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## **Melatonin in the complex treatment of gastro esophageal reflux disease in children**

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*This article deals with the problem of gastroesophageal reflux disease (GERD) in children, which has an enormous medical and social importance. Despite recent advances in therapy, the disease is characterized by recurrent exacerbations with the development of complications, which dictates the need of finding a new pathogenically supported esophagitis treatment. In this regard, the effectiveness of melatonin was evaluated in the treatment of the gastroesophageal reflux disease in 20 patients. During the intake of this medicine a clear positive trend was set, which included: the elimination of pain, lack of palpable pain in the epigastria and pyloric duodenal areas, reduction of the frequency of dyspeptic symptoms, a significant reduction in gastroesophageal reflux during dynamic endoscopic examination, and improvements of the function of gastric acid, regulatory processes in the digestive tract due to the normalization of melatonin levels. Scientific evidence shows that the inclusion of the drug in the complex treatment of GERD patients can improve the effectiveness of therapy by 2.5 times.*

**Key words:** *gastroesophageal reflux disease, melatonin, the treatment of children.*

Despite recent advances of gastroesophageal reflux disease (GERD) treatment, it is characterized by recurrent exacerbations with the development of complications, which dictates the need of finding new pathogenically based treatment for child esophagitis.

Clearly, GERD is a multifaceted disease with violations of the regulation of the digestive tract including the humoral oral mechanism [1]. An important role is played by gastrointestinal hormones, such as melatonin, which affects the processes of motility, secretion, microcirculation, cell proliferation, and cellular protection [2-4]. In the world medical practice some experience of its use has been already gained in the treatment of various diseases: disorders of sleep and circadian rhythms, hypertension and coronary heart disease and prevention of aging [5-8]. The positive effect of the inclusion of melatonin in the complex treatment of duodenal ulcer and irritable bowel syndrome in a therapeutic clinic [9, 10] was proved. However, studies on its use in GERD in adults and children have not been met. The purpose of this study is to evaluate the effectiveness of melatonin in the treatment of gastroesophageal reflux disease in children.

### **Patients and Methods**

Studies were performed on 40 children with GERD aged 12 to 18 years. Depending on the treatment scheme the patients were divided into 2 groups. 20 patients (main) of the 1<sup>st</sup> group received a complex therapy, including diet, intake of esomeprazole (Nexium) 40 mg per day, domperidone (Motilium) 150 mg three times a day and Melatonin (Melaxen "Unipharm" U.S. registration certificate: P № 015325/01 dated 02.02.2004) before going to bed 3 mg once a day. In the 2<sup>nd</sup> (control) group 20 patients received only standard therapy (esomeprazole and domperidone). According to the testimony, all patients were prescribed symptomatic agents. The duration of therapy was 1 month. Both groups did not differ significantly among themselves by age, gender, the nature of clinical and laboratory-instrumental violations.

Monitoring of the therapy effectiveness was carried out according to the dynamics of clinical manifestations, morphological and functional mucosal changes of the esophago-gastro-duodenal area and the percentage of melatonin in the urine. The diagnosis of gastroesophageal reflux disease was based on clinical and laboratory research tools according to the classification by G. Tytgat in the modification of V.F. Privorotskiy (1999) [11].

The quantity of melatonin was evaluated in terms of its main metabolite - 6-sulfatoksimeatoninine - in the urine by the method of «BUHLMANN 6-Sulfatoxymelatonin ELISA».

All diagnostic and treatment activities that were conducted in the hospital are approved by the Ethics Committee of FGU "Institute of Pediatric Gastroenterology" in 2008 and were performed with the informed consent of parents and children over 15 years.

Inclusion criteria were: the presence of gastroesophageal reflux disease, age over

12 years, clinically stable condition with no physical illnesses at the stage of decompensation, parental consent for treatment.

Exclusion criteria were: the impossibility of endoscopy, age younger than 12 years, the presence of somatic diseases in a decompensating stage, the emergence of side effects requiring withdrawal of therapy during treatment, parental rejection.

In this paper we apply modern methods of statistical analysis, integrated into the program Statistica 6.0 for Windows XP. Descriptive statistics included the mean value of trait (M) and the mean error (m). Mann-Whitney, Wilcoxon, and Spearman criteria were used for comparisons between groups. Differences were considered significant at a significance level achieved for the appropriate statistical test,  $p < 0.05$ , as it is customary in biology and medicine.

### **Results of the study and discussion**

Prior to treatment most patients had an abdominal pain which was localized mainly in the epigastria region, particularly: 19 (95%) children of Group 1 before the appointment of melatonin and 20 (100%) patients of the control group. Palpable epigastria and pyloric duodenal pain of varying severity occurred in 20 (100%) and 15 (75%) children in both groups, respectively. The manifestations of dyspeptic syndrome in the form of heartburn and regurgitation were recorded in 16 (80%) and 11 (55%) patients in Group 1, 12 (60%) and 8 (40%) - Group 2. Nausea and vomiting after a meal were determined in 7 (35%) and 10 (50%) cases, respectively (Table 1). From the astheno-vegetative complaints: 3 (15%) patients of the 1<sup>st</sup> group and 4 (20%) of the control group reported headache. Various behavioral disorders were clear: irritability, anxiety, fatigue occurred equally often in 8 (40%) patients.

Therapy gave a clear positive change in the form of improved general health, a significant reduction or elimination of pain and dyspeptic syndromes of the disease in all the children carried out by the end of the course. Thus, there were no complaints of abdominal pain in all core patients ( $p = 0.001$ ) and 16 of the control group ( $p = 0.001$ ) groups. Regardless of the treatment epigastria tenderness and soreness of pyloric duodenal area has not been determined. However, dyspeptic manifestations, namely heartburn and regurgitation were stopped, respectively, in 19 (95%,  $p = 0.001$ ) and 18 (90%,  $p = 0.003$ ) out of the 20 children in the study group, and clearly less - in 9 (45%) and 8 (40%) cases ( $p = 0.006$ ,  $p = 0.001$ ) - in the control group. Only after taking melatonin in all patients the absence of vomiting after eating ( $p = 0.004$ ) was determined.

Among the vegetative complaints in the study group breaches of conduct were registered less (2 times compared with baseline) in 2 out of 20 (10%) observed ( $p = 0.03$ ). The appointment of esomeprazole and domperidone kept these complaints more often - in 8 (40%) patients,  $p = 0.03$  (see Table. 1).

Thus, in patients with GERD combined treatment with the inclusion of melatonin detected clinically positive dynamics, characterized not only by the relief of pain with a more frequent normalization of dyspeptic disorders, but also a distinct decrease in the number of vegetative complaints - increased irritability, anxiety, fatigue compared with patients the standard treatment.

While taking medicines positive changes in endoscopic performance were set. For example before treatment, all children showed signs of nonspecific inflammation of the mucous membrane of the esophagus, such as swelling, redness, erosion were determined with the same frequency in 9 (45%) patients; multiple erosions of the esophagus were recorded in 5 (25%) and 7 (35 %); ulcerative process - in 1 (5%) and 2 (10%) respectively. Destructive changes were seen in 6 (30%) and 4 (20%) patients as the form of initial manifestations of epithelialization.

Observed children also had violations of the motor-evacuation function of the digestive tract. Gastroesophageal reflux and lack of cardiac closure of the esophagus were noticed in 18 (90%) and 4 (20%) patients of the main group and in 19 (95%) and 7 (35%) - in control.

After completing the course of therapy regardless of the complex, according to the endoscopic examination, the following were revealed: decreased the severity of hyperemia and edema of the mucosa of the esophagus; decreased the number of erosions and ulcers of the esophagus; and absence of patients with an initial stage of destructive changes in the mucous membranes. It should be noted that the above breach of esophageal motility had a distinct positive trend in patients who received melatonin compared with standard treatment. Thus, the number of children diagnosed with GER has declined by half and made eight (40%,  $p = 0.008$ ) patients in the intervention group, whereas in the control pathologic reflux was maintained in the majority - 16 (80%,  $p = 0.02$ ) cases.

Consequently, during therapy, regardless of the assigned the positive dynamics of endoscopic mucosal inflammatory changes of the esophagus was obvious.

However, only combined treatment with melatonin promoted the normalization of motor disorders of esophagus gastro duodenal??? due to hum??? oral regulation of digestive functions.

Stomach pH-measure showed that the average pH of the stomach fundi of fasting main and control groups was  $1,36 \pm 0,06$  and  $1,6 \pm 0,24$  TE, which corresponded to hyperacid state. After treatment the pH level decreased to  $2,7 \pm 0,59$  ( $p = 0.027$ ) and  $2,58 \pm 0,4$  TE pH, respectively, with a more pronounced positive dynamics of the appointment of melatonin.

Thus, the use of melatonin in the treatment of gastroesophageal reflux disease is effectively for correction of acid.

The study of melatonin metabolite in urine revealed decrease in its level up to 33,

$67 \pm 3, 43$  ( $p = 0.04$ ) prior to treatment in the study group and  $37, 04 \pm 3, 09$  mg. / ml. ( $p = 0.02$ ) - in the control compared to the norm, which confirmed the deregulation of functions esophagus gastro duodenal zone (Table 2).

After treatment the quantity of 6-sulfatoksimeletonina in urine increased in patients who received melatonin, to  $45, 32 \pm 2, 2$  mg / ml ( $p = 0.02$ ), reaching the standards. At the same time standard scheme didn't change its dynamic, 6-sulfatoksimeletonina equaled to  $35, 77 \pm 3, 46$  mg / ml (see Table. 2).

Consequently, the use of melatonin in the complex treatment of patients with gastroesophageal reflux disease contributed to the improvement of regulatory processes in the digestive tract due to the normalization of hormone levels.

Thus, the therapy in both groups showed a significant clinical reduction in the number of complaints of abdominal pain with a decrease in palpable pain. Among the vegetative signs headache bothered rarely. The resulting shifts were confirmed by a significant reduction in edema and hyperemia of the esophageal mucosa and epithelialization process improvement, reduction of hyperacidity. Its use has led to the positive dynamics of regulatory violations by the normalization of neural humoral effects of melatonin, which were associated with improvement of the morph functional state esophago-gastro-duodenal area.

The inclusion of this drug in the complex treatment of gastroesophageal reflux disease in children makes it clearly possible to reduce the dyspeptic signs and autonomic dysfunction in the form of increased irritability, anxiety, and fatigue. The dynamic observation of patients within 1 month confirmed the efficacy of melatonin, as indicated by a pronounced decrease (2 times) the number of children with gastroesophageal reflux preservation.

In accordance with the basics of evidence-based medicine its evaluation by using the method of "case-control" was carried out. Scientific evidence shows that the inclusion of melatonin in the complex treatment of GERD can improve the efficiency of therapy with a decrease in 2 times the number of registered gastroesophageal reflux by endoscopic examination, which is the basis for the formation of the disease, due to the normalization of the regulation of gastrointestinal motor function.

When comparing the effectiveness of treatments for gastroesophageal reflux saving option for dynamic observation was chosen as a clinical sign to represent the effect of interfering with the identification of patients who needed treatment for some time to get a favorable outcome (NNT) (A. Spiegel, 2004 .) Table 3 shows the key performance indicators, and an interference in the 1<sup>st</sup> and 2<sup>nd</sup> group.

The results shown in the table characterize the reduction of adverse outcomes during treatment with melatonin as compared to using only the standard treatment in children with gastro esophageal reflux disease 2 times, respectively, up to 40

and 80%.

Relative risk reduction of 50% with a confidence interval 1,4-5,5 (CI greater than 1) means the number of patients with gastroesophageal reflux disease, who needs to be treated with the proposed therapeutic complex for 1 month to prevent an adverse outcome ( maintaining GER), equal to 2.5, CI 2.23 to 2.77. Thus, every second patient during combined treatment with the inclusion of melatonin had a positive effect compared to baseline therapy. Consequently, CHBNL indicator shows that the effectiveness of proposed treatment increases conventional.

### **Conclusion**

The inclusion of melatonin in the complex treatment of gastroesophageal reflux disease in children is accompanied by distinct positive dynamics in the form of elimination of pain in all observed patients, the absence of palpable pain in the epigastria and pyloric duodenal regions expressed by reduction of the frequency of dyspeptic symptoms, improvement of the acid-forming function of the stomach, the correction of regulatory violations with the normalization of melatonin levels, and a significant reduction in gastroesophageal reflux registration under dynamic endoscopic examination. Its use in the complex of therapeutic measures of GERD patients can improve the efficiency of therapy by 2.5 times.

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**Table 1.** Dynamics of changes in the frequency of clinical findings during treatment in children with GERD (%)

<b>Groups of children</b>  <b>Indicators</b>	<b>Main, n =20</b>		<b>Control, n=20</b>		<b>p</b>		
	Before treatment	After treatment	Before treatment	After treatment			
	1	2	3	4	1-2	3-4	2-4
Abdominal pain	19 (95)	0	20 (100)	4 (20)	<b>0,001</b>	<b>0,001</b>	
Palpation pain	20 (100)	0	15 (75)	0	<b>0,001</b>	<b>0,001</b>	
Heartburn	16 (80)	1 (5)	12 (60)	11 (55)	<b>0,001</b>		<b>0,006</b>
Belching	11 (55)	2 (10)	8 (40)	8 (40)	<b>0,003</b>		<b>0,001</b>
Nausea and vomiting	7 (35)	0	10 (50)	5 (25)	<b>0,004</b>		<b>0,02</b>
Headache	3 (15)	1 (5)	4 (20)	1(5)			
Behavior disorders	8 (40)	2 (10)	8 (40)	8 (40)	<b>0,03</b>		<b>0,03</b>

**Notice:** p - The reliability of differences between groups, n - number of children surveyed.

**Table 2:** The dynamics of the frequency of changes in the level of melatonin during the treatment in children with GERD (M ± m)

Groups of children  Indicators	Norm n=18	Main, n =20		Control, n=20		p	
		Before treatment	After treatment	Before treatment	After treatment		
		1	2	3	4	1-2	2-4
6 sulfatoksime latoninurine ng/ml	43,52 ±1,43	33,67 ±3,43*	45,32 ±2,20	37,04 ±3,09*	35,77 ±3,46*	<b>0,02</b>	<b>0,02</b>

Notice. p - the reliability of differences between groups, n - number of children surveyed \* - reliability with a group of healthy children, p <0

**Table 3.** Performance evaluation of combined treatment with respect to the acceptance of standard drugs

Compared groups	Indicators						
		Chick %	SOR %, 95% DI	CHBNL 95% DI	OSH 95% DI	x2	p
1	40	80	50	40	2,5	0,02	<0,05
2			1,4-5,5	13-67	2,23-2,77		

Notice: Chill - the frequency of outcomes (save GER) in patients with gastroesophageal reflux disease treated with the inclusion of melatonin; Chick - the frequency of outcomes (save GER) in patients who received standard therapy, GRA - the relative risk reduction; CAP - an absolute risk reduction, odds ratio - the ratio of chances