Original Article

Is there any Benefit with Pantoprazole Treatment in Infantile Hypertrophic Pyloric Stenosis?

Natasha Fourie, Marion Arnold[1], Behrouz Banieghbal, Samantha Lynn Marchant[2]

Division of Paediatric Surgery, Tygerberg Hospital, University of Stellenbosch, Stellenbosch, [1]Division of Paediatric Surgery, Red Cross War Memorial Children's Hospital, University of Cape Town, [2]Department of Surgery, Groote Schuur Hospital, Cape Town, South Africa

Abstract

Context: Previous studies demonstrated faster correction of metabolic derangement associated with hypertrophic pyloric stenosis with pre-operative intravenous (IV) histamine-2 receptor antagonists. **Aims:** We investigated if similar outcomes are achieved with IV pantoprazole, a proton-pump inhibitor (PPI), including the subgroup of delayed presenters in the South African setting. **Settings and Design:** A 5-year retrospective record review (January 2014–December 2018) compared the rate of metabolic correction in patients with hypertrophic pyloric stenosis at two tertiary centres. **Subjects and Methods:** One centre routinely administers IV pantoprazole (1 mg/kg daily) preoperatively (PPI group) and the other does not (non-PPI group). Fluid administration, chloride supplementation and post-operative emesis were evaluated. **Statistical Analysis:** Spearman's rank correlation coefficient was used to calculate statistical significance for discrete dependent variables. Continuous variables were compared between the groups using the Student *t*-test. Fisher's exact contingency tables were used to classify categorical data and to assess the significance of outcome between two treatment options. $P < 0.05$ was considered statistically significant. **Results:** Forty-two patients received IV pantoprazole and 24 did not. The mean time of metabolic correction was 8 h shorter in the PPI group ($P = 0.067$). Total pre-operative chloride administration correlated to the rate of metabolic correction in both cohorts ($P < 0.0001$). Profound hypochloraemia (chloride <85 mmol/l) was corrected 23 h faster in the PPI group ($P < 0.004$). Post-operative emesis was noted: 0.45 episodes/patient in the PPI group and 0.75 episodes/patient in the non-PPI group ($P = 0.01$). **Conclusions:** Pre-operative IV pantoprazole administration showed a faster correction of metabolic derangements, and in profound hypochloraemia, the correction occurred substantially faster in the PPI group. Post-operative emesis was significantly less frequent in the PPI group.

Keywords: Hypertrophic pyloric stenosis, pantoprazole, post-operative emesis, serum chloride, shorter resuscitation time

Introduction

Infantile hypertrophic pyloric stenosis (IHPS) is a disorder affecting infants usually between 3 and 8 weeks of age. Pyloric channel muscle becomes abnormally thickened causing progressive vomiting due to gastric outlet obstruction. Loss of hydrochloric acid (HCl) leads to dehydration and metabolic alkalosis with hypochloraemia and hypokalaemia. Appropriate fluid resuscitation with intravenous (IV) 0.45% saline is required before corrective surgery.[1,2]

Compensatory mechanisms to normalise the pH include hypoventilation, renal bicarbonate excretion and hydrogen ion retention with compensatory excretion of potassium.[3-7] In rare cases of delayed presentation, sodium is preferentially reabsorbed to hydrogen ion reabsorption due to renin–angiotensin–aldosterone system, worsening hypokalaemia and increased bicarbonate reabsorption maintaining the alkalosis. Prolonged vomiting leads to sodium reabsorption in exchange for hydrogen ions, producing paradoxical aciduria.[8] The quantity of bicarbonate that can be reabsorbed is limited by hypochloraemia. Consequently, chloride administration can reverse the pattern of electrolyte abnormalities and metabolic alkalosis associated with loss of gastric content.[3-6,9] The amount was calculated to be

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Address for correspondence: Dr. Natasha Fourie, University of Stellenbosch, Tygerberg Campus, Francie Van Zyl Drive, Tygerberg, 7505, Cape Town, South Africa.
E-mail: natashfourie@gmail.com

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10 mmol/kg of chloride required for every 3 mmol/L reduction in plasma bicarbonate in neonates and infants.[10]

Suppression of HCl production by IV proton-pump inhibitors (PPIs) may result in faster improvement of alkalosis by reducing loss of hydrogen ion and chloride loss and hence earlier correction.[11,12] One study investigated the rapid correction of pH with IV cimetidine (a histamine-2 receptor antagonist) in infants with HPS, whereas another author demonstrated the same with ranitidine.[13,14]

Cimetidine is no longer available in this country, therefore, we investigated whether IV PPI had the same effect of correcting pH and electrolytes as cimetidine. This detailed study investigates pH correction in infantile HPS with IV pantoprazole therapy including a subgroup of delayed presenters often seen in the African setting.

Subjects and Methods

This retrospective observational cohort study reviewed all cases with IHPS at two tertiary paediatric surgical referral centres in Cape Town, South Africa, for the period January 2014–December 2018. This study was approved by local human ethics committees from both centres (Centre A HREC study number: #N19/01/006 and Centre B HREC study number: 059/2019).

Centre A routinely administers IV pantoprazole 1 mg/kg/day to all infants with HPS (PPI group), whereas Centre B does not (non-PPI group).

Acid-base status was measured by arterial blood gas and baseline serum electrolytes and urea were checked on admission. Fluid resuscitation was started with 5% dextrose in 0.45% sodium chloride. Potassium chloride was added to resuscitation fluid, appropriately adjusted to serum potassium results.

Serum electrolytes and arterial blood gas were repeated every 6–12 h, and surgery was only carried out when metabolic derangements were within acceptable range, i.e., pH below 7.5, serum bicarbonate <28 mmol/L, chloride level more than 95 mmol/l and a normal serum potassium.

Patients who had interruption of IV fluid administration for more than 8 h or incomplete data were excluded.

The primary outcome was time to surgery in both the groups, and the secondary outcomes were incidents of post-operative vomiting, rate of fluid resuscitation received and chloride administered preoperatively (mmol/kg). The groups were compared for heterogeneity with respect to patient age, gestation at birth, duration of pre-admission vomiting, rate and volume of IV fluid received from admission to pre-surgical correction of metabolic parameters, total potassium administration, time to surgery, time to tolerance of full feeds post-surgery and intra- and post-operative complications.

Spearman's rank correlation coefficient was used to calculate statistical significance for discrete dependent variables. Continuous variables were compared between the groups using the Student t-test. Fisher's exact contingency tables were used to classify categorical data and to assess the significance of outcome between two treatment options. $P < 0.05$ was considered statistically significant.

Results

A total of 47 patients were operated on for IHPS in Centre A, of which 5 cases were excluded due to overnight interruption of IV fluid therapy (PPI group). Twenty-five cases were operated on at Centre B and did not receive PPI and one was excluded due to incomplete records (non-PPI group).

Gender ratios were similar between the two groups: 36 male and 6 female infants in the PPI group and 20 male and 4 female infants in the non-PPI group. There was a delay from onset of vomiting to hospital admission by more than 8 days in 17 cases (41%) in the PPI group and 8 cases (38%) in the non-PPI group. This difference did not reach statistical significance ($P = 0.38$).

The rate of fluid administration was equivalent between the groups. The volume of fluid administered preoperatively was a mean of 6.6 ml/kg/h in the PPI group (range, 4.6–10.4 ml/kg/h) and a mean of 6.3 ml/kg/h in the non-PPI group (range, 3.1–11.9 ml/kg/h). This value was insignificant at statistical analysis ($P = 0.24$).

Total pre-operative chloride administration was assessed between the two groups. There was a range of chloride administered according to the admitting physician's preference and tailored according to laboratory results. The total mmol/kg/day of chloride administered preoperatively was a mean of 60.4 mmol/kg/day in the PPI group and a mean of 78.2 mmol/kg/day in the non-PPI group. There was no significant difference between these two means of chloride administration ($P = 0.15$). However, total chloride administered was positively correlated with reduced time to pH correction [Figures 1 and 2].

Time to correction of pH was 8 h and 20 min faster in the PPI group, however, this was not statistically significant either ($P = 0.067$).

Thirteen cases of delayed presentation were recorded with a profound hypochloraemia (chloride <85 mmol/L) (31%) in the PPI group compared to five (21%) in the non-PPI group; in this subgroup, correction occurred 23 h faster in the PPI group ($P = 0.004$).

Admission arterial blood pH was severely alkalotic (pH >7.65) in 19/42 (45%) in the PPI group and in 9/24 (38%) in the non-PPI group. Correction occurred 10 h faster in the PPI group ($P = 0.16$).

Post-operative vomiting occurred in 19/42 (45.2%) patients in the PPI group (0.45 episodes/patient) and in 18/24 (75%) patients in the non-PPI group (0.75 episode/patient). This represents a 30% reduction in post-operative vomiting in the PPI group compared to the non-PPI group ($P = 0.01$).

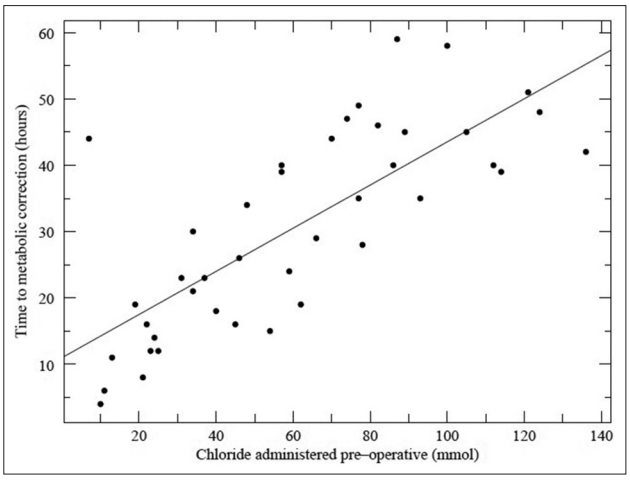

Figure 1: Proton-pump inhibitor group: Chloride administered pre-operative (mmol/kg) versus time to metabolic correction

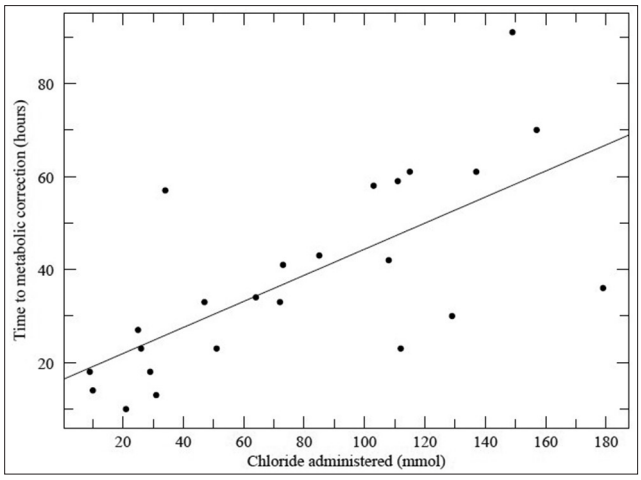

Figure 2: Non-proton-pump inhibitor group: Chloride administered pre-operative (mmol/kg) versus time to metabolic correction

In both the groups, similar feeds were administered before and after hospital admission. The PPI group was breastfed in 23/42 (55%), received formula feeds in 15/42 (36%) and mixed feeds in 4/42 (10%). The non-PPI group received breastfeeds in 13/24 (54%), formula feeds in 9/24 (38%) and mixed feeds in 2/24 (8%). *P* value was insignificant between these groups.

The mean duration of post-surgical hospital stay in the PPI group was 2.9 days (range, 1–7 days) and 2.4 days (range, 1–7 days) in the non-PPI group ($P = 0.93$). Non-medical delay in discharge occurred due to lack of immediately available transport in seven patients in the PPI group and three in the non-PPI group.

There were two minor surgical complications recorded: one wound dehiscence in the PPI group and one wound infection in the non-PPI group.

Discussion

The incidence of IHPS in Southern Africa is much lower than that in Western Europe and North America.[13,15-17] Since patients with IHPS are not frequently seen by healthcare workers, thus causing a low index of suspicion leading to delayed diagnosis, additional delays occur due to socioeconomic factors due to lack of secondary level care, large distances between medical centres and the absence of reliable transport. For example, Italy which has the same population as South Africa but has four times the smaller surface area of land has twice as many hospitals.[18] Furthermore, 80% of population have private transport compared to 33% in South Africa.[19] This results in admission of infants who at times present with substantial dehydration and severe metabolic alkalosis, unlike those seen in European countries.

Correction of the electrolyte abnormalities in this subgroup of patients can take up to 10 days with appropriate fluid resuscitation, before corrective surgery.[1,2,16,17] Compensatory mechanisms to normalise the pH include hypoventilation, renal bicarbonate excretion and hydrogen ion retention with compensatory excretion of potassium.[3-7] The quantity of bicarbonate that can be reabsorbed is limited by hypochloraemia. Consequently, chloride administration can reverse the pattern of electrolyte abnormalities and metabolic alkalosis associated with loss of gastric content.[3-7,9] The calculation of chloride dose to reduce plasma bicarbonate on average by 3 mmol/L equals 10 mmol/kg body weight in neonates and infants.[10]

Metabolic alkalosis in IHPS is caused by excessive loss of HCl, therefore, its reduced production may result in its correction. The pharmacologic effect of PPI relies on cyclic adenosine monophosphate-driven H, K-ATPase translocation from the cytoplasm to the canalicular membrane of the parietal cell.[20] This hypothesis was based on a previous study that investigated the rapid correction of pH with IV cimetidine in HPS in infants.[13] IV PPI therapy has superseded histamine-2 antagonist in acute treatment of gastric acid hypersecretion due to its better clinical side effect profile and ease of once-daily administration, with comparable rapid onset of action for IV formulations.[12,21,22]

In the current study, administration of chloride (in mmol/kg/h) during pre-operative resuscitation correlated closely with correction of pH, in keeping with previous research.[10] We also showed that chloride correction can be achieved much faster with PPI in severe cases but were unable to demonstrate the same with pH improvement. However, in a previous study by the senior author, the pH corrected 16 h faster when cimetidine was used.[13] This may be due to the shorter half-life of daily PPI dosage (2-h half-life) compared to 8-h cimetidine administration (8-h half-life).[22]

The observed difference in rapid improvement in chloride level may also be due to its single source of maintenance by the renal system, whereas hydrogen ion has two regulatory components (respiratory and renal).

It is relevant to note the safety of PPIs for long-term management of peptic ulcer and reflux oesophagitis for decades. They are also often used for gastro-oesophageal reflux

in infants, and over 50% of infants in the USA received it as treatment for reflux.[23]

Post-operative emesis was significantly less in the PPI group. Oesophagitis caused by prolonged vomiting is possibly resolved by PPI, which was demonstrated by a previous study to be a significant factor in post-operative vomiting in infants with IHPS.[24] This reduction in post-operative vomiting in the PPI group did not correlate to a decrease in duration of hospital stay in the PPI group. This could possibly be due to differences in feeding policies and discharge procedures between Centre A and Centre B, which were not evaluated as part of the study. Post-operative stay was affected by non-clinical factors such as availability of transport and thus cannot specifically be compared between the two groups.

Limitations and confounding factors in the study include:

1. A small sample size due to lower incidence of IHPS in Africa[13,15]
2. Higher number of male infants in the PPI group who are known to increase their pH less in response to pantoprazole in comparison to females[24]
3. Discharge time was unfavourably affected in both the groups due to lack of transport. The patients in both the groups were in the lower socioeconomics of the population group, as they could not afford private transport
4. Retrospective nature of the study does not allow the establishment of a causal effect due to confounders.

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Conflicts of interest

There are no conflicts of interest.

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