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ROLE AND EFFICACY OF CHRONIC INTERMITTENT INTRAVENOUS INSULIN INFUSION THERAPY IN PATIENTS WITH DIABETIC GASTROPARESIS

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ABSTRACT
Diabetic gastroparesis is characterised by a delay in gastric emptying after a meal in the absence of a mechanical gastric outlet obstruction. Chronic intermittent intravenous insulin therapy (CIIIT) involves delivering insulin intravenously in an infusion over a 6-12 hour period in a pulsatile fashion adjusting the dosages based on frequent blood sugar monitoring. The aim of the study was to evaluate the efficacy of CIIIT in patients of diabetic gastroparesis. Fifty euglycemic cases of diabetes mellitus having signs and/or symptoms of diabetic gastroparesis not relieved with conventional pharmacotherapy were considered for the study. CIIIT was given and the symptoms were compared at the commencement of the study, after 6 sessions of CIIIT (i.e. after 3 months) and finally after 6 months by asking the patient to grade their symptoms on the Visual Analogue Scale (VAS) on each visit. At the conclusion of our study, we found that patients who were previously refractory to conventional pharmacotherapy, showed considerable response to CIIIT with most patients giving history of improvement in their symptoms after therapy and during follow up. The VAS scores showed significant decline in all symptoms and HbA1c levels also remained in the euglycemic range throughout. Therefore, it is recommended that patients presenting with complaints of diabetic gastroparesis should be managed by CIIIT rather than the conventional pharmacological therapies.

Keywords: CIIIT, Diabetes Mellitus, Gastroparesis

INTRODUCTION
Diabetes mellitus is the most common endocrine disease worldwide. It is a syndrome characterised by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiencies in insulin secretion and/or insulin action. Its long term complications lead to significant morbidity and mortality. Gastroparesis is one such complication and is a disorder characterised by a delay in gastric emptying after a meal in the absence of a mechanical gastric outlet obstruction (Parkman *et al.,* 2004). It typically occurs in association with other diseases, is more common in females and causes considerable impact on the quality of life (Soykan *et al.,* 1998; Revicki *et al.,* 2004; Farup *et al.,* 1998). Diabetes mellitus is the most common systemic disease associated with gastroparesis, and symptoms suggestive of gastroparesis occur in 5-12% of the patients with diabetes, the cardinal ones being nausea and vomiting (Holloway *et al.,* 1985). Patients with diabetes presenting with gastroparesis often have had diabetes for at least 10 years. Gastroesophageal scintiscanning at 15 min intervals for 4 hours after food intake is considered as the gold standard for measuring gastric emptying. Retention of more than 10% of the meal after 4 hours is considered an abnormal result, for which management is required (Holloway *et al.,* 1985).
Improved metabolic control is beneficial not only for the prevention but has also been seen to improve the symptomatology in patients with diabetic gastroparesis (Soykan *et al.,* 1998). Multi dose insulin (MDI) injections provide flexibility in adjustment of insulin dose and injection timing according to meals. However, in patients with gastroparesis, a mismatch between insulin action and glucose absorption can still result in wide fluctuations in glucose levels despite MDI use. Although, the rate of gastric emptying does not affect the insulin secretion directly, it does regulate the delivery of carbohydrates and other macronutrients to the small intestine. This significantly impacts both, the timing and magnitude of blood glucose excursion and intestinal incretin peptide secretion, thereby modulating insulin release indirectly.

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The effects of gastric emptying on both the peak and initial rise in blood glucose are direct. As a result, the insulin requirement to sustain normoglycemia after a standard meal is substantially lower in diabetes patients with rather than without gastroparesis.

Chronic intermittent intravenous insulin therapy (CIIIT), also referred to as Pulsatile IV Insulin Therapy (PIVIT) involves delivering insulin intravenously in an infusion over a 6 to 12 hour period in a pulsatile fashion adjusting the dosages based on frequent blood glucose monitoring. The pulses are designed to deliver a higher, more physiologic concentration of insulin to the liver than is delivered by traditional subcutaneous injections. This higher level of insulin is thought to mimic the body's natural levels of insulin and delivery to the latter more closely. It is hoped that this therapy ultimately results in improved glucose control through improved hepatic activation (American Diabetes Association, 2006).

CIIIT is typically delivered once weekly as outpatient therapy. It is designed principally to normalize the hepatic metabolism of glucose and although the exact physiologic mechanism is unclear, Aoki *et al.,* (2001), one of the principal investigators of the technique, proposes that in diabetic patients, lower level of insulin in the portal vein are associated with a decreased concentration of the liver enzymes required for hepatic metabolism of glucose. Once weekly, 6 to 12 hourly intravenous pulsatile infusions of insulin are designed to increase the portal vein concentrations of insulin, ultimately stimulating the synthesis of glucokinase and other insulin-dependent enzymes.

Aims and Objectives
The aim of the study was to evaluate the efficacy of CIIIT in patients of diabetic gastroparesis.

MATERIALS AND METHODS
Fifty cases of diabetes mellitus with different duration of diabetes, drawn from the diabetic clinic, OPD and indoors of the Post Graduate Department of Medicine, S.N. Medical College, Agra constituted the material for the present study. Cases having the signs and/or symptoms of diabetic gastropathy like belching, nausea, vomiting, bloating/discomfort, constipation and diarrhoea, who were euglycaemic, and were not relieved with conventional pharmacotherapy for the same (taken for at least 6 months), were considered for the study. A written, informed consent was obtained from all the patients and the permission for the study was obtained from the institutional ethics committee. CIIIT was given to all the patients as a neutralizing drip with regular insulin (8 U in 500 ml dextrose), over 6 hours with regular blood sugar monitoring, once in every 2 weeks (+/- 1 day as per patient convenience) for a period of 3 months (6 sessions) using a normal infusion set and the symptoms were compared at the commencement of the study, after 6 sessions of CIIIT (i.e. after 3 months) and finally after 6 months. This was done by asking the patient to grade their symptoms on the Visual Analogue Scale (VAS) on each visit.

Any patient who was found to have another alternative explanation for his symptoms (eg: mechanical obstruction of the gastrointestinal tract) was excluded from the study.

The patients were subjected to detailed history and clinical examination and the following symptoms were noted: belching, nausea, vomiting, abdominal fullness/ bloating, diarrhoea and constipation and were graded on the Visual Analogue Scale in the range of 0-10 on the basis of severity. Routine investigations including blood sugar (fasting and post prandial), upper G.I. endoscopy, USG abdomen, urine ketodiastix (to rule out diabetic ketoacidosis), serum creatinine, SGPT and glycosylated haemoglobin (HbA_1c) at the beginning and end of the study were also done for all the patients.

RESULTS AND DISCUSSION
The findings of this work are being discussed under the headings of demographic profile, clinical features and outcome.

Demographic Profile
The majority of our cases were of type 2 diabetes mellitus (90%).

The mean age of our study was 46 years with the minimum age of 31 years and the maximum age of 59 years. The majority of our patients (40%) were in the age group of 51-60 years.

The male to female ratio in our study was 2.33:1 (males-35; 70% and females-15; 30%).

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Clinical Features

Belching, nausea, vomiting, abdominal discomfort/ bloating, constipation and diarrhoea were the presenting complaints in our patients. Amongst these symptoms, belching was the most common (80%) followed by nausea (70%), abdominal discomfort (64%), vomiting (62%) and constipation (32%). Diarrhoea (20%) was the most infrequent symptom.

All the patients had multiple symptoms (100%). Most patients presented with 3 or 4 symptoms (38% each), followed by 2 symptoms (20%). Four percent patients had 5 out of the 6 symptoms. No patient had either one or all the six symptoms.

Belching was the severest symptom of the six with a mean VAS score of 8 followed by nausea which had a mean VAS score of 7. These were followed by abdominal discomfort, constipation and diarrhoea which had mean VAS scores of 6.75, 6.37 and 5.20 respectively. Vomiting was the least severe symptom with a VAS score of 5.00.

All patients were euglycaemic at presentation with a mean HbA_1c score of 6.66% and remained so throughout the study.

Table 1: Symptomatic Improvement (Mean Values of VAS)

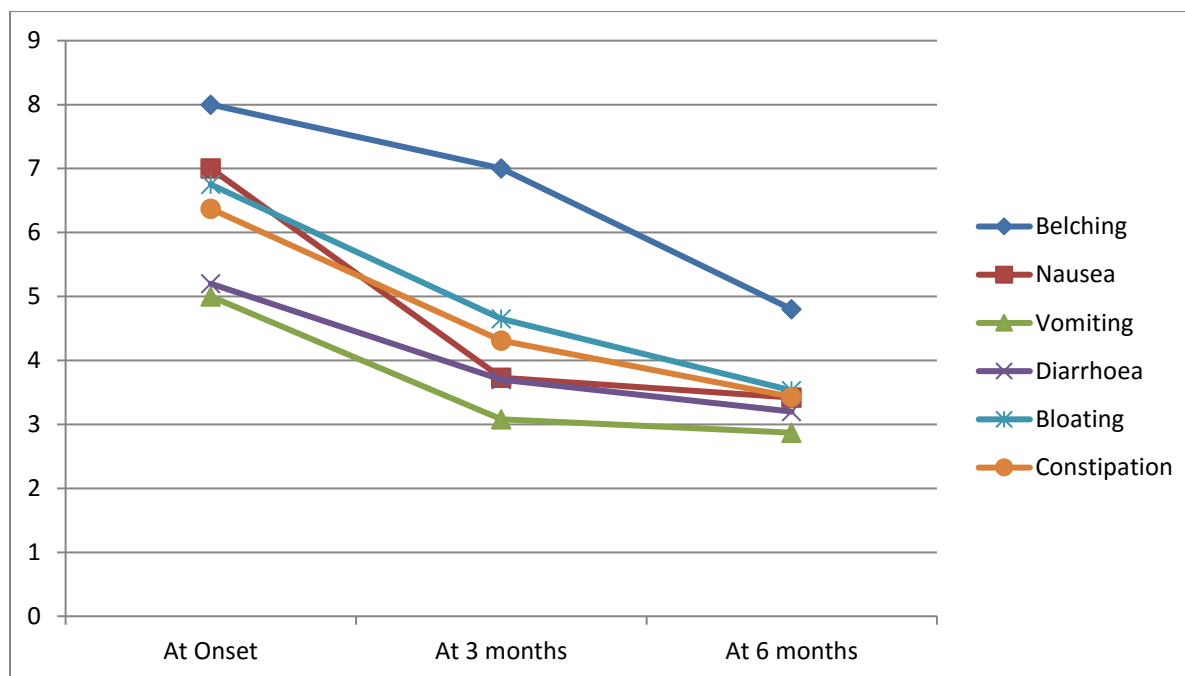| Symptoms	At Presentation	At 3 Months	At 6 Months
Belching	8.00	4.80	4.00
Nausea	7.00	3.73	3.42
Vomiting	5.00	3.08	2.87
Diarrhoea	5.20	3.70	3.20
Abdominal Discomfort/ Bloating	6.75	4.65	3.53
Constipation	6.37	4.31	3.43

Figure 1: Analysis of Symptomatic Improvement at 3 and 6 Months

Outcome

All the symptoms, which were previously refractory to the patients' conventional pharmacotherapy, showed considerable response to our therapy with CIIIT with most patients giving history of

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improvement in their symptoms after therapy and during follow up. The VAS scores showed significant decline in all symptoms. However, no patient gave history of complete recovery, with nearly all of them complaining of at least some residual symptoms. HbA1c levels also remained in the euglycemic range throughout the study with mean values of 6.59% and 6.56% at 3 and 6 months respectively.

In the literature available to us, although no long term study to date has been conducted with the use of CIIIT in diabetic gastroparesis per se, several studies on various diabetic complications have supported its use for the same. A study by Aoki *et al.,* (2001) studied the effect of long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus and found that it not only decreased the mean HbA1c values from 8.5 to 7.0 but also decreased the occurrence of both major and minor hypoglycemic episodes. A decrease in the anti-hypertensive dosage was also observed in the same study and it indicated that CIIIT markedly improves BP control in subjects with IDDM and hypertension, probably by improving the vascular smooth muscle tone. Aoki *et al.,* (2001), Aoki *et al.,* (1993), The Diabetes Control and Complications Trial Research Group (1993) also concluded through a retrospective, longitudinal study that CIIIT could successfully stabilize renal function in patients with diabetic nephropathy. Several studies Aoki *et al.,* (1995) have demonstrated a blunted diurnal variation in blood pressure in patients with diabetic autonomic neuropathy which lead to decreased target organ damage. Dailey *et al.,* (2003) through a multi-institutional prospective, randomized, controlled study evaluated the effect of CIIIT in patients with diabetic nephropathy and found that the treatment group (CIIIT) patients had a statistically significant improvement in renal function as compared to the control group.

CIIIT when given to diabetic gastroparesis patients not only improves their glycemic control, which may itself bring about symptomatic relief and also prolong the development of other micro and macrovascular complications of diabetes mellitus, but also brings about symptomatic improvement by other poorly understood mechanisms.

Conclusion
All our patients treated with CIIIT showed improvement in their symptomatology. They did not develop hypoglycaemia and also showed sustained benefit. The sustainability of the benefit over the next 2 years is under study. Therefore, it is recommended that patients presenting with complaints of diabetic gastroparesis should be managed by CIIIT rather than the conventional pharmacological therapies like metoclopramide, domperidone, levosulpride and erythromycin as it more efficacious, cheaper and more convenient. Further work with a longer study with many more subjects is required to properly quantify these changes and understand the exact mechanism how CIIIT acts.

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