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S.A. Huseynov, E.H. Azimov, M.J. Sultanova
Republican Clinical Hospital named after M.A. Mirqasimov, Baku, Azerbaijan

RATING THE PERFUSION OF THE LARGE INTESTINE SEGMENT IN PATIENTS WITH A HISTORY OF LAPAROSCOPIC TOTAL MESORECTAL EXCISION

e-mail: mic_amu@mail.ru

The purpose of the study was to assess the perfusion of the large intestine segment with the angiography in quality and quantity during the laparoscopic total mesorectal excision. The work was carried out on the basis of the analysis of the results of fluorescent images of 28 patients who were diagnosed with adenocarcinoma of the rectum of various degrees and underwent laparoscopic total mesorectal excision. Using the fluorescence curve, T½max and the time ratio (TR=T½ max/T max) from the graphs, the fluorescence intensity of the colon was assessed as weak, medium or high. Of the patients under our supervision, T½max<18 sec was observed in 75 % of patients, T½max>18 sec–in 21.4 % of patients. In 16.7 % of cases in patients with low perfusion (TR<0.4) who underwent a safe anastomosis, narrowness of the anastomosis was noted, in 33.3 % of cases in patients with average perfusion (0.4<TR<0.6) (critical zone) complications associated with anastomosis. With Tmax 51.5>, T½max 19.8>, slope 1.7<, the likelihood of complications also increases. These indices are considered independent criteria. The use of quantity indexes as ½T max and TR during the study of perfusion with indocyanine green, assisted in finding the intestinal segment with weak perfusion.

Key words: laparoscopic total mesorectal excision, fluorescence imaging, quantity indices T½max and TR, colorectal cancer.

С.А. Гусейнов, Е.Х. Азімов, М.Дж. Султанова

ОЦІНКА ПЕРФУЗІЇ СЕГМЕНТУ ТОВСТОГО КИШЕЧНИКА У ПАЦІЄНТІВ, ЯКІ ПЕРЕНЕСЛИ ЛАПАРОСКОПІЧНУ ТОТАЛЬНУ МЕЗОРЕКТАЛЬНУ ЕКСЦИЗІЮ

Метою дослідження було оцінити перфузію сегмента товстої кишки за допомогою ангіографії у якісному та кількісному відношенні при лапароскопічній тотальній мезоректальній ексцизії. Роботу проведено на підставі аналізу результатів флюоресцентних зображень 28 хворих з діагнозом аденокарцинома прямої кишки, які перенесли лапароскопічну тотальну мезоректальну ексцизію. Використовуючи криву флуоресценції, T½max та співвідношення часу (TR=T½ max/Tmax) з графіків, інтенсивність флуоресценції товстої кишки оцінювали як слабку, середню або високу. З хворих, що знаходяться під нашим спостереженням, T½max<18 с спостерігали у 75 % хворих, T½max>18 с – у 21,4 % хворих. У 16,7 % випадків у хворих з низькою перфузією (TR<0,4), які перенесли безпечний анастомоз, відзначена вузькість анастомозу, у 33,3 % випадків у хворих із середньою перфузією (0,4<TR<0,6) (критична зона) відзначено ускладнення, пов'язані з анастомозом. При Tmax 51,5>, T½max 19,8>, нахилі 1,7< також зростає ймовірність ускладнень. Ці показники вважаються незалежними критеріями. Використання кількісних показників у вигляді T½max і TR при дослідженні перфузії за допомогою ангіографії з індоціаніном зеленим сприяє визначенню сегмента кишечника зі слабкою перфузією.

Ключові слова: лапароскопічна тотальна мезоректальна ексцизія, флюоресцентна візуалізація, кількісні індекси T½max та TR, колоректальний рак.

Colon pathology is characterized by high incidence and mortality rates [7, 11]. Rectal carcinoma is one of the most common neoplasms. The frequency of occurrence of carcinomas of this localization is increasing every year. Therefore, the whole world is trying to improve the results of treatment of rectal cancer with the use of new treatments and chemotherapy regimens. Despite the use of modern technologies and methods of surgical treatment, complications associated with the imposition of anastomosis still account for 10-20 % of cases [3, 5, 7].

The collateral venous network developed weakly in the level of splenic flexure of rectum in 10 % of the population. This anatomical type might lead to the occurrence of ischemia and the appearance of complications (anastomotic attack, necrosis, narrowness etc.) associated with anastomosis during the total mesorectal excision (TME) [4, 6, 10].

The most important method for determining rectal circulation is that the surgeon sees a change in color and pulsation on the rectal wall [1, 13].

Microcirculation disorders observed on the wall of the rectum are sometimes impossible to determine visually. If the veins on the rectal wall are edematous and the organ wall is excessively oily, then even the most experienced surgeon may have difficulty assessing such perfusion [12, 15]. Circulation in a segment of the colon can be easily visualized within a short period of time (1–3 min) using indocyanine green (ICG) robotic and laparoscopic fluorescent cameras. In the literature, quantitative and qualitative indicators have not been explained in detail when using ICG [1, 3, 5]. For example, it has even been found that the intestinal segment examined by ICG fluorescence may not meet physiological requirements and, as a result, serious complications may occur in the anastomosis zone. Quantitative indicators given in the fluorescence of the ICG to predict complications that may occur in the area of the anastomosis turned out to be unsatisfactory [12]. At the same time, new directions in the application of this technique are emerging [4, 6].

The purpose of the study was to define a reliable index that can minimize the complications associated with anastomosis by using indocyanine green angiography during the laparoscopic total mesorectal excision.

Materials and methods. The study was carried out as a result of the treatments and examinations of 28 patients diagnosed with rectal adenocarcinoma of different localization in 2012–2015. The materials of the American Hospital of the Turkish Republic were used during the study. The superior ligation of the inferior mesenteric artery (IMA) was conducted and the mobilization of the splenic flexure was implemented in all patients. Laparoscopic TME was conducted in all of the patients and colorectal anastomosis was created with circular steps (28 and 31) after assessing the perfusion of a large intestinal segment with the ICG and double-tube ileostomy was put. The ICG gives an image with the PINPOINT endoscopic fluorescence imaging system (Novadaq, Mississauga, ON, Canada) due to the effect of ultraviolet rays at certain wavelengths.

First, we clipped and visually registered the border in the usual way to determine the border of perfusion in the colon, and then performed ICG angiography. To do this, the ICG powder in the amount of 25 mg/kg was dissolved in 10 ml of saline and injected into the peripheral vein in the amount of 4.0 ml. Fluorescent images of 803 nm ICG waves after some time were monitored in the mode of the infrared radiation spectrum at a wavelength of 800 nm using a special mode in the laparoscopic apparatus. The perfusion of the colonic segment was monitored in the ICG fluorescence mode of the laparoscopic apparatus for 2 minutes (sometimes for 4 minutes when good perfusion was not obtained). In addition, the perfusion of the intestinal segment was assessed qualitatively and quantitatively using a special method.

Results of the study and their discussion. We used the clipping method for assessing the obtained results qualitatively. Our observations show a difference exists between the perfusion the border seen visually and the border visualized with ICG fluorescence in 8 (29.6 %) out of 28 patients. This difference was disclosed to be about 1.5–3.0 cm. The same difference was insignificant in the remaining patients (16 in total) (0.1–0.6 cm). Despite ICG, we believe that the cause of the complications (anastomosis (2 patients) and stenosis (1 patient)) associated with the anastomosis in 3 patients is our inability to assess perfusion qualitatively. A complication associated with the imposition of anastomosis in 19 patients who did not undergo ICG by performing laparoscopic TME was noted in 4 (20 %) patients. The reason for the occurrence of complications associated with the imposition of the anastomosis was the impossibility of assessing perfusion at the microcirculatory level.

Fluorescence videos were recorded to assess rectal perfusion qualitatively, and graphical curves were generated using a simulation method to visually describe changes in fluorescence intensity.

Fluorescence factors and perfusion factors were used for assessing the perfusion in the rectal segment by using the graphical curves. The fluorescence intensity factors mean minimum (Fmin) and maximum (Fmax) fluorescent intensity, base intensity (▲F) and fluorescence difference in the direction of fluorescence (slope=▲F/▲T=Fmax/Tmax). The fluorescence in the maximum intensity from the first fluorescence appeared during the ICG perfusion (Tmax=▲T) as they passed as it is seen and the indexes like the time (T½max) and time correlation (TR=Tmax½/Tmax) spent on the maximum half of the fluorescence increase, were investigated and analyzed. Anastomoses were predicted by using certain clinical factors and perfusion factors for assessing the efficacy of the phases of the ICG perfusion. The fluorescence intensity (density), TR time correlation, ▲F/▲T fluorescence slope were considered important quantities. The connection of the weak perfusion with T½max, TR and fluorescence slope in the diagram. The ICG fluorescence intensity, minimum limits, maximum ascend and descend were mentioned in the fluorescence diagram depending on the time. Our observations show that the ICG gives maximum fluorescence image by beginning from the 40th second and increasing up to 60 seconds after being injected intravenously. The fluorescence intensity also falls down from this time section in the higher and lower cases. It would be more correct to assess the perfusion in T max and T½max time. Complications associated with anastomosis in patients who underwent an ICG test with laparoscopic TME in the first 10 and 30 days were analyzed. This time, analyses were made by using clinical symptoms, roentgen examinations, computer tomography and colonoscopic examinations. Colectomy was conducted in a patient experiencing anastomotic attack (necrosis of the anastomotic zone) and ileostomy was formed but the drainage of the anastomotic zone was conducted in another patient. It was impossible to pass through the zone of narrowness led from the ileostomy to the endoscopy in a patient with anastomotic narrowness and the narrowness was dilated in a transanal way. We tried to define the connection among the complications occurred in the anastomotic zone with some indexes.

The analysis of the clinical factors shows that multifactoral reasons stand on the basis of the complications occurred in connection with anastomosis. Only satisfactory level of the blood circulation with the ICG is not enough for preventing of this type of complications. It was defined while investigating the correlation between the perfusion factors and anastomotic complications that the fluorescence factors and fluorescence slope fall down in the complication groups to a considerable extent (Table 1).

Table 1

Correlation between anastomosis complications and perfusion factors

		N	Mean	Std. Deviation	Std. Error	95 % Confidence Interval for Mean		Minimum	Maximum	PU
						Lower Bound	Upper Bound			
Tmax	no	25	30.1	18.4	3.7	22.5	37.7	1.6	58.6	0.013
	yes	3	63.0	9.8	5.7	38.5	87.5	52.0	71.0	
	Total	28	33.6	20.4	3.9	25.7	41.5	1.6	71.0	
T½max	no	25	11.6	7.0	1.4	8.7	14.5	,5	22.6	0.013
	yes	3	41.1	22.7	13.1	0.0	97.4	19.9	65.0	
	Total	28	14.8	13.0	2.5	9.8	19.8	,5	65.0	
TR	no	25	0.402	0.192	0.038	0.322	0.481	,02	,64	0.063
	yes	3	0.607	0.091	0.052	0.381	0.832	,51	,69	
	Total	28	0.424	0.194	0.037	0.348	0.499	,02	,69	
Fmin	no	25	10.4	5.6	1.1	8.1	12.7	1.0	19.5	0.911
	yes	3	10.9	4.1	2.4	0.7	21.1	6.8	15.0	
	Total	28	10.4	5.4	1.0	8.3	12.6	1.0	19.5	
Fmax	no	25	57.1	23.0	4.6	47.6	66.6	22.9	90.3	0.110
	yes	3	33.8	12.9	7.4	1.9	65.7	22.0	47.5	
	Total	28	54.6	23.1	4.4	45.6	63.6	22.0	90.3	
Slope	no	25	2.70	1.43	0.29	2.11	3.29	,5	4.9	0.023
	yes	3	0.73	0.67	0.38	0.00	2.39	,3	1.5	
	Total	28	2.49	1.50	0.28	1.91	3.07	,3	4.9	

Note: Pu – coefficient of statistical significance of differences according to Mann-Whitney U test

As it is seen from the table, Tmax, T½max, slope is more correct index. The statistical importance of TR, F_{min}, F_{max} indexes is not so much.

Receiver operating characteristic index was used for predicting the complications associated with anastomosis (ROC–Recerver Operating Characteristic). The ROC curves were used to define the concrete values of the perfusion factors with high sensitivity and specificity. Analyzes were made with logarithm model for define the relationships among the perfusion factors and prevent the complications that may occur in connection with anastomosis. ROC analyzes were made for defining the concrete values of the perfusion factors to predict the complications in connection with anastomosis. Our observations show that the area under T½max and TR curves (AUC–area under curve) is more than 0.9 that it shows the possession of certain indexes of an important value in predicting of complications associated with anastomosis. The fluorescence slope is associated with complications on anastomosis. The ROC-curves for parameters studied are shown in Fig. 1.

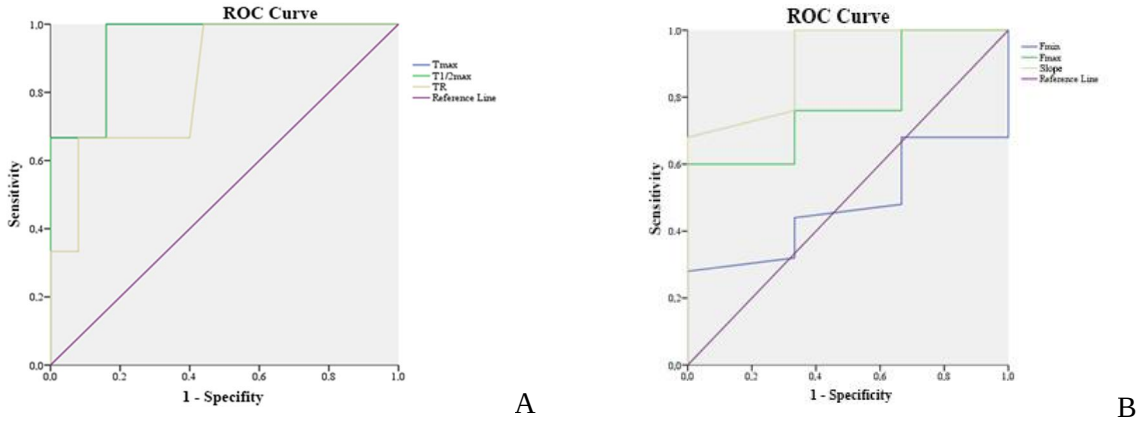

Fig. 1. ROC-curves for parameters of perfusion. A – ROC-curve for Tmax, T½max and TR. **B –** ROC-curve for Fmin, Fmax and slope.

AUROC for Tmax was 0.947±0.054; 95 % Confidence Interval (95 %CI):0.841–1.000; p=0,013); for T½max–0.947±0.054; 95 %CI: 0.841–1,000; p=0.013; for TR–0.833±0.117; 95 %CI: 0.604–1.000; p=0.063. As it is seen, the TR index shows the lower level of the sensitivity and specificity of the index. AUROC for Fmin was 0.480±0.124; 95 %CI:0.236–0.724; p=0,911); for Fmax–0.787±0.114; 95 %CI: 0.563–1,000; p=0.110; for slope–0.907±0.086; 95 %CI: 0.739–1.000; p=0.023.

In our study it is considered, that slope (fast >1.0 AU/sec, low>0.7 AU/sec), T½max (fast<10 sec, low>18 sec), TR time correlation (fast<0.4, low >0.6). The perfusion factors had high specificity and exactness for predicting the complications associated with anastomosis. T½max was used by us as high sensitivity but TR as specific and exact index (Table 2).

Table 2

Predictive values of parameters of perfusion for complications

No.	Tmax	T½max	TR	Fmin	Fmax	Slope
n	28	28	28	28	28	28
min	1.6	0.5	0.02	1	22	0.3
max	71	65	0.69	19.5	90,3	4.9
bound	51.5	19.8	0.6	15.5	51	1.7
	>	>	>	<	<	<
n+	3	3	3	3	3	3
++	3	3	2	3	3	3
Sn	100.0	100.0	66.7	100.0	100,0	100.0
±mp	0.0	0.0	27.2	0.0	0,0	0.0
n-	25	25	25	25	25	25
--	21	21	23	7	15	17
Sp	84.0	84.0	92.0	28.0	60,0	68.0
±mp	7.3	7.3	5.4	9.0	9,8	9.3
ODV	24	24	25	10	18	20
%	85.7	85.7	89.3	35.7	64,3	71.4
±mp	6.6	6.6	5.8	9.1	9,1	8.5
pPV	42.9	42.9	50.0	14.3	23,1	27.3
±mp	18.7	18.7	25.0	7.6	11,7	13.4
nPV	100.0	100.0	95.8	100.0	100,0	100.0
±mp	0.0	0.0	4.1	0.0	0,0	0.0
LR+	6.25	6.25	8.33	1.39	2,50	3.13
	good	good	good	insufficient	sufficient	sufficient
LR-	0.00	0.00	0.36	0.00	0,00	0.00
	excellent	excellent	sufficient	excellent	excellent	Excellent

Note: Sn – sensitivity; Sp – specificity; ODV – overall diagnostic value; pPV (nPV) – positive (neqativ) predictive values; (LR+) positive likelihood ratio; (LR–) negative likelihood ratio. Slope (low<0.7 A4/sec), T ½ max (low >18 sec), TR (low>0.6).

In case T½max and TR are high (that is, slow flow), the probability of occurrence of complications regarding the anastomosis was high.

It was shown that the transaction line was slipped to the proximal for about 2–3 cm because of the existence of segments without fluorescence in the zone close to the rectal wall after the transection of the mesentery of the large intestine. In case the perfusion status was violated in the distance of 5–10 cm, then it would be more logical to avoid of putting of anastomosis and using of alternative measures. It was necessary for changing of the transaction line in 8 of the patients under our observation. No complication was noted in 7 out of these patients but anastomotic attach was observed in only 1 patient. In general, the fluorescence intensity of the left half of the large intestine was lower in the same patient. Colectomy was performed by having another operation in the 8th day after the operation. Thus, we may tell about the occurrence of complications on anastomosis with the T½max and TR indexes beforehand. The aim here was to identify the patients with weak perfusion and include in certain treatment program. We differed 4 risk zones according to the perfusion degree. If anastomosis is put in the critical region, the probability of attack will be over 10 %. In general, we consider it advisable to put ileostomy during the mobilization of splenic flexure and superior ligation of the IMA. In case anastomosis is put in the dangerous zone, the probability of anastomotic attack will make up 70 %. In such cases, the operations may be completed by relocation of the transaction line towards the proximal and application of colostomy. We offer the following scheme for predicting anatomoses by using T½max and TR (Fig. 2).

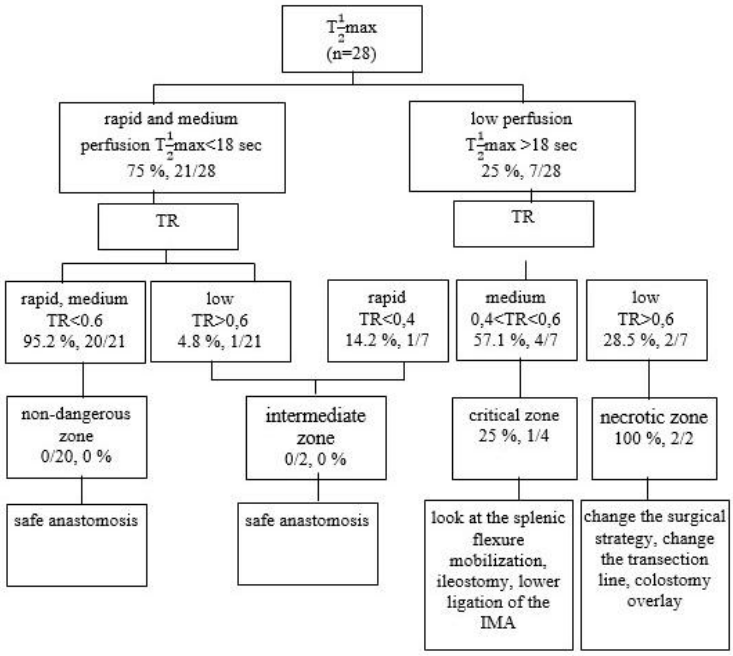

Fig. 2. Algorithm of predicting colorectal anastomoses during the TME

According to our results, we can say the following: the circulation of the left half of the colon, including the intestinal segment used in anastomoses, is considered as external arteries. But observations show that the closure of the IMA from the root leads to a decrease in pressure in the splenic curve and, as a result, to good nutrition of the anastomotic area in 10-30 % of cases. Therefore, knowledge of the state of blood circulation in the intestinal wall assumes critical importance.

The incorporation of ICG into clinical medicine has revolutionized the field [9, 14]. But this method is not flawless either. It could not show perfusion in the anastomosing segments of the intestine in terms of quantity, but he did so in terms of quality. For example, it is necessary to analyze the blood flow by quantity in order to correctly interpret changes in the microcirculation on the wall in order to predict the vital activity of the intestine. A new direction in the development of the fluorescent ICG method has emerged with the introduction of Fmax and T½max into clinical practice. The study of Wada T, et al, showed Fmax to be an important factor and explained the role of T ½ max and TR perfusion values in anastomotic complications [15].

We think that we should consider not only the anatomic properties of a patient but also the properties of fluorescence camera system and conditions of video filming during the assessment of perfusion by quantity. Besides it, the factors like the fluorescence light source, colored development mode, camera distance of an operation room are considered as the factors influencing the intensity of fluorescence. The dangerous complications were 10.7 % in the research work carried out by us. In the different researches (Kamiya K, et al, 2015; Blanco-Colino R, et al, 2018), this percent in 2015 was 40%, 2.8 % in 2016, 2.5 % in 2017 and 7 % in 2018 [2, 8]. The reason for occurring of the complications more in the first times, it was the formation of anastomoses in the patients with weak ICG fluorescence. As the interpretation was not conducted in the first times correctly, the creation of colored image during the fluorescence in the patients with violated blood circulation in the living eyes, caused errors. It was called as delayed perfusion. Therefore, measurements not made within right time, may lead to serious complications by giving wrong fluorescence image [12].

Conclusions

1. ICG perfusion is the most effective quality index used for safe application of anastomoses during the TME.

2. It is possible to avoid wrong transection in 29.7 % by ICG imaging.

3. It is possible to predict the anastomoses beforehand by using the perfusion factors like T½max, TR and Fmax.

4. 16.7 % cases in the patients with lower perfusion TR<0.4, complications on anastomosis were noted in 33.33 % cases in the patients with the anastomotic narrowness, medium perfusion (0.4<TR<0.6) in the patients applied anastomoses safely.

5. In case of Tmax 51,5>, T1/2max 19,8>, slope 1,7<, the probability of complication is also high. The above-said indexes are considered as independent criteria.

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Ya.O. Yemchenko, I.P. Kaydashev, K.Ye. Ishcheykin, O.V. Bezeha, K.V. Vasylyeva, Ya.O. Oliinichenko, L.A. Bolotna[1]
Poltava Medical State University, Poltava, [1]Kharkiv National Medical University, Kharkiv

THIAZOLIDINEDIONES IN THE TREATMENT OF PSORIASIS IN PATIENTS WITH OBESITY

e-mail: yanaumsa@ukr.net

Psoriasis is the most common chronic, genetically determined autoimmune polyetiologic inflammatory disease with impaired epidermal proliferation, provoked by exogenous and endogenous factors and manifested by erythematous scaly elements, papules and plaques. Despite the widespread prevalence of psoriasis and a large number of studies on this problem, there is still no single view of the pathogenesis of this dermatosis. For an objective understanding of the pathogenesis of psoriasis, it is necessary to consider the insufficiently studied comorbidity of this pathology. Recently, an undeniable link between psoriasis and obesity has been proven. Taking into account the current data on the role of systemic inflammation underlying the development of both psoriasis and obesity, the study of molecular mechanisms of its development, and taking into account the role of proinflammatory nuclear transcription factors, thiazolidinediones are the pathogenetically determined drug of choice for the treatment of these diseases. In this study, we determined the efficacy of using 45 mg of pioglitazone once daily for six months in the complex treatment of patients with moderate vulgar psoriasis with concomitant alimentary obesity of I-II degree by clinical and immunological studies of systemic inflammation. Analyzing the study results, it was found that long-term use of 45 mg of pioglitazone was effective, led to a decrease in systemic inflammation, and contributed to a milder course of psoriasis in case of recurrent relapse of the disease.

Key words: psoriasis, alimentary obesity, systemic inflammation, treatment.

Я.О. Ємченко, І.П. Кайдашев, К.Є. Іщейкін, О.В. Безега, К.В. Васильєва, Я.О. Олійніченко, Л.А. Болотна

ТІАЗОЛІДИНДІОНИ У ЛІКУВАННІ ПСОРІАЗУ У ПАЦІЄНТІВ З ОЖИРІННЯМ

Псоріаз є найбільш розповсюдженим хронічним, генетично детермінованим аутоімунним поліетіологічним запальним захворюванням з порушенням епідермальної проліферації, що провокується екзогенними і ендогенними факторами та проявляється еритематозно-лускатими елементами, папулами і бляшками. Незважаючи на значне поширення псоріазу та на велику кількість робіт з цієї проблеми, до сих пір немає єдиного погляду на патогенез цього дерматозу. Для об'єктивного розуміння патогенезу псоріазу необхідно враховувати недостатньо вивчену коморбідність цієї патології. Останнім часом доведений безперечний зв'язок між псоріазом і ожирінням. Враховуючи сучасні данні ролі системного запалення, що лежить в основі розвитку як псоріазу, так і ожиріння, вивчення молекулярних механізмів його розвитку та беручи до уваги роль прозапальних ядерних транскрипційних факторів патогенетично обумовленим препаратом вибору для лікування цих захворювань є тіазолідиндіони.У цьому досліджені ми визначали ефективність використання 45 мг піоглітазону 1 раз на добу протягом 6 місяців у комплексному лікуванні хворих на розповсюджений вульгарний псоріаз середнього ступеня тяжкості перебігу з супутнім аліментарним ожирінням I-II ступеня шляхом клінічного та імунологічного дослідження показників системного запалення. Аналізуючи результати проведеного дослідження було встановлено, що тривале використання 45 мг піоглітазону виявилось ефективним та призвело до зниження показників системного запалення і сприяло більш легкому перебігу псоріазу при повторному рецидиві захворювання.

Ключові слова: псоріаз, аліментарне ожиріння, системне запалення, лікування.

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Psoriasis is a systemic immune-associated disease of multifactorial nature with a predominance of genetic factors in the development, characterized by accelerated proliferation of epidermocytes and impaired differentiation, immune reactions in the dermis and synovial membranes, an imbalance between pro- and anti-inflammatory cytokines, chemokines, and frequent pathological changes in the musculoskeletal system.