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EFFECTIVENESS OF PRUCALOPRIDE EITHER AS MONOTHERAPY AND COMBINATION THERAPY AND THE QUALITY OF LIFE IN PATIENTS WITH CHRONIC IDIOPATHIC CONSTIPATION

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INTRODUCTION
Prucalopride is a 5 HT -4 receptor agonist used for the treatment of Chronic Idiopathic Constipation (CIC) where laxatives fail to show its effectiveness. CIC is a common condition defined by infrequent stools, difficulty in passing stools without any underlying cause and it was diagnosed based on Rome IV criteria. The clinical efficacy of Prucalopride was found to be > 3 SCBMs (Spontaneous complete bowel movements) / week over 4 week treatment. The most common treatment associated side effects are head ache, nausea, vomiting, abdominal pain and cramps. The neurological side effect of the drug includes suicidal ideation, visual hallucination and in some cases loss of memory is also reported. The quality of life in patients with CIC is evaluated based on PAC –QOL (Patient assessment of constipation – Quality of life) Questionnaire. This study aims to determine the QoL, and to analyse the effectiveness of Prucalopride either as monotherapy or combination therapy. This is an Observational Cohort study done for a period of 6 months involving 100 patients. From this study among 100 patients, 59 % of the total population has their SCBM increased more than 3 per week over 4 week treatment and 71% of the total population are extremely satisfied after the treatment. From our study effect of Prucalopride as Monotherapy is effective than combination therapy.

KEYWORDS: Chronic Idiopathic Constipation(CIC), Spontaneous Complete Bowel Movement (SCBM), Quality Of Life (QoL), Monotherapy, Combination therapy.

INTRODUCTION

Chronic Constipation is a very common gastrointestinal disorder which causes difficulty in passing stools. It is associated with pain and stiffness.[1] It is considered as a complicated condition among the adults since the estimated prevalence is 1% to 80 % worldwide.[2] It is classified into idiopathic and functional constipation.[3] Functional constipation is the impaired colonic motility that results in decreased frequency and duration of propagating contractions leads to reduced mass movements.[4.5] Whereas Chronic Idiopathic constipation(CIC) is a condition that occur without any underlying cause .The typical symptom of this condition is assessed through passing fewer than 3 spontaneous complete bowel movements (SCBM) per week for more than 6 months.[6] Rome IV criteria defines constipation as two or more of the following symptoms for 12 weeks including.[7,8,9]

At least 25% of defecations:

1. Straining, lumpy or hard stools,
2. Sensation of incomplete evacuation,
3. Sensation of anorectal blockage,
4. Manual maneuvers to facilitate defecations,
5. Fewer than three defecations per week

Other gastrointestinal symptoms includes[6-10,11]

- Abdominal distension
- Vomiting
- Blood in the stool
- Hematochezia
- Weight loss
- Anemia
- Rapid worsening of constipation

There are 3 subtypes of CIC such as [9]

- Normal transit constipation (NTC)
- Slow transit constipation (STC) or colonic inertia
- Disorders of defecation (DD)

1. Normal transit constipation (NTC) – Stool become harder than normal but moves through the colon at a normal rate along with abdominal pain and bloating. It is normally associated with psychological stress

and medical therapy includes fiber supplementation or laxatives are suggested.

2. Slow Transit constipation (STC) – Stool moves through the colon more slowly than the usual movement rate along with abdominal bloating and pain. The medical therapy includes fiber supplementation and laxatives are suggested.
3. Disorders of defecation includes.[7,9]

- ✓ Rectocele – It is a condition results in the bulging of rectal walls into the walls of vagina.
- ✓ Rectal prolapse – It is a condition results in the protrution of rectum through the anus to outside.
- ✓ Dyssynergic function(Pelvic floor dysfunction) – It is a condition occurs due to the abnormality in co-ordination of internal and external anal sphincters, perianal muscles, pelvic floor muscles, abdominal muscles and the muscles in the rectum .Biofeedback therapy is suggested.
- ✓ Other causes of CIC includes[11] is caused due to medications, medical conditions.

Medications which cause CIC are antacids, iron supplements, opiods, and calcium channel blockers.
Medical condition in which CIC occurs is in cerebrovascular disease, colon cancer, and cognitive impairment.

There is a relative relationship between patient's quality of life (QoL) and CIC. Thus it is important to measure QoL in patients with CIC. PAC –QOL (Patient assessment of constipation quality of life) questionnaire is the most validated measuring tool for evaluating QoL by taking patient interviews .PAC –QOL questionnaire consists of 28 items grouped into 4 subscales.[21]

1. Physical discomfort
2. Psychosocial discomfort
3. Worries and concerns
4. Treatment satisfaction

For the diagnosis of constipation medical history of the patient should be analyzed including surgical history, faecal consistency, frequency of defecation, straining while defecating, incomplete defecation, abdominal pain and discomfort, diet and life style conditions.[12,13]

The Bristol Stool scale is a diagnostic tool used for the assessment of constipation severity among individuals. It was developed by Bristol Royal Infirmary in 1997.[14] 5 HT-4 receptor agonists are mainly preferred for the treatment of CIC .Cisapride is the first drug in this class popularly used in the management of gastrointestinal disorders but it was withdrawn from the market in 2000 due to its side effect ,cardiac arrhythmias.[15,16] It occurs due to the interaction of the drug with cardiac human ether a –go-go (hERG) encoded potassium channels results in the blocking of these channels leads to the prolongation of QT interval.Tegaserod is an another partial 5-HT 4 agonist was also withdrawn from the market in 2007 due to the occurrence of ischemic cardiac events.[17]

Prucalopride is a dihydrobenzofurancarboxamide derivative from benzofuran family selectively stimulates 5 –HT4 receptors and promotes enterokinetic properties.[18] It was developed by Shire Development LLC and approved for use in Europe in 2009,[19] in Canada on December 7, 2011. Then on December 14, 2018 the Food and drug administration (FDA) approved Prucalopride (trade name Motegrity) for the treatment of Chronic Idiopathic Constipation.[20] It was used in the condition were other laxatives failed to produce adequate relief and it does not interact with hERG encoded potassium channels. The primary efficacy end point of Prucalopride is calculated on the basis > 3SCBMs / week over 4 week treatment.[21]

MATERIALS AND METHODS

Aim of the study

- To determine the QoL and analyse the effectiveness of Prucalopride either as Monotherapy or combination therapy in adult with Chronic Idiopathic Constipation (CIC).

Objectives

- To determine QOL in patients with Prucalopride treatment.

To analyse the effectiveness of Prucalopride either as Monotherapy or with other laxatives. The observational cohort study was planned to be carried out for a period of six months (October 2019 to March 2020).

The IEC approval was obtained and detailed literature review was performed. After the approval from the IEC, study began with data collection. Patients diagnosed with CIC and treated with drug Prucalopride was identified from the gastroenterology department of tertiary care hospital, Ernakulam. Case records were reviewed retrospectively and prospectively .QoL of the patients undergoing Prucalopride treatment was assessed by providing PAC –QOL questionnaire.

Statistical analysis was conducted with the aid of Python Libraries including SciPy, Pandas and Numpy

Methodology

Study method

- ➢ **Study design:** Observational cohort study
- ➢ **Study setting:** Ernakulum Medical Centre Hospital, Palarivattom, Kochi, Kerala.
- ➢ **Study duration**: 6 month duration study
- ➢ **Study population:** In order to be statistically significant we required a minimum of 100 cases.

Inclusion and Exclusion criteria

Inclusion criteria

- Constipation of functional type i.e.; idiopathic in nature

- Male and female patients above 18years.
- Patients prescribed with Prucalopride.
- All patients having less than 3 SCBM

Exclusion criteria
- Patients with impaired renal function.
- Constipation thought to be drug induced.
- Presence of secondary causes of constipation.

Outcome measures
Spontaneous complete bowel movement greater than 3 per week over 4 week treatment.

Data collection and management:
Patients diagnosed with idiopathic constipation and treated with the drug Prucalopride will be identified from the gastroenterology department of tertiary care hospital, Ernakulam over 6 months period .Case records were collected retrospectively and prospectively .QOL of patients undergoing Prucalopride treatment was assessed by providing PAC-QOL questionnaire to the patients receiving Prucalopride treatment.

Data analysis
Statistical Analysis is done using exploratory data analysis, Mann-Whitney U test, Kruskal –Wallis test, Wilcoxan Signed Rank test

Data Confidentially and Ethical issue
Informed consent is not obtained since no individual patient data is revealed in the study. Approval from the respective hospital′s IRB will be obtained prior to the study. The collected data will be accessible to the clinical guide, academic guide and co guide. The information will be released to the IRB of EMC Hospital, Ernakulam. The study will be monitored every 2 months by the College Research Committee.

RESULTS AND DISCUSSION

Result
An observational cohort study was conducted to determine quality of life, effectiveness of monotherapy or combination therapy of Prucalopride in adults with chronic idiopathic constipation. In the study, we have considered sample size as
$N=Z^2 *p\ (100-p)/d^2$

According to the inclusion criteria Here, the study of Prucalopride efficacy will help to determine whether this drug administered over 3 weeks exhibits disease modifying properties (SCBM >3 per week) in CIC when other laxatives are failed to produce the effect.

The analysis is mainly divided into two parts:
1. Descriptive part
2. Inferential part

In the descriptive part, we described the patient's age wise characteristics, gender wise characteristics and type of therapy followed.

In the inferential part, we compared the effect of drug age wise, gender wise and during different periods of treatment. At the end, we studied the Patient Assessment of Constipation – Quality of Life (PAC-QOL) and Patient's degree of satisfaction after the completion of treatment.

In Statistics EDA is an approach to analysing datasets to summarise their main characteristics often with visual methods. EDA is also used for seeing what the data can tell us beyond the formal modelling or hypothesis testing.

Descriptive part
In our investigation the patient characteristics were described with respect to the following variables
- Age
- Gender
- Type of therapy
- PAC-QOL Score
- Duration of treatment

1.1 Classification according to age range
Age wise distribution of the study population

Table 1

Age range	Nomenclature	Percentage
0-14	Paediatric	0
15-47	Youth	42
48-67	Middle aged	34
More than 64	Elderly	24

Inference: Most of the cases reported were of the age group 14-47%. Patients below 14 years are not reported to be affected during the study.

1.2 Classification according to patient's gender
Gender distribution of the study population

Table 2

Gender	Percentage
Male	67
Female	33

Inference: 67% of the patients diagnosed in the study were male.

1.3 Classification according to therapy type
Type of therapy followed

Table 3

Type of therapy	Percentage
Monotherapy	59
Combination therapy	41

Inference: In the study population, 59% underwent Monotherapy and the rest Combination therapy.

1.4 Patient assessment of constipation and quality of life before admininstering the drug

Bar diagram showing PAC-QOL of the study population

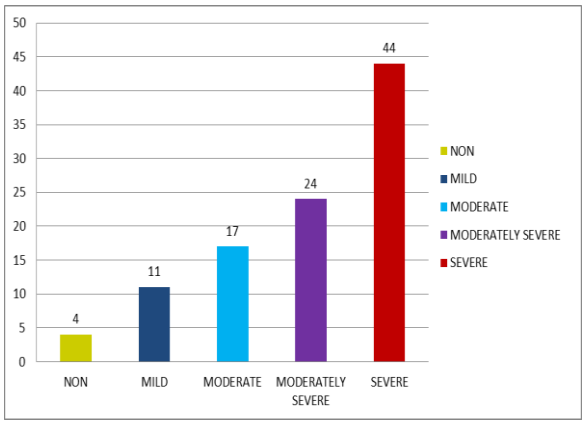

Figure 1

Inference: About 44% of the study population have severe health problems and only 4% have better quality of life.

1.5 Classification according to duration of treatment the study population has undergone

Table showing duration of treatment the study population has undergone

Table 4

Duration of treatment	Percentage
Over 4 weeks	59
Over 6 weeks	27
Over 8 weeks	14

Inference: 59% of the study population has undergone the treatment only for 4 weeks.

Inferential part

Testing of hypothesis

To determine clinical efficacy and quality of life in patients with Prucalopride treatment and to analyse its effectiveness either as monotherapy or with other laxatives, the following statistical tests are being used.

1. Mann–Whitney U Test
2. Kruskal–Wallis H Test
3. Wilcoxon Signed Rank Test

To conduct the above mentioned statistical tests we have transformed the given *discrete* data to *continuous* data by applying *square root* transformation.

For carrying out these studies we have used *Jupyter Notebook*. It is an interactive development environment based on *Python 3.7*, which is mainly used to configure and arrange the user interface to support a wide range of workflows in data science, scientific computing, and machine learning.

Python has a wide rangeof libraries used in scientific and numeric computing. We have predominantly used the following Python libraries for our study.

- SciPy
- Pandas
- Numpy

Wilcoxon signed rank test on scbm per week before administering prucalopride and after 4 weeks of treatment

Null Hypothesis (H_0): SCBM per week of the study populationbefore administering Prucalopride is equal to SCBM per week after 4 weeks of treatment.

Alternative Hypothesis (H_1): SCBM per week of the study population before administering Prucalopride is less than SCBM per week after 4 weeks of treatment

Inference: After administering Prucalopride SCBM per week has increased.

Kruskal-wallis h test for testing the effectiveness of prucalopride for 3 different duration of treatment

H_0: The effect of Prucalopride for three different durations of treatment is the same.

H_1: The effect of Prucalopride is different for at least one treatment period.

Inference: The effect of Prucalopride is different for at least one treatment period.

Mann-whitney u test for testing the effectiveness of prucalopride for each treatment period

1. **H_0:** The effect of Prucalopride over 4 weeks of treatment is the same as that of 6 weeks period.
   H_1: The effect of Prucalopride over 4 weeks of treatment is higher than that of 6 weeks period.

Inference: The effect of Prucalopride over 4 weeks of treatment is higher than that of 6 weeks period.

2. **H_0:** The effect of Prucalopride over 4 weeks of treatment is the same as that of 8 weeks period.
   H_1: The effect of Prucalopride over 4 weeks of treatment is higher than that of 8 weeks period.

Inference: The effect of Prucalopride over 4 weeks of treatment is higher than that of 8 weeks period.

3. **H_0:** The effect of Prucalopride over 6 weeks of treatment is the same as that of 8 weeks period.
   H_1: The effect of Prucalopride over 6 weeks of treatment is not same as that of 8 weeks period.

Inference: The effect of Prucalopride over 6 weeks of treatment is not same as that of 8 weeks period.

CONCLUSION

The administration of Prucalopride is found to be effective within 4 weeks of treatment for the study population.

Scbm per week over different durations of treatment

Diagram showing SCBM per week over different durations of treatment of the study population

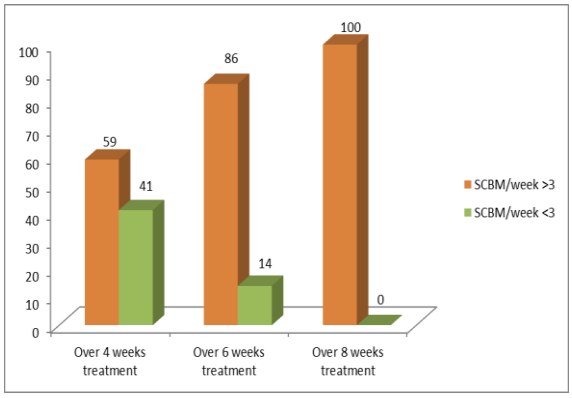

Figure 2

Inference: 59% of the total study population has their SCBM increased more than 3 per week just after 4 weeks medication. After 6 weeks 86% of the total population has their SCBM increased more than 3 per week. Then after 8 week the whole population has their SCBM increased more than 3 per week. Therefore, the administration of Prucalopride is found to be effective within 4 weeks of treatment for majority the study population.

Mann-whitney u test for testing the effectiveness of prucalopride either as monotherapy or with other laxatives

H_0: The effect of Prucalopride as monotherapy the same as Prucalopride with other laxatives

H_1: The effect of Prucalopride as monotherapy better than Prucalopride with other laxatives

Inference: The effect of Prucalopride as monotherapy is better than Prucalopride with other laxatives.

Mann-whitney u test for testing the effectiveness of prucalopride gender-wise over 4 weeks of treatment

H_0: The effect of Prucalopride over 4 weeks of treatment in Male is the same as that of Female.

H_1: The effect of Prucalopride over 4 weeks of treatment in Male is not same as that of Female

Inference: The effect of Prucalopride over 4 weeks of treatment in is not same as that of Female.

Diagram showing gender-wise satisfaction level over 4 weeks of treatment.

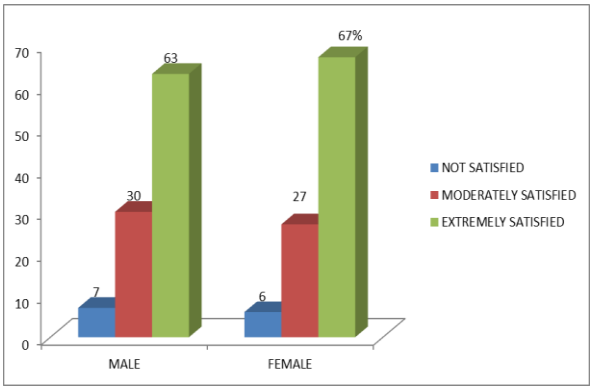

Figure 3

Kruskal-wallis h test for testing the effectiveness of prucalopride for different age groups over four weeks of treatment

H_0: The effect of Prucalopride over 4 weeks of treatment for each age-group is the same.

H_1: The effect of Prucalopride over 4 weeks of treatment is different for at least one age group.

Inference: The effect of Prucalopride over 4 weeks of treatment for each age-group is the same.

Diagram showing age-wise satisfaction level over 4 weeks of treatment

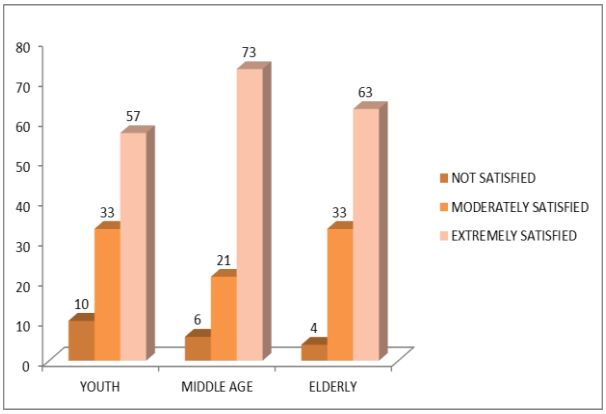

Figure 4

Patient's degree of satisfaction after treatment

Diagram showing Satisfaction of the study population

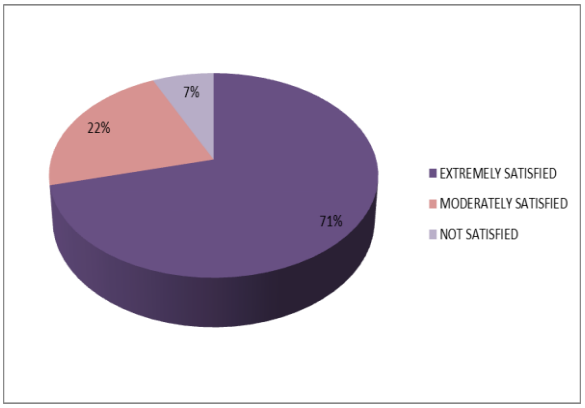

Figure 5

Inference: 71% of the patients are extremely satisfied after the treatment. Only 7% are not satisfied.

DISCUSSION

An observational cohort study was conducted to determine the QoL and effectiveness of monotherapy and combination therapy of Prucalopride in adult with chronic idiopathic constipation. A total of 100 patients was diagnosed with chronic idiopathic constipation and treated with Prucalopride from the gastroenterology department of tertiary care hospital, Ernakulam over 6 months period. Case records were retrospectively and prospectively reviewed for evaluating the treatment. QoL of the patients undergoing Prucalopride treatment were assessed by providing PAC QOL questionnaire.

In the present study exploratory data analysis was conducted to describe the patient's age wise characteristics, gender wise characteristics and the type of therapy followed which belongs to descriptive part of the study. In the inferential part we compared the effect of drug age wise, gender wise and during different periods of treatment. At the end we studied the patient assessment of constipation – QOL (PAC-QOL) and patient's degree of satisfaction after the completion of the treatment.

The percentage of age wise distribution of study population is as follows:
42% youth, 34% paediatrics, and 24% elderly. Thus most of the cases reported were of the age group 14- 47. Among 100 patients' 67 % of patients diagnosed in the study were male and the remaining 33% were females. In the study population 59% underwent monotherapy and 41% combination therapy. Based on the duration of the treatment 59%, 27%, 14%, attained >3 SCBM/ week over 4 week, 6 week and 8 week treatment respectively. Among them 59% of the patients achieved >3 SCBM/week over 4 week treatment reveals primary efficacy of the drug. Patient's assessment of constipation and quality of life before administering the drug was evaluated with PAC- QOL Questionnaire. It showed about44% of the study population have severe health problems and only 4% have better quality of life. 71% of the patients are extremely satisfied after the treatment attained better quality of life. This result was having a close resemblance to the study conducted by M.C. Ruiz – Lopez.

CONCLUSION

Prucalopride is a selective, high affinity 5HT receptor agonist used for the treatment of CIC in adults where other laxatives failed to provide adequate relief. A total of 100 patients were studied to evaluate the quality of life and effectives of monotherapy and combination therapy.. In conclusion Prucalopride can exhibit disease modifying properties (>3 SCBM /week over 4 week treatment) in patients with CIC when other laxatives failed to produce the effect. This provides an important advancement in treating the disease.

Investigation of Prucalopride efficacy determines whether this drug administered over 3 weeks exhibits disease modifying properties (SCBM>3/Week) in CIC when other laxatives failed to produce the effect. This provides an important therapeutic advancement in treating this disease.

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