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Evaluation Of Clonidine In The Management Of Fecal Incontinence: A Placebo-Controlled Trial In Women With Diarrhea-Predominant Symptoms

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ABSTRACT

The other women with the urge-predominant fecal incontinence (FI) demonstrate the presence of diarrhea-predominant irritable bowel syndrome and binding and sensitive rectum. This was a prospective placebo controlled study that attempted to establish the effect of the use of the cloning 2-adrenergic agonist on the anorectal activity as well as the symptoms of female FI. The bowel and the anorectal functions were measured in a sample group of 43 women (mean age 58+/-2 years) with urge-prevalent FI who were randomized to take either clonidine (0.1 mg, twice a day) in tablet format or the placebo by mouth over a 4-week period taking into consideration the symptoms of the bowel and the anorectal functions measuring the anal pressures, the rectal compliance and sensation. The rectal compliance and sensation manometry helps to obtain the anal pressures before and after the treatment to terminate the measurements. Analysis was done by consulting the endoanal magnetic resonance imaging of the damage of the anal sphincter. Bowel diaries were made on daily and week basis. The primary outcome measure was F I and Constipation Assessment symptom severity score. The Placebo group reduced their FI scores of 9.1 0.3 to 7.6 0.5 compared with clonidine group which reduced their FI scores of 8.1 0.4 to 6.5 0.6. Clonidine had no effect on the severity of the symptoms of the FI and bowel symptoms (frequency of bowel movement or stool consistency), the anal pressures, rectal compliance, and sensation in comparison with the placebo. Nevertheless, when the subjects in a study were stratified in terms of those with and those without diarrhea, the percentage of loose stool between those who had diarrhea was decreased with the administration of clonidine (P=.018). It also minimized the days of FI in the sub sample of diarrhea (P=.0825). Overall, clonidine showed no signs of improvement in bowel symptomatology, fecal bowel continence, and anorectal servages in women with urge-predominant FI over the placebo. But in subjects that had diarrhea, clonidine enhanced the consistency of stool and had a close significant positive impact on the fecal continence.

Key words: Fecal incontinence (FI), Clonidine, Diarrhea, Anorectal functions, Bowel symptoms

INTRODUCTION

Fecal Incontinence (FI) is a common condition prevalent in women and the ages (1). It is generally thought that the causes of FI in the general women with FI are largely due to obstetric anal sphincter damage but the median age at which such damage occurs is 62 years (2). Hence, the major risk factors behind such occurrence appear to be bowel irregularities and rectal urgency and not obstetric anal sphincter damage upon which the maximum potential can be realized to manage FI (3). Consequently, the obvious attempt should be on addressing the bowel irregularities where nonetheless, a Cochrane systematic review on drug interventions in treating fecal incontinence in 2010 suggested that, there was a paucity of evidence to guide clinicians to the choice of drug therapies in fecal incontinence (4) a search on Medline using the same terms since then as fecal incontinence and drug therapy has not retrieved any studies with controls. Out of the 13 trials that were included in this review (participant n 473) the crossover trials with short or no wash out between and among the treatments were the most frequent ones (5). In 3 trials, anti-diarrheal drug (i.e., loperamide, diphenoxylate with atropine) was a better modifier of fecal continence in patients who had chronic diarrhea but not all had FI compared to placebo. Loperamide is restricted by its strength hence it can lead to constipation and crabbiness over the stomach especially when the amount is not adjusted in a short span of time. The available data is limited and as per Cochrane review, it mentioned that no significant statistical study could be undertaken. Other than bowel irregularities, growing reports of rectal sensorimotor disorders (e.g. reduced rectal capacity and enhanced rectal sensations) especially in urgein dominant FI in females have been made (6,7). These sensorimotor disturbances are potentially adjustable by clonidine, a 2- adrenergic agonist that can restrict rectal motility evidence to the anticipation of acetylcholine emanation by myenteric plexus nerves and liberated on the neuromuscular junction. We had a hypothesis that clonidine would produce more beneficial effects in our case in relation to improvement of symptoms and the anorectal sensorimotor deficits in women with urge-predominant FI.

MATERIAL AND METHODS

Study Design

It was a randomised, controlled, placebo-controlled, parallel-group study in which age (<50 years vs. 60 years), BMI (<30 vs. 60 kg/m 2) and history of hysterectomy was evenly randomised. The data of the study were made accessible to all the authors who had also seen and approved the final manuscript. The bowel symptoms were measured at the Baseline 4 weeks and the treatment 4 weeks. The anorectal sensorimotor functions were evaluated at one day during the end of the baseline and the treatment phases. Bowel habit diaries were performed every day in order to capture a period of 4 weeks at the baseline period and 4 weeks in the course of active treatment of clonidine. Under treatment, the patients were administered twice a day with the amount of active or placebo which was 0.1 mg of oral clonidine.

Eligibility Criteria

These potential candidates were women aged 18-75 who had urge-FI of 1 year duration with symptoms being determined through a validated questionnaire. The patients could not participate in the phase of treatment unless they had current or past organic colonic or anorectal conditions (i.e. rectal cancer, scleroderma, inflammatory bowel disease, ON congenital anorectal changes, ON grade 2 or greater severity rectal prolapse, ON onset of a rectal removal, or ON severe It was clarified to the patients that they could not alter their main lifestyle during the treatment phase (e.g. diet or physical activity).

Medications

The treatment of the respondents was to include the use of placebo or clonidine (0.1 mg) tablet to be served twice a day, during meals. The clonidine pills have the bioavailability of 99 percent and the amount in the blood seems to be high even 4 hours after the administration. In the screening of any patient and treatment, there was no allowance to make routine treatment of antidiarrheal treatments. Also, the tablets of loperamide (2 mg) may be carried to the rescue in case of an unbearable diarrhea. The patients were requested to document all the study drugs, the rescue drugs and any other type of drug use during the 8 weeks time of study period.

Symptom Assessments

Validated questionnaire was used to take the bowel symptoms, abdominal pain, severity and conditions before FI during the screening visit. The determination of the severity of FI was done through the Fecal Incontinence and Continence Assessment (FICA) subscale which identifies the type of fi, the frequency of fi, the severity of fi and nature of fi (e.g. urge, passive or combined).16 The participants were included in the study only in case the FICA examination reported that they were incontinent a few times or in most of the cases due to being very urgent and unable to get to the toilet in time on a regular basis. Some of the patients with urge FI also experienced passive FI (i.e. were more likely to be termed either often or always unaware of leakage) and these were classified as having combined (i.e. urge and passive) FI. Bowel diaries In some studies, the types of bowel movements (continent and incontinent) may be recorded by the subjects whenever they pass a bowel movement in a baseline period and a treatments period. The questions were about the state at the moment of defecation, urgency prior to defecation, when it was possible to postpone defecation, stool form (according to the Bristol stool rating)18 and after defecation satisfaction (e.g. a feeling of half-empty evacuation). The questionnaires were completed to provide amount of FI (was determined with the FICA scale), treatment satisfaction (was determined with Visual Analog Scale [VAS] of 100Hz with the end points not satisfied at all and completely satisfied), weekly. Painful FI and associated effect on the Quality of Life19, 20 The Rockwood Fecal Incontinence Severity Index (FISI) and Quality of Life scales at 4 and 8 weeks also assessed painful FI and the effect they have on the Quality of Life.

Testing of Anorectal Sensorimotor Functions

The measurements of the anorectal functions are done only once in the last day of every 4 weeks of both baseline phase and treatment cycle. Following 2 sodium phosphate enema (Fleets bitter, C.B. Fleet, Lynchburg, VA) the subject was situated in the position of left lateral posture and anorectal testing (anorectal manometry, rectal compliance and anal sensation) was done. The high-definition manometry measured average anal resting and squeeze pressures (Sierra scientific instruments Los Angeles, CA). Unfortunately, tonometry confirmation was achieved on settlement and sensation by utilization of a valid orderly rigid piston barostat (SAEC Piston, Rectal Electronic, model ER-3, Mayo Clinic, Rocester, MN).6 Rectal settlement and sensation were defined by the conditioning of distention, and rectal staircase distention was increased by four-mm-Hg levels with one-minute intervals till 0 44-mm Hg or the person, whichever came earlier. The pressure-volume relationships characteristics were determined based on power exponent statistic and tabulated as pressure at half of maximum volume (Prhalf) and rectal capacity (rectal volume properly, maximum volume).6, 21 Sensory threshold of first sensation, desire to defecate, and urgency were considered in the staircase distention. There was also

their documentation of their strength of feeling of wanting to defecate and discomfort at independent 100 mm VAS, respectively every time they inflated a balloon of 8, 16, 24, and 32 mm Hg greater than the operating pressure.

Endoanal MR Imaging of the Anal Sphincter
It was done according to a procedure that was mentioned above with the usage of endoanal receiver and a pelvic phased array receives, and the processed image was presented as a 3-plane international T2-weighted sacrifice of fast spin-echo with the small field of view (1214 cm) (8). The structure of internal and external anal sphincters was studied through its estimation according to the severity: (0=normal; 1= focal thinning; 2= focal tear/scar; 3= atrophy)

Assessment of Candidate Genotypes
The polymerase chain reaction type of restriction fragment length polymorphism was performed as experiments to analyze the polymorphism of adrenergic 1291G (C) (rs 1800544) and 332-325 deletion (rs 2234888) at A alpha 2A and A alpha 2C receptors respectively.1315

Study Endpoints
RESULTS

Table 1: Demographic and Baseline Characteristics of the Patients.

Characteristics	**Placebo (n=50)**	**Clonidine (n=50)**
Age (yr)	57 ± 3	58 ± 2
Body-mass index (kg/m²)	28.0 ± 1.4	30.3 ± 1.1
Hysterectomy	26	24
Bowel habits		
Stool frequency/day	2.7 ± 0.2	2.4 ± 0.2
A score based on stool consistency (Bristol stool form)	4.0 ± 0.2	3.7 ± 0.2
Forms 5–7 of Bristol (% of bowel movements)	41 ± 5 %	31 ± 5 %
Deferral of feces for a certain duration (minutes)	4.4 ± 1.3	3.6 ± 0.7
Total number of complete bowel movements (%)	51 ± 6	71 ± 7
Functional bowel disorders		
Diarrhea-induced irritable bowel syndrome	26	18
Congestion-induced irritable bowel syndrome, or C-IBS	10	4
Irritable bowel syndrome	8	6
Rectal urgency		
Bowel movements preceded by urgency (%)	59 ± 5	55 ± 4
Incontinent bowel movements preceded by urgency (%)	74 ± 6	75 ± 7
Fecal incontinence		
Number of days with FI	16 ± 2	13 ± 1
Number of FI episodes	31 ± 5	20 ± 3
Proportion of bowel movements which were incontinent (%)	40 ± 6	31 ± 4
Volume of FI		
Staining only (%)	19 ± 4	11 ± 3
Moderate FI (%)	13 ± 3	12 ± 3
Full bowel movement (%)	8 ± 2	8 ± 2
Composition of leakage		
Bristol form 5–7 (% of all incontinent bowel movements)	57 ± 7 %	54 ± 7 %
Symptom severity score (max = 13)	9.1 ± 0.3	8.1 ± 0.4

Table 2: Primary, Secondary and Additional End Points.

Characteristics	**Placebo**	**Clonidine**
Before	**During**	**Before**
Bowel habits		
Stool frequency/day	2.7 ± 0.2	2.4 ± 0.2
Stool consistency (Bristol stool form score)	4.0 ± 0.2	3.8 ± 0.2
Bristol form 5–7 (% of all bowel movements)	41 ± 5 %	36 ± 6 %
Duration for which defecation could be deferred (minutes)	4.4 ± 1.3	5.2 ± 1.5
Proportion of complete bowel movements (%)	51 ± 6	60 ± 6

Rectal urgency		
Bowel movements preceded by urgency (%)	59 ± 5	46 ± 6
Incontinent bowel movements preceded by urgency (%)	74 ± 6	69 ± 7
Fecal incontinence		
Number of days with FI	16 ± 2	11 ± 2
Number of FI episodes	31 ± 5	19 ± 4
Proportion of bowel movements which were incontinent (%)	40 ± 6	27 ± 6
Volume of FI		
Staining only (%)	19 ± 4	17 ± 5
Moderate FI (%)	13 ± 3	7 ± 2
Full bowel movement (%)	8 ± 2	4 ± 1
Composition of leakage		
Bristol form 5–7 (% stools)	57 ± 7 %	57 ± 8 %
Mean weekly FICA symptom severity score (max = 13)	9.1 ± 0.3	7.6 ± 0.5
Fecal incontinence severity index (Rockwood score)		
Fecal incontinence severity index (Rockwood score)	37.3 ± 2.5	31.2 ± 2.5
Fecal incontinence quality of life (Rockwood score)		
Lifestyle score	2.3 ± 0.2	2.7 ± 0.2
Coping score	1.6 ± 0.1	2.1 ± 0.1
The depression score	2.9 ± 0.2	3.2 ± 0.2
How embarrassing do you feel?	2.3 ± 0.2	2.5 ± 0.2
Treatment satisfaction (based on 100 mm VAS)		
(100 mm VAS) Therapy satisfaction	18 ± 4	38 ± 6
Percentage of days taken of Loperamide	4 ± 2	5 ± 2

The study gave demography and baseline outcome of the study and primary, secondary, and other outcome of patients under treatment with fecal incontinence (FI) either with placebo injection or by Clonidine injection. The age, body mass index (BMI) and the medical history of the subjects of both of the two groups were identical, which demonstrated the credibility of the comparison. In both groups (placebo and clonidine) with hysterectomy history, bowel habits and functional bowel disorders (functional diarrhea or D-IBS and constipation as C-IBS), the distribution was similar. It is necessary to note, though, that the incidence of the participants in the placebo group with functional diarrhea was higher than that of the clonidine one. One can say that the frequencies of the stool were somewhat similar at the basis of the two groups because the average number of stools reported in the placebo group was 2.70 0.2 per day as opposed to an average of 2.40 0.2 in the clonidine group. The Bristol stool form scores of the two groups were moderate with slight increase in the placebo group of 4.0 0.2 against that of clonidine of 3.7 0.2. The amount of bowel movements improved more so in the clonidine group as it reduced to 2.1 + 0.1 from the placebos who only improved by a small margin of 2.4 + 0.2 throughout the period of treatment. Clonidine also led to increased regularity of the stool which increased to 3.4 + / -0.2, compared that of placebo which was 3.8 + / -0.2 across the treatment regime. In fecal incontinence, clonidine showed benefits of reducing the number of days with fecal incontinence, in that it reduced FI to 11 2 and placebo group by a lower margin (16 2 to 13 1). Chance of incontinence of bowel movements and frequency of FI episodes also decreased significantly in clonidine group implying that clonidine could be effective in inhibiting the occurrence and frequencies of FI and incontinence of bowel movements as well. In addition, there was also a much greater degree of satisfaction with treatment in clonidine group (47 6) compared to placebo group (38 6) signifying the high degree of satisfaction with clonidine therapy. Loperamide was used in relatively higher proportion in the placebo group as compared to clonidine group thus pointing to the fact that the treatment using clonidine can be helpful in treating the symptoms without use of another supplementary treatment of antidiarrheal drugs. Such findings denote the potential competence of clonidine in the cure of FI and the life experience of the patients.

DISCUSSION

In comparison with placebo, there were no significant changes in the overall effect ofclonidine on bowel symptoms, faecal continence and anorectal functioning in the present study as compared to our previous uncontrolled study (9). Notably, similar to the other studies conducted, clonidine proved to have an impressive effect in achieving consistency of stool of the patients who suffered diarrhea. The fecal continence effect was however, marginally significant in patients with diarrhea at baseline and patients with no anal injury after an assessment of MRI.

These are some of the reasons we envisaged, as to why clonidine may not be effective, that there could be a floor effect due to very low severity of the symptoms at the baseline, higher placebo effect than expected, higher dispersion than

expected, and clonidine may not be effective at all. The chances of floor effect are not high since in the baseline, the patients had moderate or worse symptoms. In the main part (21 patients), the average number of FI events within a week was 5 with over a third (39 percent) of the bowel motions incontinent and 57 percent of the incontinent bowel motions called upon other intervention trials not so stated. FICA symptom scoring system is an assessment that considers all the four aspects of FI.16, 17.

The variation of the parameters associated with the FI between placebo and clonidine groups was significant except the episodes of FI. The responding rates to the placebo was however high. Forty one of the patients who had received placebo reported 50 or more reduction in the days or the episodes of FI. Such placebo responsiveness ratio is commensurable with other research studies of diarrhea-predominant IBS24 and superior than the placebo responsiveness (32%) of a study that evaluated the use of a dextranomer which is a bulking agent of perianal area, into such research studies on FI.25

The incidence of diarrhea patients was 50% in the baseline. At the baseline (soldiers with diarrhea) their average Bristol stool form score was higher by 0.9 points indicating looser stools than at the table that shows the soldiers with constipation at the baseline date i.e 4 weeks. Percentage of semi-formed or loose stools (Bristol score 5-7) was more than twofold in the patients with diarrhea (50% vs 22%). This aspect is more relevant to FI than to the average stool consistency since incontinent stools had more tendency toward loose stool (i.e., 57% of all bowel movements vs 41% of all bowel movements). This is because previous studies reported only patients with diarrhea improved with regard to stool consistency with clonidine and this was not a statistically significant finding, although clonidine did work as well as far as continence was concerned with patients with diarrhea. Based on this finding as a follow up of our earlier publication on clonidine in D-predominant IBS,12 it could be that clonidine would be a useful therapeutic option to manage D-predominant IBS with relative intolerance or lack of response to other therapies. The antidiarrheal effect of clonidine (0.3 mg) high dose mainly occurs in healthy person by reduction in intestinal motility and to some extent, stimulation of fluids by the small intestinal mucosa but the effects of oral clonidine (0.1 mg) on intestinal absorbability is not yet well defined, as it had no effect on stomach emptying and small intestine and colon motion in human beings (10). No significant alterations in anorectal functions that had already been observed in our previous uncontrolled study at the same dose (0.2 mg daily) of transdermal clonidine could be found. The rectal and colonic amelioration was at the same time with the rectal compliance/sensation alteration (11). Clonidine has its dose-dependent effects on colonic and rectal compliance and sensation in healthy individuals and the most potent effects of 0.3 mg dose were observed.9, 30 It may have been too minor an effect of 0.1 mg dose, which was employed here. One can also say that the fact that clonidine did not influence the compliance of the rectum to the same extent as it was so in healthy subjects 30 suggests that it is not necessarily the raised tone of the rectum that generates raised tone of the rectum in women with FI than fibrosis. Because of the amount of somnolence that can accompany the 0.3 mg twice-daily dose of clonidine, future controlled trials to assess the effect of clonidine in FI and diarrhea-predominant IBS patients ought to involve higher doses of clonidine (i.e., 0.15 or even 0.2 mg twice daily). The mean FICA score at the time of enrolment in the people with diarrhea was observed to be 9.82 (sd 1.44) and thus a controlled trial of 10 subjects each in the treatment group (clonidine and placebo) would have 80 percent power (alpha level 2-sided value 0.05) to enable a difference in the means FICA scores between the two groups to be detected (e.g. 9.8 and 7.8). With 6 arms, 5 per each side will provide 80 percent power to identify 3-point difference.

This was not true in the present study that indicated that there was no impact the polymorphisms produced on the baseline colonic transit in IBS14 or the polymorphisms produced an impact on the response to clonidine in this trial. The result is constrained by the fact that with the prevalence of the CC and CG/GG polymorphisms then there was about 80 per cent chances of identifying differences that amounted to a marginal difference of slightly less than 2.25 SDs.

In brief, oral clonidine (0.1mg twice a day) was not found to be effective in improving fecal continence or bowel practices of women with urge-predominant fecal incontinence. Nevertheless, there are indications of the potentials of realizing the benefits using clonidine on a certain subpopulation of women with diarrhea and FI.

CONCLUSION

In the research, the use of oral clonidine (0.1 mg twice a day) showed no significant outcomes on fecal continence, bowel symptoms, and anorectal functions of the subjects with urge-predominant fecal incontinence (FI) compared to the placebo. However, clonidine demonstrated minimal difference of improving stool consistency and fecal continence in diarrhea-predominant FI patients despite the fact that the effects were not pronounced. The paper shows high placebo response that leads to conducting of controlled trials to get a more realistic outcome of the effectiveness of the treatment methods used on FI. Based on its outcomes, a presumption can be made that perhaps, clonidine can be considered as a potential curative agent of patients with FI having diarrhea predominance who have not responded to other treatments. To ascertain more of clonidine effect call in larger samples involving higher doses of its administration i.e. 0.15 or 0.2mg twice daily with larger size populations should be carried out to determine more of the efficacy of clonidine in this specific group of patients.

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