Original Research Paper

Volume - 10 | Issue - 12 | December - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Surgery

COMBINATION OF ITOPRIDE AND ERYTHROMYCIN FOR TREATMENT OF GASTROPARESIS - LONG TERM FOLLOW UP

Jayesh Kalbhande*	Consultant Surgeon, BARC Hospital, Anushakti Nagar, Trombay, Mumbai. *Corresponding Author
Vicky Kuldeep	PGRMO Surgery, DNB General Surgery, BARC Hospital, Anushakti Nagar, Trombay, Mumbai.
Dr Hozefa Bohra	General Surgery Resident, BARC Hospital, Anushakti Nagar, Trombay, Mumbai.
Dr Sneha Sriram	General Surgery Resident, BARC hospital, Anushakti Nagar, Trombay, Mumbai.

ABSTRACT Gastroparesis is a chronic condition and requires long term treatment. Diabetes and idiopathic cause are one of the commonest causes of gastroparesis. Gastroparesis may present with predominant symptoms of pain which is more common in idiopathic gastroparesis or predominant symptoms of vomiting which is more common in diabetic gastroparesis. Gastroparesis requires long term medical management. Gastroparesis symptoms may remain static or may progress with time. In few cases of gastroparesis, not responding to medical treatment, surgical intervention may be required. We present a case of Gastroparesis which did not respond to individual motility agent when used separately. However, there was near complete symptomatic improvement when the motility agents were combined for the treatment. The symptomatic improvement remain constant over a period of 6 years.

KEYWORDS : Refractory Gastroparesis, Treatment Of Gastroparesis

INTRODUCTION

Gastroparesis results in decreased contractility of gastric muscles leading to decreased gastric emptying. It may result in pain in abdomen, vomiting and weight loss. It is a chronic condition and requires regular monitoring and long-term treatment. In severe Gastroparesis not responding to medical management, Gastric electrical stimulation devise or surgical treatment in form of gastrectomy, Gastric peroral endoscopic myotomy may be required. In this article we describe long term follow up of a case of intractable Gastroparesis treated with combination of itopride and erythromycin.

CASE REPORT

45 years old female patient, non-diabetic and non-hypertensive, presented with severe epigastric pain, more after eating food since 4 yrs. She complained of distention of abdomen after eating food. She had nausea and decreased appetite secondary to pain in epigastric region. She did not give history of vomiting or constipation. Her stool for occult blood test was found to be negative on multiple occasions. She had significant weight loss of 8 kg over a period of 1 year. Her weight was reduced to 52 kg from 60 kg because of significantly decreased appetite secondary to severe pain in abdomen associated with food intake. She was investigated by Oesophago gastro duodenoscopy which showed, mild antral gastritis. Her rapid urease test for Helicobacter pylori was negative. Her Colonoscopy with Ileoscopy showed normal finding.

Her blood investigation was reported as, Hb 11.5 mg/dl, WBC count 4,600 /cmm, Platelet count 2,40,000/cmm. Her liver function test showed normal finding with Total bilirubin 0.3 mg/dl, Direct bilirubin 0.1 mg/dl, SGOT 25 U/ml, SGPT 19 U/ml. Her serum electrolyte was S. Sodium was 136 meq/L, S. Potassium was 3.6 meq/L, Serum Chloride was 106 meq/L. Total albumin was 6.5 gm% and Total albumin was 4.1 gm%. Serum creatinine was 0.6 mg/dl. Her fasting blood sugar was 100 mg/dl and post lunch blood sugar were 124 mg/dl. Acid peptic disease was considered as one of differential diagnosis for which she was given Proton pump inhibitor. She did not respond to treatment with proton pump inhibitor. She was then added prokinetic medication T. Itopride 50 mg TDS. However, she continued remain symptomatic. After Itopride failed to improve her symptoms it was stopped and she was given Erythromycin 250 mg three times a day. Once again, she continued to remain severely symptomatic. Then she was given combination of itopride and Domperidone however it failed to improve her symptoms.

In view of persistent symptoms, she was further investigated. S. Vit D3 was normal 37.21 (7.6 – 75 ng/ml). S. Vit B 12 was normal – 613.53 (normal 200 – 900 pg/ml), Her CT Chest abdomen and pelvis showed normal finding, CT angiography was done to rule out Coeliac artery stenosis – It revealed no abnormality. Capsule endoscopy showed normal Small Bowel study. Her ECG, 2 D echo and stress test also showed normal finding. FDG PET CT was done, It showed low grade metabolic activity in both lobes of thyroid gland suggestive of thyroiditis, however her S. T3, T4 and TSH values were normal (TSH 1.99 Micro IU/ml). Her S. Chromogranin A was 2030 (Normal was below 100 ng / ml), it was found to be raised. However, Urinary 5 HIAA level was normal - 5.81 mg / 24 hrs. (Normal 2 – 9)

Her Technetium 99m Hynic TOC scan was done in view of raised S. Chromogranin A level, to rule out neuroendocrine tumor. It showed that there was no evidence of somatostatin expressing lesion. Her raised S. Chromogranin A level was attributed to use of proton pump inhibitor. Her Gastric Emptying scintigraphy was done. Static views were acquired at 30, 60, 90, 120 and 180 minutes after consumption of standard radiolabeled solid meal. It showed Gastric emptying time of 453.36 min (Normal = 60 – 110 min), Significant retention of tracer was seen in stomach with Delayed Gastric emptying time noted. Based these finding she was diagnosed as having Gastroparesis not responding to medication. She was severely symptomatic in spite of treatment with multiple motility agents.

As a last resort, she was started on treatment with combination of multiple motility agents. Itopride 50 mg three times a day, Domperidone 10 mg three times a day and erythromycin 250 mg 4 times a day. After starting this combination, her symptoms improved dramatically. Pain in abdomen disappeared and her appetite also improved significantly. Her Gastric motility agents were tapered from combination of itopride, Domperidone and erythromycin to only Itopride and erythromycin. Dose of erythromycin was reduced to 250 mg TDS from 250 mg QDS. She remained asymptomatic after reduction of medication. She had weight gain of 6 kg over 8 months. Gastric Emptying study repeated after 1 year of completion of treatment showed gastric emptying time of 112 min which suggestive of normal gastric emptying.

Her combination therapy of itopride 50 mg TDS and erythromycin 250 mg TDS was continued. Any attempt to reduce the medication further resulted in return of symptoms of Gastroparesis. Therefore, combination of itopride and erythromycin was continued. Today 7 years after diagnosis of her condition of Gastroparesis, she continues to be on combination of erythromycin and itopride. With these medications she continues to remain asymptomatic. She has good appetite and she has maintained weight of 60 kg.

Her blood test was done regularly to check for development of hepatotoxicity due to long term use of erythromycin. Her liver function test done on multiple occasions showed normal values. She has been

evaluated regularly by doing ECG to check for QT interval prolongation. Her ECG done on multiple occasions was found to be normal. She developed type II diabetes mellitus since last 2 years and she was started on medication for same.

DISCUSSION

Gastroparesis is a condition in which there is decreased contractility of gastric muscles which result in decreased gastric emptying without any evidence of gastric outlet obstruction. It is usually associated with symptoms of abdominal fullness after eating food, nausea, vomiting, decreased appetite and pain in abdomen after eating food.(1)

There are many causes of gastroparesis. Diabetes is one of the most common cause for gastroparesis.(2)(3) Other causes include viral infections, hypothyroidism, autoimmune conditions, neuromuscular diseases, post radiotherapy gastroparesis, surgery of the upper gastrointestinal tract and others. Idiopathic gastroparesis is also one of the most common cause of gastroparesis. It is a type of gastroparesis in which the etiology of gastroparesis is not found.(3)(4)(5) Abdominal pain is more common symptom in a case of Idiopathic Gastroparesis. Abdominal fullness associated with pain was found more commonly in idiopathic gastroparesis whereas nausea associated with retching and vomiting was more common in diabetic gastroparesis. (6)(7) Our patient had predominant symptoms of severe abdominal pain after eating food. She did not have history of vomiting. This description is fitting into diagnosis of idiopathic gastroparesis. At the time of diagnosis, no etiological factor for gastroparesis was found in her, therefore she was labelled as idiopathic gastroparesis.

Erythromycin acts on motilin receptor which results in increased contractility of gastric muscles.(8) It has been found that erythromycin used in oral as well as intravenous form results in increased gastric motility.(9) Erythromycin was found to be useful in treatment of idiopathic Gastroparesis as well as diabetic Gastroparesis.(10)

Itopride is a prokinetic agent which improves gastric motility by its action of antagonizing dopamine D2 receptor and inhibiting acetyl choline esterase.(11) Itopride has been studied for treatment of Diabetic gastroparesis and there was significant symptomatic improvement after use of Itopride.(12)(13)(14) Itopride showed improved symptoms and improved quality of life in patients with gastroparesis. It also showed improvement in glycemic indices of diabetic patients in a small study.(15) Domperidone act peripherally by selectively antagonizing dopamine D2 and D3 receptors, which results in increased contractility of muscles of stomach.(16) Domperidone has been found to be useful in symptomatic improvement in patients with diabetic gastroparesis.(17)

Our patient was having refractory Gastroparesis, which was not responding to use of single motility agent. Itopride, erythromycin when used separately did not result in symptomatic improvement. When she was started on a combination of itopride, Domperidone and erythromycin there was significant symptomatic improvement. Her medications were later on tapered to combination of itopride and erythromycin. She responded well to this combination regimen and has remained asymptomatic for last 6 years after starting the treatment.

Hepatotoxicity, in the form of a mixed hepatic injury with predominant cholestasis, has been reported with the use of erythromycin stearate and erythromycin ethyl succinate, but the highest incidence of hepatotoxicity appears to be associated with erythromycin estolate.(18) Our patients liver function test were monitored over a period of last 7 years and all liver function test were within normal limit. It has been reported that erythromycin is associated with prolonged QT interval.(19) Our patient's ECG was monitored over a period of 7 years and it has been found to have normal QT interval. It has also been reported that prolonged QT interval is seen more commonly if erythromycin is used in form of antibiotic when it is used in large dose. Gastroparesis usually requires smaller dose of erythromycin and it has not been associated with hepatotoxicity.(20) In our case prolongation of QT interval was not observed in spite of long term use, this may be because of low dose of erythromycin used.

CONCLUSION

Use of combination of itopride and erythromycin is useful in treatment of refractory Gastroparesis. However, Complications associated with long term use of erythromycin and its drug to drug interaction need to be monitored. More long-term studies are needed on this subject.

REFERENCES

1. Camilleri M, Bharucha AE, Farrugia G. Epidemiology, mechanisms, and management of diabetic gastroparesis. Clin Gastroenterol Hepatol. 2011;9(1):5–12.
2. Koch KL. Diabetic gastropathy (gastric neuromuscular dysfunction in diabetes mellitus a review of symptoms, pathophysiology, and treatment). Dig Dis Sci. 1999;44(6):1061–75.
3. Soykan I, Sivri B, Sarosiek I, Kiernan B, Mccallum RW. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. Dig Dis Sci. 1998;43(11):2398–404.
4. Parkman HP, Yates K, Hasler WL, Nguyen L, Pasricha PJ, Snape WJ, et al. Similarities and differences between diabetic and idiopathic gastroparesis. Clin Gastroenterol Hepatol. 2011;9(12):1056–64.
5. Parkman HP, Yates K, Hasler WL, Nguyen L, Pasricha PJ, Snape WJ, et al. Clinical features of idiopathic gastroparesis vary with sex, body mass, symptom onset, delay in gastric emptying, and gastroparesis severity. Gastroenterology. 2011;140(1):101–15.
6. Cherian D, Parkman HP. Nausea and vomiting in diabetic and idiopathic gastroparesis. Neurogastroenterol Motil. 2012;24(3):217-e103.
7. Cherian D, Sachdeva P, Fisher RS, Parkman HP. Abdominal pain is a frequent symptom of gastroparesis. Clin Gastroenterol Hepatol. 2010;8(8):676–81.
8. Feighner SD, Tan CP, McKee KK, Palyha OC, Hreniuk DL, Pong S-S, et al. Receptor for motilin identified in the human gastrointestinal system. Science (80-). 1999;284(5423):2184–8.
9. Janssens J, Peeters TL, Vantrappen G, Tack J, Urbain JL, De Roo M, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin: preliminary studies. N Engl J Med. 1990;322(15):1028–31.
10. Richards RD, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. Am J Gastroenterol. 1993;88(2).
11. Rai Ramesh R BTK. N. Int J Curr Med Pharm Res. vol 3(issue 10):2549–58.
12. Venkatesh V, Kulkarni KP. Itopride and pantoprazole outcomes in diabetic gastroparesis trial (IPOD trial). J Indian Med Assoc. 2008;106(12):814–5.
13. Kostitska I. Efficacy of Itopride in Treatment of Gastroparesis Considering the State of Carbohydrate Metabolism in Patients with Type 2 Diabetes Mellitus. Lviv clinical bulletin. 4. 28-33. 10.25040/lkv2015.04.028. 2015.
14. Basque, Jean-Rene Ph.D.; Kikuchi, Y.; Ohtsubo, T.; Sarashina, G.; Nakamura H. Efficacy of Itopride Hydrochloride on Gastric Emptying in Patients with Diabetic Gastroparesis. In: Supplement Abstracts Submitted for the 70th Annual Scientific Meeting of the American College of Gastroenterology: FUNCTIONAL BOWEL DISORDERS 885.
15. Rai RR, Choubal CC, Agarwal M, Khaliq AM, Farishta FJ, Harwani YP, et al. A prospective multicentric postmarketing observational study to characterize the patient population with reduced gastrointestinal motility among indian diabetic patients receiving itopride: The progress study. Int J Appl Basic Med Res. 2019;9(3):148.
16. Takahashi T, Kurosawa S, Wiley JW, Owyang C. Mechanism for the gastrokinetic action of domperidone: in vitro studies in guinea pigs. Gastroenterology. 1991;101(3):703–10.
17. Farup CE, Leidy NK, Murray M, Williams GR, Helbers L, Quigley EMM. Effect of domperidone on the health-related quality of life of patients with symptoms of diabetic gastroparesis. Diabetes Care. 1998;21(10):1699–706.
18. Westphal JF, Vetter D, Brogard JM. Hepatic side-effects of antibiotics. J Antimicrob Chemother. 1994;33(3):387–401.
19. Brandriss MW, Richardson WS, Barold SS. Erythromycin-induced QT prolongation and polymorphic ventricular tachycardia (torsades de pointes): case report and review. Clin Infect Dis. 1994;18(6):995–8.
20. Curry JI, Lander TD, Stringer MD. Erythromycin as a prokinetic agent in infants and children. Aliment Pharmacol Ther. 2001;15(5):595–603.