

Is Abandonment of Nonoperative Management of Hypertrophic Pyloric Stenosis Warranted?

Marija Lukac^{1,2} Sanja Sindjic Antunovic^{1,2} Dragana Vujovic² Polina Pavicevic^{1,3} Milos Jesic^{1,4}
Tamara Krstajic⁴ Ivana Petronic^{1,5} Dejan Nikolic⁵

¹Faculty of Medicine, University of Belgrade, Belgrade, Serbia

²Department of Neonatal Surgery, University Children's Hospital, Belgrade, Serbia

³Department of Radiology, University Children's Hospital, Belgrade, Serbia

⁴Department of Neonatology, University Children's Hospital, Belgrade, Serbia

⁵Department of Physical Medicine and Rehabilitation, University Children's Hospital, Belgrade, Serbia

Address for correspondence Marija Lukac, MD, PhD, Department of Pediatric Surgery, Faculty of Medicine, University of Belgrade, Dr Subotica 8, Belgrade 11000, Serbia
(e-mail: marija.lukac@udk.bg.ac.rs; mlukac13@gmail.com).

Eur J Pediatr Surg 2013;23:80–84.

Abstract

Aim Evaluation of the effectiveness of oral atropine versus surgical therapy for hypertrophic pyloric stenosis (HPS).

Methodology A total of 66 consecutive patients with HPS were treated at the University Children's Hospital between January 2006 and December 2011. The diagnosis was initially based on medical history and confirmed by ultrasonography (US). The patients were divided into two groups according to the treatment preferred by their parents. The conservatively treated group, consisting of 33 boys and 7 girls, mean age 22.25 days, was given water-soluble atropine sulfate therapy at an initial dose of 0.05 mg/kg/day divided into 8 single doses, and administered after stomach decompression, 20 minutes prior to feeding. If vomiting persisted, the daily dose was progressively increased up to 0.18 mg/kg. If vomiting did not stop and full oral feeding was not reestablished in a week, surgery was done. The second group of 26 patients, mean age 20.86 days, underwent an operative procedure, Ramstedt extramucosal pyloromyotomy after the initial resuscitation. US evaluation was performed on days 7, 14, and 21. The outcome of the treatment was tested by Yates modification of the χ^2 test.

Results In the group of patients treated with atropine sulfate, 10 (25%) failed to respond to therapy, therefore, 8 boys and 2 girls underwent surgical treatment between the fifth and seventh day following institution of therapy. The remaining patients who received atropine sulfate (75%) were discharged when vomiting ceased, between the sixth and eighth day. They continued to take oral medication for 4 to 6 weeks, and were followed up by an ultrasound examination. The operated patients were discharged between the third and fifth day after surgery. There was a significant statistical

Keywords

- ▶ hypertrophic pyloric stenosis
- ▶ conservative treatment
- ▶ atropine sulfate
- ▶ pyloromyotomy

received
May 18, 2012
accepted after revision
October 17, 2012
published online
February 2, 2013

© 2013 Georg Thieme Verlag KG
Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0032-1333114>.
ISSN 0939-7248.

difference between the groups regarding the outcome at a significance level of $p < 0.05$ (Yates $\chi^2 = 5.839$), with no complications regardless of the treatment option. However, at the significance level of $p < 0.01$ (Yates $\chi^2 = 7.661$), these methods demonstrate a difference in favor of surgical treatment.

Conclusion Further investigation of oral, intravenous or combined atropine sulfate treatment may clarify its position as an alternative to pyloromyotomy.

Introduction

Hypertrophic pyloric stenosis (HPS) is the most common surgical cause of vomiting in newborns. Conservative management of the condition remains controversial. The Fredet-Ramstedt operative technique is easy for a skilled pediatric surgeon to perform, with both classical and laparoscopic approaches yielding excellent results and fast recovery of patients. The cause of HPS is unknown; it is generally accepted that the condition results from a pronounced pylorospasm, with rare and immature ganglion cells in the pylorus wall having some potential role. Progredient stenosis of the pyloric channel causes intensive peristaltic gastric waves, which lead to antral elongation and thickening of the pyloric channel wall.¹

Since there is a prevailing opinion that a muscle spasm underlies its etiology,^{2,3} the success of medical-oral or venous therapy using the antispasmodic atropine sulfate has been reinvestigated. Medical treatment of HPS with oral antispasmodics was abandoned in the mid-1960s, but reappraised in the 1990s mainly by a group from Osaka, Japan.^{4,5}

Here, we analyze the justification of the treatment and role of oral atropine sulfate therapy in comparison to surgical treatment using the classical technique, (extramucosal pyloromyotomy by Fredet-Ramstedt), the gold standard for the treatment of HPS since the mid-1960s.

Materials and Methods

We performed a retrospective cohort study, in the period between January 2006 and December 2011, with 66 patients, divided into two groups according to the mode of treatment: conservative and surgical. The prerequisite for inclusion was an ultrasonographically verified diagnosis of HPS according to the criteria by Haller and Cohen.⁶ HPS was defined if the thickness of the pyloric muscle was 4 mm or more, diameter was 15 mm or more, and length was 18 mm or more.

The parents were previously informed of the therapeutic options of both conservative and surgical treatment, as well as the attitude of the attending surgeon toward the specific type of treatment. Both treatment protocols were presented to the parents in detail, and their informed consent for the chosen method was obtained. Patients in the conservative group were administered oral atropine sulfate solution. The surgical group underwent extramucosal pyloromyotomy (Fredet-Ramstedt). The conservative and surgical treatment involved 40 (33 boys and 7 girls) and 26 (20 boys and 6 girls)

patients, respectively. On admission, all patients underwent complete laboratory analyses (blood count with differential, acid-base status, electrolytes, bilirubin, glycemia, C-reactive protein (CRP), transaminases, urea, and creatinine level). No patient had associated abnormalities of the gastrointestinal tract.

The atropine sulfate protocol of treatment included the insertion of a nasogastric tube (NG), and decompression of the stomach on admission, followed by an initial correction of water and electrolyte imbalance as per the patient. A total daily dose of atropine sulfate was divided into 8 carefully titrated equal doses comprising of 1 mL of solution. Atropine was given in the form of an aqueous solution via the NG tube at the initial dose of 0.05 mg/kg/day, 20 minutes before feed, following aspiration of gastric content and measurement of residual food. If the meal was tolerated, indicated by the amount and appearance of residual feed (up to 10% of previous feed volume, without evidence of milk, was considered normal and returned through the tube), the same atropine dose would be repeated in 3 hours. Vomiting was tolerated a maximum of two times a day. The initial meal was 10 mL of 5% glucose solution, and subsequent meals included breast milk or formula. The newborns who responded well to therapy were gradually given bigger meals, with feed volumes increased by increments of 10 mL for each meal until an oral intake of 120 mL/kg/24 hours was achieved. If vomiting occurred, the atropine dose would be increased in the following meal by 0.01 mg/kg/day without changing the oral intake, up to 0.18 mg/kg/day. If the subsequent meal was tolerated, progressive increase of intake would be continued.

The patients were discharged for home treatment when they tolerated feeds for 2 days without vomiting, and parents were trained for continuation of oral drug administration at home. The patients were clinically assessed once a week during drug administration, together with an ultrasound examination and body weight measurement. Atropine was used for 6 to 8 weeks after the vomiting ceased, irrespective of the degree of reduction of the pyloric muscle hypertrophy. The atropine sulfate concentration on discharge was given without any dose adjustment if oral feed was tolerated. If possetting occurred, the dose was adjusted to body weight. Newborns for whom a maximal daily dose of 0.18 mg/kg/day had been attained but who still experienced postprandial projectile vomiting were withdrawn from therapy.

Ten newborns from the conservatively treated group (eight males and two females) had an inadequate response to therapy and thus were excluded from further follow-up.

They underwent surgical treatment by pyloromyotomy in less than 5 to 7 days from the onset of treatment to finish the therapy. Pyloromyotomy was performed via a supraumbilical right transverse incision. The NG tube was left for 12 hours after surgery in the operated patients, and feeds were started 3 hours after its withdrawal: initially with 10 mL of 5% glucose solution, and subsequently replaced by breast milk or formula. If the meal was tolerated, it was progressively increased; otherwise, the previously tolerated volume was reintroduced.

The Board of Experts of the University Children's Hospital approved the application of oral atropine sulfate as a therapeutic option in 2000.

The significance of difference by distribution of sex and age was analyzed by means of nonparametric χ^2 test. For analyzing the difference in the outcome of HPS treatment between the conservatively and surgically treated groups, the nonparametric χ^2 test modified by Yates was used.

Results

HPS was managed by oral atropine sulfate therapy in 40 patients, including 33 boys and 7 girls. The patients were assessed on a daily basis by a neonatal surgeon and neonatologist. Until they had attained full oral intake, they had fluid and electrolyte supplementation, Vaminolact (amino acid solution for intravenous nutrition). The mean age of this group was 22 days. The primary surgically treated group included 26 newborns (20 boys and 6 girls; mean age, 21 days). The distribution by sex of the patients, 53 boys and 13 girls, was statistically significant, in a ratio of 4:1 ($p < 0.01$). There was no significant difference (p value, χ^2 test) in distribution by age, weight (on admission and discharge), and pyloric measures (length and thickness of pyloric muscle) between the atropine and pyloromyotomy group (→Table 1).

It appeared that oral atropine sulfate was well tolerated in all patients. In the medically managed-group, 30 cases were

successfully treated with oral therapy (25 boys and 5 girls, 75%). No patient required surgical treatment after discharge, and the established oral intake was continued at home for a duration of 6 to 8 weeks. No significant complications during medical treatment were reported. Serial ultrasound controls performed on days 7, 14, 21, and 6 weeks from the beginning of treatment did not show regression of the pyloric muscle wall to normal, although the passage of content from stomach to duodenum was unobstructed. Once a week, parents were supplied with a prepared solution of atropine sulfate, and its concentration was adjusted to the patient's body weight in the first 4 weeks. After 4 weeks, atropine concentration remained the same and given the increase in the patient's body weight, it was gradually decreased, and was completely discontinued at week 6.

Vomiting did not cease and there was no satisfactory oral intake in 10 out of 40 (8 boys and 2 girls, 25%) patients from the conservatively treated group in the expected interval of 7 days, and therefore, surgical treatment by the Fredet-Ramstedt technique was performed. The atropine sulfate therapy originally planned for 7 days was terminated in 2 patients at day 5, as parents requested for surgery. Both patients were discharged on postoperative day 3 upon re-establishment of full oral intake.

The Fredet-Ramstedt technique, used for the 26 primary surgically treated patients, included a supraumbilical incision in the right upper quadrant. Experienced pediatric surgeons operated on all patients. Full oral intake (120 mL/kg/day) was achieved between postoperative days 2 and 3, and the patients were discharged between postoperative days 3 and 5. The postoperative period was uneventful.

Statistical analysis showed that at the significance level of $p < 0.05$, there was a difference in the choice of method of treatment in relation to its outcome (Yates $\chi^2 = 5.839$); however, at the significance level of $p < 0.01$ (Yates $\chi^2 = 7.661$), these methods demonstrate a difference in favor of surgical treatment.

Table 1 Summary of patients with HPS

	Atropine sulfate group (<i>n</i> = 40)	Pyloromyotomy group (<i>n</i> = 26)	<i>p</i> value
Number of males	33	20	0.06 ^b
Number of females	7	6	
Male to female ratio	11:4	10:3	
Age on admission (days)	22.25 ± 6.75	20.86 ± 6.14	0.40 ^a
Weight on admission (g)	3,680.2 ± 510.6	3,560 ± 523.3	0.36 ^a
Weight on discharge (g)	3,870 ± 505.2	3,610 ± 533.1	0.05 ^a
Pyloric muscle thickness US (mm)	4.9 ± 0.5	4.9 ± 0.7	1.00 ^a
Pyloric muscle length US (mm)	17.2 ± 2.8	17.6 ± 2.5	0.56 ^a
Successful therapy	30 (75%)	26 (100%)	0.02 ^b

Abbreviations: HPS, hypertrophic pyloric stenosis; US, ultrasonography.

^at test.

^b χ^2 test.

Discussion

After 40 years of almost exclusive domination by surgical treatment of HPS, medical therapy with atropine sulfate has been sporadically employed in some institutions⁷ worldwide, and has mostly generated a negative view among the majority of pediatric surgeons.⁸ Given the excellent results of the Fredet-Ramstedt surgical technique—with few complications if performed by a competent pediatric surgeon, and complete cure in a short period of time—it still represents the method of choice for HPS treatment. In the last ten years, laparoscopy-assisted pyloromyotomy, a minimally invasive procedure, has been advocated by many experts, although one meta-analysis⁹ shows that an open method has less complications and higher effectiveness.

Atropine sulfate has been used for HPS treatment at the University Children's Hospital since 2000,¹⁰ and has been applied by a group of pediatric surgeons who practice neonatal surgery and cooperate with a team of neonatologists engaged in the treatment of these patients.

The success of patients exclusively treated by oral atropine sulfate in our study (initial dose of 0.05 mg/kg/24 hours, progressively increased to 0.18 mg/kg/24 hours) was 75%. This proportion of 75% of treated patients by oral atropine sulfate therapy in our study was smaller in comparison to data from other studies using combined oral and intravenous therapy.^{11–13} Nevertheless, opting for exclusively oral administration, we wished to evade the possibility of side effects, which are more probable in intravenous atropine sulfate injection.

Other studies have combined oral and intravenous atropine sulfate administration and the percentage of success has been higher. Yamataka et al¹¹ reported 85% success with medical treatment of patients (initial oral atropine sulfate dose 0.05 mg/kg/24 hours, adjusted in case of continual vomiting to 0.1 mg/kg/24 hours). Two patients were converted to intravenous injection on day 3, because the atropine was not tolerated. Kawahara et al¹² reported that the success of a combination of intravenous atropine followed by oral intake (initial injection dose of 0.01 mg/kg six times a day, until vomiting stopped, and afterward oral 0.02 mg/kg six times a day with progressive reduction until the patient was cured) was 87%. The difference in maximal oral doses is remarkable, for instance in our study, it was 0.18 mg/kg/24 hours. The upper limit in our study was not exceeded, but in cases where atropine failed, and vomiting could not be stopped till day 7 (in our series—25% of patients), the disease was managed by surgical procedure. Out of the 12 patients treated, conversion to surgery was required in 2 (on day 5, according to the parent's wishes). No side-effects of atropine sulfate were reported in any of cases.

No recurrence of disease was recorded in our conservative treatment group after successful completion of therapy, comparable with the other available data.^{10–13} The mean hospital stay was 4 to 8 days for surgical and medical treatment, respectively. A shorter hospitalization in the operated group of patients and quicker time to achieve full enteral intake have been consistently found in all studies dealing with either oral or venous atropine sulfate administration.^{10,11,13}

Ultrasonographic follow up was done in all cases on days 7, 14, and 21, but there were no significant changes in the pyloric muscle thickness or channel length. However, an improvement in the passage of content from the stomach to the duodenum was apparent. Further ultrasound controls were sporadic because the clinical condition of patients was stable, vomiting-free, and characterized by weight gain.

When classical or laparoscopy-assisted pyloromyotomy is used, the major advantages are the success of the operation, shorter hospitalization, and few complications. Nevertheless, the postoperative length of stay varies in different parts of the world (in western countries, the stay is only 1 day, while in Serbia, it is 4 days, i.e., until complete cessation of vomiting). In our study, the operated group (all patients were operated by qualified surgeons mostly engaged in neonatal problems, and with over 10 years of experience in surgical practice), had no postoperative complications. However, reference data report that the percentage of incomplete pyloromyotomy ranges from 0 to 5.5% in laparoscopic interventions, and from 0 to 0.9% in open pyloromyotomy cases.^{14–17}

Langer and To,¹⁵ as well as Safford et al¹⁸ found that the length of postoperative treatment and a lower degree of duodenal perforation depended on the surgeon's experience. The percentage of postoperative complications varies in relation to institutions and the surgeon's expertise and experience.

The major disadvantage of atropine sulfate application is that it requires an experienced and motivated team to observe and monitor the patient's condition, and follow changes of the disease process—for instance, adjust the dose regime in case of vomiting. From the perspective of the pediatric surgeon, an HPS operation is easier and less time consuming than conservative treatment, whose prognosis is additionally uncertain. For the parents, there is broad satisfaction across all 75% of parents whose children were successfully treated by medical therapy, thus avoiding surgery and its associated risks, no matter how small they might be.

The value and place of oral, intravenous or combined atropine sulfate treatment for HPS must be investigated. A multicenter prospective randomized study is necessary to provide a uniform and safe protocol that will resolve the dilemma about the most successful application of the drug (oral, venous, or combined), and its optimal dose. Further investigations of oral or intravenous atropine treatment may clarify its position as an alternative to pyloromyotomy.

Conflict of Interest

None

References

- 1 Batcup G, Spitz L. A histopathological study of gastric mucosal biopsies in infantile hypertrophic pyloric stenosis. *J Clin Pathol* 1979;32(6):625–628
- 2 Imura K, Kawahara H, Yagi M, Oue T, Okada A. Pyloric motor abnormality in patients with infantile hypertrophic pyloric stenosis. *Pediatr Surg Int* 1998;14(3):178–181

- 3 Oue T, Puri P. Smooth muscle cell hypertrophy versus hyperplasia in infantile hypertrophic pyloric stenosis. *Pediatr Res* 1999;45(6):853–857
- 4 Nagita A, Yamaguchi J, Amemoto K, Yoden A, Yamazaki T, Mino M. Management and ultrasonographic appearance of infantile hypertrophic pyloric stenosis with intravenous atropine sulfate. *J Pediatr Gastroenterol Nutr* 1996;23(2):172–177
- 5 Nagita A, Yoshimoto Y. Medical treatment of hypertrophic pyloric stenosis with atropine sulfate. *Jpn J Pediatr Surg* 1998;30:837–840
- 6 Haller JO, Cohen HL. Hypertrophic pyloric stenosis: diagnosis using US. *Radiology* 1986;161(2):335–339
- 7 Aspelund G, Langer JC. Current management of hypertrophic pyloric stenosis. *Semin Pediatr Surg* 2007;16(1):27–33
- 8 Meissner PE, Engelmann G, Troeger J, Linderkamp O, Nuetzenadel W. Conservative treatment of infantile hypertrophic pyloric stenosis with intravenous atropine sulfate does not replace pyloromyotomy. *Pediatr Surg Int* 2006;22(12):1021–1024
- 9 Hall NJ, Van Der Zee J, Tan HL, Pierro A. Meta-analysis of laparoscopic versus open pyloromyotomy. *Ann Surg* 2004;240(5):774–778
- 10 Sretenović A, Smoljanić Z, Korać G, Sindjeć S, Lukac M, Krstić Z. [Conservative treatment of hypertrophic pyloric stenosis in children]. *Srp Arh Celok Lek* 2004;132(Suppl 1):93–96
- 11 Yamataka A, Tsukada K, Yokoyama-Laws Y, et al. Pyloromyotomy versus atropine sulfate for infantile hypertrophic pyloric stenosis. *J Pediatr Surg* 2000;35(2):338–341, discussion 342
- 12 Kawahara H, Takama Y, Yoshida H, et al. Medical treatment of infantile hypertrophic pyloric stenosis: should we always slice the “olive”? *J Pediatr Surg* 2005;40(12):1848–1851
- 13 Kawahara H, Imura K, Nishikawa M, Yagi M, Kubota A. Intravenous atropine treatment in infantile hypertrophic pyloric stenosis. *Arch Dis Child* 2002;87(1):71–74
- 14 van den Ende ED, Allema JH, Hazebroek FW, Breslau PJ. Can pyloromyotomy for infantile hypertrophic pyloric stenosis be performed in any hospital? Results from two teaching hospitals. *Eur J Pediatr* 2007;166(6):553–557
- 15 Langer JC, To T. Does pediatric surgical specialty training affect outcome after Ramstedt pyloromyotomy? A population-based study. *Pediatrics* 2004;113(5):1342–1347
- 16 Yagmurlu A, Barnhart DC, Vernon A, Georgeson KE, Harmon CM. Comparison of the incidence of complications in open and laparoscopic pyloromyotomy: a concurrent single institution series. *J Pediatr Surg* 2004;39(3):292–296, discussion 292–296
- 17 Kim SS, Lau ST, Lee SL, et al. Pyloromyotomy: a comparison of laparoscopic, circumumbilical, and right upper quadrant operative techniques. *J Am Coll Surg* 2005;201(1):66–70
- 18 Safford SD, Pietrobon R, Safford KM, Martins H, Skinner MA, Rice HE. A study of 11,003 patients with hypertrophic pyloric stenosis and the association between surgeon and hospital volume and outcomes. *J Pediatr Surg* 2005;40(6):967–972, discussion 972–973