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Database analysis of oral atropine treatment of infantile hypertrophic pyloric stenosis. A ten-year single-center experience

Analiza baze podataka o lečenju infantilne hipertrofične stenoze pilorusa oralnom primenom atropina. Desetogodišnje iskustvo jednog centra

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Abstract

Background/Aim. Infantile hypertrophic pyloric stenosis (IHPS) is the most common cause of surgery in newborns and young infants. Conservative treatment of IHPS is of great importance because it spares the newborn from stress caused by surgery and general anesthesia. The aim of this study was to evaluate the impact of various oral administration regimens of atropine on its efficacy in treating IHPS. **Methods.** The study included 45 patients with IHPS, conservatively treated by atropine sulfate in the period from 2006 to 2016. Clinical examination, laboratory analysis, and ultrasonography were performed on all patients on admission. The efficacy of treatment with different oral dosage regimens was analyzed and potential predictive factors of the negative outcome were defined. The evaluation of the success of the treatment was statistically analyzed by the method of the multivariate logistic regression model. **Results.** Out of 45 patients, 36 (80%) were successfully cured (p = 0.0008, without the need for surgery and without any complications. Gender prevalence, age, birth weight, body weight on admission, duration of symptoms, pyloric muscle thickness, and length had no statistically significant individual effect on the success of the atropine treatment. Patients who received a progressively increased dose of atropine had an 18 times higher risk of surgery, patients with hypochloremic alkalosis (HCA) had a 15 times higher risk, while others, with more than 5 vomitings within the first three days of the therapy, were 9 times more likely to be surgically treated. **Conclusion.** High success rate and no side effects represent an orally administered atropine treatment as a valid alternative choice for non-operative management of IHPS. Administration of initially high doses was shown to be more effective in relation to gradually increased oral doses of atropine sulfate. HCA and continued vomiting are considered as potential predictive factors of negative outcomes of the atropine treatment.

Key words:
atropine; infant; muscarinic antagonists; pyloric stenosis, hypertrophic; risk factors; surgical procedures, operative; treatment outcome.

Apstrakt

Uvod/Cilj. Infantilna hipertrofična stenoza pilorusa (IHSP) je najčešći razlog za hiruršku intervenciju u uzrastu novorođenčeta i mladog odojčeta, a efikasan konzervativni tretman je od velikog značaja, jer se na taj način novorođeno dete ne izlaže stresu uzrokovanom hirurškom intervencijom i opštom anestezijom. Cilj rada bio je procena uticaja različitih režima oralne primene atropina na njegovu efikasnost u lečenju IHSP. **Metode.** Studijom je bilo obuhvaćeno 45 bolesnika konzervativno lečenih oralnom primenom atropin sulfata zbog IHSP, u periodu od 2006. do 2016. godine. Klinički pregled, laboratorijske analize i ehosonografija urađeni su kod svih ispitanika na prijemu. Analizirana je efikasnost konzervativnog tretmana, s posebnim naglaskom na efekat doziranja leka i definisanje potencijalnih prediktivnih faktora negativnog ishoda. Procena uspešnosti lečenja analizirana je korišćenjem modela multivarijantne logističke regresije. **Rezultati.** Konzervativno je lečeno 45 bolesnika, od kojih je 36 (80%) bilo uspešno izlečeno (p = 0,0008, bez potrebe za hirurškom intervencijom i bez komplikacija. Polna zastupljenost, uzrast, porođajna telesna masa, telesna masa na prijemu, trajanje simptoma, kao i dužina i debljina pilorusnog mišića nisu imali statistički značajan

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pojedinačni uticaj na uspeh medikamentnog lečenja. Ispitanici kod kojih je primenjeno progresivno povećanje doze atropina imali su 18 puta viši rizik da će biti operisani, ispitanici koji su na prijemu imali hipohloremijsku alkalozu 15 puta viši rizik, dok su oni sa više od 5 povraćanja u prva tri dana od početka primene atropina imali 9 puta viši rizik od primene hirurškog lečenja. **Zaključak.** Visoka stopa uspešnosti lečenja oralnom primenom atropin sulfata čini ga validnim alternativnim lekom za neoperativni tretman IHSP. Pokazalo se da je primena inicijalno visokih doza efikasnija u odnosu na postepeno povećavane oralne doze atropin sulfata.

Ključne reči:
atropin; odojče; antimuskarinici; pilorus, stenoza, hipertrofička; faktori rizika; hirurgija, operativne procedure; lečenje, ishod.

Introduction

Infantile hypertrophic pyloric stenosis (IHPS) is the most common cause of surgical procedures in newborns and young infants [1]. The inability of gastric emptying, due to progressive hypertrophy of the pyloric circular muscle, causes postprandial, missile, non-bilious vomiting, resulting in body weight loss and the development of metabolic alkalosis. It is reported with an incidence of 4/1,000 live-born children, 4 times more often in boys [2]. Prolonged spasm of the pyloric muscle leads to its hypertrophy, but whether the absence of relaxation is caused by a genetic factor, a smaller number of ganglion cells and/or a lower level of nitrogen-monoxide (NO) synthetase with the neutrality of the gastric contents in the newborn, is not completely clarified [3–5]. The diagnostic method of choice is ultrasonography and extramucosal pyloromyotomy is the superior method of treatment of IHPS, whose outcome is a rapid providing lifelong resolution of symptoms [6–9]. Pyloromyotomy by the laparoscopic approach is equal to an open surgical method, although it is followed by a slightly higher percentage of mucosal perforations and incomplete pyloromyotomies [10]. Medication treatment, which implies treatment with atropine sulfate, is accepted as an alternative to pyloromyotomy, primarily in children with comorbidity. In some countries, like Japan, it is the first line of therapy. Initially, according to literature data, atropine was administered intravenously with higher efficacy on the treatment of IHPS but with more side effects. Also, the harmful effects of orally administered atropine were not recorded [11].

The aim of the study was to evaluate the impact of various oral administration regimens of atropine on its efficacy in treating IHPS, as well as to define potential predictive factors of its negative outcome.

Methods

A retrospective and prospective nonrandomized study was conducted in a ten-year period (2006–2016). Forty-five patients with IHPS were treated by orally administered atropine sulfate. The study included patients with a missile, non-bilious vomiting in a typical age group, while the IHPS was confirmed after the clinical and ultrasound examination. The inclusion criteria were positive ultrasound findings of the hypertrophic pylorus, defined by the Haller and Cohen criteria that considered the thickness of the muscle wall ≥ 4 mm, the total diameter of pylorus ≥ 15 mm, and pyloric muscle length ≥ 18 mm. The data were obtained by processing existing medical documentation for the retrospective group and complete diagnosis on admission and during hospitalization for patients from the prospective part of the study. Gender distribution, age, birth weight, and body weight were analyzed on admission, whereby the body weight gain was considered poor if it was < 10 g/kg/day. The analysis also included symptom duration and its correlation with the ultrasound findings (pyloric muscle thickness and length) and the incidence of hypochloremic alkalosis (HCA) on the admission, which considered pH > 7.35, Cl^- < 95 mmol/L, and base excess (BE) > 2 mmol/L. Conservative treatment implied the placement of a nasogastric tube, aspiration of gastric content before administration of atropine and a meal, 20 min after administration of the drug. Episodes of vomiting > 5 in 3 days were indications of switching to surgical treatment. Successful conservative treatment involved discharging the child without surgery, with a milk intake of 120 mL/kg/day and body weight gain. The patients were divided into two subgroups upon the concentration of the drug they received: subgroup Ia received gradually increased doses of atropine from 0.05 mg/kg/day to 0.18 mg/kg/day, with a continuous increase of 0.02 mg/kg/day, for 7 days from the day of admission. Subgroup Ib received the maximum dose of atropine (0.18 mg/kg/day) from the beginning, with an evaluation of the effectiveness of the therapy after three days, based on the total number of projectile vomiting during that period. A successful treatment implied discharge without operation. A comparative analysis of the obtained results was made. The aforementioned analysis examined the influence of predictive factors on the outcome of conservative treatment, enabling the definition of a negative one that signifies a withdrawal from the medicament therapy.

Statistical analysis

The statistical analysis was performed using SPSS statistical package for Windows, version 22. The descriptive statistics, including mean, median, and standard deviation of numerical variables, and numbers and percentages of categorical variables were used to characterize the study sample. For categorical data, the Pearson χ^2 test or the Fisher exact test were employed, and

for numerical data, the independent samples *t*-test or the Mann-Whitney *U* test were used. Multiple logistic regression model, with atropine treatment outcome as the dependent variable, included all variables with $p < 0.05$ from univariate analysis. In all analyses, the significance levels were set at 0.05.

Results

A group of patients on atropine treatment included 45 patients, 34 (75.6%) boys and 11 (24.4%) girls. This means that there was a significantly higher number of male children in total ($p = 0.0054$), although there is no statistically significant effect of the gender distribution on the success of the medication treatment ($p = 0.416$) (Table 1).

undergo surgery had less than 5 episodes of vomiting in 3 days, which proved to be statistically significant compared to 4 out of 9 (44%) patients who were surgically treated ($p = 0.002$).

The subgroup Ia included 15 (33.3%) patients initially treated with gradually increased doses, and the subgroup Ib included 30 (66.7%) patients, who received the maximum dose of atropine ($p = 0.0702$). Twenty-eight out of 36 (78%) patients who did not undergo surgery were treated with an initially high dose of atropine, which was statistically significantly higher than 8 (22%) non-operated patients who were treated with a gradually increased dose of atropine ($p = 0.003$). Twenty-eight (93%) out of 30 patients from the subgroup Ib were successfully cured by atropine, while only 2 (7%) underwent surgery, with a very

Table 1

Clinical characteristics of patients with infantile hypertrophic pyloric stenosis treated by atropine sulfate

Parameter	Atropine sulfate only – no surgery required	Atropine sulfate followed by surgery	*p*
Gender, n (%)			
male	26 (72)	8 (89)	0.416
female	10 (28)	1 (11)	
Age (days), mean ± SD	31.9 ± 12.6	27.8 ± 13.4	0.392
Birth weight (kg), mean ± SD	3.3 ± 0.6	3.6 ± 0.2	0.197
Body weight on admission (kg), mean ± SD	3.9 ± 0.8	3.9 ± 0.7	0.869
Duration of symptoms (days), median (range)	4 (2–10)	4 (2–15)	0.542
Pyloric muscle length, mean ± SD	17.5 ± 1.8	18.2 ± 3.8	0.407
Pyloric muscle thickness, mean ± SD	4.2 ± 0.7	4.4 ± 0.7	0.385
Hypochloremic alkalosis, n (%)	2 (6)	4 (44)	0.010
Aspiration from the nasogastric tube, n (%)	15 (42)	9 (100)	0.002
Number of vomiting, n (%)			
≤ 5	34 (94)	4 (44)	0.002
> 5	2 (6)	5 (56)	
Length of stay in hospital (days), median (range)	10 (4–22)	12 (11–17)	0.023
Atropine sulfate dose, n (%)			
initially high	28 (78)	2 (22)	0.003
progressively increased	8 (22)	7 (78)	

SD – standard deviation.

Successful treatment with atropine was achieved in 36 (80%) patients with very high statistical significance ($p = 0.0008$).

Age, birth weight, body weight on admission, duration of symptoms, pyloric muscle thickness, as well as pyloric muscle length had no statistically significant individual effect on the success of the atropine treatment or the need for converting to surgery (Table 1).

Patients who did not go for surgery had statistically significantly less frequent HCA on admission in 2 out of 36 patients (6%) compared to 4 out of 9 patients (44%) ($p = 0.010$) who were shifted to surgical treatment. Aspiration of gastric content from the nasogastric tube prior to atropine administration was observed in a statistically significantly lower number of patients, in 15 out of 36 (42%) non-operated compared to all 9 (100%) operated patients ($p = 0.002$). Thirty-four (94%) patients who did not

high statistically significant difference ($p = 0.0001$) demonstrating a significant influence of the initially high dose of atropine on the success of conservative treatment. Eight (53%) out of 15 patients from the subgroup Ia were successfully cured by atropine and 7 (47%) underwent surgery, which means that there was no statistically significant difference between the observed patients, indicating lower efficacy of the initially lower dose of atropine (Table 1).

In the multivariate logistic regression model, a statistically significant predictor was the regimen of atropine-dosing patients, who received an initially lower dose of atropine with its progressive increase. They had an 18 times greater risk of surgery [odds ratio (OR) 17.9; $p = 0{,}033$]. The HCA values and the number of vomiting episodes were at the margin of statistical significance – patients who had HCA were at a 15 times greater risk of

surgery (OR 15.06; $p = 0.084$), and ones who experienced vomiting > 5 times within the first 3 days from the onset of atropine administration were at a 9 times greater risk of surgery (OR 9.45; $p = 0.059$) (Table 2).

Table 2

Multivariate logistic regression model of the impact of predictive factors on the atropine treatment outcome of infantile hypertrophic pyloric stenosis

Parameter	OR (95% CI)	*p*
Gender		
male	1	
female	1.30 (0.08–20.2)	0.853
Age	0.96 (0.87–1.06)	0.404
Hypochloremic alkalosis	15.06 (0.69–326.8)	0.084
Number of vomiting		
≤ 5	1	
> 5	9.45 (0.92–97.3)	0.059
Atropine sulfate dose		
initial high	1	
progressively increased	17.9 (1.26–254.0)	0.033

OR – odds ratio; CI – confidence interval.

During the course of the study, no harmful effects of orally administered atropine were observed.

Discussion

Attempts to find an approximate or equally effective conservative method of IHPS treatment have lasted for several decades. The first reason is the generally accepted assumption that prolonged pyloric muscle spasms lead to muscle hypertrophy. However, it is still unclear whether the cause of the spasm is the deficiency of nerve endings in the pyloric muscle, a lower level of NO synthetase, or a reduced number of intestinal Kajal cells [12–15]. The fact that progression of content through the pyloric channel occurs shortly after atropine administration or after pyloromyotomy confirms that muscle spasm, not only hypertrophy, is the main cause of pyloric obstruction, even though ultrasound reveals pyloric muscle hypertrophy continuing to exist for months after healing [16].

Most articles on non-operative treatment of IHPS promote atropine sulfate medical treatment. Medical treatment with atropine sulfate as a non-operative alternative to pyloromyotomy is suggested in 62.5% of these articles [12].

As atropine is parasympatholytic with a strong antimuscarinic effect, which reduces peristaltic contractions and relaxes smooth musculature, in this particular case, its use is completely justified and logical [17].

Although the surgical treatment of IHPS is 100% effective, avoiding the stress for a newborn child that comes with surgery and general anesthesia is also essential. One cannot rule out with certainty the existence of adverse effects of repeated general anesthesia in the neonatal age on the cognitive and motor development of the child [18, 19].

Besides, the complication rate after surgical treatment is about 7.3% ($p < 0.01$) concerning the mucosal perforation, wound infection, or incomplete pyloromyotomy [10].

Since 1991, when the first laparoscopic pyloromyotomy was done, no significant advantage of this approach has been defined in relation to open surgery. However, a slightly higher percentage of incomplete pyloromyotomy with the laparoscopic approach (0.87%) is shown concerning the open surgical method, which is statistically significant ($p = 0.046$) [10]. Atropine treatment of prolonged vomiting due to insufficient pyloromyotomy leads to symptom resolution very quickly and should certainly have an advantage over redo-pyloromyotomy [20–26].

Initial intravenous administration of atropine, with a subsequent transition to the oral route, recommended in most articles, has a higher percentage of efficiency but requires more serious patient monitoring due to the effects on the central nervous system, possible tachycardia, and face blushing [1, 16]. The harmful effects of atropine administered orally were not recorded in the literature nor our patient series. These were the reasons why our patients received atropine orally. The use of a maximum dose of atropine from the very beginning of the treatment was proven to be very safe and with a higher percentage of successful healing [27, 28].

Our study showed that HCA could be considered as a potential predictive factor of the negative outcome of atropine treatment. The literature also reveals the mutual relationship between duration of symptoms and HCA, with the same negative effect on the outcome of atropine treatment of IHPS [29].

Continued vomiting, more than five times in the first three days of the therapy, as well as in the Koike et al. [30] series, was a potential predictive factor of the negative outcome of atropine treatment in our series of patients. The influence of the pyloric muscle thickness is of no statistical significance on the outcome of atropine treatment [31].

There are only a few articles that mention other options of non-operative treatment such as spasmolytic treatment, dating from 1950–1986, balloon catheter dilatation of pyloric stenosis, dating from 1990, and tetrahydrobiopterin for the restoration of nitric oxide synthase activity in pyloric muscle, dating from 1997 [32–34]. Although these few options have been adopted by some researchers, their significance is minor and marginal, with no use in clinical practice.

Conclusion

High success rate and no side effects represent the orally administered atropine treatment as a valid alternative indication for non-operative management of IHPS, allowing discharge from the hospital without an operation. Administrating initially high doses was shown to be more effective in relation to gradually increased oral doses of atropine sulfate. HCA and continued vomiting, more than five times in the first three days of therapy, were considered as potential predictive factors of the negative outcome of atropine treatment.

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