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The Effect of Proximal Colonic Irrigation (King's 3-2-1 Bowel Cleansing Regime) on Motor and Nonmotor Symptoms in Parkinson's Disease: A Cross Racial Retrospective Review

Vinod Metta

vinod.metta@nhs.net

King's College London

Georgios Kapsas
King's College Hospital London Dubai

Hasna Hussain
King's College Hospital London Dubai

Afsal Nalarakettil
King's College Hospital London Dubai

Therese Masagnay
King's College Hospital London Dubai

Clarissa Sangilan
King's College Hospital London Dubai

Karolina Poplawska-Domaszewicz
Poznan University of Medical Sciences

Vinay Goyal
Medanta Hospital

Rajinder K Dhamija
Lady Hardinge Medical College

Rupam Borgohain
Yashodha hospitals

Rukmini Mridula
Yashodha hospitals

Sampath Kumar
Narayana Medical College

Carmen Rodrigues Blazquez
The Carlos III Health Institute (ISCIII)

Huzaifa Ibrahim
Parkinson's UAE

Kallol Ray Chaudhuri
King's College Hospital London Dubai
Guy Chung-Faye
King's College Hospital London Dubai

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Vinod Metta[1,2*], Georgios Kapsas[2], Hasna Hussain[2], Afsal Nalarakettil[2], Therese Masagnay[2], Clarissa Sangilan[2], Karolina Poplawska-Domaszewicz[3], Vinay Goyal[4], Rajinder K. Dhamija[5], Rupam Borgohain[6], Rukmini Mridula[6], Sampath Kumar N S[7], Carmen Rodrigues Blazquez[8], Huzaifa Ibrahim[9], Kallol Ray Chaudhuri[2], Guy Chung-Faye[1, 2]

Affiliations:

1. King's College London, Department of Neurosciences, Institute of Psychiatry, Psychology & Neuroscience and Parkinson's Foundation Centre of Excellence, King's College Hospital, London, United Kingdom.
2. Parkinson's Foundation Centre of Excellence, King's College Hospital London, Dubai, United Arab Emirates.
3. Institute of Neurological Disorders, Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland.
4. Institute of Movement Disorders & Parkinson's Centre of Excellence, Medanta Hospitals, New Delhi, India.
5. Institute of Human Behaviour and Allied Sciences, Lady Hardinge Medical College and SSK Hospital, New Delhi.
6. Institute of Movement Disorders & Parkinson's centre of excellence, Yashodha hospitals, Hyderabad, India.
7. Institute of Movement Disorders & Parkinson's centre of excellence, Narayana Medical College, Nellore, India.
8. National Centre of Epidemiology and CIBERNED, Institute of Salud Carlos III, Madrid, Spain
9. Parkinson's UAE, United Arab Emirates.

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***Corresponding author:**
Name : Dr Vinod Metta
Email : vinod.metta@nhs.net
ORCID **:** 0000-0002-8970-8595

Authors' Role: Credit
Conceptualization: Vinod Metta, Georgios Kapsas, Kallol Ray Chaudhuri
Formal analysis: Karolina Poplawska-Domaszewicz, Carmen Rodrigues Blazquez
Investigation: Guy Chung-Faye
Methodology: Vinay Goyal, Rajender K Dhamija, Rukmini Mridula, Rupam Borgohain, Sampath Kumar N S
Project administration: Hasna Hussain, Afsal Nalarakettil
Resources: Hasna Hussain, Therese Masagnay, Clarissa Sangilan
Writing-original draft: Vinod Metta, Georgios Kapsas, Kallol Ray Chaudhuri
Writing-review & editing: Kallol Ray Chaudhuri

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Abstract:
Parkinson's disease (PD) is associated with widespread gastrointestinal (GI) dysfunction including gut microbiota dysbiosis affecting the entire gastrointestinal tract with fecal impaction and constipation being a common symptom. We initiated a pathway of proximal colonic irrigation with standard colonoscopy and targeted irrigation followed by bowel preparation with polyethylene glycol 3350 in a 3-2-1 bowel cleansing pattern to help levodopa absorption and consequent motor and nonmotor symptoms (NMS) in a cross racial cohort of PD patients with fecal impaction (Leech score) and constipation since 2022. The pathway has been used in PD patients referred for dopamine replacement therapy (DRT) optimisation with refractory motor fluctuations as well as GI symptoms (constipation, bloating, abdominal discomfort). Patients undergo proximal colonic irrigation and subsequent 3-2-1 bowel cleansing regime with assessment of motor and nonmotor scores (baseline, 3 and 6 months). Review of outcome measures shows significant improvements in constipation and NMS burden and Leech scores at 3 months persisting at 6 months follow-up. In addition, Unified Parkinson's Disease Rating Scale (UPDRS) Part III and Part IV scores, wearing-off symptoms, and Levodopa Equivalent Daily Dose (LEDD) decreased significantly across all racial groups. Controlled prospective studies are required to validate proximal colonic irrigation followed by the 3-2-1 bowel cleansing strategy in PD cases with poor response to DRT, fecal loading and constipation.

Introduction:
PD is the second most common neurological disorder and a steep rise in numbers is projected with almost 25.2 million people likely to be diagnosed with PD worldwide by 2050 [1]. The neurodegenerative changes associated with PD lead to significant GI dysfunction in advanced stages of the disease which manifests as gastroparesis, constipation, and difficulties with defecation and fecal impaction [2, 3]. Fecal impaction with constipation can interfere with oral absorption of levodopa and lead to refractory motor and non-motor fluctuations and the need for switching to non-oral therapies [4, 5]. In addition, constipation and gut dysbiosis can be a feature of prodromal PD and can be present prior to the onset of motor symptoms in PD [3, 6].

Growing evidence suggests that gut dysbiosis and motility issues may impair the oral absorption of levodopa, thereby contributing to delayed-on and no-on phenomena following oral levodopa administration in patients with PD [7]. Findings from both preclinical rodent models and clinical human studies indicate that alterations in the gut microbiota may be associated with increased motor fluctuations and abnormal gut motility [8]. Baizabal-Carvallo et al. reported improvement in dyskinesias and other motor complications in PD following a "bowel cleansing" regime consisting of saline colon enemas with sodium phosphate Fleet, combined with oral rifaximin and polyethylene glycol-3350 (17 g/day dissolved in water for 10 days) [8]. Another study suggested that bowel cleansing by enema may reduce intestinal microbiota load by approximately 31-fold [9]. In another study, Doi et al. investigated 31 patients with PD and demonstrated that delayed gastric emptying was correlated with altered orally administered levodopa pharmacokinetics, implicating gastric dysmotility to be related to gut dysbiosis and to be an important factor in delayed-on episodes [10]. Prolonged gastric retention may delay delivery of levodopa to the small intestine, where absorption primarily occurs, thereby reducing bioavailability and contributing to inconsistent therapeutic responses [11].

There are also ethnic differences in levodopa response in PD which has been shown in several studies. A study of levodopa responsiveness in Black and South Asian subjects in the UK showed levodopa hyporesponsiveness in Black and Asian PD patients [12]. Studies led by Metta et al from United Arab Emirates (UAE) have also highlighted the need for "ethically aware" personalised drug regimens for non-white South Asian and Black subjects with PD which may not follow the protocol or guidelines for White Caucasian subjects, and the issue has also been highlighted in relation to ethnic inclusion in clinical trials [13, 14]. Another study by Metta et al. highlighted the heterogeneity of Parkinson endophenotypes in the UAE population and the importance of prompt diagnosis and dopaminergic dose optimisation [15].

We noticed severe gastrointestinal symptom load in PD cases in UAE who are referred for optimisation of oral DRT at the Parkinson's centre at Kings College Hospital, Dubai as evident in the gastrointestinal domain scores in PD nonmotor symptoms scale (NMSS) from the Empark study [15]. Based on this local clinical experience we started a pre-screen protocol of screening these PD cases with abdominal X-Rays, performing

Leech scores and then undertaking a proximal colonic wash regime once the Leech score exceeded 5 or if there was significant clinically intrusive constipation and or large bowel related symptoms. As is usual in our clinic, motor, nonmotor, wearing off, quality of life and levodopa equivalence dose (LEDD) data are routinely collected as part of good clinical practice and in these cases with the 3-2-1 bowel cleansing regime outcome was collected at 3 and 6 months supplemented by repeat abdominal X-Rays and Leech scores.

In this retrospective review of 100 cases (99 evaluable) we have reviewed pre and post outcome scales based and LEDD data at 3 and 6 months. The proximal colonic irrigation and 3-2-1 bowel cleansing regime is described in Methods. We also, for the first time, provide a comparative analysis of the effects of the 3-2-1 bowel cleansing regime in a cross racial (Arab versus, South Asian versus White Caucasian) PD population.

Objectives:

This is retrospective review of outcome measures collected in our cohort of PD cases who underwent proximal colonic irrigation with fecal impaction followed by the 3-2-1 bowel cleansing regime. Pre-post (baseline, 3 and 6 months) assessments of motor and NMS scale data are presented along with constipation and fecal loading which were used as the main anchor outcome supported by using and analysing Leech scores on abdominal X-Ray [16]. The Specific objectives of the study were twofold: First to assess the effect of the King's 3-2-1 bowel cleansing regime on constipation and Leech score from abdominal X-Ray, motor and nonmotor function and wearing off as well as changes in levodopa equivalent dose (if any). In addition, we were able to compare the effect of this intervention on Arabic, South Asian and White Caucasian Parkinson's patients who make up the patient population at KCH Dubai making this the first cross racial study of this kind.

Study subjects and Inclusion/Exclusion criteria:

This retrospective data based real life PD review included patients with PD who visited the Parkinson's Centre of Excellence at King's College Hospital London, Dubai between 2022-2026. Ethnicity in all the subjects was recorded using established UK government criteria (Office for National Statistics methodology on identification of ethnicity) [17].

The inclusion criteria of patient included were as follows:

1) Age at or above 18 years (yrs).

Clinical diagnosis of PD per the revised movement disorders society criteria [18]

2) Symptoms of constipation and levodopa refractory motor fluctuations (as judged by clinicians) and wearing off response to oral levodopa
3) Abdominal X-Ray with Leech score >5
4) Clinically recognizable ON/OFF states and ability to commit to a 6-months bowel preparation regime
5) Ability to provide informed consent for the clinical pathway

The exclusion criteria were as follows:

1) Hoehn & Yahr (H&Y) stage V and institutionalized patients with PD
2) Patients with no fluctuations, or constipation
3) pregnant or nursing patients and or childbearing age
4) chronic conditions interfering with assessments (e.g., dementia and Mini-Mental State Examination (MMSE) score less than 21.

The Proximal Colonic Irrigation (3-2-1 bowel cleansing) Regime:

The regime used in this study was developed after review of the relevant literature and through the cumulative clinical experience of several authors of this paper (VM, GCF, KRC) which included a Parkinson specialist gastroenterologist (GCF) as well observation of high bowel dysfunction scores in NMSS in the local population as shown in the Empark study [15]. Therefore, the underpinning "rationale" for the review was the observation that in our local clinical practice, "high" colonic irrigation appeared to be particularly useful in relieving constipation and fecal loading, with secondary improvement in a range of motor and non-motor symptoms in

PD patients referred to the centre. In addition, the regime was developed following discussions and focus group meetings with key stakeholders, including neurologists, PD nurse specialists (PDNS), gastroenterologists, nutritionists, and expert patient group (Parkinson's UAE) whose chairman (HI) is an author in the paper. The specific protocol consisted of colonic irrigation performed by a senior gastroenterologist after obtaining informed consent followed by discharge of patient on the 3-2-1 bowel cleansing regimen (fig 1). Fecal loading and constipation were assessed using Leech scores [16], and overall motor and non-motor status was evaluated with validated tools as listed below. This protocol included colonic irrigation which combines standard colonoscopy with targeted irrigation under mild sedation. The procedure washes out the high rectal area and extends irrigation distally, proximally, and throughout the entire colon followed by bowel preparation with polyethylene glycol 3350 in a 3–2–1 regimen (17 g/day dissolved in water). During Week 1, the patient received three doses daily (before breakfast, before lunch, and before dinner). In Week 2, dosing was reduced to two doses daily (before breakfast and before dinner). In Week 3, dosing was further reduced to a single dose daily (before breakfast). Thereafter, bowel preparation continued once daily for 6 months. This is the basis of the 3-2-1 bowel cleansing regime (Fig 1). Clinical outcomes were evaluated at 3 months and 6 months.

Figure 1: The Proximal Colonic Irrigation (3-2-1 bowel cleansing) regime.



Clinical Assessments: The assessments performed were:

- Constipations as denoted by the gastrointestinal domain (domain 6) of the Parkinson's Disease Non-Motor Symptoms Scale (PD NMSS) [20].
- The 9-item Wearing-Off Questionnaire (WOQ-9), a validated patient self-administered screening tool used to detect the "wearing-off" phenomenon in PD [21]
- Abdominal X-Ray and evaluation by Leech Scores [16]
- Hoehn & Yahr Stage (H&Y) and Unified Parkinson's Disease Rating Scale (UPDRS) III and IV subitems.
- LEDD [22]

Diet and concomitant medications:

During the study period the patient and caregivers were advised keep concomitant oral therapies as stable and constant as possible and concomitant therapies that bypass the gastrointestinal tract, such as transdermal

Rotigotine, inhaled levodopa, apomorphine pen injections, or sublingual formulations were not used as this may influence the outcome of this study. Medications and supplements affecting gastrointestinal transit such as domperidone, laxatives, dietary supplements, antacids, or other gastrointestinal medications were not allowed unless deemed essential clinically. Similarly, dietary and hydration factors were kept as constant as possible as this may potentially influence gastrointestinal function and the outcomes assessed in the study.

Safety Monitoring:
Adverse Events (AE) and Serious Adverse Events (SAE) were documented with: - Onset, duration, severity - Outcome - Causality assessment. An independent oversight committee (King's Dubai Research Advisory Committee) addressed the occurrence of AE specially any Serious Adverse Events (SAE).

Data Collection:
The baseline demographic characteristics and LEDD of the participants were retrieved from their medical records. The Leech score was recorded on abdominal X-ray and those scoring above 5 were selected. Informed written consent was obtained for the study. Racial characteristics were recorded as per self-identification supported by the Office for National Statistics methodology on identification of ethnicity [23]. Patients underwent baseline assessment with clinical scales as detailed above as well as a baseline Leech score. The 3-2-1 bowel cleansing regime was administered and data collected at 3 and 6 months following the interventions. During the study duration the patients were asked to keep all concomitant Dopamine Replacement Therapy (DRT) constant unless the clinical scenario changed and clinicians and patients agreed to changes in DRT such as reduction or increase. Lifestyle, especially diet and water intake were kept stable and at baseline level as far as possible.

Data analysis
Descriptive statistics were calculated for all study variables. Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as means and standard deviations (SDs).

To evaluate changes in administered scale scores across the three assessment time points (baseline, T0; 3 months, T1; and 6 months, T2), repeated-measures one-way analyses of variance (ANOVAs) were performed. Pairwise post hoc comparisons were adjusted using the Bonferroni correction for multiple testing.

To account for disease severity (Hoehn & Yahr [H&Y] stage) and ethnicity (Asian, Arab, and Caucasian patients), mixed-design ANOVA models were additionally conducted for NMSS constipation and Leech scores. These models included time as the within-subject factor and H&Y stage or ethnicity as the between-subject factor, together with the time × group interaction term. Where significant effects were identified, Bonferroni-adjusted post hoc comparisons and polynomial within-subject contrasts were performed to further characterize longitudinal changes.

Ethical Approval:
All Participants underwent neurological evaluations and specific assessments for PD, conducted by qualified healthcare professionals. This review received ethical approval from King's College Hospital London, Dubai Research Ethics Committee (REC/K22(2026). It was also carried out in compliance with the General Data Protection Regulation (GDPR) as endorsed by the UAE Parkinson's expert group and the Parkinson's Association UAE. Patients recruited for the study were invited to attend a baseline visit for assessments alongside their caregivers. Caregivers were required to provide informed consent and maintain regular contact with the patient for a minimum of 20 hours per week.

Results:
A total of 100 patients with Parkinson's disease (PD) and fecal loading and constipation were audited, and the baseline characteristics of the study participants including ethnic distributions are shown in Table 1. Data is for 99 patients as in 1 patient full set of data was not available.

Table 1 Baseline characteristics of the 3-2-1 bowel cleansing regime participants including ethnic distributions.

		N	%
Sex	Man	59	59.6
	Woman	40	40.4
Ethnicity	Arab	47	47.5
	Asian	26	25.3
	White Caucasian	27	27.3
;	AKD	50	50.5
	TD	36	36.4
	Mixed	14	13.1
H&Y	2	4	3.0
	2.5	19	19.2
	3	55	55.6
	3.5	22	22.2
	Range	**Mean**	**SD**
Age (years)	50-88	67.34	7.84
PD Duration (years)	2-17	7.41	2.25
Weight (kg)	46-80	60.8	8.84
BMI (kg/m^2)	12-30	22.2	3.59
LEDD (baseline) (mg)	350-2675	1143.78	348.70

PD= Parkinson's Disease, H&Y= Hoehn & Yahr, BMI= Body Mass Index, LEDD = Levodopa Equivalent daily dose,, AKD=Akinetic-Dominant, TD= Tremor dominant

Among the PD patients, 47.5% were of Arabic origin, 25.3% South Asian and 27.3% were white Caucasian. 50.5% were of the akinesia dominant (AKD) motor subtype of PD while 36.4% with tremor dominant (TD) subtype and rest mixed pattern. H&Y stage ranged from stage 2 (only 3%) to 3.5, most being at stage 3 while age ranged from 50 to 88 yrs. Other variables such as duration of PD, body mass index (BMI) as well as LEDD are shown in Table 1.

Clinical improvement rates in key outcome variables (NMSS (constipation), Leech scores after 3-2-1 bowel cleansing regime implementation).

In our study, evaluation 99 patients (table 2) at baseline (T0), 3 months (T1) and 6 months (T2) Using the Wilcoxon-Mann-Whitney test to compare T0 vs T1 and T0 vs T2 we report significant differences (all P *<0.001)* between baseline and follow-up in all assessments, implying that the primary outcome measures (constipation and Leech scores) improved significantly in addition to all other scales-based assessment scores and the effects were associated with a significant reduction in LEDD scores after treatment. In particular, motor symptoms, as measured by the UPDRS Part III, showed significant improvement, as did dyskinesia severity, assessed with UPDRS Part IV. Scores related to wearing-off phenomena also decreased, and the LEDD was reduced following treatment, suggesting a beneficial therapeutic effect (Table 2).

Table 2 Data from all assessment parameters at baseline (T0), 3 months (T1) and 6 months (T2).

	T0 (baseline)		T1 (3 months)		T2 (6 months)		p[a]
	Mean	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**	
UPDRS-3	27.96	4.01	22.21	2.96	21.06	3.29	<0.001
UPDRS-4	15.29	3.13	8.45	2.32	6.39	2.24	<0.001
NMSS Constipation	10.6	0.97	5.45	1.01	3.52	1.12	<0.001
Leech score	11.33	1.46	5.9	1.16	4.32	0.67	<0.001
WOQ	6.81	1.16	3.95	0.92	2.16	0.56	<0.001
LEDD (mg)	1143.78	348.70	632.83	164.84	611.62	141.61	<0.001

[a] *One-way ANOVA with Bonferroni correction.*

UPDRS=Unified Parkinson's Disease Rating Scale, NMSS= Non-Motor Symptoms Scale, WOQ= Wearing-Off Questionnaire, LEDD= Levodopa Equivalent daily dose

Constipation was the key outcome clinical variable and association between NMSS domain 6 related constipation item and clinical assessments, LEDD, age, PD duration and BMI were also examined using Spearman´s rank correlation coefficients and no correlation between NMSS constipation and the rest of variables at baseline or follow-up were noted.

Association between NMSS Constipation score, Leech scores and H&Y stage:
Association of constipation (as assessed by NMSS constipation item), Leech score changes in patients at H&Y stage 2 and stage 3 (for analysis purposes, H&Y stages 2 & 2.5 and 3 & 3.5 are merged) were examined and shown in Table 3. NMSS constipation scores improved significantly over time (p<0.001), comparing T0, T1 and T2, in both groups of patients. A subgroup analysis by H&Y stage showed that constipation improved at 3 and 6 months in both stage 2 and stage 3 patients, but the benefit was greater in stage 2, especially at 6 months. The linear *time × HY level* interaction was significant (F (1, 97) = 5.24, p = .024, ηp^2 = .051). (Table 3). In relation to Leech score, while there were significant differences in NMSS constipation scores over time (p<0.001), comparing T0, T1 and T2, in both groups of patients, the linear *time × HY level* interaction was not significant (F(1, 97) = 1.18, p = .280, ηp^2 = .012).

Table 3: Association of NMSS constipation and Leech scores changes in PD patients at H&Y stage 2 and stage 3 following the proximal colonic irrigation and 3-2-1 bowel cleansing regime.

	T0 (baseline)		**T1 (3 months)**		**T2 (6 months)**		
NMSS Constipation	**Mean**	**SD**	**mean**	**SD**	**mean**	**SD**	***p*[a]**
H&Y2	10.50	1.01	5.09	0.68	2.91	1.15	*<0.001*
H&Y3	10.60	0.96	5.56	1.07	3.69	1.06	*<0.001*
Leech score							
H&Y2	11.45	1.50	6.09	1.11	4.14	0.83	*<0.001*
H&Y3	11.30	1.45	5.84	1.71	4.38	0.61	*<0.001*

[a] *Mixed ANOVA with post-hoc testing*
H&Y= Hoehn & Yahr

Association between constipation and Leech score and ethnicity:
When patients were stratified by ethnicity, both the NMSS constipation score and the Leech score showed significant improvement over time in all three groups: Asian, Arab, and Caucasian patients (all p< 0.001) (Table 4). In relation to constipation, there were significant differences in NMSS constipation scores over time (p<0.001), comparing T0, T1 and T2, in the three groups of patients. However, the linear *time x ethnicity* interaction was not significant for NMSS constipation (F (2, 96) = 2.32, p = .103, ηp^2 = .046). Leech scores also showed significant differences over time (p<0.001), comparing T0, T1 and T2, in all three groups of patients (table 4). However, the linear *time x ethnicity* interaction was not significant for NMSS constipation (F (2, 96) = 2.32, p = .103, ηp^2 = .046) or for Leech score (F (2, 96) = 0.506, p = .605, ηp^2 = .010).

Table 4 Changes after treatment and association of NMSS constipation and Leech scores stratified by ethnicity

	T0 (baseline)		**T1 (3 months)**		**T2 (6 months)**		
NMSS Constipation	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	***p*[a]**
Arab	10.79	1.02	5.62	1.26	3.57	1.17	*<0.001*
South Asian	10.48	0.87	5.04	0.73	3.12	1.13	*<0.001*
Caucasian	10.37	0.93	5.56	0.58	3.78	0.93	*<0.001*
Leech scores	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	***p*[a]**
Arab	11.49	1.44	6.04	1.14	4.32	0.73	*<0.001*
South Asian	10.92	1.29	5.64	0.86	4.08	0.57	*<0.001*
Caucasian	11.44	1.60	5.89	1.40	4.56	0.58	*<0.001*

Discussion:

The present study represents the first evaluation of clinical improvement rates in constipation and a range of motor parameters as well as Leech scores among a cross racial PD cohort especially patients with advanced Parkinson's disease (APD)with refractory constipation managed by a locally developed and specific proximal colonic irrigation intestinal decontamination programme (the 3-2-1 bowel cleansing regime). In addition, we also show tolerability and efficacy of this regime in Arab, South South Asian and White Caucasian cohorts over a 6-month period although in an uncontrolled, unblinded study. These findings suggest that targeted modulation of the gut environment may have sustained therapeutic value in PD, particularly in individuals with APD usually characterised by troublesome motor fluctuations, constipation and complications of long-term oral dopaminergic therapy. Targeting the large bowel microbiota has been topical and widely attempted including a recent double-blind placebo-controlled study of fecal microbiota transplantation and therefore, our large bowel focused bowel cleansing strategy seems a feasible pragmatic option to use [3].

The key finding is the improvement of severe and troublesome constipation and fecal loading (as shown by abdominal X-Rays and Leech scores) which in turn is associated with significant improvements in UPDRS Parts 3 and 4 at both 3- and 6-months following implementation of 3-2-1 bowel cleansing regime. There is increase in time to ON after levodopa but also reduction in motor fluctuations such as wearing off and dyskinesia. Importantly, the persistence of this effect over 6 months suggests that the observed benefit was not merely transient but may reflect a durable and sustained change in symptom control. This is consistent with the concept that GI dysfunction and intestinal dysbiosis may contribute to impaired levodopa response and fluctuation severity in APD which can be managed by strategies focussed on intestinal decontamination and more recently fecal transplantation [3].

Our results are broadly in keeping with the findings of Baizabal-Carvallo et al. who reported improvement in dyskinesias and motor complications following a "bowel cleansing" approach combining saline colon enemas with sodium phosphate (Fleet®), oral rifaximin, and polyethylene glycol-3 in 14 patients at 10 days of follow-up. In that study, significant improvement was observed in MDS-UPDRS Part IV, functional impact of motor fluctuations, and complexity of motor fluctuations, with marked to moderate improvement in dyskinesia in 57% of cases [8]. Although the intervention and follow-up duration differed from ours, both studies support the hypothesis that intestinal decontamination or microbiome-directed therapy may positively influence motor complications in PD as well as constipation.

In our cohort, the magnitude of improvement in both UPDRS Part 3 and Part 4 was evident at 3 months and remained significant at 6 months, indicating a sustained therapeutic response after 3-2-1 bowel cleansing. This improvement was accompanied by a marked, significant reduction in LEDD, the reduction in dopaminergic burden, together with improved clinical ratings, suggests enhanced responsiveness to levodopa and improved overall control of parkinsonism. Such findings are particularly important in APD, where escalating oral medication doses often fail to provide stable symptom control and device aided non-oral therapies are required.

The improvement in UPDRS Part 4 is especially relevant, as this section captures motor fluctuations and levodopa-related complications that substantially affect quality of life in APD. The parallel improvement in WOQ scores in our study suggests that the benefit of 3-2-1 bowel cleansing may be driven in part by reduced end-of-dose wearing off and more consistent levodopa effect. This interpretation is supported by reports showing that gut-directed interventions, including probiotics such as Symprove, may improve time to ON and levodopa pharmacokinetics such as time to on after levodopa intake in PD [24-26]. Taken together, these findings strengthen the emerging view that GI factors and changes in gut microbiota are not merely secondary consequences of PD but may actively contribute to disease expression and therapeutic variability.

Several mechanisms may explain the beneficial effects observed. Intestinal decontamination may reduce bacterial overgrowth, improve gut motility, alter microbial metabolism of levodopa, and decrease inflammation-related impairment of gut–brain signalling. But these are speculations. In APD, delayed gastric emptying, small intestinal bacterial overgrowth, and dysbiosis may all contribute to erratic levodopa absorption and fluctuating motor response [27]. By addressing these factors, 3-2-1 bowel cleansing regime may improve

both levodopa bioavailability and the consistency of symptom control although this is speculative. The sustained reduction in LEDD observed in our study further supports the possibility that improved intestinal function can translate into lower medication requirements without loss of symptomatic benefit.

Sub analysis of the data as presented in Tables 3 and 4 merit discussion. An additional important finding from this study relates to the effect of the 3-2-1 bowel cleansing on constipation, which was clinically assessed using the constipation subitem of the PD NMSS. The NMSS is a validated instrument comprising 30 items across nine domains, including a GI domain that specifically captures constipation [20]. Each item is scored according to both severity and frequency, with total scores ranging from 0 to 360. In our cohort, the NMSS constipation sub score improved significantly from baseline to both 3 and 6 months, with each comparison reaching statistical significance.

To complement the symptom-based assessment, we also used Leech scoring, an abdominal radiographic scoring system that provides an objective measure of faecal loading and impaction and is therefore a useful surrogate marker of constipation [16]. Importantly, the improvement observed in the constipation subitem of the NMSS was mirrored by a concurrent and significant reduction in Leech scores at both 3 and 6 months (Tables 3), supporting the clinical relevance of the intervention and suggesting that symptom improvement was accompanied by objective improvement in bowel loading.

The observed improvement in constipation after implementation of the 3-2-1 bowel cleansing regime is also consistent with recent evidence from a four-strain probiotic trial in Parkinson's disease, which similarly reported benefit in constipation outcomes as well as a single fecal microbiota transplantation trial which showed improvement in nonmotor symptoms [3, 26]. Taken together, these findings support the growing concept that interventions targeting the gut environment may have beneficial effects not only on GI symptoms but also on broader clinical outcomes in PD.

The mechanism by which 3-2-1 bowel cleansing regime may lead to sustained improvement in motor state, motor fluctuations, and constipation remains highly speculative and cannot be determined from the present study. However, several biological pathways may be relevant. Preclinical data suggest that lipopolysaccharide (LPS), an endotoxin derived from gut microbiota, may contribute to motor dysfunction and fluctuations, potentially through inflammatory pathways, and that such effects may be attenuated by gut decontamination [30]. Other plausible mechanisms include reduced release of tumour necrosis factor-α, which may be induced by LPS, as well as modulation of nitric oxide synthase activity within the nervous system [33]. Another possible explanation is the successful treatment of Small Intestinal Bacterial Overgrowth (SIBO), which has been associated with motor fluctuations in PD. In a study of 182 patients, SIBO was linked to fluctuations in motor performance [34]. It is possible that the 3-2-1 bowel cleansing reduced SIBO in our cohort, although this was not specifically measured. Moreover, unlike the study by Baizabal-Carvallo et al we did not use targeted luminal antibiotics, so the contribution of SIBO eradication in our study remains inferential rather than proven [8].

A subgroup analysis by H&Y stage showed that while constipation improved at 3 and 6 months in both stage 2 and stage 3 patients the benefit was greater in stage 2 as measured by the NMSS (Table 3). Clinically this may suggest that the effect of the 3-2-1 bowel cleansing can be started as early as H&Y stage 2 PD and that bowel decontamination and GI "cleansing" strategies are more effective earlier in the disease course, when autonomic dysfunction and enteric pathology may be less advanced. However, larger studies are needed to confirm this observation.

A unique aspect of this study is the examination of these effects on gut function in a cross racial cohort, a fact that is increasingly recognised as an unmet need in PD research and care, especially clinical trials [14]. The fact that our findings were observed in a cross-racial cohort, albeit in a small sample size also increases their potential generalizability [35]. PD is a heterogeneous disorder with motor and nonmotor subtypes and it could be speculated that responses to GI interventions may vary across different populations due to differences in diet, microbiome composition, disease phenotype, and access to treatment. For the first time we show statistically significant benefit of the 3-2-1 bowel cleansing in APD across 3 racial group thus demonstrating benefit across

racial groups and signpost the fact that this intervention may have broad applicability, although clearly, larger controlled cross racial studies are needed to confirm this.

The issue of racial and ethnic variation in treatment response across chronic diseases, including stroke, pain, arthritis, and PD, is increasingly recognised [28-33]. The American Thoracic Society has proposed a multilevel framework to improve the inclusion of minority populations in clinical research across pulmonary, critical care, and sleep medicine, and similarly there is an urgent need to include under-represented groups in PD studies [34]. Our dataset is notable in that it includes a relatively diverse population of Arabic, South Asian, and White Caucasian patients who underwent 3-2-1 bowel cleansing. We have previously reported on the efficacy of device-aided therapies for APD in a similarly diverse patient population from our centre [27].

Including diverse populations in studies of gut microbiota-targeted interventions is particularly important, as diet, environment, hydration, and cultural lifestyle factors may influence gut microbial composition and function across racial groups [35, 36]. In our analysis, constipation scores improved significantly over time in all three ethnic groups at baseline, 3 months, and 6 months .The reasons for these intergroup differences are not clear. They may reflect variation in dietary patterns, fluid intake, environmental exposure, or other lifestyle-related factors that affect GI transit and microbiota composition, but this is speculative. Weather and hydration status may also be contributory, especially in hotter climates where constipation burden may be influenced by reduced water intake. These observations warrant further investigation in larger, adequately powered studies.

Several limitations of this study should be acknowledged. First, the study design being an exploratory single-arm intervention study without a comparator does not allow definitive causal inference, and placebo effects or regression to the mean cannot be excluded. Second, the sample size was limited although this is the world's first cross racial study of this kind. The cohort likely represents patients with advanced disease, which may reduce generalizability to earlier stages of PD. Third, the intervention was multimodal, making it difficult to determine the relative contribution of each component of 3-2-1 regime. Finally, a longer follow-up will be required to determine whether the observed benefits persist beyond 6 months and whether repeated treatment is necessary to maintain effect.

Despite these limitations, our findings provide further evidence that intestinal decontamination may represent a promising adjunctive strategy for managing motor fluctuations and reducing dopaminergic burden in APD. The consistency of improvement across motor scores, fluctuation measures, and LEDD suggests a meaningful clinical effect across all 3 racial groups. Further randomized, controlled studies are warranted to clarify the efficacy, mechanism, and durability of this approach, and to determine which subgroups of patients are most likely to benefit.

Clinical Implications:

The clinical implications of these findings are potentially important. First, our data strengthen the evidence that intestinal decontamination strategies, including the 3-2-1programme, may improve constipation in APD, particularly in patients with marked faecal loading. Second, the concordance between symptom-based improvement and radiographic reduction in faecal impaction suggests that abdominal X-Ray assessment using Leech scoring may serve as a useful adjunct in routine clinical care, especially for identifying patients who may benefit from bowel-targeted intervention.

Third, the findings support the broader therapeutic concept that modulation of the gut microbiota may improve not only GI symptoms but also motor fluctuations and possibly levodopa responsiveness in APD as recently showed in a probiotic trial. Finally, our results suggest that 3-2-1 can be applied across ethnically diverse patient groups, although response patterns may vary between populations. This reinforces the need for personalised management approaches and for future studies to examine whether demographic, dietary, or microbiome-related factors influence treatment response.

Conclusion:
In summary, our findings suggest that screening for faecal impaction using abdominal radiography may be a valuable component of the care pathway in APD, particularly in patients with high Leech scores and prominent constipation. A structured bowel decontamination strategy may therefore represent an important adjunctive intervention in the multidisciplinary management of APD.

Disclosure of potential conflicts of interest
The authors have no competing interests to declare that are relevant to the content of this article. The authors have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript, financial or proprietary interest in any material discussed in this article.

Compliance with Ethical Standards
All procedures performed in studies involving human participants were in accordance with the ethical standards of King's College Hospital London Dubai, UAE and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the patients included in the study.

Data Availability Statement:
The datasets are available from the corresponding author (vinod.metta@nhs.net) upon reasonable request.

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