Treating Infantile Hypertrophic Pyloric Stenosis with Atropine Therapy: A Systematic Review and Meta-Analysis

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Abstract

Background: Infantile hypertrophic pyloric stenosis (IHPS) is a common condition affecting neonates and young infants, clinically characterized by progressive projectile non-bilious vomiting due to a thickened pyloric antrum (1). The incidence of IHPS is 2-5 per 1000 live births (2,3). Ramstedt's surgical pyloromyotomy (4) is the current standard of treatment with a near perfect success rate and has remained relatively unmodified for over a century (1). Prior to pyloromyotomy, the oral intake of atropine or other antispasmodic drugs were used as non-invasive forms of treatment (5). While this option has been reappraised in certain countries, avoiding invasive surgery in newborns, the approach has not been broadly accepted due to a varying reported proportion of success and a prolonged hospital stay (1). The rationale for drug therapy stems from the decreased function of acetylcholine and muscarinic receptors in the pathophysiology of IHPS, whereby atropine reduces peristalsis of the intestine through smooth muscle relaxation (6). Higher success rates in medical management have been attributed to initial intravenous administration as opposed to oral, stronger dosages as well as specific patient characteristics (5,7–9). While drug therapy does not require a surgeon or a sterile setting, which is not globally available, and avoids the risks associated with surgical and anesthetic stress, especially in infants with contraindications for pyloromyotomy, it is unlikely that it would replace surgery in Western countries (9). The majority of studies that have investigated the use of atropine therapy for IHPS treatment have had relatively small sample sizes and the predictive factors of negative outcomes are not well established. The use of the drug as a treatment appears advantageous in low-resource settings, however remains controversial due to a lack of empirical evidence and differentiation between administration method and regimen.

Objectives: The primary objective of this study is to systematically review the literature and evaluate the pooled efficacy as well as compare the hospital stay of conservative medical (atropine therapy) and operative (pyloromyotomy) treatment of IHPS. The secondary objective is to investigate and analyze the influence of predictive factors involved in the outcome of intravenous atropine therapy (IAT) to treat IHPS.

Hypothesis: We anticipate that IAT may be a suitable alternative to pyloromyotomy dependent on the infant's clinical factors including age, bodyweight and pyloric muscle thickness.

Methods: This review was conducted according to PRISMA guidelines. Major electronic databases were searched for studies that utilized atropine therapy for IHPS treatment. Scientific articles published from after 1990 were targeted, with no language restrictions. Case reports, case series with less than 5 patients, letters, editorials and abstracts were excluded. Studies with intravenous and/or oral administration of atropine sulfate were considered for inclusion in the systematic review, with success rate as the main outcome of interest. The first meta-analysis compared the length of hospital stay between pyloromyotomy and IAT groups. A second meta-analysis focused on age, body weight and pyloric muscle thickness on hospital admission between patients who were successful and unsuccessful from IAT. The quality of evidence for all outcomes

was evaluated using the Cochrane Risk of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool. The meta-analyses determined the inverse variance (IV) of mean differences (MDs) and standardized mean differences (SMDs) as well as 95% confidence intervals (CIs) for continuous variables, which were calculated using random-effects models.

Results: Of 2605 abstracts screened, 73 full-text articles were analyzed and 20 were deemed eligible for the qualitative analysis. Out of 1199 infants, 917 (76.5%) reported successful treatment of IHPS using atropine therapy. The seven articles in the first meta-analysis found that the mean length of hospital stay was significantly longer in patients treated medically (n = 845, 10.3 days) in comparison to surgically (n = 1809, 5.36 days; MD 4.92, 95% CI 3.74 to 6.10, $p < 0.00001$; $I^2 = 81\%$). The six articles that were included in the second meta-analysis directly compared predictive factors of successful IAT (n = 527) in infants to unsuccessful IAT (n = 188). The quantitative data revealed significant differences in age on hospital admission [SMD 0.52, 95% CI 0.17 to 0.88, $p = 0.004$; $I^2 = 48\%$], and in bodyweight on admission [SMD 1.04, 95% CI 0.51 to 1.59, $p < 0.0001$; $I^2 = 75\%$] between the two groups. Success of IAT was not significantly associated with the thickness of the pyloric muscle [SMD -0.34, 95% CI -1.39 to 0.72, $p = 0.53$; $I^2 = 88\%$].

Conclusion: IAT is a viable alternative to pyloromyotomy in low-resource settings or in infants with a congenital anomaly or co-morbid conditions, however younger age and even more crucially, lighter bodyweight at diagnosis, are both significant clinical factors that contribute towards unsuccessful IAT in IHPS. Pyloric muscle thickness is not associated with the outcome of IAT. These results provide valuable information for parents and health care professionals that can aid to increase the success rate of medically managed IHPS in countries that utilize this technique.

Résumé

Contexte: La sténose pylorique hypertrophique infantile (SPHI) est une maladie courante affectant les nouveau-nés, caractérisée cliniquement par des vomissements progressifs non bilieux dus à un antre pylorique épaissi (1). L'incidence de la SPHI est de 2 à 5 pour 1000 naissances vivantes (2,3). La pyloromyotomie chirurgicale de Ramstedt (4) est la norme actuelle de traitement avec un taux de réussite presque parfait et est restée relativement inchangée pendant plus d'un siècle (1). Avant la pyloromyotomie, la prise orale d'atropine ou d'autres médicaments antispasmodiques étaient utilisées comme traitement non invasive (5). Même si cette option a été réévaluée dans certains pays, évitant la chirurgie invasive chez les nouveau-nés, l'approche n'a pas été largement acceptée en raison d'une proportion de succès rapportée variable et d'un séjour hospitalier prolongé (1). La justification du traitement médicamenteux comprends la physiopathologie de la SPHI qui peut être due en partie à une altération de la fonction de l'acétylcholine et des récepteurs muscariniques, par laquelle l'atropine diminue le péristaltisme intestinal en relaxant les muscles lisses (6). Des taux de succès plus élevés dans la prise en charge médicale ont été attribués à l'administration intraveineuse initiale par opposition aux doses orales plus fortes ainsi qu'aux caractéristiques spécifiques des patients (5,7–9). Même si la pharmacothérapie ne nécessite pas de chirurgien ni un environnement stérile, qui n'est pas disponible dans le monde entier, et évite les risques associés au stress chirurgical et anesthésique, en particulier chez les nourrissons avec des contre-indications à la pyloromyotomie, il est peu probable qu'elle remplace la chirurgie dans les pays occidentaux (9). La majorité des études qui ont examiné l'utilisation du traitement par l'atropine pour le traitement de la SPHI ont eu des échantillons relativement petite et les facteurs prédicatifs de résultats négatifs ne sont pas bien établis. L'utilisation du médicament pour le traitement semble avantageuse dans les milieux à faibles ressources, mais reste controversée en raison d'un manque de preuves empiriques et de la différenciation entre la méthode d'administration et le régime.

Objectifs: L'objectif principal de cette étude est de passer systématiquement en revue la littérature et d'évaluer l'efficacité combinée ainsi que de comparer l'hospitalisation du traitement médical conservateur (thérapie à l'atropine) et opératoire (pyloromyotomie) de la SPHI. L'objectif secondaire est d'étudier et d'analyser l'influence des facteurs prédicatifs impliqués dans le résultat de la thérapie intraveineuse à l'atropine (TIA) pour traiter la SPHI.

Hypothèse : Nous prévoyons que la TIA peut être une alternative appropriée à la pyloromyotomie en fonction des facteurs cliniques du nourrisson, notamment l'âge, le poids corporel et l'épaisseur du muscle pylorique.

Méthodes : Cette revue a été menée conformément aux directives PRISMA. Les principales bases de données électroniques ont été recherchées pour les études utilisant la thérapie à l'atropine pour le traitement de la SPHI. Les articles scientifiques publiés après 1990 ont été ciblées, sans restrictions linguistiques. Les rapports de cas, les séries de cas avec moins de 5 patients, les lettres, les éditoriaux et les résumés ont été exclus. Les études avec l'administration intraveineuse et / ou orale de sulfate d'atropine ont été envisagées pour inclusion dans la revue systématique, le taux de

réussite étant le principal résultat d'intérêt. La première méta-analyse a comparé la durée du séjour à l'hôpital entre les groupes pyloromyotomie et TIA. Une deuxième méta-analyse s'est concentrée sur l'âge, le poids corporel et l'épaisseur du muscle pylorique à l'admission à l'hôpital entre les patients qui ont réussi et qui n'ont pas réussi à la TIA. La qualité des preuves pour tous les critères de jugement a été évaluée à l'aide de l'outil Cochrane Risk of Bias In Non-Randomized Studies - of Interventions (ROBINS-I). Les méta-analyses ont déterminé la variance inverse des différences moyennes (DM) et des différences moyennes standardisées (DMS) ainsi que des intervalle de confiance à 95% pour les variables continues, qui ont été calculés à l'aide de modèles à effets aléatoires.

Résultats : 2605 résumés ont été examinés, 73 articles en texte intégral ont été analysés et 20 ont été jugés éligibles pour l'analyse qualitative. Sur 1199 nourrissons, 917 (76,5%) ont réussi le traitement à l'atropine pour la SPHI. Les seps articles de la première méta-analyse ont montré que la durée moyenne du séjour à l'hôpital était significativement plus longue chez les patients traités médicalement (n = 845, 10,3 jours) par rapport à la chirurgie (n = 1809, 5,36 jours; DM 4,92, IC à 95% 3,74 à 6,10, p <0,00001; I^2 = 81%). Les six articles qui ont été inclus dans la deuxième méta-analyse comparaient directement les facteurs prédictifs de la réussite de la TIA (n = 527) chez les nourrissons à la défaillance de la TIA (n = 188). Les données quantitatives ont révélé des différences significatives d'âge à l'admission à l'hôpital [DMS 0,52, IC à 95% 0,17 à 0,88, p = 0,004; I^2 = 48%], et en poids corporel à l'admission [DMS 1,04, IC à 95% 0,51 à 1,59, p <0,0001; I^2 = 75%] entre les deux groupes. Le succès de la TIA n'était pas significativement associé à l'épaisseur du muscle pylorique [DMS -0,34, IC à 95% -1,39 à 0,72, p = 0,53; I^2 = 88%].

Conclusion : La TIA est une alternative viable à la pyloromyotomie, dans les milieux à faibles ressources ou chez les nourrissons présentant une anomalie congénitale ou des conditions comorbides, même si les moins âgées et, plus important encore, le poids corporel plus léger au moment du diagnostic, sont deux facteurs cliniques qui contribuent à l'échec de la TIA dans la SPHI. L'épaisseur du muscle pylorique n'est pas associée au résultat de la TIA. Ces résultats fournissent des informations pertinentes aux parents et professionnels de la santé qui peuvent aider à augmenter le taux de réussite de la SPHI gérée par médicament dans les pays qui utilisent cette technique.

Contribution of Authors

Noah Cohen (Thesis Candidate):

I generated the original thesis topic idea upon consultation with my supervisor. I was responsible for the article selection, data collection, analysis, and writing of this thesis document.

Dr. John. S. Sampalis (Supervisor):

Dr. Sampalis was responsible for collaborating on the development of the thesis topic and provided insight into the study design, methodology, and statistical plan. Dr. Sampalis acted as a reviewer for article selection, data extraction, and quality assessment of the included articles. He also reviewed the thesis document and manuscript.

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1. Introduction

Infantile hypertrophic pyloric stenosis (IHPS) is a gastrointestinal condition affecting neonates and young infants, clinically characterized by progressive “projectile” non-bilious vomiting (10). Typically, these infants are born showing no symptoms, whereby emesis develops during the first few weeks of life. IHPS inhibits the movement of stomach contents through the pyloric canal into the duodenum, which causes the inadequate digestion of food and as a result, the accumulation of stomach contents (11).

Infantile hypertrophic pyloric stenosis (IHPS) is one of the most common conditions requiring surgery in newborns (12). It is therefore highly familiar among pediatric practitioners. Gastric outlet obstruction from IHPS is dangerous as it leads to emaciation may result in death if it is left untreated (13). Since the 20th century, a comprehensive understanding of the condition as well as advances in treatment have reduced the mortality rate of IHPS from over 50% to nearly 0% (13).

IHPS is not a surgical emergency as it first requires aggressive intravenous resuscitation in dehydrated and metabolically unbalanced infants (14). Upon fluid correction, extramucosal pyloromyotomy is the standard method of treatment, which is a surgical procedure that has remained relatively unmodified for over a century (15). Slight changes include minimally invasive access modifications such as the circumbilical incision method by Tan and Bianchi in 1986 (16) and the laparoscopic approach by Alain and Grousseau in 1991 (17). Despite a high success rate and a low risk of associated complications, there exists a pharmacological alternative, which is used in low-income countries such as Japan, that avoids surgery and the unnecessary use of general anesthesia in newborns. In 1996, a Japanese study by Nagita et al. showed strong results (a 95.6% success rate) through the use of atropine sulfate as a treatment method for IHPS, however mean days to arrest vomiting was 5 ± 2 days (18). During this time, parenteral nutrition is generally initiated in order to meet the nutritional needs of the infant (19). A number of other Japanese studies reported relatively high success rates, however they also reported an average length of hospital stay of 12 or 13 days (20). While the statistic regarding the efficacy of the drug alternative may sound promising, the length of hospital stay for medical management greatly exceeds that of the surgical procedure. This is one of the main reasons it is not the first line of treatment in North

America. Additionally, the parental care and strict medication regime required after discharge further explain why atropine therapy is not used to any significant extent in high income settings.

In recent years, numerous studies have tested the efficacy of the pharmacological method, however the majority of investigations utilizing atropine have had relatively small sample sizes and use varying administration forms (oral versus intravenous intake) and dosages, stop criteria, as well as overall procedures. Drug therapy is useful for families who do not have access to expert pediatric surgeons, as they are not universally available (21). Additionally, it has been published in the literature that atropine therapy is a more cost effective option compared to surgery in Japan, in terms of medical expenditure, despite a longer duration of treatment (14). This conservative option, however, has not been widely researched, despite having been reappraised in some Asian and European countries.

A relatively recent review article by Lauriti et al., (22) in the European Journal of Pediatric Surgery that compared atropine therapy to pyloromyotomy found no evidence-based literature to support its use in infants over the operation as a treatment method for IHPS. The authors came to the conclusion that atropine therapy be reserved solely for patients with contraindications for general anesthesia or surgery. This study, however narrowly compared medical management directly to surgical management, without providing an overview of the differences among successful and unsuccessful atropine therapy populations.

In order to improve the efficacy of atropine therapy, understanding which infants have successful outcomes from this less invasive form of treatment is of utmost importance for developing clinical guidelines in low-resource settings. To the best of our knowledge, to date, there is no review paper that has considered the patients' predictive factors that may be involved in the positive or negative outcome of atropine therapy. This would be of primary relevance for creating a recommendation, and thus we propose to generate a systematic review with meta-analysis to critically evaluate the literature and summarize the evidence regarding drug therapy as a treatment method for IHPS. Length of hospital stay between surgically and medically managed patients will be compared as well as possible predictive factors for the success of drug therapy. Focusing on the personal characteristics of the infants with negative outcomes from medical management will assist in formulating an informed decision in selecting the best treatment option for newborns on a case by case basis in countries that may utilize drug therapy.

Thus, the main objectives of the systematic review in the present thesis are to determine the efficacy of atropine administration as an intervention in comparison to pyloromyotomy in the treatment of IHPS and analyze the difference in hospital stay between the two groups. The secondary objective is to compare the clinical factors of patients with IHPS who were successful in intravenous atropine therapy (IAT) as a treatment method to patients who were not. This information will establish whether the variables of interest (age, bodyweight and pyloric muscle thickness on admission) have significant effects on the treatment outcome. It is hypothesized that these personal characteristics can be used to help determine which infants are most likely to have an unsuccessful result from IAT. This review will follow the principles of the PICO framework and evaluate the pooled efficacy while elucidating an up to date evidence based assessment of the options available to manage this disease including evidence gaps in drug therapy from the best available data.

2. IHPS Background and Review of the Literature

2.1 Definition and History

Infantile hypertrophic pyloric stenosis (IHPS), simply known as pyloric stenosis is an idiopathic hypertrophy of the circular and longitudinal muscular layers of the pylorus in newborns (1). This causes the pyloric channel to narrow and elongate, resulting in a partial obstruction of the gastric outlet (23). A hundred years ago, very few infants with this disease survived.

2.1.1 Early Descriptions

The history of what we now refer to as IHPS dates back to the early 1600s. In 1627, a German surgeon by the name of Fabricious Hildanus described the first clinical case as spastic, uncontrolled vomiting (13). Dr. Patrick Blair has also been attributed to an earlier account of the condition, having published an autopsy report consisting of a general post-mortem description of a male infant with pyloric stenosis in 1717 (24). In 1758, a similar explanation was published for a female infant by Dr. Christopher Weber (25). The pathological anatomy of the altered pylorus was explained by Landerer in 1879 and Mayer in 1885, with Landerer being the first to use the term "congenital defect" when discussing hypertrophic pyloric stenosis (26).

Harald Hirschsprung, a Danish pediatrician, is notable for his description of the clinical course and pathology of IHPS in his 1888 seminal article of two post-mortem cases. This provided the first rigorous and complete overview of the condition, which led to its modern understanding (13). Hirschsprung also believed that IHPS was a congenital failure of the fetal pylorus and named it *angeborener pylorusstenose*, which translates to congenital pyloric stenosis (27). Case reports multiplied exponentially after his work became known and by the end of the first decade of the 20th century, there were nearly 600 published cases (28). In 1907, Dr. Henry Dufour and Dr. Pierre Fredet split the pyloric muscle until the submucosa layer with a transverse closure of the muscle. This was the first definition of a surgical correction and the successful operation was presented to the Société Médicale des Hôpitaux de Paris (25). In 1910, Dr. Fredet along with Dr. Louis Guillemot reviewed the world's literature on pyloric stenosis and reported the clinical signs of the condition as increased gastric peristalsis, projectile vomiting and weight loss from an enclosing pyloric tumor. They also overviewed the high frequency of IHPS in boys (15). The team recommended reducing feedings, introduced gastric lavage and the use of atropine as an initial treatment method (25).

2.1.1 The First Surgical Interventions

In the late nineteenth and early twentieth centuries, IHPS treatment consisted of three major surgical interventions: dilatation of the pylorus, gastroenterostomy and pyloroplasty. These were implemented in an attempt to either bypass the obstruction altogether or alleviate it by directly attacking the pyloric muscle (26). Dilatation of the pyloric orifice, designed to relieve the obstruction, was initially described in 1882 by Loreta, an Italian professor, specifically in adult patients (28). This later became adopted for pediatric patients in 1899, the first attempt to relieve obstruction by divulsion of the pylorus (28). After gaining access to the distal portion of the stomach through an incision or the insertion of a mechanical Hegar dilator, the pyloric sphincter was dilated using just one or two fingers (29). This technique was eventually discarded due to substandard results with high recurrences and fatal peritonitis caused by pyloric rupture (6). Gastroenterostomy, performed in extreme cases is a procedure that involves the surgical construction that links the stomach and the jejunum, which bypasses the obstruction of the gastric outlet. This was the first successful operation, performed by Lobker in 1898 (28). Despite the mucosa being left intact in this practice, there remains an unsatisfactorily high associated mortality rate of approximately 50% (25). Dr. Clinton Thomas Dent, a British surgeon, performed the first successful pyloroplasty in 1902. He incised the pylorus longitudinally, left the mucosa intact and proceeded to suture the muscle transversely (29). This method did not durably disrupt the pyloric ring or relieve the obstruction and thus was not deemed satisfactory.

2.1.2 History of Modern Treatment

The gold standard of treatment for IHPS is Ramstedt's surgical pyloromyotomy. The very first pyloromyotomy was not actually performed by Ramstedt, but by a British surgeon by the name of Sir Harold Jalland Stiles in 1910 (17). However, the operation became well known through the work of Dr. Conrad Ramstedt, a German surgeon, who operated on the first case of pyloric stenosis he encountered, on August 23rd 1911 (4,13). Ramstedt initially planned to perform a pyloroplasty, however after incising the pylorus muscle longitudinally, he attempted to close the defect transversely, but the suture tore out through the muscle. He corrected this problem by covering it with an omental patch and the patient made a successful recovery (6). A year later, in 1912, Ramstedt performed another pyloromyotomy, but this time he incised the pylorus muscle longitudinally without covering the mucosal bulge (13). This was a simplified version of the

previously mentioned Fredet procedure by skipping the transverse suture, leaving the mucosa uncovered (15). Most surgeons approach the pylorus either through the right upper quadrant or an upper midline incision as both techniques provide optimal access. The downside, however, is that the cosmetic result is unsatisfactory (30).

Ramstedt's pyloromyotomy has seen a major shift in success rate across the 1900s. The very first Ramstedt operation in England took place at the Belgrave Hospital by Dr. Ramsay in July of 1918. The child died 1 week later, despite having relieved the stenosis post-mortem. Ramsay performed this operation more than 200 times but the initial results were not very successful. His paper in 1921 described the outcome of the first 10 pyloromyotomies he treated IHPS patients to be only 50% successful, with the other half not surviving the procedure. The poor level of nourishment and hydration of these patients as well as the standards of perioperative care at that time masked the true value of the procedure (26). Years later, the procedure became one of the most successful in the practice of surgery. In 1957, Pollock conducted a review of 1422 IHPS cases operated on at the Los Angeles Children's Hospital between 1934 and 1955 (31). The mortality rate was extremely low, with a mere 25 deaths (1.7%). Many of these were due to unrelated pre-existing conditions such as meningitis and multiple sclerosis (31).

IHPS was first diagnosed by ultrasound imaging in the late 1970s, which over time became the method of choice (13,32). More recent developments of the pyloromyotomy procedure itself include the circumbilical incision method in 1986 for the open approach (16) and the introduction of the laparoscopic approach in 1991 (17). The advantages and disadvantages of the two techniques continue to be debated.

2.2 Embryology, Anatomy and Function

2.2.1 The Stomach

The stomach performs a number of functions in the body including the digestion of food, immune defense, and hormonal regulation of metabolic homeostasis, which makes it an evolutionary diverse structure (33). Stomach development begins from a spindle-shaped, small dilatation in the distal portion of the pre-enteron in the fourth week of fertilization (34). This is also when the enlarged lumen is established, as the dorsal border grows at a faster rate than the ventral side, forming the greater curvature (13).

The stomach is located in the upper left quadrant of the abdominal cavity, which can change its size depending on the amount of food that is ingested, through the folds located within its wall (23). The stomach is the enlarged portion of the digestive tract which joins the esophagus through the cardia (13). The anatomical structure of the stomach consists of the body whose upper portion forms the fundus of the stomach as well as the lower portion called the pylorus, as seen in Figure 1. These two sections are divided by the angular notch (incisura angularis). The sulcus intermedius splits the pyloric vestibule, simply identified as pylorus (represented by the outward convex of the greater curvature) and the pyloric antrum. The pyloric sphincter (or valve) at the end of the pyloric canal (or antrum), is a ring of smooth muscle that constricts to limit the release of stomach contents through the orifice and marks the opening of the stomach into the duodenum (6). In a regular newborn, the length of the pyloric antrum is approximately 2.5 cm and ends at the pyloric orifice and sphincter, which means guard (13). The pyloric sphincter receives sympathetic innervation from the celiac ganglion and is a separate entity from the esophagogastric junction, which is the portion where the stomach meets the esophagus (1).

2.2.2 The Pylorus

The pylorus means the gate, and pyloric stenosis is a narrowing of the opening from the stomach to the duodenum (1). The pyloric portion of the stomach is caudal and moves to the right and upwards, while the cranial or cardiac section rotates to the left and slightly downwards (1). An ultrasound of a fetal stomach can be visualized as early as the ninth week of gestation, where macroscopic measurements can be performed. The formation of the pylorus can be seen as of the fourteenth week (34). The pylorus plays important roles in the gastrointestinal tract including the regulation of digestion rate and the direction of chyme movement. The pyloric sphincter regulates

the flow and controls the exit of chyme (a thick, acidic liquid made up of food and gastric juice) through the pyloric canal into the duodenum for additional digestion (35). The stomach is emptied intermittently, once the intragastric pressure has overcome pyloric resistant (35). The pyloric sphincter is normally contracted so that the orifice remains small and food is broken down in the stomach for a sufficient period of time. After the stomach has completed digestion, the sphincter begins to convulse in waves of peristalsis by pressure gradient changes generated by the diaphragm (36). Gastric peristaltic waves slowly empty the stomach over a 30 minute to an hour time period. The sphincter also blocks any regurgitation of chyme from the duodenum (35).

In the longitudinal section of the pylorus where the greater curvature continues, two muscular loops are clearly distinguished which make up both the longitudinal and circular fibers and define the anatomical boundaries of the pylorus (6). The contraction of the circular fibers narrows the lumen of the pyloric canal, while the contraction of the longitudinal ones approach the distal middle sphincter and functions as a whole. In the mucous membrane of the pylorus, unlike gastric mucosa, there are fewer parietal cells, and most glands secrete mucous (13). There are a number of gastrin-secreting G cells, and enteroendocrine cells are present, which secrete serotonin and somatostatin (37).

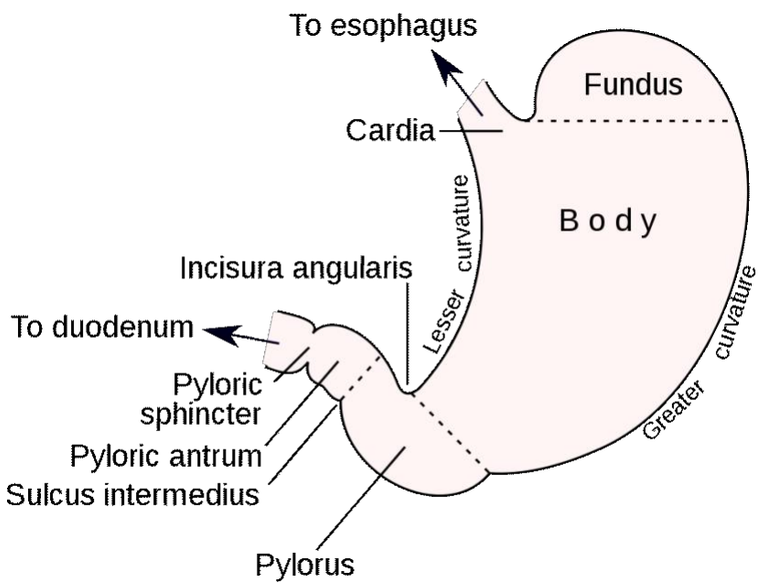


Figure 1. The outline of the stomach showing its anatomic landmarks *(Anatomy of the Human Body)*

2.3 Epidemiology and Genetic Disposition

IHPS is the most common gastrointestinal disease among infants and the most common condition producing emesis during infancy (13). The exact incidence range of IHPS is not known, however it is estimated to be between 2 to 5 per 1000 live births in Caucasian infants and is slightly less prevalent in Hispanic, African-American and Asian children (1,2). It is well recognized that IHPS is more common in males, with a ratio to females of approximately 4:1 (1,39). It can be hypothesized that the cause for this distribution is linked to a genetic factor related to the skewing or inactivation of the X-chromosome (40). Up until now, however, this has not been proven. According to Schwartz, although pyloric stenosis is more common in boys, the risk of an infant developing IHPS from their mother is greater than if their father once suffered from it (27). As many as 7% of cases appear in children whose parents were affected (1). There is an increased risk for first-born infants, who are affected about four times as often, whereby first-born males comprise of about 30% of patients with IHPS (3). The opinion that the condition is more common in first-born than later-born children has generally been supported, but the focus has been the comparison of first-born with subsequent infants as a group (3). The genetic predisposition of the condition is commonly associated with people of Jewish ancestry and there is geographic variability (1). In terms of hereditary factors, IHPS is known to run in families, however no specific pattern of inheritance has been demonstrated aside from the dominance in firstborn white males (1). Over 20% of affected infants display at least one coexisting congenital anomaly. Cardiovascular anomalies are the most common (over 50%), followed by additional gastrointestinal anomalies (about 25%) and anomalies of the central nervous system (over 15%) (41). IHPS is said to be rare among premature infants (1).

2.4 Etiology and Pathogenesis

Despite extensive research that has been conducted about plausible etiological factors and pathophysiological mechanisms, the exact cause of IHPS remains unclear. It is well known that the pylorus has an elevated high-pressure zone that relaxes with the peristalsis of the antrum and contracts as a response to duodenal stimulation. This mechanism prevents the regressive movement of duodenal contents to the stomach (15).

Hirschsprung's explanation was that a congenital, organic defect that causes pathological development of the pyloric wall, leads to a narrowing of the pyloric canal (29). This theory, however could not explain the absence of changes in the pylorus of the fetus and newborn in the first few weeks of life, or the later onset of the disease. Thompson states that hypertrophy is a consequence of the pylorospasm. He believed that there was an innate disharmony between the stomach and the pylorus, in the sense that gastric relaxation is not accompanied by contraction of the pylorus and vice versa (26). This miscoordination leads to the muscular hypertrophy and elements of Thompson's statement are present in all later theories. The exact cause that leads to muscle hypertrophy has not yet been precisely defined, however it has been suggested that it is multifactorial through environmental and hereditary factors such as genetic or immunohistochemical abnormalities as well as hyperacidity (13).

2.4.1 Environmental Factors

In terms of environmental factors, feeding method, erythromycin exposure and maternal age have all been implicated. Firstly, formula fed babies have been shown to have an increased risk in comparison to bottle fed ones (22). In a study conducted in 2012 by Krogh and colleagues, formula-fed infants exhibited a 4.6-fold increased risk of developing IHPS when compared to breastfed infants, even after statistical adjustment for other known risks and confounders. The increased risk was identified in all infants who were formula fed at any point during development (42). This could also cause infantile hypergastrinemia from repeated pyloric contract in response to hyperacidity (1). Several studies have shown that infants exposed to erythromycin (a motilin agonist inducing gastric and pyloric contractions) have an increased risk for developing IHPS especially when the drug is administered in the first few weeks of life (28,43–45). While erythromycin is indicated to be safe to prescribe to neonates, a meta-analysis published in 2016 showed that some studies identify an 8 to 10 time increased risk of developing IHPS (43). Maternal

age can also be a significant contributing factor given that younger mothers (who are less than 20 years of age) display a 40% increased risk of having a child who develops IHPS when compared to mothers that are 25 to 29 years of age. The risk of IHPS in mothers older than 30, on the other hand further decreases (46). Finally, maternal smoking raises the risk of IHPS two-fold over non-smokers, deeming it a critical environmental factor influencing the incidence of IHPS (11).

The stomach is made up of a complex system involving smooth muscle fibers, the enteric nerve plexus, gastrointestinal hormones and interstitial cells of Cajal (28). In recent years, through technological advancements, evolving theories have formed concerning the pathogenesis of IHPS. They consist of abnormalities in hormonal control such as gastrointestinal peptides, altered nitric oxide production, neurotrophins, pyloric innervation and the extracellular matrix. This constellation leads to the failure of pylorus relaxation, increased synthesis of growth factors and results in hypertrophy of the muscle (11).

A number of gastrointestinal peptides or growth factors have been associated with IHPS by a causal relationship with gastrin, substance P, epidermal growth factor (EGF), transforming growth factor-a (TGF-a), insulin-like growth factor-I, somatostatin, secretin, enteroglucagon, and neurotensin. Substance P is a neurotransmitter known to be highly concentrated in the pylorus of infants with IHPS (27,47). It is responsible for enteric muscle contraction and can produce chronic pylorospasm, leading to hypertrophy of the pylorus. In an article by Shima and Puri, an increase in the gene expression of EGF, TGF-a, and insulin-like growth factor-I production as well as an increase in immunostaining for EGF and TGF-a was observed (47). Thus, increased insulin-like growth factor production and platelet-derived growth factors have also been implicated in the etiology of IHPS, however their roles have not been substantiated (13).

The pyloric muscle in IHPS exhibits an irregular distribution of nerve terminals, a reduced intramuscular nerve supporting cells and an abnormal peptidergic innervation (48). Neurotrophins, important for neural development, differentiation and survival are decreased in IHPS (49). Glial-derived growth factors are deficient, potentially due to the immature development of the enteric nervous system. Tyrosine kinase A receptor c-kit is also not present in the tissue (49). In combination, these factors contribute to the pathogenesis of IHPS by causing reduced muscular relaxation and promoting muscular hyperplasia, hypertrophy, and pyloric canal obstruction. Even 120 years later, the underlying mechanism of IHPS is debated and has not yet reached a final

conclusion, however it is evident that it roots from a collective influence of the genetic and environmental factors that contribute to the disease.

2.4.2 Nitric Oxide Pathway

The nitric oxide (NO) pathway has also been associated with the etiology of IHPS. NO relaxes smooth muscle of the myenteric plexus upon its release as it is a major inhibitory non-adrenergic and non-cholinergic neurotransmitter in the gastrointestinal tract (19). Thus, impairment or deficiency of neurons containing NO synthase could be the root of the condition. More specifically, IHPS occurs, in part, from the insufficient progression of inhibitory neurons in the myenteric plexus that stimulate intestinal polypeptide and NO. As a result of this, the tonicity of the pyloric sphincter is diminished (35). It has been observed in literature outlining the immunocytochemistry of IHPS that patients show decreased markers for nerve supporting cells and peptide-containing nerve cells (50). IHPS patients also show decreased levels of NO and mRNA for NO synthase, which are caused by alterations in the regulatory region of the NO synthase gene (51,52).

A study conducted by Piotrowska et al. that evaluated ultrastructural abnormalities of enteric nerves found that IHPS patients have a decreased amount of interstitial cells of Cajal, the pacemaker cells of the smooth muscles of the gastrointestinal tract. IHPS patients are also heme oxygenase-2 deficient, which affects communication between the interstitial cells of Cajal and smooth muscle cells (51). Another study measured nicotinamide-adenine dinucleotide phosphate (NADPH) diaphorase activity (identical to that of NO synthase) of the hypertrophied pyloric muscle wall from IHPS patients (53). While the activity in the longitudinal muscle was unchanged, there was no NADPH diaphorase activity in the hypertrophied circular muscle. Thus, the lack of NO synthase in pyloric tissue may be liable for pylorospasm, leading to IHPS (53). Taken together, the neurotransmitter that has gained the most attention in IHPS research is NO, a key player in the pathway mediating pyloric relaxation, and consequently deficient in IHPS patients.

2.5 Clinical Features and Differential Diagnosis

2.5.1 Symptoms and Signs

In infants with IHPS, the pylorus of the stomach becomes abnormally thickened, causing a narrowed and elongated pyloric channel, as seen in Figure 2. This gastric outlet obstruction is characterized by hypertrophy, hyperperistalsis and compensatory dilation of the stomach (14,25). Typically, IHPS patients present forceful or projectile non-bilious vomiting after feeding in the first 2 to 6 weeks of life (1). The usual presentation is at the 3 week mark and approximately 95% of IHPS cases are diagnosed in those aged 3 to 12 weeks (1). A study conducted by Schärli et al. on 1215 patients with IHPS showed that the vomiting initiated directly after delivery in 20%, 1–2 weeks of age in 60%, and after 4 weeks of age in 20% of the patients (54). This narrow diagnosis window may be caused by enteral feeding, which acts on the atypical tissue of the pylorus. The distinction of bilious vomiting in the newborn is crucial, because if present it may suggest a more serious pathology such as malrotation with volvulus, which would require a time-sensitive intervention (12). The emesis may become blood-tinged, brown or coffee-ground secondary to gastritis or a Mallory-Weiss tear at the gastro-esophageal junction (21). Many parents mistakenly believe their infant has a food allergy or gastroesophageal reflux (15).

Despite infants being constantly hungry, eating and nursing on a regular basis, dehydration is common and can cause the baby to cry without tears and/or have diapers less wet than normal from a decreased amount of urination (1). Jaundice is encountered in 2–5% of infants with IHPS, characterized by indirect hyperbilirubinemia due to a deficiency of glucuronyl transferase (27). On physical examination, the infant may already display signs of dehydration including sunken/depressed eyes (anterior fontanelles), prolonged capillary refill time, cool peripheries, poor skin turgor, and lethargy (11). This is dependent on the delay in diagnosis. A careful inspection of the area while the infant is in a supine position can help with diagnosis, performed after a test feed of milk, dextrose or air, administered orally or through a nasogastric tube (40). Visible abdominal distention (epigastric fulness) and gastric peristalsis are often observed due to the dilated stomach, migrating from the left upper quadrant inferomedially towards the right side (12). The hypertrophied pyloric muscle, which is occasionally observed, is known as a palpable “olive-shaped” mass directly above the umbilicus at the lateral border of the rectus muscle below the edge of the liver. Optimally, the abdominal wall can be relaxed by hip flexion and the abdomen should

be gently palpated while concentrating on the area halfway between the umbilicus and the xiphoid, among the two rectus muscles (21).

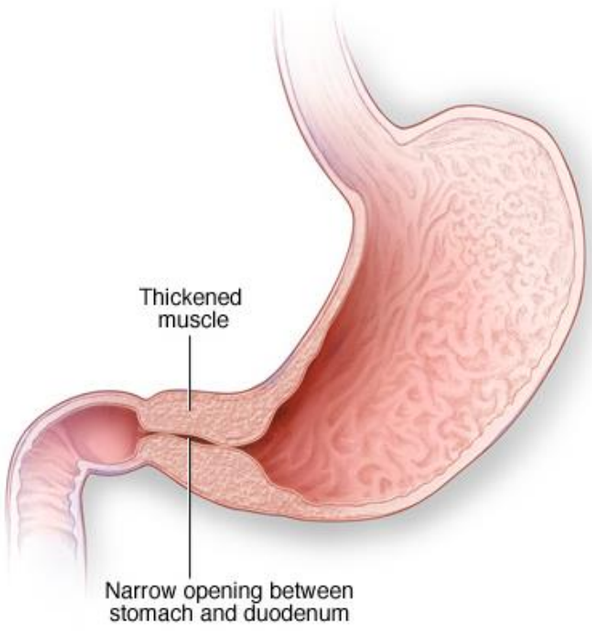


Figure 2. Visualization of pyloric stenosis depicting where food is blocked from entering the small intestine of an infant *(Mayo Foundation for Medical Education and Research)*

2.5.2 Ultrasonography

While the diagnosis can sometimes be made clinically, abdominal ultrasound has become the most common and effective imaging modality, as seen in Figure 3 (13,14). It is a dynamic scan and the presence or absence of flow through the pyloric channel is observed (12). Ideally this is performed by a specialist to ensure a sufficient level of specificity and sensitivity from the investigation. In cases with gastric overdistention, the pylorus can be difficult to visualize due to the displacement of the pylorus dorsally by the gas- and fluid-filled stomach (55). In order to correct this issue, the infant can be turned over into a right lateral decubitus position, causing the pylorus to rise anteriorly for a clearer image (55). Using a high resolution linear probe, measurements of the length of the pyloric channel (canal) and pyloric muscle thickness are taken. The generally accepted criteria for a positive ultrasound are a pyloric muscle thickness of 3.5 (in premature infants) to 4 mm or more and a pyloric channel length of 15 mm or greater (13,27). Some institutions also determine pyloric diameter and consider more than 14 mm to be abnormal (13). In patients without IHPS, the pyloric muscle thickness typically does not measure more than 3 mm (13) Thus, if the diagnosis is inconclusive due to measurements that are extremely close to

diagnostic values and symptoms continue for a few days, the ultrasound can be retaken. Fluoroscopic upper gastrointestinal contrast studies were also once used for diagnosis, because the canal of the pylorus in patients with IHPS is bordered by a sequence of contrast material (56). This method can take quite long, involves exposure to radiation and the sensitivity level will vary based on the skill of the examiner. Thus, real-time ultrasonography has replaced fluoroscopy as the diagnostic procedure of choice as it can visualize the thick and elongated pyloric muscle quite easily (21).

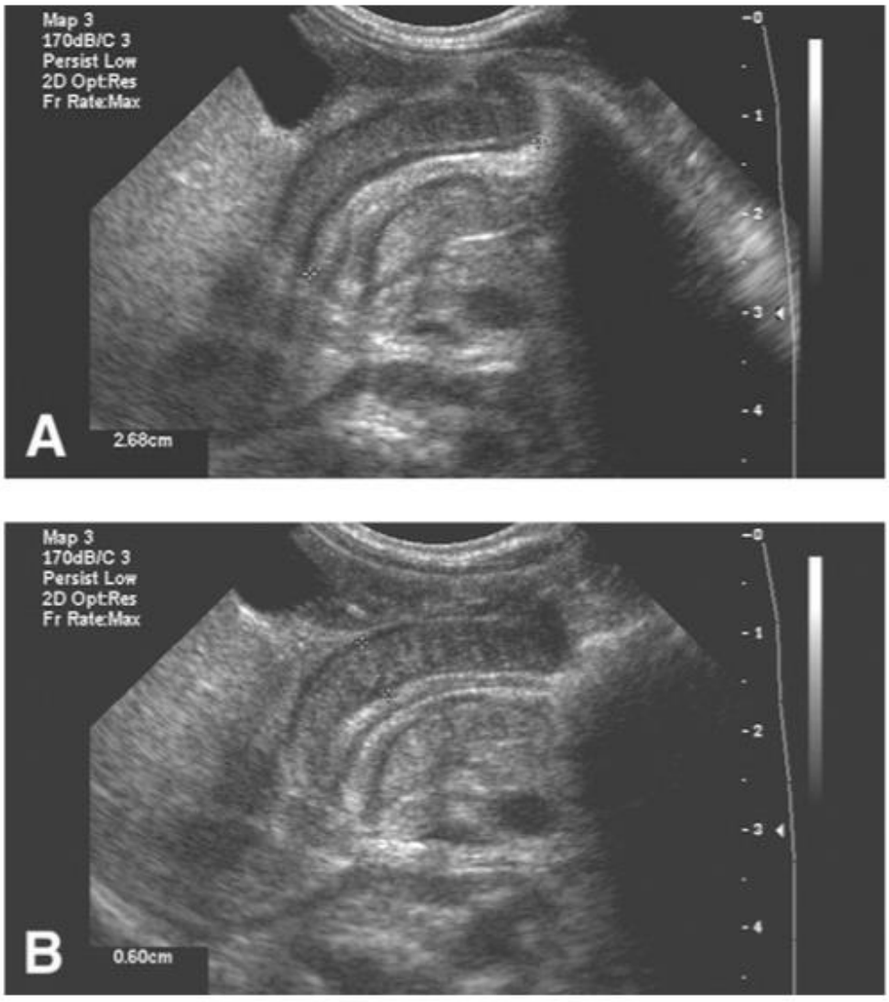


Figure 3. Ultrasound images of the hypertrophied pylorus in a 5-week-old infant (A) pyloric length measuring 26.8 mm and (B) pyloric muscle thickness measuring 6.0mm *(Seminars in Pediatric Surgery)*

2.6 Management and Treatment of IHPS

2.6.1 Preoperative Management

IHPS is not a surgical emergency, but may be a medical emergency in infants requiring aggressive intravenous resuscitation due to dehydrated that remains untreated and develops an electrolyte disturbance (57). Acknowledging that the main priority before treatment of IHPS itself is the fluid and nutritional correction of the infant is crucial. Sufferers of the condition are not able to digest sufficient from persistent vomiting, patients are at risk of an electrolyte imbalance, more specifically hypochloremic metabolic alkalosis (11). Prompt assessment of serum electrolytes and pH are therefore essential.

Best practices include discontinuing oral feedings and setting the infant up on an intravenous solution in order to replenish electrolytes lost from emesis (57). This will also help prepare the infant for surgery, ensuring they are able to withstand the general anaesthetic used during pyloromyotomy. If the contraindication is left uncorrected, it can pose significant risks including perioperative arrhythmias, seizures, vascular collapse and potentially apnea (58). In severe cases of dehydration, infants with IHPS can suffer from hypochloremic, hypokalemic, hyponatraemic, metabolic alkalosis due to hydrogen and chloride being lost through persistent vomiting. Benson and Alpern defined the three stages of severity based on serum carbon dioxide (HCO_3) levels (I. slight < 25 mmol/L, II. Moderate 26-35 mmol/L, III. Severe > 35 mmol/L) (59). According to the literature, decreasing serum bicarbonate values less than 30 mEq/L represents an improvement of alkalosis (27). Most patients will not necessarily have a complete gastric outlet obstruction, thus should be able to tolerate their gastric secretions. Thus, no nasogastric tube is required as it would remove additional fluid and hydrochloric acid from the stomach, which contributes towards the imbalance of electrolytes (27).

The pathophysiology of the imbalance is well understood, given that vomiting results in the losses of hydrogen (H^+) and chloride (Cl^-) ions (60). The pancreas secretes bicarbonate when it is stimulated by H^+, but without this stimulus, alkalosis occurs due to the overall increase in serum bicarbonate (61). In order to buffer the pH change, hydrogen exits the cells in exchange for potassium (K^+), creating hypokalemia (62). Additionally, the kidneys excrete any excess bicarbonate (58). The extracellular volume decreases, which causes contraction alkalosis and

stimulates the renin angiotensin aldosterone pathway to reabsorb Na+ in exchange for K+. This worsens hypokalemia, corrected by an increase in bicarbonate reabsorption to maintain alkalosis (58).

Current trends in the diagnosis of IHPS have shown that the majority of infants are diagnosed early on, prior to significant electrolyte abnormalities (63). This is likely due to the increased use of abdominal ultrasound to establish the diagnosis (61). According to Papadakis et al., in the modern era, given the early suspect, increase in use of ultrasonography as well as fast hospitalization process, up to 88% of infants with IHPS have normal electrolyte levels at presentation and very rarely present with bicarbonate levels > 35 mmol/L, and do not show clinical evidence of dehydration on admission (64). Nonetheless, approximately one fourth of patients are still diagnosed after over 1 week of symptoms, and therefore continued improvement in awareness is required (63).

2.6.2 Surgical Management

Ramstedt's pyloromyotomy was introduced in 1912 and is one of the most important surgeries of the twentieth century as it marked a transition in prognosis from rare survival to rare mortality (4). This method is renowned for not extending the incision through the mucosa and not re-opposing the muscle coats transversely (30). While this form of treatment remains widely practiced and relatively unchanged, the technique involved in gaining access to the abdomen has been modified considerably. Open pyloromyotomy (OP) practices include the lateral oblique muscle-splitting incision, the transverse right upper quadrant incision, and more recently, the right semicircular umbilical incision and the supraumbilical semicircular incision (15). Tan and Bianchi introduced the use of a circumbilical incision, which is cosmetically superior, in 1986, however there can be difficulty in delivering the pylorus as well as the risk of a serosal tear, whereby the incision needs to be extended (15). This three-quarter semi-circular incision follows the curve of the umbilicus and is known for its better cosmetic results (21). The lining of the pylorus protrudes through the incision and a channel is opened from the stomach to the small intestine, as seen in Figure 4. Regardless of the incision method, the pyloric muscle is pulled through the wound and pyloromyotomy is performed through the extramucosal longitudinal splitting of the thickened or hypertrophied pyloric which allows the submucosal layer to bulge out of the serosa (14).

Surgical procedures have undergone an evolution of changes, one of which is the increase in minimally and less invasive procedures. In the case of IHPS, the laparoscopic pyloromyotomy (LP) in lieu of OP has been utilized, which has a wider diffusion (65). This approach was first described by Alain et al. in 1991 and advantages of this technique have been cited to include less emesis, a sooner hospital discharge and a more rapid post-operative recovery when compared to OP (66). Recent RCTs have reported conflicting evidence as to which procedure is superior. In a double-blind multicentre RCT by Hall et al. (2009), analysis of primary outcomes showed that after LP, infants achieved full enteral feed more quickly and were discharged earlier than those who underwent OP (67). According to Taylor et al. in their review from 2013, LP was associated with a higher rate of wound infection, but no statistically significant evidence was found of an earlier return to normal feeding or discharge (29). LeClair and colleagues' RCT that compared LP with the open circumbilical approach also did not observe any difference in the incidence of post-operative vomiting (68). In a 2011 RCT by Siddiqui et al., no difference in operating time, hospital stay or patterns of refeeding were observed between LP and OP groups. Long-term cosmetic results, however, were significantly superior after LP (69). A systematic review and meta-analysis conducted in 2016 by Sathya et al. that evaluated OP versus LP in infants also showed no significant differences in primary outcome of major complications, perioperative complications, operative time or length of hospital stay (65). Thus, according to the literature, despite the technological advances and the general increase in popularity of laparoscopic surgery, there is no concrete evidence supporting a recommendation of one procedure over the other; ultimately the choice can be left to the surgeon.

The vast majority of IHPS patients have excellent short-term and long-term outcomes given the level of care in fluid resuscitation and advances in anesthesia for the surgical approach. Thus, mortality has been practically eliminated (14). After the outflow tract is enlarged, the pylorus is returned to the abdominal cavity and the area is closed, leaving a slightly visible scar. An early short-lived increase in muscle thickness is generally observed within the first few postoperative days, followed by a slow decrease that will eventually reach normalization (< 3 mm). The gradual decrease in length is associated with the healing of the pylorus and return of function (70). The thickness of the pyloric muscle restores to the normal level at 6 weeks to 6 months after the operation (71,72).

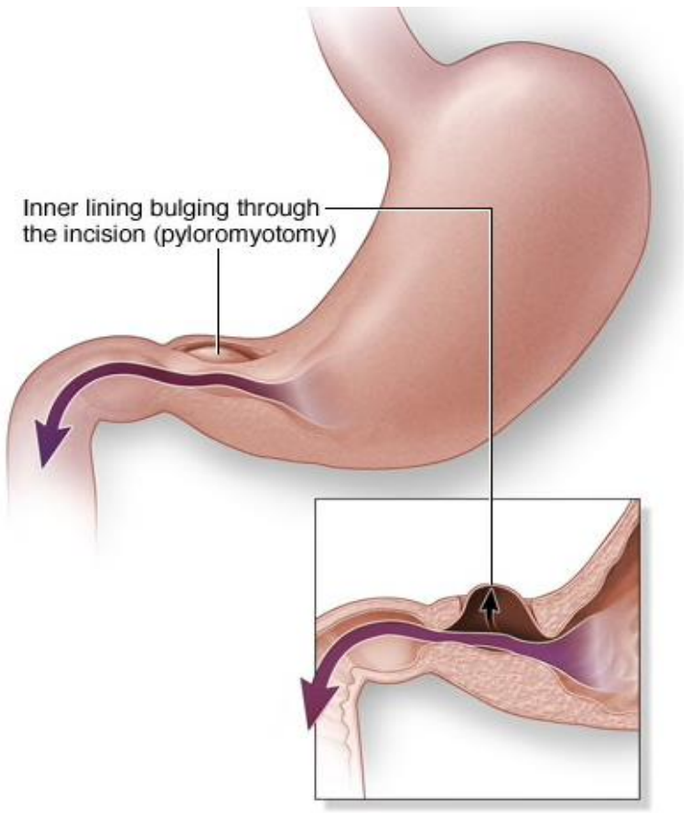


Figure 4. Channel opened from stomach to small intestine *(Mayo Foundation for Medical Education and Research)*

2.6.3 Operative Complications

Pyloromyotomy is associated with an extremely low incidence of morbidity, and mortality is almost not encountered (25). The most serious intraoperative complication is the opening of the full thickness of the pyloric wall with mucosal perforation, which is a result of a myotomy extension beyond the pyloric-duodenal junction. It is caused by the rapid ballooning of the mucosal lining accompanied by the substantially thinned serosal surface of the pylorus, as it transitions to the duodenal bulb (6). Recognizing this intraoperatively is crucial, as the perforation can lead to sepsis, postoperative peritonitis or even death. Extensive mucosal perforations are solved by suturing followed by a rotation of the pylorus 90 degrees to 180 degrees to repeat the pyloromyotomy at an alternate location (6). The reported range of risk of performance is between 0.4-10% in LP and from 0-6% for OP (73). Wound infection is another complication with a reported range of 0-6% for LP and 0-7% for OP (6). A meta-analysis conducted by Oomen et al. in 2012 concerning complications of pyloromyotomy has indicated major complication rates of 4.9% and 2% for LP and OP, respectively (74).

Postoperative hemorrhage, wound dehiscence, incisional hernia and serosal tears have been cited as rare complications (14,15). The use of general anesthesia for pyloromyotomy creates a relatively high-risk situation as the infant is less than 3 months of age, may have had a major

disturbance of fluid and electrolytes and has gastric outlet obstruction. Thus, stomach emptying is prevented and there is an increased danger of pulmonary aspiration of gastric secretions (57,75).

The diagnosis or exclusion of an incomplete myotomy is officially made when postoperative vomiting persists for more than seven days (53). Incomplete pyloromyotomies are generally caused by an inadequate disruption of the muscular fibers on the gastric end of the pyloric incision and require repeat surgery. This can also be due to a postoperative pyloric edema or gastric atony from chronic obstruction, despite an adequate pyloromyotomy (15,77).

2.6.4 Postoperative Care

Postoperative length of stay is country dependent and varies mostly based on the postoperative feeding regimen. In the western world, the hospital stay may be less than 1 day, while in Serbia for example, it is generally 4 days (78). According to Hajiran et al., in their review of 6693 pyloromyotomies performed in the US, the average length of hospital stay was 2.47 days (112). While many surgeons impose a period of no feeding, a variety of regimens have been used after pyloromyotomy. According to Schwartz (2012), feeding can begin within 4 hours of the surgical procedure. A prospective randomized study found post-surgery vomiting to be self-limited and independent of the structure of three feeding regimens (79). A retrospective study reported shorter post-operative hospital stay in patients receiving accelerated feedings, with no increase in vomiting (80). A meta-analysis from 2016 on feed-post pyloromyotomy found that ad libitum feeding is the best recommendation for patients after pyloromyotomy as it contributes toward a decreased hospital stay (81). Given that the majority of infants are brought to the hospital earlier in the course of the condition and diagnosis is made quickly through ultrasonography, most should be able to withstand early and accelerated feedings (13).

2.6.5 Medical Management

Drug therapy as a treatment method for IHPS was based on the belief that pyloric obstruction rooted from the spasm of the pylorus. Historically, gastric lavage was used to quantify and treat gastric outlet obstructions in order to release a muscular spasm in the pylorus through electrical stimulation (30). Adolph Kussmaul attempted to reduce excessive sympathetic nerve stimulation in IHPS by gastric lavage with a sodium bicarbonate solution which encouraged acid loss (30). Despite difficulties intubating an obstructed pylorus, in 1912, Hess used duodenal catheters to diagnose marked stenosis in an attempt to relieve the pylorospasm (30).

Antispasmodic drugs were another management method for those who believed the pathology stemmed from a pylorus in systole (30). Atropine was first introduced by Strümpel in 1904 and was deemed marginally helpful by Hutchison in 1910 (30). Pharmacological management became well-known through Haas in 1922, who published an article that brought atropine back on the table citing that it suppresses pyloric contractions and decreases gastric peristalsis, which in combination, are responsible for the symptoms of IHPS (26). The theory is that atropine, a muscarinic acetylcholine inhibitor, reduces muscular contraction and gastrointestinal peristalsis, breaking the cycle which caused these symptoms (21). More specifically, atropine induces relaxation of the pylorus to re-establish the normal passage of food. Given that the muscles of the pylorus are enlarged, the opening is narrowed and eventually, food from the stomach is prevented from moving to the intestine. Atropine is an anticholinergic and antimuscarinic agent that can decrease intestinal peristalsis by relaxing hypertrophic musculature (14). According to Kawahara et al. the collection pyloric contractions are abolished for a short period of time by an IAT injection of 0.01 mg/kg (9). This dose of atropine is said to improve transpyloric flow by inhibiting pylorospasm. Literature has also shown that oral atropine is less effective on its own in comparison to the initial intravenous intake followed by oral treatment (22,82,83). This can be explained by the fact that gastric outlet obstruction prevents drugs like atropine sulfate from reaching the small intestine, in which they are absorbed (84). IAT however, requires more serious monitoring of patients in comparison to oral.

Atropine sulfate had previously been used in rare cases as a rescue therapy for an incomplete pyloromyotomy (85). Antimuscarinic agents including scopolamine were used in the 1950s and 60s as medical management for IHPS (86). Jacoby and Lond's study reported in 1962 that oral atropine (methyl nitrate) had a positive outcome in roughly 90% of infants with IHPS (87). Medical management was also associated with a longer duration of therapy and a slower resolution of symptoms (88). Thus, the effects of said medications were not dramatic enough to warrant their use as a substitute for operation, at that time.

Beginning in the 1990s, medical treatment started to become reappraised, primarily outside North America (22). Nagita and coworkers published a study in 1996 with encouraging results, which resulted in a renewed interest in medical management (18). Intravenous atropine sulfate was administered until vomiting ceased at which point parents were given oral atropine sulfate to treat

their children with at home at twice the effective intravenous dose for a period of 2 weeks. Ultrasound was repeated until pyloric muscles normalized. 22 out of 23 infants ceased vomiting after 1 to 8 days of IAT. This study also reported that on average, 5 hospital days elapsed before were free from vomiting. At least 2 more hospital days elapsed before the efficiency of IAT was confirmed and parents were able to administer oral atropine at home (18). While atropine can be a successful medicine for IHPS, the mean duration of hospital stay in the surgical approach is incomparable. Kawahara et al. utilized a similar approach with intravenous atropine which was then converted to oral atropine once the infant was able to tolerate full feeds (89). The treatment was successful in 17/19 patients, with no major complications reported. However, the duration of the hospital stay of patients who underwent initial surgical treatment was significantly shorter than that of the successful atropine group (5 [4-29] vs 13 [6-36] days, $p < 0.001$). Three weeks after the completion of oral atropine, pyloric muscle thickness decreased significantly from 5 to 3 mm. By 6 months, the pyloric canal length had shortened. The authors published a more recent non-randomized follow-up study in 2005, which confirmed their preliminary results (9).

A number of retrospective studies were published in the early 2000s with varying efficacy and a recent meta-analysis comparing pyloromyotomy to atropine found a success rate of roughly 80% from medical management compared to 100% from operation amongst 12 studies with 500 patients. The review found that although the incidence of complications is comparable between the two groups, IAT is not effective for all patients and the length of hospital stay remains significantly longer with the atropine therapy. More specifically, mean hospital stay in patients treated with pyloromyotomy was 5.6 ± 2.3 days while those treated with atropine was 10.3 ± 3.8 days. The use of drug therapy has not gained wide acceptance in Western countries not only due to said prolonged hospital admission, but also due to parenteral nutrition, which is the feeding of nutritional products intravenously, generally required until vomiting is arrested (85). According to Meissner et al., clinical improvement is seen on the 6^{th} or 7^{th} day and in their study utilizing IAT, vomiting ceased by the 9^{th} day (90). Atropine in the management of IHPS also requires at-home oral doses once the child has been discharged. While it is the only non-operative form of treatment, according to Lauriti and colleagues it is recommended that atropine therapy solely be reserved only for selected infants with IHPS such as those who are not well suited for surgery and may not be able to undertake anesthesia (22).

An additional non-operative technique worth noting is endoscopic or image-guided balloon dilatation of the pyloric channel, which has previously been described for IHPS patients (15). The first reported study with balloon dilatation targeted six patients with IHPS, where only one case was resolved, however a mucosal rupture occurred (91). There are some articles that suggest the technique for recurrent pyloric stenosis after pyloromyotomy and for IHPS that has a late onset (36,92). Nonetheless, this treatment method has not been widely adopted due to a high rate of perforation and failure to relieve the obstruction (15).

2.6.6 Long-Term Outcome Differences Between Treatment Method

When comparing the value of conservative to operative treatment, it is relevant to consider the long-term changes and effects on the pylorus between the two methods. Pyloromyotomy itself can lead to certain changes in the functioning of the pylorus muscle as a sphincter. In a long-term follow up study performed 16 to 26 years after the treatment, no significant difference in rate for gastric emptying between the atropine therapy or surgery was observed (93). Additionally, comparison of pyloric flow rate between those operated on and treated with atropine did not show a significant difference in adulthood, although the volume of dense flow through the pylorus after pyloromyotomy is slight lower (93). In terms of the time taken to show normalization of pyloric muscle thickness, the majority of studies have similar results irrespective of surgical or medical management. In a study by Fan et al. that specified details on the follow up of the two groups at 6 months post-treatment, no recurrent vomiting was found and all of the children developed well (5). The mean body weight of the children who underwent IAT was 7.8 ± 1.5 kg, which was not significantly different as compared with the operation group (mean: 8.1 ± 1.8 kg). The mean thickness of the pyloric muscle was 2.2 ± 0.3 mm in the IAT group, which was also not significantly different as compared with the operation group (mean: 2.0 ± 0.3 mm). Nonetheless, this is an internal restoration that has no effect on the infant's ability to eat as they would have been symptom free for quite some time.

3. Methods

3.1 Systematic Review

Our study utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (94) and the Cochrane Handbook for Systematic Reviews of Interventions (95) as guides. All inclusion criteria and outcomes of interest were determined a priori by the authors, as seen in Table 1; however, there is no published protocol. The systematic review of the literature was conducted by selecting studies using a defined research strategy (see supplementary table S1). A comprehensive search of major electronic scientific databases took place (including PubMed, MEDLINE and Embase via OVID, The Cochrane Library (via Wiley), Scopus (via Elsevier). The initial search was conducted in December 2019 and was re-run prior to thesis manuscript submission in December 2020. Case reports, case series with less than 5 patients, letters, editorials and abstracts were excluded. The full text of the potentially eligible studies was retrieved and independently assessed and screened by two reviewers who came to a final consensus regarding inclusion. These publications mostly comprised of retrospective and prospective studies, with two nationwide databases also included. The main outcome measure of the systematic review is atropine success rate (%) between surgically treated and drug therapy groups.

Table 1. Inclusion criteria for eligibility in the systematic review

Publication	
Language	Any
Date	After 1990
Subject	Human studies
Study type	Case-control
	Cohort
	Prospective
	Randomized clinical trial
	Retrospective
Excluded	Case reports and small series
	Letters
	Editorials
	Abstracts
Keywords (including MeSH terms)	Infantile hypertrophic pyloric stenosis
	Atropine

3.2 Quality Assessment

Due to the nature of our study, it is important to critically appraise the quality of studies in order to assess the risk of bias. Two investigators independently assessed the quality and then came to a consensus of all publications that met inclusion criteria. The methodological quality of the systematic review was evaluated via the AMSTAR measurement tool (see supplementary table S2) (96). For the studies that were quantitatively synthesized, the Cochrane Collaboration's Risk of Bias Tool in Non-Randomized Studies – of Interventions (ROBINS-I) (obtained from http://methods.cochrane.org/bias/risk-bias-non-randomized-studies-interventions) was used to assess the risk of bias in detail with examples from each of the publications (see supplementary table S3) (95). This guide provided assessment criteria including subject selection, exposures, outcomes, confounding variables and analysis methods, which were compared for investigation across studies. This information was then summarized into a visualization tool for risk-of-bias assessments known as a "traffic light" plot on Review Manager (Rev Man) 5.4, which provides domain-level judgments for each individual result as 'low risk' of bias, 'high risk' of bias or 'unclear risk' of bias, as seen in Figure 6.

3.3 Data Synthesis for Meta-Analyses

The first meta-analysis (A) covered studies that compare length of hospital stay (days) between pyloromyotomy and IAT in infants with IHPS. Studies that directly compare patient characteristics of successful and unsuccessful intravenous atropine therapy were included in the second meta-analysis (B). Outcome measures comprised of age on hospital admission (days), bodyweight on hospital admission (g) and thickness of pyloric muscle before management (mm). Both meta-analyses were performed using inverse variance random effects models on Rev Man 5.4 (97). Meta-analysis A produced mean differences (MDs) and meta-analysis B produced standardized mean differences (SMDs). All variables are continuous and 95% confidence intervals (CI) were computed. I^2 values were calculated to assess and quantify statistical homogeneity between studies and p-values were computed to show the overall effect. Data are expressed as mean ± standard deviation. Publication biases were considered as part of the quality assessment. Had a more substantial number of studies were identified for inclusion per outcome (≥ 10), funnel plots would have been created to help assess the risk of reporting bias and other biases. Findings were also summarized narratively.

4. Results

Literature database search identified 2605 articles for potential inclusion; 1603 articles were screened and 74 full-text articles were assessed for eligibility, as seen in Figure 5. Twenty studies fulfilled the eligibility criteria for the qualitative synthesis and 11 of these were included in the quantitative analysis. From the 11 scientific articles that were brought forward, meta-analysis A (n = 7) contained all studies that directly compared IAT to surgery and meta-analysis B (n = 6) encompassed those that compared successful and unsuccessful IAT patients. Kawahara et al. (9), and Fujiogi et al. (98) studies overlapped within both meta-analyses. The results of the systematic review were largely consistent with published systematic reviews and provided up-to-date information on more than double the number of patients in the last review on this topic (22,82,83). 917 infants reported success with intravenous atropine for IHPS resolution out of 1199 (76.5%) patients (Table 2). Seven of the studies were conducted in Japan, six in Europe, three in India, two in China, one in Korea, one in Saudi Arabia and one in Egypt. The year of publication ranged from 1996 to 2019. It can been observed from the data that studies that incorporate IAT as the initial treatment with higher dosages in combination with oral administration tend to have higher success rates (86.5-96.2%). There was one outlier study, Riccabona et al., which utilized an unknown dosage (1 drop of oral atropine) and had an extremely low success rate of 31.2% [7/22 patients] (56).

The seven articles that were included in meta-analysis A compared IAT (845 infants) with surgery (1809 infants), as seen in Table 3. IHPS patients treated with IAT had a significantly longer mean length of hospital stay (10.3 days) than those treated surgically with pyloromyotomy (5.36 days; MD 4.92, 95% confidence interval (CI) [3.74-6.10]; $p < 0.00001$; Fig. 7). However, there was significant heterogeneity between the studies ($I^2 = 81\%$; $p < 0.001$).

The six articles that were included in meta-analysis B directly compared predictive factors of successful IAT (527 infants) to unsuccessful IAT (188 infants), as seen in Table 4. The results of this meta-analysis revealed a significant association in age on hospital admission of IHPS [SMD 0.52, 95% CI 0.17 to 0.88, $p = 0.004$, $I^2 = 48$ %, Fig. 8] and bodyweight on admission of IHPS [SMD 1.04, 95% CI 0.51 to 1.58, $p = 0.0001$, Fig. 9] between successful and unsuccessful cases of atropine treatment. However, there was significant heterogeneity between the groups in bodyweight on admission ($I^2 = 75$ %, $p < 0.00001$). The results of this meta-analysis revealed no

significant differences in the thickness of the pyloric muscle at diagnosis [SMD -0.34, 95% CI -1.39 to 0.72, p = 0.53, I^2 = 88 %, Fig. 10) between successful and unsuccessful atropine treatment groups.

In terms of the sensitivity analyses, all of the studies possessed a risk of bias in one or more domains of the ROBINS-I tool, as seen in Figure 6 and detailed in supplementary table S3. Of the eight relevant factors, each of the studies showed a high risk of bias in either 3 or 4 categories. These were adequate sequence generation, allocation concealment, blinding of participants and other bias. In certain cases, some of the criteria were deemed unclear and left blank.

Table 2. Studies reporting atropine treatment in infantile hypertrophic pyloric stenosis

Author	Year	Country	Study type	Atropine dosage and time period	Administration method (route)	Atropine, *n*	Success, *n* (%)
Nagita et al. (18)	1996	Japan	R	0.04-0.11 mg/kg/d for 1-6 d (i.v.), then doubled (o)	Intravenous + Oral	23	22 (95.6)
Lim et al. (99)	2000	Korea	R	0.04-0.07 mg/kg/d	Intravenous	14	12 (85.7)
Yamataka et al. (6)	2000	Japan	R	0.05-0.10 mg/kg/d for 1-5 d Home: 0.2-6.3 m	Oral	14	11 (78.6)
Kazuko et al. (100)	2001	Japan	R	0.05-0.10 mg/kg/d for 1-6 d, Home: 4.8 ± 1.9 m	Oral	18	16 (88.9)
Riccabona et al. (56)	2001	Austria	R	1 drop 6-8x/d	Oral	22	7 (31.8)
Singh et al. (101)	2001	India	P	0.06-0.26 mg/kg/d for 1-12 d 0.12-0.66 mg/kg/d (o) for 21 d	Intravenous + Oral	52	50 (96.2)
Sretenović et al. (103)	2004	Serbia	P	0.05–0.10 mg/kg/d	Oral	22	18 (81.8)
Singh et al. (104)	2005	India	R	0.18 mg/kg/d	Oral	12	11 (91.7)
Kawahara et al. (9)	2005	Japan	R	0.06 mg/kg/d for 7 d 0.12 mg/kg/d (o) for 23-128 d	Intravenous + Oral	52	45 (86.5)
Meissner et al. (90)	2006	Germany	R	0.04–0.11 mg/kg/d (i.v.) doubled (o)	Intravenous + Oral	33	25 (75.8)
Almaramhy et al. (105)	2013	Saudi Arabia	P	0.01 mg/kg/4h (i.v.) doubled (o)	Intravenous + Oral	12	8 (66.7)
Koike et al. (106)	2013	Japan	R	0.04–0.1 mg/kg/d (i.v.) doubled (o)	Intravenous + Oral	31	18 (58.1)
Lukac et al. (78)	2013	Serbia	R	0.05–0.18 mg/kg/d	Oral	40	30 (75.0)
Takeuchi et al. (20)	2013	Japan	R, ND1	Varied (n.r.)	Intravenous + Oral	180	142 (78.9)
Fan et al. (5)	2016	China	P	0.06 mg/kg/d step-up (i.v.) step-down (o)	Intravenous + Oral	26	23 (88.5)
Mhatre et al. (107)	2017	India	R	0.01 mg/kg/d (i.v.), every 4h	Intravenous + Oral	4*	4 (100)
Elekiabi et al. (7)	2018	Egypt	P	0.01 mg/kg (i.v.), 6x/d then 0.02 mg/kg (o), 6x/d	Intravenous + Oral	25	20 (80.0)
Fujiogi et al. (98)	2019	Japan	R, ND2	Varied (n.r.)	Intravenous + Oral	526	386 (73.4)
Ono et al. (8)	2019	China	R	0.1 mg/kg/d (i.v.) 8x/day 0.2 mg/kg/d 8x/d (o)	Intravenous + Oral	48	33 (68.8)
Vujović at al. (102)	2019	Serbia	R	Ib 0.18 mg/kg/d max (o)	Oral	30	28 (93.3)
				Ia 0.05-0.18 mg/kg /d, 0.02 incr for 7d	Oral	15	8 (53.3)
TOTALS						**1199**	**917 (76.5)**

Key: R = retrospective, P = prospective
ND1 = nationwide database Japan 2006-2008

ND2 = nationwide database Japan 2010-2016
d = day(s), m = month(s); i.v. = intravenous, o = oral, n.r. = not reported
*Mhatre et al. 2017 was included because the overall study population was 10 patients (≥ 5 patients)

Table 3. Studies directly comparing hospital stay between surgically and medically treated patients (meta-analysis A)

		Infants treated, *n*		Mean hospital stay (d)	
Author	**Year**	**IAT**	**Surgery**	**IAT**	**Surgery**
Yamataka et al.	2000	14	20	5.3 (1-10)	2.7 (2-3)
Kawahara et al.	2005	45	33	13 (6-36)	5.0 (4-29)
Almaramhy et al.	2013	14	14	10 ± 2.0	3.0 ± 1.0
Lukac et al.	2013	40	26	8.0 (n.r.)	4.0 (n.r.)
Takeuchi et al.	2013	180	397	13.5 ± 9.0	8.0 ± 4.0
Fan et al.	2016	26	23	9.5 (6-11)	6.8 (5-9)
Fujiogi et al.	2019	526	1296	13 (9-17)	8.0 (6-10)
TOTALS		**845**	**1809**	Mean: **10.3**	Mean: **5.36**

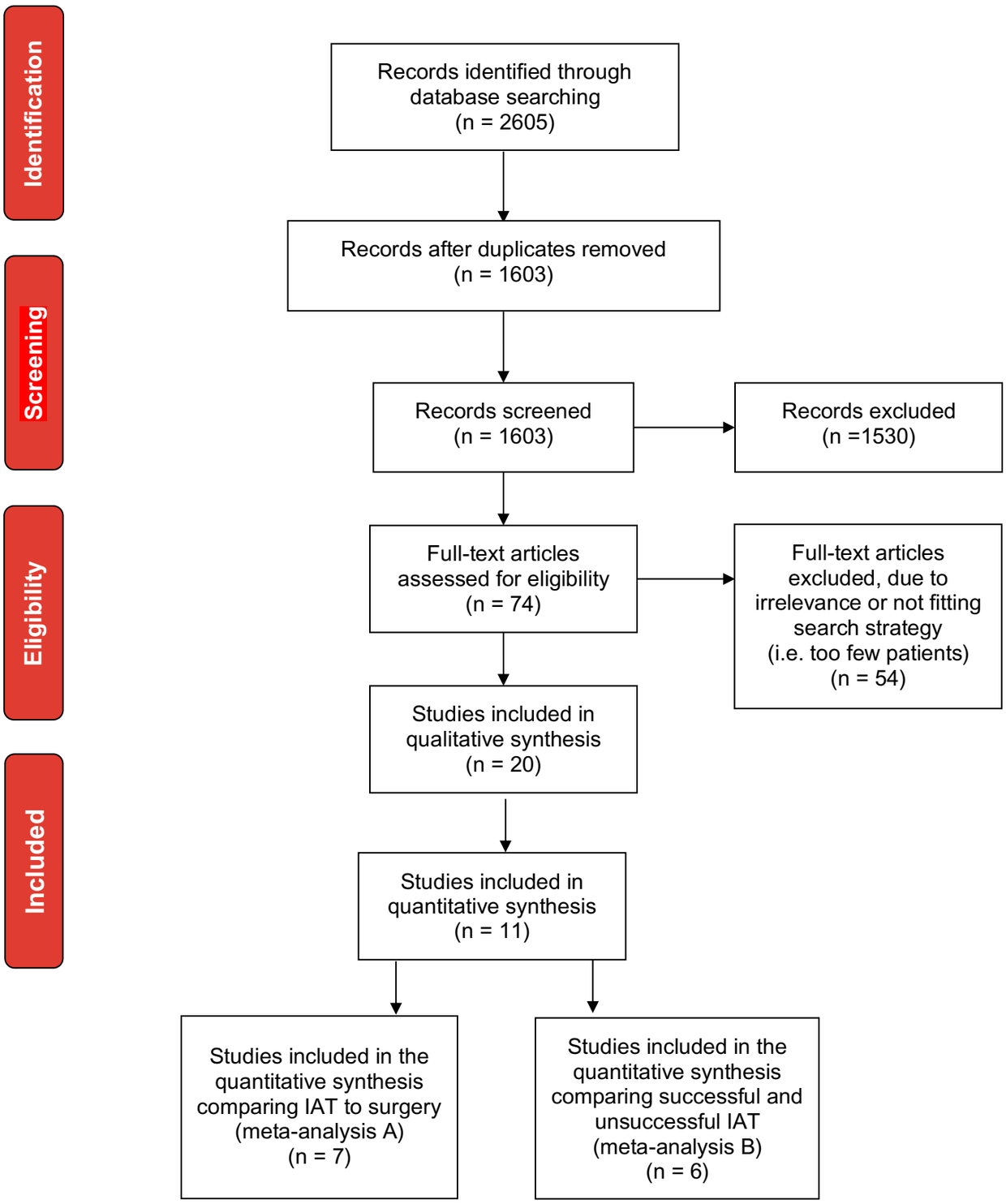
Note: Kawahara et al. ranges were calculated into SD by [(max-min)/4)
For values reported as mean (IQR), estimates were calculated using mean=median and SD = IQR/1.35
Lukac et al. SD was estimated based on the highest SD in that category

Table 4. Studies directly comparing successful versus unsuccessful IAT (meta-analysis B)

Author	**Year**			**Age on admission (d)**		**Body weight on admission (g)**		**Thickness of pyloric muscle on admission (d)**	
		Successful IAT, n	**Unsuccessful IAT, n**	**Successful IAT**	**Unsuccessful IAT**	**Successful IAT**	**Unsuccessful IAT**	**Successful IAT**	**Unsuccessful IAT**
Kawahara et al.	2005	45	7	41 (10-132)	38 (16-75)	3885 (2323-5410)	3230 (2615-4175)	5 (3-7)	5 (3-7)
Meissner et al.	2006	25	8	39.9	29.4	4050	3670	5.3	4.8
Koike et al.	2013	18	13	29.7 ± 9.13	29.1 ± 12.9	3961 ± 132.8	3702 ± 121.8	4.85 ± 0.18	4.69 ± 0.16
Elekiabi et al.	2018	20	5	37.5 ± 18.1	13.0 ± 2.91	3756 ± 576.3	2508 ± 338.6	3.90 ± 0.78	7.20 ± 0.83
Fujiogi et al.	2019	386	140	40 ± 17	34 ± 16	3946 ± 774	3592 ± 671	n.r.	n.r.
Ono et al.	2019	33	15	50.1 ± 18.8	30.9 ± 11.8	4201 ± 867	3388 ± 667	4.8 ± 1.0	4.8 ± 0.9
TOTALS		**527**	**188**						

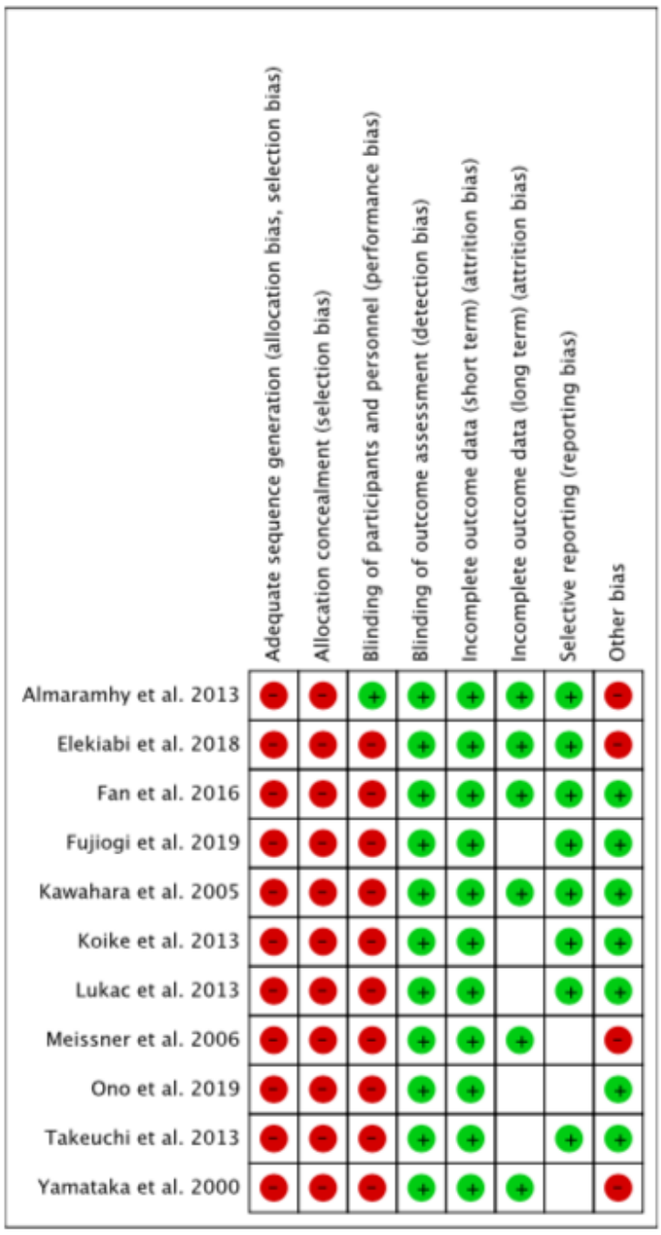
Key: n.r. = not reported
Kawahara et al. ranges were calculated into SD by [(max-min)/4)
Meissner et al. SD was estimated based on the highest SD in each respective category

Figure 5. Diagram of workflow in the systematic review and meta-analysis *(Prisma, 2009)*



Note that there are two overlapping studies in meta-analysis A and B

Figure 6. Risk of bias traffic-light plot summary for the studies in the (quantitative) meta-analysis



Key: ([+] refers to 'low' risk of bias, [-] refers to 'high' risk of bias, and [blank] squares refers to 'unclear' risk of bias)

Figure 7. Forest plot comparison of length of hospital stay among infantile hypertrophic pyloric stenosis patients who were treated intravenously with atropine or surgically via pyloromyotomy (meta-analysis A)

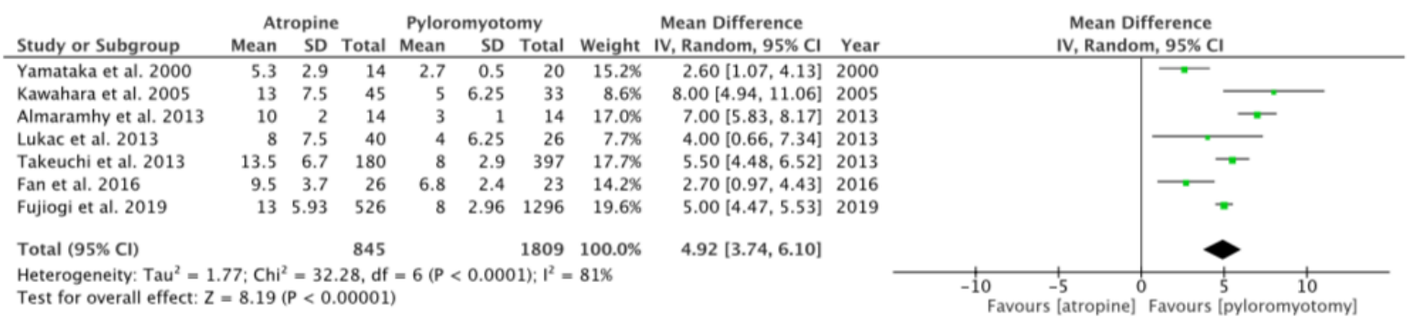


Figure 8. Forest plot comparison of age on hospital admission of patients with infantile hypertrophic pyloric stenosis who were successfully and unsuccessfully treated intravenously with atropine (meta-analysis B)

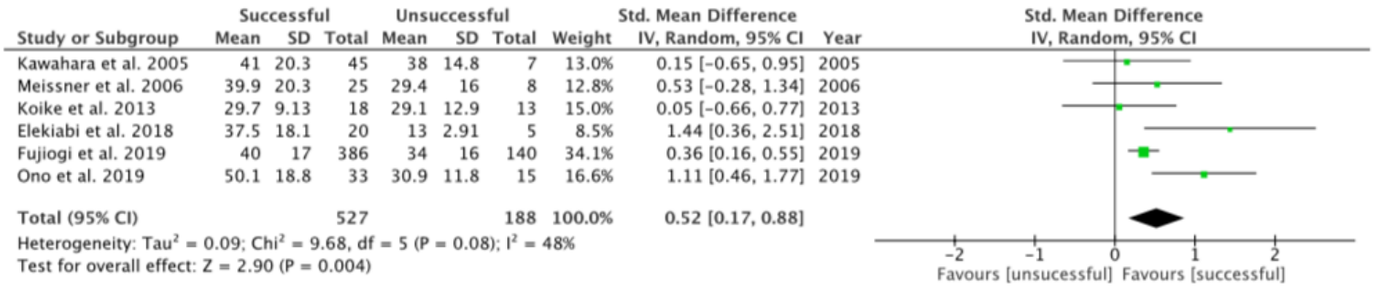


Figure 9. Forest plot comparison of bodyweight on admission of infantile hypertrophic pyloric stenosis in patients who were successfully and unsuccessfully treated intravenously with atropine (meta-analysis B)

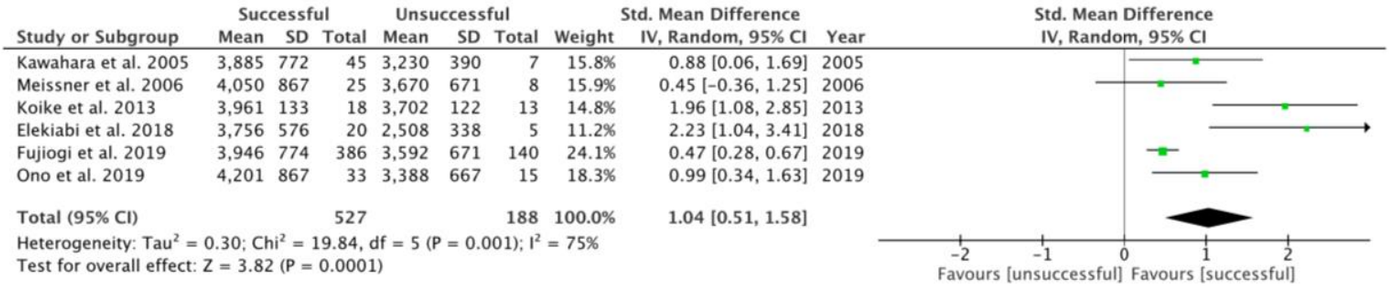
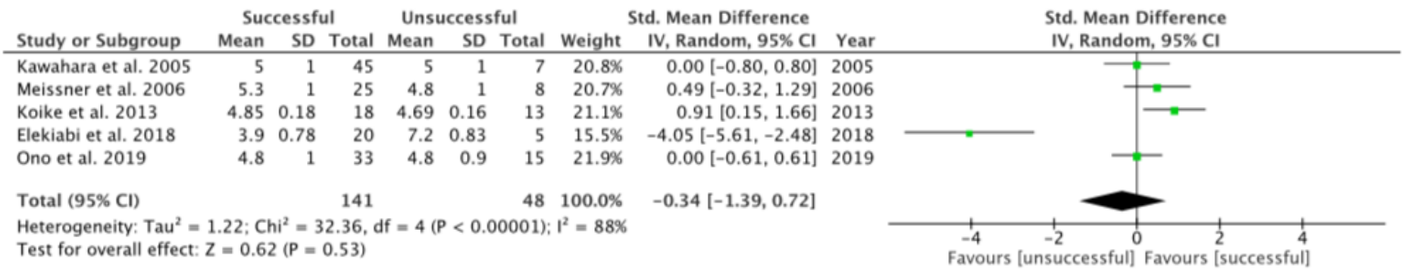


Figure 10. Forest plot comparison of pylorus muscle thickness on admission (before treatment) in infantile hypertrophic pyloric stenosis patients who were successfully and unsuccessfully treated intravenously with atropine (meta-analysis B)



5. Discussion

5.1 Summary of Main Results

This systematic review shows that atropine therapy is effective in 76.5% of cases. However, atropine success rate among the included studies ranged between 31.8 and 100% and was found to be more effective when initially administered intravenously followed by oral treatment. If the one outlier study that solely utilized oral atropine at an unknown dose was omitted, the success rate range for studies remains inhomogeneous, but becomes 53.3-100%. The reason for such a wide reported proportion of success is likely due to the variability of effective dosages, which is linked to alterations in the muscarinic sensitivity of muscle or the uneven distribution of atropine in the pylorus as a result of compromised blood flow secondary to spasm (18).

In analyzing the treatment results according to the method of drug administration, it can be observed that a higher proportion of success is recorded in series' that utilize initial IAT as opposed to the oral form. The rationale behind initially administering atropine intravenously is because orally it does not directly reach the site of absorption, the intestine. It has been suggested that the pharmacologic activity of IAT is 2 to 3 times greater than that of the oral route (21). Thus, to achieve effective blood concentration, atropine must be administered orally at a dose twice as high as the effective intravenous dose (18). However, IAT may be associated with certain adverse effects, whereby transient tachycardia and mild facial flushing are the most common (22). These complications are generally minor and disappear spontaneously, resolving themselves without treatment (18). Oral atropine, on the other hand, is not associated with as many complications as it is not directly absorbed by the intestine. Given the short half-life of atropine in children less than 2 years old, dosing should be individualized and guided by the appearance of adverse events (108). One study from the systematic review with a lower success rate did not escalate the IAT dose to overcome unresponsiveness (105). Studies with higher success rates generally adjusted dosages accordingly, whereby the dose was increased in increments of 0.01 mg/kg/d, known as the step-wise approach, until vomiting was controlled, as long as no serious adverse reactions occurred (5, 18, 101). Regardless of the cause, the optimal or maximal dosage of IAT for this condition is dependent on the case, with incremental increases as a treatment method showing the most promise.

Given that IAT reached satisfactory results and a near perfect efficacy in some studies, it can be inferred from the data that acetylcholine plays a significant role in the pathophysiology of IHPS. It was initially used based on the assumption that the isolated pseudo-obstruction at the pyloric level is caused by a motor abnormality of the gastroduodenal joint and frequent muscle contractions due to hyperacidity, which result in pyloric muscle hypertrophy (19). The etiology of IHPS, however, remains ambiguous although several hypotheses have been proposed based off the initial literature review. This includes a potential genetic basis, impaired function of acetylcholine and muscarinic receptors, and decreased NO synthase activity (11). It is known that atropine sulfate works through an cholinergic blocking agent. Drug dosage may be influenced by a lack of NO synthase or poor innervation of the circular musculature of the pylorus in patients with IHPS (13).

The definition of success varied greatly amongst the studies, which likely had an effect on the percent efficacy. Some studies considered IAT to be unsuccessful if projectile vomiting continued after one week of treatment. Not all studies waited this long as surgery was opted for midway through atropine treatment according to parent's wishes. For example, in the Fan et al., study (5), which had a success rate of 23/26 patients (88.5%), and was also included in meta-analysis A, two patients underwent surgery at the request of their parents before completing the 7 days of IAT. In a study with a lower success rate (58.1%), 9 out of 13 of the "unsuccessful IAT patients" changed their course of treatment on the 6th day, which is earlier than most studies (106). Other studies referred patients to pyloromyotomy as early as the fourth or fifth day of treatment, which in some cases were the sole patients to be deemed unsuccessful (78,88,103). Thus, a possible reason for failed IAT cases may be the insufficient duration of the treatment. Furthermore, Meissner et al. found that the seventh day is considered a turning point for symptom cessation, in patients with a positive response to atropine therapy (90). Elekiabi and colleagues considered atropine treatment unsuccessful if the infants failed to tolerate half of the full feeding volume within 7 days or the full feeding volume within two weeks (7). In most of the studies, the parents were also given the option to withdraw from IAT in the case that they were uncomfortable or if clinical symptoms worsened such as an increased amount of projectile vomiting (90,105,106). Switching the patient to pyloromyotomy voluntarily makes these results less reliable. It is important that families are made aware before taking the decision to opt for atropine therapy that a short treatment duration will generally not judge the effectiveness of IAT sufficiently, as at least

7 full days of IAT may be required in order to observe improvements. Some patients, however, may require an even longer period of time to achieve the full effect of the drug, which prolongs the duration of symptoms and hospitalization.

As expected, IAT patients had a significantly increased mean length of hospital stay compared to those treated with pyloromyotomy (10.3 days vs. 5.36 days; $p < 0.00001$). This is partially due to the previously mentioned extended amount of time required for IAT to take effect, and is one of the major reasons as to why IAT has not gained acceptance in Western countries. Parenteral nutrition as well as the continuous at home oral treatment required upon hospital discharge for medically managed IHPS patients are additional disadvantageous factors. Once an infant is able to tolerate full feeding without vomiting, atropine is given orally at the same dose as the intravenous dose. Patients were generally discharged from the hospital when vomiting was controlled and full feeding (120-150 ml/kg, study protocol dependent) could be maintained with oral atropine administration, which was continued at home by their parents (5,78,88,105). The length of hospital stay reported by the studies included in meta-analysis A used the intend to treat approach for IAT patients. Thus, if an unsuccessful IAT patient was converted to surgery, hospitalization time for the latter procedure was generally included. The results from Kawahara et al. (9), however, reported length of stay among successful and unsuccessful patients, therefore the recorded statistic and the value used in meta-analysis A for this study strictly refers to successful IAT patients. Another one of the included studies reported the length of hospital stay equivalent to the average time to return to full feeding of 120 mL/kg/d rather than the actual number of days until patient discharge (88).

The results of meta-analysis A indicate a relatively long mean hospital stay of 5.36 days for surgical patients in comparison to the earlier cited mean of 2.47 days in a study of nearly 7000 patients in the US (112). Surgically treated patients are discharged once they achieve remission of vomiting, however specific descriptions of recovery procedures after pyloromyotomy were not provided in the studies from meta-analysis A, as their focus was primarily on drug therapy. While hospital stay is partially determined by the time taken to achieve full enteral feeding, the difference across countries might be explained by the variation in post-operative management procedures. According to Jobson et al., recent evidence has demonstrated that post-operative regimentation of treatment optimizes both care and length of hospital stay after pyloromyotomy (19). A review conducted in 2013 by Graham et al., found evidence suggesting a period of starvation

postoperatively may decrease the frequency of postoperative emesis and decrease length of hospital stay. This study provided a recommendation to delay feeds by at least 4 hours, postoperatively, followed by the initiation of ad libitum feedings (109). There remains an ongoing dispute whether ad libitum or incremental protocol driven feeding is more superior. Ultimately, irrespective of the post-operative feeding schedule, it is evident that hospital stay is significantly shorter for pyloromyotomy in comparison to those treated with IAT and explains why this method has not been adopted as a valid alternative to surgery in high-resource settings.

While the results show that the length of hospital stay was longer on average in the atropine group in comparison to the surgical group, studies in China and India suggest that drug therapy remains the cheaper option. This is not necessarily applicable in North America where hospital stay for pyloromyotomy can be less than one day, however cost differences between medical and surgical management in Asian counties have shown to favour atropine (5,88,101,104). For example, Fan and colleagues cited the the medical expenditure to be significantly lower in the drug therapy group of 26 patients (mean: 2373.5 ± 327.9 Yuan; ranged from 1374.5 to 3347.8 Yuan) than in the operation group of 23 patients (mean: 12 487.6 ± 1098.2 Yuan; ranged from 10 328.9 to 14 338.6 Yuan) (5). However, in a nationwide database study conducted in Japan, by Takeuchi et al., it was determined that despite the total cost of medically treated (including patients converted to surgery) was $5330 ± $3970 USD versus $6510 ± $2060 USD, the difference was not statistically significant. The cost of patients who were successfully treated with IAT (not including those who were converted to surgery), however was lower, costing $4570 ± $2950 USD (20).

Meta-analysis B focused on pre-treatment data to clarify the limitations of IAT for IHPS in the early stages through predictive factors for negative outcomes. This is especially useful in low resource settings where medical management is sometimes used as the first line of treatment. The results of our study found that IHPS patients who weigh less on hospital admission tend to have an unsuccessful outcome from IAT. It was also observed that infants who were younger on admission were significantly less successful with the conservative approach in comparison to their older counterparts.

The effect of age might be explained by the previously mentioned innervation abnormality of the smooth muscles of the pylorus in IHPS patients. In a study that determined the distribution pattern of neural cell adhesion molecule (NCAM) positive fibers in biopsy specimens of pyloric muscle, it was suggested that the innervation normalizes with age and that this normalization

precedes the normalization of the muscular hypertrophy (110). Additionally, age dependent improvement of structural immaturity of the pylorus was observed in full-thickness muscle biopsy specimens from IHPS patients (49). Taken together, age-related innervation deficiency may have an influence on the pylorus' responsiveness against atropine, which acts as an inhibitory agent to the cholinergic nerve, the excitatory effector of the pyloric muscle.

The results concerning age contradicted the findings of one study conducted by Riccabona et al., who noticed a better response in the subgroup consisting only of younger patients, up to the age of 42 days, promoting the possibility of an initial conservative medical approach in these patients (56). Nevertheless, this study was noted as an outlier due to an abnormally low efficacy rate of 31.8%, and did not specify oral dosage amounts, as previously mentioned.

Contrary to our hypothesis, we found that the thickness of the pylorus obtained by ultrasound prior to treatment had no effect on the outcome of IAT, based on the data of the studies that reported this characteristic. Length of pyloric thickness among successful and unsuccessful conservatively managed populations was not included in the meta-analysis as there were not a sufficient number of studies that compared this information. It can be inferred from the data that the dimensions of the pylorus do not determine the degree of obstruction of the canal, and thus cannot be accepted as an absolute predictive factor.

The results of Singh et al.'s study, included in the systematic review, suggests that the level of pyloric hypertrophy has an influence on the length of hospital stay in conservative treatment. The subjects in this study were divided into three groups based on their pylorus dimensions at hospital admission. It was observed that in patients with a mild degree of hypertrophy (3-5.5 mm thick and 16.5-19.4 mm long) the symptoms of IHPS disappeared after 1-3 days. Patients with ultrasonographic evidence of moderate hypertrophy (5.6-8 mm thick and 19.5-22.4 mm long) became and remained free of vomiting after 4-7 days of IAT, whereas those with severe hypertrophy (8.1-9.4 mm thick and 22.5-26 mm long) took 8 to 12 days of IAT to become and remain vomiting free for 24 hours (104). While pyloric length and thickness may not have an influence on the efficacy of IAT in IHPS patients, this study suggests that dimensions may be predictive of the length of hospital stay for drug therapy.

The results of the present study indicate that age and body weight are the only variables that correlate with outcomes. We recognize that age and weight are co-linear variables (younger

patients will typically weight less) as the effect of age might be masked by bodyweight, and vice-versa. Firstly, it should be noted that each of these studies possess a relatively high potential for bias based off the ROBINS-I tool and the retrospective and prospective nature of the included studies are not the highest level of evidence. The level of heterogeneity differs between the two models whereby age is only moderately heterogeneous (I^2 = 48%) versus bodyweight, which is considerably heterogeneous (I^2 = 75%) as per the results of meta-analysis B.

Adjusting for collinearity and confounding is only possible when patient level data are available. This is not the case with meta-analysis. When stratified data are reported consistently across all or many of the studies, a meta-regression analysis may be helpful in delineating the independent effects of age and weight. Unfortunately, individual patient data is not available in the present study as the results are reported independently. It can, however, be inferred from our results that bodyweight is more crucial than age in the success of IAT. This can be observed by virtue of the magnitude of the standardized effect. The inverse variance SMD value is much higher for bodyweight 1.04 [0.51-1.58] in comparison to age 0.52 [0.17-0.88], as seen in Figures 8 and 9, and in fact, the value for age is just within the lower bound confidence of the effect of bodyweight. Descriptively, it can also be observed from the data in Figure 8 exploring age, that 3 out of the 6 studies cross the line of null effect between successful and unsuccessful cases. Two out of three of these studies, however, do not cross this line in their confidence interval calculation for bodyweight, as seen in Figure 9. Thus, we can infer that weight has a stronger association, independently of the age of the patient (which according to the data merely approaches statistical significance). While no definite conclusion about confounding or collinearity effects can be drawn based off the limited data available from the six studies in meta-analysis B, it can be deduced that an infant's bodyweight is likely more important than age in their probability for success with IAT.

The only study to stratify IAT patients into bodyweight and age groups based on their hospital admission data was the one published by Fujiogi and colleagues (98)**,** who found that bodyweight was more important than age. In this study, it was reported that the successful IAT group had a significantly higher mean (SD) age at admission in the successful IAT group than in the unsuccessful IAT group (40(17) vs. 34(16) days, $p < 0.0001$). While the bivariate analyses in this study determined both age and weight were significant predictors of successful outcome, the multivariate analysis, in which both age and weight were included as covariates, showed that only

weight remained significantly associated with outcome. These results are in line with our assessment, that weight is a more important predictor of outcome than age.

As a general estimate based on the findings of the present study, IHPS patients who are much lighter than 4000 g have a stronger likelihood to not respond as well to IAT. As a secondary consideration, infants who are younger than 40 weeks also show an increased risk to fail IAT and be converted to surgery. Given that these predictive factors are obtained at admission, it might be possible to select which patients are most likely to have a negative outcome of IAT. Moreover, patients considered to be of high risk for a negative outcome and who are not responding well to the treatment could be transferred to pyloromyotomy sooner than those who would have a stronger likelihood to succeed in medical management. Nonetheless, as previously discussed, it can take up to 7 days to observe the effects of IAT, which helps explain the prolonged hospital stay.

Jacoby and Lond first introduced the idea of selective treatment in 1962 (87). They outlined criteria that would indicate cases where medical treatment was more likely to be satisfactory, but where even if it failed, surgery performed later would not be more dangerous than it would have at the beginning. These criteria were not intended to distinguish cases that would respond to medical treatment from those that would not, but simply to select a group that might be safely treated medically. They included indications for surgical treatment such as vomiting beginning in the second week or earlier and severe dehydration. Indications for medical treatment included vomiting beginning in the fourth week of later (87). Rudolph in his editorial comment in 1996 suggested that it would be important to define a patient selection criteria to determine which infants are most likely to respond to medical therapy (111). To the best of our knowledge, our review is the very first to directly compare studies that provide data on the personal characteristics of successful and unsuccessful IAT patients, in an attempt to deem certain infants as weaker candidates for atropine.

There exists other clinical factors in the literature that could be relevant to consider in the prediction of a negative outcome for IAT. Jacoby and Lond introduced the idea of the duration of symptoms (i.e. vomiting) prior to admission and its effect on IAT by showing that this was significantly different between positive and negative outcomes of IAT whereby the successful group had a mean of 18 ± 16.3 days and the unsuccessful group had a mean of 9 ± 7 days (87). Ono et al. found similar results stating that the patients in the unsuccessful group had a significantly shorter duration of symptoms prior to admission (8.7 ± 7.4 days vs 18.1 ± 16.3 days, $p = 0.04$) (8).

Other studies, however, found that there was no difference in the duration of symptoms between the two groups and thus did not have an effect on the outcome of conservative treatment (90,102). This outcome was not included in the meta-analysis as there was not a sufficient number of studies that provided this data.

Another apparent predictive outcome observed in a study that was included in the meta-analysis was significant differences in urine potassium level at admission between successful and unsuccessful IAT groups (106). This information would also relate to metabolic alkalosis as elevated urinary potassium is one of the compensatory mechanisms for a long-term electrolyte disturbance. This data can be obtained relatively easily upon admission and would be highly appropriate to measure in a future study. This study also cited projectile vomiting that occurred more than five times by day 3 an independent predictive factor of a negative outcome for IAT. This may influence a decision to convert IAT to surgery, however this factor only becomes apparent after IAT begins. Rather, it can be used as an indicator that the infant may be unfit for this medical management in conjunction with other predictive factors observed in the present study to help parents decide whether they should wait before transferring course to pyloromyotomy to treat their infant for IHPS (106).

Finally, the presence of metabolic alkalosis, while increasingly uncommon, given earlier diagnostic timelines due to the use of ultrasonography, may nonetheless be useful to compare in a future study. To the best of our knowledge, however, none of the included studies considered whether those who had electrolyte disturbances were more prone to have to convert to pyloromyotomy. This would help classify metabolic alkalosis as a potential additional factor predictive of a negative outcome of drug treatment.

5.2 Limitations and Implications

Given the small sample sizes of the studies on this topic, meta-analyses provide an excellent method of pooling the results to better examine our outcomes of interest. We acknowledge the limitations of our study, which, as with any other review paper, the quality of the evidence relies on the quality of the studies and data available in the literature. While there was no language restriction to accurately represent the existing data, the systematic review is composed of retrospective and prospective case cohorts, which are not the highest level of evidence. Additionally, there is especially a lack of studies investigating the present study topic looking at atropine as a treatment method for IHPS in general. No randomized controlled trials have been published on IAT and pyloromyotomy to treat IHPS aside from Almaramhy et al.'s prospective randomized study (105).

One of the potential sources of bias in meta-analyses is publication bias. The construction of funnel plots can aid in the assessment of this type of bias; however, our study included too few studies to accurately utilize this method. It should also be noted that risk of bias assessments revealed the potential for a variety of biases influencing the included studies, such as allocation bias, selection bias and performance bias, which may have affected the results. Furthermore, variability in atropine protocols, including drug administration route, dosage and definition of success also effected the results. Given that this practice is not widely used and the patient population who has undergone IAT is extremely low in comparison to the overall number of infants who have suffered from the condition, the data is extremely limited. Statistical heterogeneity of data was moderate to high, which is inherent in meta-analyses and this must also be considered when interpreting the results of the present study. The research quality across included trials varied, and in some trials was difficult to judge as key methodological aspects were poorly documented or omitted due to the nature of two included nationwide databases, for example. Finally, the PRISMA checklist of our study was completed (see supplementary table S4).

Our study investigated the use of medical management for IHPS in low-resource settings through an evidence-based approach. Drug treatment can be unsuccessful and end in conversion to surgery, which is why defining predictive factors, especially those that indicate its negative outcome, would mean a higher percentage of successful treatment with atropine. The use of said indicators to assist in predicting the outcome of atropine therapy in countries such as Japan or

India, for example, based on a patient's clinical characteristics before treatment is proven in the present study. The results indicated that age and size are the only variables that correlate with outcomes, and while it can be gathered that bodyweight is likely more crucial, the true confounding and collinearity effect of these two variables remains to be determined. This is due to the limitation of the available data, which does not include individual patient information. For future investigations, we recommend a study that records all relevant pre-treatment data of IHPS patients treated with IAT highlighted in this thesis. A multivariable regression analysis or stratification that divides the data would assist in determining which of these predictive factors may lead to a successful outcome from this form of treatment and can help control for said confounding.

Our up to date systematic review and meta-analysis guides health care professionals on the merits and pitfalls of the less researched drug therapy approach of atropine. The results provide a mean of summarizing and synthesizing research evidence for the common pediatric condition and suggest predictive factors to consider when pharmacological treatment for IHPS is opted for in countries that lack funds to cover health care costs and in cases where a child has a serious contraindication for surgery. This is the first meta-analysis to compile data on personal characteristics affecting the outcome of IAT. The level of efficacy of IAT is notable, but ultimately the success rate is lower than pyloromyotomy, which as previously mentioned, is nearly 100%. Drug therapy also has a significantly longer hospital stay than surgery, the basis for its rejection by many physicians in Europe and most in North America. Skilled nursing, parenteral nutrition and careful follow up are required while a patient is treated medically, and it would be unlikely that this technique would ever replace surgery in the Western world. Atropine is a less established method, however caters to a wider population as it has no requirement for a surgeon. Surgery for IHPS can be easier and less time consuming than conservative management, whose outcome is not as successful, especially in the eyes of a pediatric surgeon. Based on the limited records examining the costs associated with the two treatment methods, atropine therapy can be economically favourable in certain Asian countries. A financial analysis of cost-effectiveness between the two procedures in selected countries would be highly relevant for a future study. The present study provides useful information on predictive factors of a negative outcome for IAT that could help parents and physicians (in resource-limited environments who may opt for this technique) determine whether a child is more well-suited (or not) for conservative treatment.

6. Conclusion

In the last few decades, the effectiveness of drug therapy for IHPS has been re-examined in Asia and Europe. More recent studies have suggested that medical management be reserved for poor surgical candidates. For example, infants with a hostile abdomen or who have severe medical co-morbidities that would make them at high risk for anaesthesia and surgery such as haemophilia should opt for atropine therapy. While we demonstrate IAT to be effective in over ¾ of patients, IAT requires a significantly prolonged hospital stay compared to that of pyloromyotomy for the management of IHPS and is the main reason drug therapy is rarely utilized in North America. According to the data obtained in the present study, pre-therapy characteristics of the infants can potentially be used in a meaningful way to help select which IHPS patients are at a higher risk for a negative outcome of IAT, making the chances for success with this form of treatment greater for those who may be medically managed in low-resource settings. Our results suggest that bodyweight, most crucially, as well as age on admission are influential towards the outcome of atropine treatment. Patients who are smaller and younger at diagnosis are significantly more likely for a negative outcome from IAT, irrespective of their level of pyloric muscle thickness, which has no effect.

7. References

1. Al-Salem AH. Atlas of Pediatric Surgery: Principles and Treatment [Internet]. Cham: Springer International Publishing; 2020. Available from: http://link.springer.com/10.1007/978-3-030-29211-9

2. Blackmore CC. Evidence-Based Imaging. In: Radiology Business Practice [Internet]. Elsevier; 2008. p. 367–79. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323044523100217

3. MacMahon B. The Continuing Enigma of Pyloric Stenosis of Infancy: A Review. Epidemiology. 2006 Mar;17(2):195–201.

4. Ramstedt C. Zur operation der angeborenen pylorus-stenose. Med Klin. 1912;8:1702–5.

5. Fan J, Shi Y, Cheng M, Zhu X, Wang D. Treating idiopathic hypertrophic pyloric stenosis with sequential therapy: A clinical study: Hypertrophic pyloric stenosis. J Paediatr Child Health. 2016 Jul;52(7):734–8.

6. El-Gohary Y, Abdelhafeez A, Paton E, Gosain A, Murphy AJ. Pyloric stenosis: an enigma more than a century after the first successful treatment. Pediatr Surg Int. 2018 Jan;34(1):21–7.

7. Elekiabi OA, Eraky ME, Gertallah LM, Hassanin AM. Efficacy Medical Treatment as an Alternative to surgical treatment in Management of Infantile Hypertrophic Pyloric Stenosis (IHPS). 2018;6.

8. Ono S, Takenouchi A, Terui K, Yoshida H, Terui E. Risk factors for unsuccessful atropine therapy in hypertrophic pyloric stenosis. Pediatr Int. 2019 Nov;61(11):1151–4.

9. Kawahara H, Takama Y, Yoshida H, Nakai H, Okuyama H, Kubota A, et al. Medical treatment of infantile hypertrophic pyloric stenosis: should we always slice the “olive”? J Pediatr Surg. 2005 Dec;40(12):1848–51.

10. Hussain M. Sonographic Diagnosis of Infantile Hypertrophic Pyloric stenosis- Use of Simultaneous Grey-scale & Colour Doppler Examination. 2008;2(2):7.

11. Galea R, Said E. Infantile Hypertrophic Pyloric Stenosis: An Epidemiological Review. Neonatal Netw. 2018 Jul;37(4):197–204.

12. Ross A, Johnson PRV. Infantile hypertrophic pyloric stenosis. Surg Oxf. 2016 Dec;34(12):609–11.

13. Hernanz-Schulman M. Infantile Hypertrophic Pyloric Stenosis. Radiology. 2003 May;227(2):319–31.

14. Ranells JD, Carver JD, Kirby RS. Infantile Hypertrophic Pyloric Stenosis: Epidemiology, Genetics, and Clinical Update. Adv Pediatr. 2011 Jan;58(1):195–206.

15. Bertozzi M, Magrini E, Appignani A. Hypertrophic Pyloric Stenosis and Other Pyloric Affections. In: Lima M, Reinberg O, editors. Neonatal Surgery [Internet]. Cham: Springer International Publishing; 2019. p. 225–38. Available from: http://link.springer.com/10.1007/978-3-319-93534-8_16

16. Tan KC, Bianchi A. Circumumbilical incision for pyloromyotomy. Br J Surg. 1986 May;73(5):399–399.

17. MacKinlay GA, Barnhart DC. Laparoscopic Pyloromyotomy. 2008;6.

18. Nagita A, Yamaguchi J, Amemoto K. Management and Ultrasonographic Appearance of Infantile Hypertrophic Pyloric Stenosis with Intravenous Atropine Sulfate. Journal of Pediatric Gastroenterology & Nutrition. 1996;23(2):172–7.

19. Jobson M, Hall NJ. Contemporary management of pyloric stenosis. Semin Pediatr Surg. 2016 Aug;25(4):219–24.

20. Takeuchi M, Yasunaga H, Horiguchi H, Hashimoto H, Matsuda S. Pyloromyotomy versus i.v. atropine therapy for the treatment of infantile pyloric stenosis: Nationwide hospital discharge database analysis: Atropine therapy for pyloric stenosis. Pediatr Int. 2013 Aug;55(4):488–91.

21. Aspelund G, Langer JC. Current management of hypertrophic pyloric stenosis. Semin Pediatr Surg. 2007 Feb;16(1):27–33.

22. Lauriti G, Cascini V, Chiesa P, Pierro A, Zani A. Atropine Treatment for Hypertrophic Pyloric Stenosis: A Systematic Review and Meta-Analysis. Eur J Pediatr Surg. 2018 Oct;28(05):393–9.

23. Lima M, editor. Pediatric Digestive Surgery [Internet]. Cham: Springer International Publishing; 2017. Available from: http://link.springer.com/10.1007/978-3-319-40525-4

24. Thomas J. Is Dr. Patrick Blair's description of pyloric stenosis in 1717 the earliest on record? J Paediatr. 62(176).

25. Raffensperger J. Pierre Fredet and pyloromyotomy. J Pediatr Surg. 2009 Sep;44(9):1842–5.

26. Mack HC. A HISTORY OF HYPERTROPHIC PYLORIC STENOSIS AND ITS TREATMENT. :25.

27. Schwartz MZ. Hypertrophic Pyloric Stenosis. In: Pediatric Surgery [Internet]. Elsevier; 2012. p. 1021–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323072557000787

28. Georgoula C, Gardiner M. Pyloric stenosis a 100 years after Ramstedt. Arch Dis Child. 2012 Aug;97(8):741–5.

29. Taylor S. PYLORIC STENOSIS BEFORE AND AFTER RAMSTEDTP. :4.

30. Taghavi K, Powell E, Patel B, McBride CA. The treatment of pyloric stenosis: Evolution in practice: The treatment of pyloric stenosis. J Paediatr Child Health. 2017 Nov;53(11):1105–10.

31. Pollock WF, Norris WJ, Gordon HE. The management of hypertrophic pyloric stenosis at the Los Angeles Childrens Hospital. Am J Surg. 1957 Aug;94(2):335–49.

32. Teele RL, Smith EH. Ultrasound in the Diagnosis of Idiopathic Hypertrophic Pyloric Stenosis. N Engl J Med. 1977 May 19;296(20):1149–50.

33. McCracken KW, Wells JM. Mechanisms of embryonic stomach development. Semin Cell Dev Biol. 2017 Jun;66:36–42.

34. Koyuncu E, Malas MA, Albay S, Cankara N, Karahan N. The development of fetal pylorus during the fetal period. Surg Radiol Anat. 2009 Jun;31(5):335–41.

35. Ramkumar d., Schulze k. s. The pylorus. Neurogastroenterol Motil. 2005 Jun;17(s1):22–30.

36. Boybeyi Ö, Karnak İ, Ekinci S, Ciftci AO, Akçören Z, Tanyel FC, et al. Late-onset hypertrophic pyloric stenosis: definition of diagnostic criteria and algorithm for the management. J Pediatr Surg. 2010 Sep;45(9):1777–83.

37. Dick A, Ardill J, Potts S, Dodge J. Gastrin, somatostatin and infantile hypertrophic pyloric stenosis. Acta Paediatr. 2001 Aug;90(8):879–82.

38. Gray H, Lewis WH. Anatomy of the human body [Internet]. New York: Bartleby.com; 2000 [cited 2020 Aug 22]. Available from: http://www.bartleby.com/107/

39. Schechter R, Torfs CP, Bateson TF. The epidemiology of infantile hypertrophic pyloric stenosis. Paediatr Perinat Epidemiol. 1997 Oct;11(4):407–27.

40. Peters B, Oomen MW, Bakx R, Benninga MA. Advances in infantile hypertrophic pyloric stenosis. Expert Rev Gastroenterol Hepatol. 2014 Jul;8(5):533–41.

41. Feng Z, Nie Y, Zhang Y, Li Q, Xia H, Gong S, et al. The Clinical Features of Infantile Hypertrophic Pyloric Stenosis in Chinese Han Population: Analysis from 1998 to 2010. Huang L-M, editor. PLoS ONE. 2014 Feb 19;9(2):e88925.

42. Krogh C, Biggar RJ, Fischer TK, Lindholm M, Wohlfahrt J, Melbye M. Bottle-feeding and the Risk of Pyloric Stenosis. PEDIATRICS. 2012 Oct 1;130(4):e943–9.

43. Murchison L, De Coppi P, Eaton S. Post-natal erythromycin exposure and risk of infantile hypertrophic pyloric stenosis: a systematic review and meta-analysis. Pediatr Surg Int. 2016 Dec;32(12):1147–52.

44. Krogh C, Gortz S, Wohlfahrt J, Biggar RJ, Melbye M, Fischer TK. Pre- and Perinatal Risk Factors for Pyloric Stenosis and Their Influence on the Male Predominance. Am J Epidemiol. 2012 Jul 1;176(1):24–31.

45. Lund M, Pasternak B, Davidsen RB, Feenstra B, Krogh C, Diaz LJ, et al. Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis: nationwide cohort study. BMJ. 2014 Mar 11;348(mar11 8):g1908–g1908.

46. Pedersen RN, Garne E, Loane M, Korsholm L, Husby S, A Eurocat Working Group, et al. Infantile hypertrophic pyloric stenosis: A comparative study of incidence and other epidemiological characteristics in seven European regions. J Matern Fetal Neonatal Med. 2008 Jan;21(9):599–604.

47. Shima H, Puri P. Increased expression of transforming growth factor-a in infantile hypertrophic pyloric stenosis. :3.

48. Ohshiro K. Pathogenesis of infantile hypertrophic pyloric stenosis: recent progress. :10.

49. Guarino N, Yoneda A, Shima H, Puri P. Selective neurotrophin deficiency in infantile hypertrophic pyloric stenosis. J Pediatr Surg. 2001 Aug;36(8):1280–4.

50. Okazaki T, Yamataka A, Fujiwara T, Nishiye H, Fujimoto T, Miyano T. Abnormal distribution of nerve terminals in infantile hypertrophic pyloric stenosis. J Pediatr Surg. 1994 May;29(5):655–8.

51. Piotrowska AP, Solari V, Puri P. Distribution of Heme Oxygenase-2 in Nerves and Interstitial Cells of Cajal in the Normal Pylorus and in Infantile Hypertrophic Pyloric Stenosis. Arch Pathol Lab Med. 2003;127:5.

52. Saur D, Vanderwinden J-M, Seidler B, Schmid RM, De Laet M-H, Allescher H-D. Single-nucleotide promoter polymorphism alters transcription of neuronal nitric oxide synthase exon 1c in infantile hypertrophic pyloric stenosis. Proc Natl Acad Sci. 2004 Feb 10;101(6):1662–7.

53. Wang X-Y, Wong W-C, Ling E-A. Localization of nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d) activity in the gastrointestinal sphincters in the guinea pig. J Auton Nerv Syst. 1996 Apr;58(1–2):51–5.

54. Schärli A, Sieber WK, Kiesewetter WB. Hypertrophic pyloric stenosis at the children's hospital of pittsburgh from 1912 to 1967 A critical review of current problems and complications. J Pediatr Surg. 1969 Feb;4(1):108–14.

55. Copeland DR, Cosper GH, McMahon LE, Boneti C, Little DC, Dassinger MS, et al. Return of the surgeon in the diagnosis of pyloric stenosis. J Pediatr Surg. 2009 Jun;44(6):1189–92.

56. Riccabona M, Weitzer C, Lindbichler F, Mayr J. Sonography and color Doppler sonography for monitoring conservatively treated infantile hypertrophic pyloric stenosis. J Ultrasound Med. 2001 Sep;20(9):997–1002.

57. Allan C. Determinants of good outcome in pyloric stenosis. J Paediatr Child Health. 2006 Mar;42(3):86–8.

58. Jacobs C, Johnson K, Khan FA, Mustafa MM. Life-threatening electrolyte abnormalities in pyloric stenosis. J Pediatr Surg Case Rep. 2019 Apr;43:16–8.

59. Benson CD, Alpern B. Preoperative and Postoperative Care of Congenital Pyloric Stenosis. Arch Surg. 1957 Dec 1;75(6):877.

60. Miozzari H, Tonz M. Fluid resuscitation in infantile hypertrophic pyloric stenosis. 2001;5.

61. Hulka F, Campbell TJ, Campbell JR, Harrison MW. Evolution in the Recognition of Infantile Hypertrophic Pyloric Stenosis. PEDIATRICS. 1997 Aug 1;100(2):e9–e9.

62. Nmadu PT. Alterations in serum electrolytes in congenital hypertrophic pyloric stenosis: a study in Nigerian children. Ann Trop Paediatr. 1992 Jan;12(2):169–72.

63. Acker SN, Garcia AJ, Ross JT, Somme S. Current trends in the diagnosis and treatment of pyloric stenosis. Pediatr Surg Int. 2015 Apr;31(4):363–6.

64. Papadakis K, Chen EA, Luks FI, Lessin MS, Wesselhoeft CW, Deluca FG. The changing presentation of pyloric stenosis. Am J Emerg Med. 1999 Jan;17(1):67–9.

65. Sathya C, Wayne C, Gotsch A, Vincent J, Sullivan KJ, Nasr A. Laparoscopic versus open pyloromyotomy in infants: a systematic review and meta-analysis. Pediatr Surg Int. 2017 Mar;33(3):325–33.

66. Hall NJ, Van Der Zee J, Tan HL, Pierro A. Meta-analysis of Laparoscopic Versus Open Pyloromyotomy: Ann Surg. 2004 Nov;240(5):774–8.

67. Hall NJ, Pacilli M, Eaton S, Reblock K, Gaines BA, Pastor A, et al. Recovery after open versus laparoscopic pyloromyotomy for pyloric stenosis: a double-blind multicentre randomised controlled trial. 2009;373:9.

68. Leclair M-D, Plattner V, Mirallie E, Lejus C, Nguyen J-M, Podevin G, et al. Laparoscopic pyloromyotomy for hypertrophic pyloric stenosis: a prospective, randomized controlled trial. J Pediatr Surg. 2007 Apr;42(4):692–8.

69. Siddiqui S, Heidel RE, Angel CA, Kennedy AP. Pyloromyotomy: randomized control trial of laparoscopic vs open technique. J Pediatr Surg. 2012 Jan;47(1):93–8.

70. Yoshizawa J, Eto T, Higashimoto Y, Saitou T, Maie M. Ultrasonographic features of normalization of the pylorus after pyloromyotomy for hypertrophic pyloric stenosis. J Pediatr Surg. 2001 Apr;36(4):582–6.

71. Bourchier D, Dawson KP, Kennedy JC. Pyloric stenosis: A postoperative ultrasonic study. J Paediatr Child Health. 1985 Aug;21(3):189–90.

72. Sauerbrei EE, Paloschi GG. The ultrasonic features of hypertrophic pyloric stenosis, with emphasis on the postoperative appearance. Radiology. 1983 May;147(2):503–6.

73. 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 Mar;39(3):292–6.

74. Oomen MWN, Hoekstra LT, Bakx R, Ubbink DT, Heij HA. Open Versus Laparoscopic Pyloromyotomy for Hypertrophic Pyloric Stenosis: A Systematic Review and Meta-Analysis Focusing on Major Complications. Surg Endosc. 2012 Aug;26(8):2104–10.

75. Craig R, Deeley A. Anaesthesia for pyloromyotomy. BJA Educ. 2018 Jun;18(6):173–7.

76. Hall NJ, Eaton S, Seims A, Leys CM, Densmore JC, Calkins CM, et al. Risk of incomplete pyloromyotomy and mucosal perforation in open and laparoscopic pyloromyotomy. J Pediatr Surg. 2014 Jul;49(7):1083–6.

77. Muramori K, Nagasaki A, Kawanami T. Ultrasonographic Serial Measurements of the Morphologic Resolution of the Pylorus After Ramstedt Pyloromyotomy for Infantile Hypertrophic Pyloric Stenosis. J Ultrasound Med. 2007 Dec;26(12):1681–7.

78. Lukac M, Antunovic S, Vujovic D, Pavicevic P, Jesic M, Krstajic T, et al. Is Abandonment of Nonoperative Management of Hypertrophic Pyloric Stenosis Warranted? Eur J Pediatr Surg. 2013 Feb 2;23(01):080–4.

79. Wheeler RA, Najmaldin AS, Stoodley N, Griffiths DM, Burge DM, Atwell JD. Feeding regimens after pyloromyotomy. :2.

80. Gollin G, Doslouglu H, Flummerfeldt P, Caty MG, Glick PL, Allen JE, et al. Rapid Advancement of Feedings After Pyloromyotomy for Pyloric Stenosis. Clin Pediatr (Phila). 2000 Mar;39(3):187–90.

81. Sullivan KJ, Chan E, Vincent J, Iqbal M, Nasr A, for the Canadian Association of Paediatric Surgeons Evidence-Based Resource. Feeding Post-Pyloromyotomy: A Meta-analysis. Pediatrics. 2016 Jan;137(1):e20152550.

82. Wu S-F, Lin H-Y, Huang F-K, Chen A-C, Su B-H, Li C-I, et al. Efficacy of Medical Treatment for Infantile Hypertrophic Pyloric Stenosis: A Meta-analysis. Pediatr Neonatol. 2016 Dec;57(6):515–21.

83. Mercer AE, Phillips R. Question 2 * Can a conservative approach to the treatment of hypertrophic pyloric stenosis with atropine be considered a real alternative to surgical pyloromyotomy? Arch Dis Child. 2013 Jun 1;98(6):474–7.

84. Lambert DG, Appadu BL. Muscarinic receptor subtypes: do they have a place in clinical anaesthesia? Br J Anaesth. 1995 May;74(5):497–9.

85. Owen RP, Almond SL, Humphrey GME. Atropine sulphate: rescue therapy for pyloric stenosis. Case Rep. 2012 Aug 2;2012(aug02 1):bcr2012006489–bcr2012006489.

86. Mellin GW, Santulli TV, Altman HS. Congenital pyloric stenosis. J Pediatr. 1965 Mar;66(3):649–57.

87. Jacoby N. PYLORIC STENOSIS: SELECTIVE MEDICAL AND SURGICAL TREATMENT A Survey of Sixteen Years' Experience. The Lancet. 1962 Jan;279(7221):119–21.

88. Yamataka A, Tsukada K, Yokoyama-Laws Y, Murata M, Lane GJ, Osawa M, et al. Pyloromyotomy versus atropine sulfate for infantile hypertrophic pyloric stenosis. J Pediatr Surg. 2000 Feb;35(2):338–42.

89. Kawahara H. Intravenous atropine treatment in infantile hypertrophic pyloric stenosis. Arch Dis Child. 2002 Jul 1;87(1):71–4.

90. 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 Nov 21;22(12):1021–4.

91. Hayashi AH, Giacomantonio JM, Lau HYC, Gillis DA. Balloon catheter dilatation for hypertrophic pyloric stenosis. J Pediatr Surg. 1990 Nov;25(11):1119–21.

92. Nasr A, Ein SH, Connolly B. Recurrent pyloric stenosis: to dilate or operate? A preliminary report. J Pediatr Surg. 2008 Feb;43(2):e17–20.

93. Lüdtke FE, Bertus M, Voth E, Michalski S, Lepsien G. Gastric emptying 16 to 26 years after treatment of infantile hypertrophic pyloric stenosis. J Pediatr Surg. 1994 Apr;29(4):523–6.

94. Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 Jul 21;339(jul21 1):b2535–b2535.

95. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343(oct18 2):d5928–d5928.

96. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007 Dec;7(1):10.

97. Review Manager (RevMan) 5.3 (2014). Copenhagen: The Nordic Cochrane Centre, the Cochrane collaboration [Computer Program].

98. Fujiogi M, Michihata N, Matsui H, Fushimi K, Yasunaga H, Ishimaru T, et al. Factors affecting successful atropine therapy for infantile hypertrophic pyloric stenosis: a retrospective analysis using a nationwide database in Japan. :8.

99. Lim JW, Son HS, Shim KS. Infantile Hypertrophic Pyloric Stenosis Treated with Intravenous Atropine Sulfate. J Korean Pediatr Soc. 2000;43(6):763–8.

100. Kazuko O, Yokoyama Y, Honma S. Oral Treatment of Atropine Sulfate for Infantile Hypertrophic Pyloric Stenosis. J Jap Fed Soc. 105:22–8.

101. Singh UK, Suman S, Kumar R. Successful Management of Infantile Hypertrophic Pyloric Stenosis with Atropine Sulfate. Indiann Pediatrics. 2001;38:1099–105.

102. Vujovic D, Lukac M, Sretenovic A, Pejanovic J, Jovanovic B, Pavicevic P, et al. Database analysis of oral atropine treatment of infantile hypertrophic pyloric stenosis. A ten-year single center experience. Vojnosanit Pregl. 2019;(00):47–47.

103. Sretenovic A, Smoljanic Z, Korac G, Sindjic S, Lukac M, Krstic Z. Conservative treatment of hypertrophic pyloric stenosis in children. Srp Arh Celok Lek. 2004;132:93–6.

104. Singh UK, Kumar R, Prasad R. Oral Atropine Sulfate for Infantile Hypertrophic Pyloric Stenosis. INDIAN Pediatr. 2005;42:4.

105. Almaramhy HH, Alshareif HA. Use of atropine sulfate in the treatment of infantile hypertrophic pyloric stenosis. J Taibah Univ Med Sci. 2013 Dec;8(3):173–7.

106. Koike Y, Uchida K, Nakazawa M, Inoue M, Kusunoki M, Tsukamoto Y. Predictive factors of negative outcome in initial atropine therapy for infantile hypertrophic pyloric stenosis: I.v. atropine therapy for IHPS. Pediatr Int. 2013 Oct;55(5):619–23.

107. Mhatre S, Sanjay N, Kulkarni K. Comparison between medical and surgical management of infantile hypertrophic pyloric stenosis. Indian J Res. 2017;6(12).

108. Kanto J, Klotz U. Pharmacokinetic implications for the clinical use of atropine, scopolamine and glycopyrrolate. Acta Anaesthesiol Scand. 1988 Feb;32(2):69–78.

109. Graham KA, Laituri CA, Markel TA, Ladd AP. A review of postoperative feeding regimens in infantile hypertrophic pyloric stenosis. J Pediatr Surg. 2013 Oct;48(10):2175–9.

110. Kobayashi H, Wester T, Puri P. Age-related changes in innervation in hypertrophic pyloric stenosis. Journal of Pediatric Surgery. 1997;32(12):1704–7.

111. Rudolph CD. Medical Treatment of Idiopathic Hypertrophic Pyloric Stenosis: Should We Marinate or Slice the “Olive”? Journal of Pediatric Gastroenterology and Nutrition. 1996;23(4):399–401.

112. Hajiran CJ, Hobbs GR, Vona-Davis LC, Nakayama DK. Cost of Hospitalization for Infantile Pyloric Stenosis. The American Surgeon. 2016 Jan;82(1):3–5.

8. Appendix

Supplementary Table S1. Search Strategy

PUBMED, MEDLINE, and EMBASE [via OVID]
1. (Pyloric Stenosis OR Hypertrophic Pyloric Stenosis OR Pyloric Stenosis, Hypertrophic OR Infantile Hypertrophic Pyloric Stenosis OR Idiopathic Hypertrophic Pyloric Stenosis OR Primary Hypertrophic Pyloric Stenosis OR Pyloric*adj2 Stenosis OR IHPS OR Pyloromyotomy OR Pyloromyotom*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
2. (Atropine OR Atropinol OR Atropine Sulfate OR Sulfate, Atropine).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
3. 1 AND 2
THE COCHRANE LIBRARY [via WILEY]
1. Pyloric Stenosis, Hypertrophic/ OR Pyloric Stenosis/ OR Infantile Hypertrophic Pyloris Stenosis / OR ((pyloric*adj2 stenosis) / OR pyloromyotomy).mp.
2. Atropin/ OR Atropinol/ OR Atropine Sulfate OR Sulfate, Atropine
3. 1 AND 2
SCOPUS and ELSEVIER [via SCIENCE DIRECT]
1. exp Pylorus Stenosis/ OR ((pyloric*adj2 stenosis)/ OR MeSH terms OR pyloromyotomy*).mp.
2. Atropine OR MeSH terms
3. 1 AND 2

List of MeSH terms

Pyloric Stenosis

- Stenosis, Hypertrophic Pyloric
- Hypertrophic Pyloric Stenosis
- Infantile Hypertrophic Pyloric Stenosis
- Idiopathic Hypertrophic Pyloric Stenosis
- Primary Hypertrophic Pyloric Stenosis

Atropine

- Atropinol
- Atropine Sulfate
- Sulfate, Atropine

Supplementary Table S2. Risk of bias for studies in both meta-analysis A and B, based off the Cochrane bias assessment tool

Study	Bias	Judgment (High/Low)	Support for Judgment
Yamataka et al. (2000)	Adequate sequence generation (allocation bias, selection bias)	High	"Consecutive series of cases of IHPS treated either surgically (pyloromyotomy, n = 20) or medically (atropine, n = 14) at separate institutions […] between 1996 and 1998 were compared retrospectively..." Two different institutions.
	Allocation concealment (selection bias)	High	"Pyloromyotomy: Department of Pediatric Surgery, Juntendo University School of Medicine [Juntendo]; atropine: Department of Pediatrics, Tokyo Women's Medical University School of Medicine Daini Hospital [Daini Hospital]." The participants were non-randomized, one treatment per institution.
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy.
	Blinding of outcome assessors (detection bias)	Low	Outcomes: success rate, time to full enteral feeding, length of hospital stay (time taken to return to full feeding without vomiting), post-treatment complications, recurrences and costs While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	There does not appear to be any missing data.
	Incomplete outcome data (long term) (attrition bias)	Low	Outcome: recurrence "After discharge, ultrasonography (US) was performed monthly to observe changes in pyloric muscle thickness in both the atropine and pyloromyotomy groups."
	Selective outcome reporting (reporting bias)	Unclear	This was a retrospective study.
	Other sources of bias	High	There is a small number of patients (>50) enrolled and data is obtained from two separate institutions.
Kawahara et al. (2005)	Adequate sequence generation (allocation bias, selection bias)	High	"Since the introduction of intravenous atropine therapy in 1996, 87 patients with IHPS were treated at the Osaka Medical Center and Research Institute for Maternal and Child Health during the last 9 years." This was a retrospective study from the period of 1996-2004.
	Allocation concealment (selection bias)	High	"The method of treatment of IHPS, medical or surgical, was determined according to the informed choice of the patients' guardians after ample explanation of each treatment."

			The participants were non-randomized.
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy.
	Blinding of outcome assessors (detection bias)	Low	Outcomes: success rate, length of hospital stay, complications, weight gain and recurrence While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	There does not appear to be any missing data.
	Incomplete outcome data (long term) (attrition bias)	Low	Outcomes: weight gain and recurrence “The guardians of patients who were treated with atropine therapy or surgery were asked for permission to review the patient at the age of 1 year.”
	Selective outcome reporting (reporting bias)	Low	They appear to report on a priori of defined short-term outcome measures.
	Other sources of bias	Low	Adequate sample size was reached (n=87).
Meissner et al. (2006)	Adequate sequence generation (allocation bias, selection bias)	High	"Forty-two full-term infants, diagnosed with HPS, were consecutively enrolled in the study in the Pediatric Department of Heidelberg University, Germany, between 1996 and 2000." This was a retrospective study.
	Allocation concealment (selection bias)	High	"Parents were offered the choice between standard surgery or conservative therapy."; "In cases of a serious adverse event, withdrawal of consent, or in a case that there was no improvement after 7 days, intravenous treatment was stopped and the child was scheduled for pyloromyotomy the same day". The participants were non-randomized.
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy.
	Blinding of outcome assessors (detection bias)	Low	Outcomes: success rate (%), duration of i.v. atropine therapy (days), average stay in hospital, maximum dosage of i.v. atropine [mg/(kg day)], relapse and complications While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	There does not appear to be any missing data.
	Incomplete outcome data (long term) (attrition bias)	Low	Outcome: recurrence "If vomiting ceased or several fluid passages through the pyloric muscle were observed by ultrasound (7.5 MH), together with clinical improvement, infants received oral atropine sulfate at twice the last and

			effective intravenous dose up to an age of 10 weeks. Thereafter, atropine therapy was stopped and the children were followed for another 10 weeks".
	Selective outcome reporting (reporting bias)	Unclear	This was a retrospective study.
	Other sources of bias	High	There is a small number of patients (>50) enrolled.
Almaramhy et al. (2013)	Adequate sequence generation (allocation bias, selection bias)	High	A prospective study was conducted in the Pediatric Surgery Department during the period January 2008 to June 2011. Thirty-two consecutive infants (29 boys and 3 girls) in whom infantile hypertrophic pyloric stenosis was diagnosed after presentation at the emergency department fulfilled the following diagnostic criteria: a classical history of pyloric stenosis (frequent non-bilious projectile vomiting), pyloric muscle thickness >=4 mm and pyloric canal length >= 15 mm on ultrasonography.”
	Allocation concealment (selection bias)	High	Four cases were excluded from randomization (parents specifically chose medical treatment and one had a complication for surgery, opting for atropine therapy. The remaining 28 infants were randomly assigned to medical or surgical treatment.
	Blinding of participants and personnel (performance bias)	Low	Surgeons cannot be blinded to atropine or pyloromyotomy, however the patients were randomized to medical or surgical treatment by the sealed envelope method.
	Blinding of outcome assessors (detection bias)	Low	Outcomes: success rate, incidence of complications and length of hospital stay between the two groups “Response to either surgical or medical treatment was assessed clinically on the basis of cessation of vomiting, tolerating oral intake and gaining weight, and radiologically by ultrasonographic measurements of pyloric muscle thickness and pyloric canal length.”
	Incomplete outcome data (short term) (attrition bias)	Low	There does not appear to be any missing data.
	Incomplete outcome data (long term) (attrition bias)	Low	Outcomes: weight gain and recurrence “All infants were followed for 1 year to evaluate vomiting, weight gain and recurrence of symptoms.”
	Selective outcome reporting (reporting bias)	Low	They appear to report on a priori of defined short-term outcome measures.
	Other sources of bias	High	There is a small number of patients (>50) enrolled.
	Adequate sequence generation (allocation bias, selection bias)	High	"A total of 76 pediatric patients aged 13–60 days old were clinically diagnosed with IHPS and managed at the National Mie Hospital between January 1998 and December 2011."

Koike et al. (2013)	Allocation concealment (selection bias)	High	"The selection of treatment options for IHPS, medical or surgical, was determined according to the informed choice of the patient's parents after detailed explanation of each treatment, including the pros and cons of each. Informed consent was also obtained after verbal and written information had been given to parents of all pediatric patients."; "In the case of worsening clinical symptoms, such as an increasing amount of PV after IA therapy, parents were able to withdraw from this conservative therapy at any point." The participants were non-randomized.
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy.
	Blinding of outcome assessors (detection bias)	Low	Outcomes: success rate, bodyweight gain, hospital stay (days), duration of i.v. atropine (days), pyloric thickness, Hb (g/dL), BUN (mg/dL), creatinine (mg/dL), serum sodium (mEq/L) serum chloride (mEq/L), serum potassium (mEq/L), urine sodium (mEq/L) and urine chloride (mEq/L). While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	There does not appear to be any missing data.
	Incomplete outcome data (long term) (attrition bias)	Unclear	No long-term outcome data reported.
	Selective outcome reporting (reporting bias)	Low	They appear to report on a priori defined outcomes.
	Other sources of bias	Low	Adequate sample size was reached (n=76).
Lukac et al. (2013)	Adequate sequence generation (allocation bias, selection bias)	High	"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."
	Allocation concealment (selection bias)	High	"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." The participants were non-randomized.
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy.
	Blinding of outcome assessors (detection bias)	Low	Outcomes: success rate, length of hospital stay, complications, weight gain and recurrence

			While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	There does not appear to be any missing data.
	Incomplete outcome data (long term) (attrition bias)	Unclear	No long-term outcome data reported.
	Selective outcome reporting (reporting bias)	Low	They appear to report on a priori defined short-term outcomes.
	Other sources of bias	Low	Adequate sample size was reached (n=66).
Takeuchi et al. (2013)	Adequate sequence generation (allocation bias, selection bias)	High	"We extracted data from the Diagnosis Procedure Combination (DPC) Database. The DPC database is an all-payer inpatient care database in Japan containing administrative claims data. […] Data are collected over a 6 month period (between 1 July and 31 December) each year, and are maintained by a DPC Research Team." Nationwide hospital discharge database analysis.
	Allocation concealment (selection bias)	High	"Each patient was classified into one of three categories based on treatment: group 1, infants treated with i.v. atropine and discharged without requiring surgery; group 2, infants initially treated with i.v. atropine but who subsequently underwent surgery; and group 3, infants treated with surgery as first-line therapy. Patients in group 1 and group 2 were classified as having 'medical management'." The participants were non-randomized.
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy.
	Blinding of outcome assessors (detection bias)	Low	"The database contains a variety of clinical and administrative information, including data on diagnosis and procedure, drugs, devices, length of stay (LOS), complications during hospital stay, discharge status including in-hospital death, and costs. All diagnoses were coded using the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes." While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	"Past and present history, signs and symptoms, and laboratory data for each patient are not included in the DPC database."
	Incomplete outcome data (long term) (attrition bias)	Unclear	No long-term data reported.
	Selective outcome reporting (reporting bias)	Low	All outcomes were contained in a Nationwide hospital discharge database.

	Other sources of bias	Low	“The total number of participant hospitals was 262 in 2006, 926 in 2007, and 855 in 2008.” A wide range of hospitals and large number of patients were identified.
Fan et al. (2016)	Adequate sequence generation (allocation bias, selection bias)	High	“From January 2010 to June 2013, 49 children (41 boys and 8 girls) with IHPS were treated in the Children Hospital of Wuxi.” This was a prospective study.
	Allocation concealment (selection bias)	High	“All the 49 children were with the definite diagnosis of IHPS and were divided into atropine sequential therapy (ST) group (n = 26) and operation group (n = 23) according to the willingness of their guardians.” The participants were non-randomized.
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy
	Blinding of outcome assessors (detection bias)	Low	Outcomes: remission rate of vomiting, complications, hospital stay and medical expenditure While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	There does not appear to be any missing data.
	Incomplete outcome data (long term) (attrition bias)	Low	Outcomes: weight gain and recurrence “All the children were followed up after the treatments, with the mean follow-up time of 6 months.”
	Selective outcome reporting (reporting bias)	Low	They appear to report on a priori of defined short-term outcome measures.
	Other sources of bias	Low	Adequate sample size was reached (n=49).
Elekiabi et al. (2018)	Adequate sequence generation (allocation bias, selection bias)	High	"A. This is a prospective cohort study that was done in Pediatric Surgery department, Faculty of Medicine Zagazig University and department of Radiology Faculty of Medicine Zagazig University. B. Approval was obtained from the IRB committee in Faculty of Medicine Zagazig University, and a written informed consent was obtained from the patients’ guardians. C. We have included 25 infants with clinical and/or radiological evidence of IHPS that were admitted to Pediatric Surgery department, in the period September 2016 to September 2018."
	Allocation concealment (selection bias)	High	“A. All infants have the following diagnostic criteria for IHPS: (a) repeated attacks of projectile vomiting more than 2 times daily (b) Ultrasonic evidence of gastric outlet obstruction, narrow and long pyloric canal; (c) pyloric canal of more than 15 mm in

			length and pyloric muscle more than 4 mm in thickening on ultrasonography. B. Refusal of parents to perform pyloromyotomy and prefer trying medical treatment after informing them with the costs and duration of medical therapy. C. Infants with congenital anomaly for which surgery might be risky to them."
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy.
	Blinding of outcome assessors (detection bias)	Low	Outcomes: days of hospitalization, length of pylorus, pyloric thickness, weight gain While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	There does not appear to be any missing data.
	Incomplete outcome data (long term) (attrition bias)	Low	There does not appear to be any missing data.
	Selective outcome reporting (reporting bias)	Low	They appear to report on a priori defined outcomes.
	Other sources of bias	High	There is a small number of patients (>50) enrolled.
Fujiogi et al. (2019)	Adequate sequence generation (allocation bias, selection bias)	High	"Using the Diagnosis Procedure Combination (DPC) database (inpatient , we identified the pediatric population (0-100 days old) who were admitted with a diagnosis of IHPS between July 2010 and March 2016." Nationwide hospital discharge database analysis.
	Allocation concealment (selection bias)	High	"We excluded patients transferred to other hospital in the main analysis. However, if majority of patients who underwent IAT were transferred to other hospital to receive surgery, the results might be biased. We therefore classified patients transferred to other hospital to the unsuccessful group, and performed another multivariable logistic regression analysis for successful IAT as a sensitivity analysis."
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy.
	Blinding of outcome assessors (detection bias)	Low	Outcomes: bodyweight, success rate, length of hospital stay (LOS) and complications. While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	"We excluded patients whose outcome data were missing (n = 67) and those who were treated with the oral form of atropine for initial treatment (n = 17)."

	Incomplete outcome data (long term) (attrition bias)	Unclear	"Vital signs, current symptoms, and laboratory data for each patient are not included in the DPC database." No long-term outcome data reported.
	Selective outcome reporting (reporting bias)	Low	"A previous study showed that the validity of diagnoses and procedure records in the DPC database was high in general." All outcomes were contained in a Nationwide hospital discharge database.
	Other sources of bias	Low	“All 82 academic hospitals are obliged to participate in this database, but participation by community hospitals is voluntary." A wide range of hospitals and large number of patients were identified.
Ono et al. (2019)	Adequate sequence generation (allocation bias, selection bias)	High	"A total of 56 patients diagnosed with IHPS at Kimitsu Chuo Hospital between April 2002 and March 2016 were retrospectively reviewed."
	Allocation concealment (selection bias)	High	"After the diagnosis of IHPS, the guardians were informed regarding both medical treatment by IA and surgical treatment. If the guardians did not refuse medical treatment, IA therapy was performed as the first-line treatment."; "The present protocol does not have a predetermined treatment duration, but we abandoned IA therapy if projectile vomiting was observed more than three times per day. This protocol probably caused early cessation and a shorter duration of IA therapy in the unsuccessful patients."
	Blinding of participants and personnel (performance bias)	High	Surgeons cannot be blinded to atropine or pyloromyotomy.
	Blinding of outcome assessors (detection bias)	Low	Outcomes: age, sex, birthweight, gestational age, duration of symptoms before admission, clinical conditions on arrival, laboratory data, ultra-sonography, and length of hospital stay While these outcomes cannot be blinded, it is unlikely that they are influenced by bias.
	Incomplete outcome data (short term) (attrition bias)	Low	There does not appear to be any missing data.
	Incomplete outcome data (long term) (attrition bias)	Unclear	No long-term outcome data reported.
	Selective outcome reporting (reporting bias)	Unclear	This was a retrospective study.
	Other sources of bias	Low	Adequate sample size was reached (n=56).

Supplementary Table S3. AMSTAR criteria for the present systematic reviews and meta-analysis assessed by two senior authors

ITEM	NC	JS
1. Was an 'a priori' design provided?	1	1
2. Was there duplicate study selection and data extraction?	1	1
3. Was a comprehensive literature search performed?	1	1
4. Was the status of publication (i.e., gray literature) used as an inclusion criterion?	1	1
5. Was a list of studies (included and excluded) provided?	0	0
6. Were the characteristics of the included studies provided?	1	1
7. Was the scientific quality of the included studies assessed and documented?	1	1
8. Was the quality of the included studies used appropriately in formulating conclusions?	1	1
9. Were the methods used to combine the findings of studies appropriate?	1	1
10. Was the likelihood of publication bias assessed?	1	1
11. Was the conflict of interest included?	1	1
TOTALS	**10/11**	**10/11**

Abbreviation: AMSTAR Assessment of Reporting Quality for Systematic Reviews.

Note: 0, No; 1, Yes.

Supplementary Table S4. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	11
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	T1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	32
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	32, F1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	32
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	32
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	33
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	34
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	34

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	33
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	39, F5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	37-38, T2-4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	39, F6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	35, F7-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	40-41
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	63-70, S3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	43
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	50
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	52
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A