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RELIEVING TREATMENT OF BRONCHIAL ASTHMA ATTACK IN SCHOOLCHILDREN SUFFER FROM SEVERE DISEASE PHENOTYPE

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У дослідженні показано, що триденний курс системних глюкокортикостероїдів порівняно з коротшим терміном їх призначення характеризувався вірогідним ризиком регресу бальної оцінки тяжкості нападу на 7-й день стаціонарного лікування. Також продемонстровано, що довенне введення еуфіліну на тлі застосування інгаляційних β2-агоністів короткої дії та системних глюкокортикостероїдів асоціювало з ризиком зменшення тяжкості нападу на 3-й та 7-й день стаціонарного лікування

***Ключові слова**: бронхіальна астма, фенотип, діти, лікування, тяжкість нападу, метилксантини, глюкокортикостероїди, β2-адреноміметики*

1. Introduction

Asthma is a major public health problem with a huge social and economic burden affecting 300 million people worldwide. It is the most common chronic respiratory disease, affecting up to 10 % of the adults and 30 % of the children in the Western world [1].

Asthma is a chronic, heterogeneous disease with symptoms and features that include wheeze, cough (particularly at night and during exertion), dyspnoea and chest tightness, variable airways obstruction and bronchial hyperresponsiveness. The underlying chronic inflammation is often characterised by eosinophilic activity and allergic inflammation, and airways remodelling is a frequent feature of asthma, even in young children, although not in the very early stages. The longer-term risks for the patient with poor control include asthma attacks, impaired development or accelerated decline in lung function, and side-effects of treatment. Despite the availability of effective medication, many children do not have adequately controlled asthma. This has implications for quality of life (QoL) and daily physical activity, and clearly increases the burden of disease in terms of costs to the family and society.

2. Case presentation

Children with asthma frequently report limitations in activities and sports (reported in ≤ 47 % of children with asthma), nocturnal awakening due to asthma (≤ 34 %) and absence from school (≤51 %) [2].

At least 10–12 % of patients with bronchial asthma (BA) suffer from severe phenotype of the disease [3], at the same time relatively small proportion of patients with refractory severe BA to the treatment accumulates 40–50 % of health care resources among the total population of patients with BA, causing a disproportionate large share of health facilities expenses [4]. Severe asthma is singled out into a separate phenotype and requires aggressive therapeutic approaches to achieve control [5, 6].

A major part of the burden of disease is caused by acute exacerbation in general practice and emergency department in the hospitals. Despite advances in asthma management, acute exacerbation continues to occur and impose considerable morbidity on patients and constitute a major burden on health care resources [7, 8].

An increasing prevalence of pediatric asthma has led to increasing burdens of critical illness in children with severe acute asthma exacerbations, often leading to respiratory distress, progressive hypoxia, and respiratory failure [9, 10]. Exacerbations can be defined as the presence of either one of the following signs and symptoms of airflow obstruction within the past 48 hours (e. g. cough, wheezing, shortness of breath and chest tightness) and repeated use of short-acting beta-agonists within the past 48 hours [1].

Early treatment of asthma exacerbations is the best strategy for management. Important elements of early treatment at the patient's home include a written asthma action plan; recognition of early signs and symptoms of worsening; appropriate intensification of therapy by increasing short-acting β-agonists and, in some cases, adding a short course of oral corticosteroids; removal, or withdrawal from an environmental factor contributing to the exacerbation; and prompt communication between the patient and clinician, seeking emergency care for severe manifestations, or both. Despite adherence to optimal chronic asthma care, it is increasingly recognized that some patients will require an urgent office visit or even an emergency department (ED) visit for further asthma care [11].

3. Aim of research

Improving relieving treatment of bronchial asthma attacks in children of school age with a severe phenotype of the disease.

4. Material and methods

Keeping the bioethics principles on the base of pulmonological department of the Regional Pediatric Hospital (Chernivtsi) 57 school-age children with severe persistent asthma were examined. Diagnosis of the disease was verified according to the BA classification [12, 13], the attack period was determined in 48 patients (84,2 %). The proportion of boys reached 59,6 %, inhabitants of the rural area made up 61,4 %, the average age of school children reached 12,6±0,43 years.

The severity of bronchial obstruction syndrome (BOS) on patients' admission to the hospital during the exacerbation period was assessed by point scale [14], and intensification of BOS manifestations was reflected in the increasing of the total amount of points on this scale.

Therapeutic tactics in the period of attack was assigned according to the protocol for diagnosis and treatment of asthma in children approved by GINA recommendations in 2014 versions [15] and "Guidelines for BA diagnosis and treatment in children" – PRACTALL [16]. In accordance with these documents for the purpose of desobstruction short-acting β2-agonists, glucocorticosteroids (GCS) of systemic effect (1–3 mg/kg for 1 administration for prednisolone, but not more than 60 mg per day intravenously) and methylxanthines preparations (Euphylline 3–5 mg/kg for 1 administration, but not more than 200 mg per day intravenously) were used.

In assessing the probability of the indexes difference Student's coefficient (t) was calculated. For a probable difference, the index at $p<0,05$ was taken. In assessing relative indixes, Fisher's exact criterion ($p\varphi$) was used. The results were analyzed using the principles of clinical epidemiology. Risk of event realization was evaluated taking into account the probability of relative risks (RR), attributive risks (AR) and odds ratios (OR), as well as the assessment of their 95 % of confidence intervals. The effectiveness of the treatment was evaluated in terms of reduce of absolute risk (RAR) and relative risk (RRR) specifying a minimum number of patients who should be treated in order to gain one positive result (number of patients to be treated, NNT) [17].

5. Results

It was determined that in patients with severe BA for the purpose of desobstruction short-acting inhalation β2-agonists, GCS of systemic effect and methylxanthines preparations (Euphylline) were administered for oral and intravenous use in various combinations with one another. Thus, monotherapy with short-acting inhalation β2-agonists (salbutamol) and in combination with theophylline per os was used in 19,6 % of cases, addition of corticosteroids of systemic effect to the previous version – in 17,7 % of patients. It was also noticed that every second child (52,9 %) with severe BA for the purpose of effective bronchodilatation needed combined use of all three groups of desobstructive therapeutic means. That is, 80,0 % of children with severe BA received GCS of systemic effect, the average duration of the course was 2,9±0,19 days. A quarter of schoolchildren (26,8 %) received the course of GCS of systemic effect, exceeding 3 days.

Most pupils with severe BA (52,9 %) in acute period of the disease received infusion therapy with methylxanthines (Euphylline), the average duration of infusion therapy in children with severe pathology persistence lasted 3,3±0,24 days. 44,4 % of patients received infusion therapy more than 3 days.

The Table 1 demonstrates the assessment indices of the attack severity in children with severe BA when GCS of systemic effect were used during three days, compared with one- and two-day course of their application.

Table 1

Risk indices of attack severity regression at a 3-day administration of glucocorticosteroids of systemic effect in children with severe bronchial asthma compared to one- and two-day course

Point assessment regress of BA attack severity	Risk indices		
	attributive risk	relative risk (95 % CI)	odds ratios (95 % CI)
On the third day of hospital treatment – regress is more than 3 points	0,2	1,38 (0,69–2,75)	2,4 (0,65-8,80)
On the seventh day of hospital treatment – regress is more than 9 points	0,48	2,45 (1,01–5,91)	9,0 (2,08–38,7)

These data corroborate that the three-day course of GCS of systemic effect compared with a shorter term of their administration was characterized by a probable regress risk of point assessment of the attack severity on the seventh day of hospital treatment.

Against the background of relieving treatment with GCS of systemic effect during 3 days the attack severity regress was also observed on the seventh day of hospitalization compared to the first day, in particular the pronounced manifestations of BOS (over 12 points) before treatment were observed in 83 % of schoolchildren, at the end of the treatment the assessment of bronchial obstruction severity of more than 6 points occurred only in 16,2 % of cases ($p\varphi<0,05$). Thus, the RRR of preserving severe bronchial obstruction reached 80 %, the RAR was 67 % with the number of patients to be treated – 1,5 against the background of the three-day therapeutic course with GCS of systemic effect in children of the I clinical group on the seventh day of hospital treatment.

Intravenous Euphylline application in combination with GCS, short-acting inhalation β2-agonists compared to therapy with steroids, short-acting inhalation β2-adrenomimetics in children was associated with the risk of attack severity decrease on the third and seventh day of hospital treatment (Table 2).

Table 2

Indices of the risk of attack severity decrease against the background of intravenous Euphylline application in children

Regress of point assessment of BA severity attack	Risk indices		
	AR	relative risk (95 % CI)	odds ratios (95 % CI)
on the third day of hospital treatment – more than 3 points	0,32	1,8 (0,9–3,5)	4,0 (1,2–12,4)
on the seventh day of hospital treatment – more than 9 points	0,20	1,4 (0,8–2,7)	2,3 (0,7–7,6)

Note: AR – absolute risk

The received data give reason to consider the risk indices of BA attack severity decrease convincing against the background of intravenous Euphylline administration in children with severe variant of the disease on the third day of hospital treatment. Under the influence of the mentioned treatment among the children of both clinical groups the proportion of patients with severe bronchial obstruction decreased; the obstruction was estimated by more than 12 points on the first day of hospital treatment and by more than 6 points on the seventh day of hospitalization (85 % and 22 % respectively, $p\varphi<0,05$). Thus, the RRR of severe bronchial obstruction on the seventh day of hospitalization in patients with severe BA reached 74 %, RAR was 63 % with the number of patients to be treated – 1,5.

6. Discussion

Since the basis of asthma is inflammation of the airways, it is a major target of anti-asthmatic treatment [18], and glucocorticosteroids are the "cornerstone" of both achieving and retaining control in patients with persistence of the disease and a major component of the relieving therapy [19]. This assumption was confirmed by the study, when the lion's share of children (80.0 %) suffering from a severe disease phenotype, received system glucocorticosteroids in the period of attacks. It is noteworthy that the duration of use of these drugs with a positive delayed effect on the VIIth day of treatment was 3 days.

The use of theophylline derivatives to relieve pain remains disputable. The results of recent studies have allowed to justify the use of these drugs in case of severe asthma not only as bronchodilators, but also as remedies with anti-inflammatory effect that prevent bronchial remodeling [20]. The anti-inflammatory effect, in addition to inhibition of phosphodiesterase activity and adenosine receptor blockade, is implemented by activating histone deacetylase, reducing the concentration of IL-8 and enhancing apoptotic neutrophils properties, as evidenced by their reduction in the induced sputum [21]. In small doses, the theophylline drugs enhance the anti-inflammatory effects of glucocorticosteroids [22]. The combination of bronchodilator and anti-inflammatory effects might have allowed obtaining both a quick relieving effect on the third day of treatment and preservation of the bronchodilator action on day seventh day of hospitalization.

At the same time, since it was eosinophils which were targeted by the impact of glucocorticosteroids, and methylxanthines are characterized by some pro-apoptotic effect on neutrophils, it would be appropriate to discretely analyze their effectiveness in different groups of children depending on the nature of airway inflammation.

7. Conclusion

1. The patients with severe BA for the purpose of bronchial relief were administered short-acting inhalation β2-agonists, GCS of systemic effect and methylxanthines preparations (Euphylline).

2. The three-day course of steroids of systemic effect compared with a shorter term of their administration was characterized by a probable regress risk of point assessment of the attack severity on the seventh day of treatment.

3. Intravenous Euphylline application in combination with systemic steroids, short-acting inhalation β2-agonists in children was associated with the risk of attack severity decrease on the third and seventh day of treatment.

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