340 (table 5). Consequently, the CD4/CD8 ratio was proven statistically insignificant with the occupational period of workers at P-value 0.08 (Table 7). Demirhan et al demonstrated that after angiography, the rate of CD4 in patients is significantly higher than before angiographic imaging, and angiographic processing causes an increase in patient's cellular immunity. Further, an increase in the number of CD4+ T-cells after angiography suggests that this process may possibly cause damage to the vascular endothelium of patients and increase the release of some inflammatory mediators.[30]

Borzoueisileh et al discussed the regressions between exposure duration to high background radiation and CD4% ($P = 0.045$), also with CD107a+ counts ($P = 0.048$), and CD8%. They also demonstated no significant regression between exposure duration and the other studied parameters including Log CD4, Log CD8, Log NK, Log LYM, Log NEUT, Log WBC, Log MXD counts and CD4/CD8 ratio, CD8%, LYM%, NEUT%, and MXD%.[31]

Farooque et al. focused on the immune-stimulatory effects of low dose radiation at in vivo models and its clinical efficacy. They focused effects that supporting the use of low dose radiation regimens as an anticancer treatment.[32]

Since interventional angioplasty procedure is one of the highest radiation exposures among health professionals, they should be aware of the ICRP's recommendations and international Basic Safety Standards requirement for radiation protection and local rules. They must comply with the ionizing radiation regulations and other relevant legislation.[16] Recommendations and practical advice to improve staff radiation protection are also summarized by Vano.[33] The most successful means of reducing occupational exposures has been training in radiation protection. Evaluation and follow-up of occupational doses should be considered an important part of quality assurance programs.

CONCLUSION

Estimation of the risk from ionizing radiation is difficult. However, IR can be considered as a 'two-edged sword' in that it may lead to immune suppression or overreaction. Since there are some alterations in the immune system of the workers in occupational x-ray field with occupational time in our study, other immunological parameters must be measured in the next studies as T h1 (T helper), Th2, Th17, and regulatory T cells to determine other aspects of the immune involvement. The ratios of Th1/Th2 and Th17/Tregs that could reflect altered states of immune responses against foreign antigens or tumor antigens are important. Also the proportions or counts of peripheral leucocytes including monocytes and polymorph nuclear leucocytes, which also modify or even suppress antitumor immunity, have an important role.

Further studies are needed for determining of appropriateness of periodic chick-ups of immune functions and most efficient and cost- effective ways of monitoring immune functions in radiation field workers for detecting early changes in the immune system.

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