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ORIGINAL ARTICLE

White Diet with split-dose Picosalax is preferred, better tolerated, and non-inferior to day-before clear fluids with polyethylene glycol plus sodium picosulfate-magnesium citrate for morning colonoscopy: A randomized, non-inferiority trial

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Abstract

Background and Aim: Bowel preparations with polyethylene glycol (PEG) and clear fluids are often poorly tolerated. We compared an innovative low-residue White Diet and low-volume, split-dose Picosalax with the standard preparation at our institution of day-before clear fluids and combination PEG plus sodium picosulfate/magnesium citrate (SPMC).

Methods: Adults undergoing morning colonoscopy were randomized to either the White Diet and split-dose, two sachets of Picosalax (WD/PICO) or day-before clear fluids and 1-L PEG plus two sachets of SPMC (CF/PEG + SPMC). The primary endpoint was successful bowel preparation defined by an Ottawa bowel preparation score ≤ 6. An intention-to-treat analysis with a predefined non-inferiority margin of 15% was used to compare efficacy.

Results: A total of 250 patients were randomized (125 WD/PICO and 125 CF/PEG + SPMC). WD/PICO was non-inferior to CF/PEG + SPMC for successful bowel preparation by intention-to-treat analysis (58% WD/PICO *vs* 62% CF/PEG + SPMC, 95% CI: −14.2 to 6.2%) and per-protocol analysis (64% WD/PICO *vs* 65% CF/PEG + SPMC, 95%CI: −11.3 to 9.4%). Patients in the WD/PICO group reported greater satisfaction with the diet ($P < 0.001$), greater ease of following the diet ($P < 0.001$), and improved experience compared with prior colonoscopy ($P < 0.0001$), less bloating ($P = 0.02$), less weakness ($P = 0.046$), less hunger ($P < 0.0001$), and less interference with daily activities ($P = 0.001$). Procedure/withdrawal times and adenoma detection rates were similar between groups.

Conclusion: Bowel preparation with the White Diet and low-volume, split-dose Picosalax was preferred and better tolerated without detriment to bowel preparation success compared with clear fluids and combination PEG plus SPMC for morning colonoscopy.

Introduction

Colonoscopy has been shown to reduce colorectal cancer (CRC) morbidity and mortality,[1–3] but the procedure requires high-quality bowel preparation. Many standard bowel preparations consist of large volumes of poorly palatable laxatives which many patients are unable to tolerate due to nausea, vomiting, bloating, and headache. Poor tolerance of the bowel preparation may reduce compliance and completion of the bowel preparation and adversely affect the final bowel cleanliness. To improve tolerability and compliance, low-volume bowel preparations such as Picosalax are increasingly used with improved tolerability and comparable efficacy to polyethylene glycol (PEG) bowel preparation.[4–6]

Sodium picosulfate/magnesium citrate (SPMC) preparations contain two active ingredients with different mechanisms of action; sodium picosulfate is a stimulant laxative and magnesium oxide combined with citric acid acts as an osmotic laxative.[7] Combination preparations with PEG plus SPMC may be better tolerated than high-volume PEG alone[8] and are standard practice in many Australian hospitals and endoscopy centers. Several randomized controlled trials and a meta-analysis confirm that

splitting the bowel preparation dose between the day prior and the day of the procedure results in both improved bowel cleansing and patient tolerance compared with day-prior regimens.[9–12]

In addition to the type and timing of the cleansing agent used, diet may influence the tolerability and quality of bowel preparation. Typically, patients are instructed to take a clear fluid diet the day prior to colonoscopy because high-fiber foods may impair bowel preparation. Recent randomized trials, however, suggest that a low-fiber diet[13] or even regular diet[14] the day before colonoscopy with split-dose bowel preparation is associated with better tolerance of the preparation and comparable or better colon cleansing compared with a clear fluid-only diet. The White Diet is a novel, low-residue diet of white-colored foods, which is better tolerated without detriment to bowel preparation quality compared to a clear fluid diet in patients undergoing colonoscopy.[15]

As part of the implementation of "state-of-the-art" bowel preparation strategy at our institution, the aim of this prospective, single-blinded, randomized, non-inferiority trial was to determine whether an innovative low-residue White Diet and low-volume, split-dose Picosalax is better tolerated, but with comparable bowel preparation quality, to the standard preparation at our institution of day-before clear fluids and combination PEG plus SPMC for morning colonoscopy.

Methods

Study design. This was a prospective, randomized, single-blinded, non-inferiority trial comparing bowel preparation with the White Diet and low-volume, split-dose Picosalax with day-before clear fluids and combination PEG plus SPMC for morning colonoscopy. The study was carried out at a single tertiary referral hospital (The Alfred Hospital, Melbourne, Australia). The Human Ethics Committee at The Alfred Hospital approved the study protocol and all subjects gave written informed consent. The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000765729).

Study population. Consecutive patients having outpatient morning colonoscopy were invited to take part in the study from April 2013 to November 2014. Inclusion criteria were adult patients (aged ≥18 years) undergoing colonoscopy for clinically accepted indications. Exclusion criteria included severe renal impairment (estimated glomerular filtration rate < 30), severe heart failure (New York Heart Association Class III or IV), and conditions considered to be contraindications to colonoscopy such as suspected bowel perforation, gastric outlet obstruction, toxic megacolon, severe colitis, pregnancy, or lactation. Patients with hypersensitivity to PEG or SPMC including patients with phenylketonuria or glucose-6-phosphate dehydrogenase deficiency, due to the presence of aspartame or ascorbic acid in the bowel preparation, were excluded.

Study protocol. Eligible patients were randomized to one of the two treatment arms on a 1:1 basis using a computer generated block randomization list. Patients randomized to the intervention arm (White Diet and low-volume Picosalax—WD/PICO) received the White Diet for 2 days prior to the procedure, then split-dose Picosalax (consisting of 10 mg sodium picosulfate, 3.5 g magnesium oxide, and 2 g citric acid ; Ferring Pharmaceuticals, Melbourne, Australia) consisting of two sachets of SPMC taken at 21:00 h the day before and at 04:00 h on the day of the procedure with 200 mL of water per hour allowed until 06:00 h. As described previously,[15] the White Diet comprises white-colored foods of low residue (Table 1).

Patients assigned to the standard preparation at our institution (CF/PEG + SPMC) received day-before light breakfast, then clear fluids only, and combination 1 L PEG (Glycoprep-C, consisting of macrogol 3350, sodium sulfate, sodium chloride, and potassium chloride; Fresenius Kabi Pty Ltd, Pymble, Australia) taken at 18:00 h the day before plus two sachets of SPMC (PicoPrep, consisting of 10 mg sodium picosulfate, 3.5 magnesium oxide, 12.0 g citric acid, and 36 mg aspartame; Fresenius Kabi Pty Ltd) taken at 17:00 and 19:00 h the day before the procedure with fasting from midnight. All participants received a single-page handout with standardized instructions for the allocated bowel preparation and diet. Participants were asked to complete a food diary for 2 days prior to their colonoscopy and a questionnaire on the acceptance and tolerability of the bowel preparation. Endoscopists were blinded to the type of bowel preparation taken by the patient and completed a datasheet following the procedure.

The primary outcome was successful bowel preparation as defined by an Ottawa bowel preparation score ≤ 6.[16] The Ottawa scale (0–14 points) combines the preparation score (0 = excellent, 1 = good, 2 = fair, 3 = poor, and 4 = inadequate) of three bowel segments (left colon, transverse colon, and right colon) and the amount of fluid in the entire colon (0 = low, 1 = moderate, and 2 = large). Secondary outcomes included tolerability, acceptance, and compliance with the allocated bowel preparation regimen and colonoscopy outcomes such as adenoma detection and withdrawal time.

Table 1 Patient instructions for food and fluid permitted in the White Diet

2 Days before your colonoscopy only consume foods and fluids permitted in the White Diet
White Diet foods and fluids permitted
Milk (regular, low fat, skim), water, lemonade, soda or mineral water, clear (not colored) Gatorade, or other sports drinks
Regular white bread/toast, rice bubbles, white rice, regular pasta, potatoes (peeled), rice noodles, plain rice crackers, white flour, sugar
Eggs, chicken breast (no skin), white fish fillet (no skin)
Plain cream cheese, cheddar cheese, ricotta, feta, cottage, parmesan or mozzarella cheese, white sauce
White-colored yoghurt (no added fruit or inulin), mayonnaise, cream, sour cream, butter and margarine, oil for cooking
White chocolate, vanilla ice cream, lemonade icy-pole, clear jelly, custard, "milk bottles" (white confectionery)
Foods to be excluded (not allowed)
Anything not listed above
Other white foods including pears, parsnip, cauliflower, onion, high-fiber white breads, tofu, coconut, porridge, banana, mushrooms, semolina, couscous, popcorn

Sample size calculation and statistical analysis. The sample size was calculated assuming a 75% bowel preparation success rate with clear fluids and a non-inferiority margin of 15% consistent with previous non-inferiority trials for bowel preparation.[17,18] To be adequately powered with 80% power at a one-sided alpha level of 5%, 104 patients were required in each group. An intention-to-treat (ITT) analysis was used to compare efficacy for the primary outcome with non-inferiority established if the lower confidence limit for the difference in effect was above −15%. A per-protocol analysis was also carried out for the primary efficacy endpoint, in which patients with major protocol violations were excluded. Comparisons of secondary outcomes were performed using the Student's *t*-test for normally distributed continuous variables, Wilcoxon rank-sum test for non-normally distributed continuous variables, and chi-square or Fisher's exact test as appropriate for categorical variables. Two-sided *P*-values <0.05 indicated statistical significance. Statistical analyses were performed with Stata software version 14 (StataCorp, TX, USA).

Table 2 Baseline demographic and clinical characteristics of patients

	Type of preparation		*P*-value
	WD/PICO (*n* = 125)	CF/PEG + SPMC (*n* = 125)	
Age (year), mean ± SD	54.5 ± 13.4	54.0 ± 13.1	0.81
Male gender, *n* (%)	70 (56)	65 (52)	0.53
Weight (kg), mean ± SD	79.2 ± 15.7 (*n* = 94)	77.3 ± 19.4 (*n* = 99)	0.45
Height (cm), mean ± SD	171.4 ± 10.3 (*n* = 91)	169.8 ± 14.4 (*n* = 99)	0.36
Diabetes, *n* (%)	6 (5.6) (*n* = 107)	5 (4.4) (*n* = 113)	0.69
Opioids, *n* (%)	16 (15.2) (*n* = 105)	14 (12.5) (*n* = 112)	0.56
Laxative use, *n* (%)	11 (10.3) (*n* = 107)	15 (13.4) (*n* = 112)	0.48

CF, clear fluid; PEG, polyethylene glycol; PICO, picosalax; SPMC, sodium picosulfate/magnesium citrate; WD, White Diet.

Results

Two hundred and fifty patients were randomized and, after exclusions, 112 patients were included in the WD/PICO group and 118 patients in the CF/PEG + SPMC group (Fig. 1). Patient demographics and clinical characteristics were similar between groups (Table 2).

ITT analysis of the primary efficacy endpoint showed that successful bowel preparation (defined by an Ottawa bowel preparation score ≤ 6) was 57.6% in the WD/PICO group and 61.6% in the CF/PEG + SPMC group (Table 3). The difference between groups was −4.0% (95% CI: −14.2 to 6.2%), suggesting non-inferiority between groups. Per-protocol analysis showed that successful bowel preparation was 64.3% in the WD/PICO group and 65.3% in the CF/PEG + SPMC group (difference: −1%, 95% CI: −11.3 to 9.4%) indicating non-inferiority. Colonoscopy outcomes are shown in Table 4. There were no significant differences between groups with regard to insertion time, withdrawal time, cecal intubation rate, polyps removed, or detection of CRC.

Patient-reported satisfaction scores and tolerance to bowel preparation are shown in Tables 5 and 6, respectively. Patients in the WD/PICO group reported significantly higher satisfaction with the diet and greater ease in following the diet compared with the CF/PEG + SPMC group ($P < 0.001$). Patients in the WD/PICO group who had undergone previous colonoscopy reported significantly higher diet satisfaction and improved overall experience compared with their previous bowel preparation ($P < 0.0001$). Patients in the WD/PICO group also reported less bloating ($P = 0.02$), weakness ($P = 0.046$), hunger ($P < 0.0001$), and less interference to daily activities ($P = 0.001$).

Discussion

An adequate bowel preparation prior to colonoscopy is important as poor preparations are associated with missed adenomas,[19] longer and more difficult procedures, higher rates of incomplete examinations and the need for repeat procedures or shorter surveillance intervals.[20] The ideal bowel preparation would reliably cleanse the colon of all fecal material, be well tolerated by patients, be inexpensive, and have low risk of adverse events. Although a 4-L split-dose PEG preparation is considered the

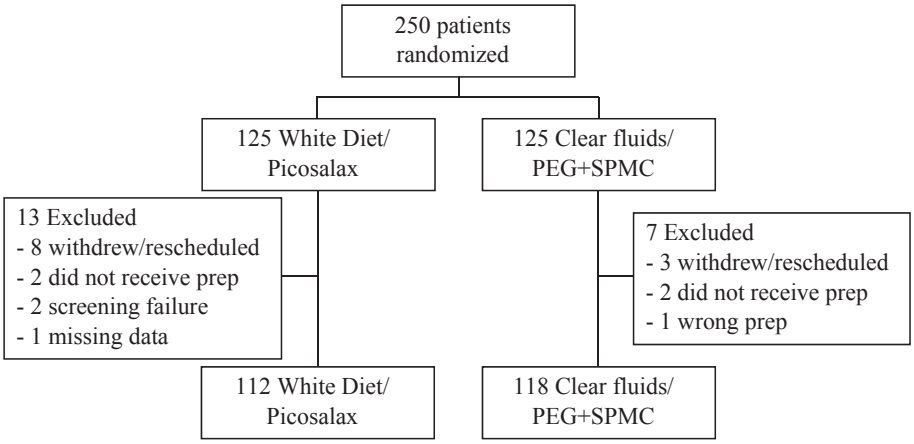

Figure 1 Enrollment flow chart. PEG, polyethylene glycol; SPMC, sodium picosulfate/magnesium citrate.

Table 3 ITT and per-protocol analyses of the primary efficacy endpoint

	Total	Type of preparation	
		WD/PICO	CF/PEG + SPMC
ITT analysis			
Number of patients in ITT analysis	250	125	125
Successful bowel preparation, *n* (%)	149 (59.6)	72 (57.6)	77 (61.6)
Difference between groups (one-sided 95% CI)		–4.0% (–14.2 to 6.2%)	
Per-protocol analysis			
Number of patients in per-protocol analysis	230	112	118
Successful bowel preparation, *n* (%)	149 (64.8)	72 (64.3)	77 (65.3)
Difference between groups (one-sided 95% CI)		–1.0% (–11.3 to 9.4%)	

CF, clear fluid; ITT, intention to treat; PEG, polyethylene glycol; PICO, picosalax; SPMC, sodium picosulfate/magnesium citrate; WD, White Diet.

gold-standard bowel preparation,[21] PEG-based preparations are often poorly tolerated, and side effects including bloating, nausea, and vomiting may lead to a failure to complete the preparation. Combination PEG and SPMC with a clear fluid diet the day before colonoscopy is the current standard bowel preparation at many Australian institutions and endoscopy centers. In this study, we performed a randomized, prospective, endoscopist-blinded, non-inferiority trial comparing a novel low-residue White Diet with low-volume, split-dose Picosalax with a standard bowel preparation of day-before clear fluids with combination PEG plus SPMC for morning colonoscopy. We found that low-volume, split-dose Picosalax with the White Diet was significantly better tolerated without detriment to bowel preparation success.

The White Diet, recently described by Butt *et al.*,[15] is a pre-colonoscopy low-residue diet of white or cream-colored foods. In that randomized controlled trial of 226 patients, the White Diet in conjunction with a 2-L PEG with ascorbate bowel preparation was preferred by patients with less hunger and interference to daily activities without detriment to bowel preparation

Table 4 Colonoscopy outcomes

	Type of preparation		*P*-value
	WD/PICO (*n* = 125)	CF/PEG + SPMC (*n* = 125)	
Past colonic resection, *n* (%)	4 (3.6) (*n* = 110)	6 (5.2) (*n* = 116)	0.75
Cecal intubation, *n* (%)	110 (98.2) (*n* = 112)	116 (98.3) (*n* = 118)	1.00
TI intubation, *n* (%)	89 (79.5) (*n* = 112)	97 (82.2) (*n* = 116)	0.60
Repeat scope due to poor preparation, *n* (%)	5 (4.5) (*n* = 111)	4 (3.4) (*n* = 118)	0.74
Insertion time (min), median (IQR)	9 (6–14) (*n* = 107)	9 (5–14) (*n* = 115)	0.95
Withdrawal time (min), median (IQR)	10 (7–14) (*n* = 95)	10 (8–15) (*n* = 87)	0.43
Total time (min), median (IQR)	20 (15–26) (*n* = 95)	20 (16–26) (*n* = 87)	0.74
Polyps removed, *n* (%)	34 (30.4) (*n* = 112)	38 (32.8) (*n* = 116)	0.70
Adenoma detection rate, *n* (%)	24 (21.4) (*n* = 112)	29 (24.6) (*n* = 118)	0.57
Colorectal cancer, *n* (%)	0 (0) (*n* = 107)	2 (1.7) (*n* = 115)	0.50

CF, clear fluid; IQR, interquartile range; PEG, polyethylene glycol; PICO, picosalax; SPMC, sodium picosulfate/magnesium citrate; TI, terminal ileum; WD, White Diet.

Table 5 Patient satisfaction with bowel preparation according to 5-point visual analog scale

	Type of preparation		*P*-value
	WD/PICO (*n* = 125)	CF/PEG + SPMC (*n* = 125)	
Understanding the diet, median (IQR)	1 (1–2) (*n* = 100)	1 (1–2) (*n* = 105)	0.76
Preparing food/fluids for the diet, median (IQR)	1 (1–2) (*n* = 100)	1 (1–2) (*n* = 104)	0.39
Sticking to/following the diet, median (IQR)	1 (1–2) (*n* = 100)	2 (1–3) (*n* = 102)	<0.001
Overall satisfaction with the diet, median (IQR)	1 (1–2) (*n* = 98)	2 (1–3) (*n* = 102)	<0.001
Previous colonoscopy, *n* (%)	54 (54.0) (*n* = 100)	65 (60.2) (*n* = 108)	0.37
Restricted to clear fluids last time, *n* (%)	48 (90.6) (*n* = 53)	54 (93.1) (*n* = 58)	0.73
Diet this time *versus* previous colonoscopy, median (IQR)	1 (1–2) (*n* = 48)	3 (3–3) (*n* = 53)	<0.0001
Overall experience this time *versus* previous colonoscopy, median (IQR)	1 (1–3) (*n* = 50)	3 (2–3) (*n* = 53)	<0.0001

CF, clear fluid; IQR, interquartile range; PEG, polyethylene glycol; PICO, picosalax; SPMC, sodium picosulfate/magnesium citrate; WD, White Diet.

Table 6 Patient tolerance to bowel preparation according to 5-point visual analog scale

	Type of preparation		*P*-value
	WD/PICO (*n* = 125)	CF/PEG + SPMC (*n* = 125)	
Bloating, median (IQR)	1 (1–1) (*n* = 88)	1 (1–2) (*n* = 100)	0.02
Abdominal cramping, median (IQR)	1 (1–2) (*n* = 89)	1 (1–2) (*n* = 101)	0.28
Nausea, median (IQR)	1 (1–2) (*n* = 92)	1 (1–3) (*n* = 101)	0.22
Headache, median (IQR)	1 (1–2) (*n* = 95)	2 (1–3) (*n* = 101)	0.13
Weakness, median (range)	1 (1–4) (*n* = 91)	1 (1–5) (*n* = 101)	0.046
Sleeping difficulty, median (IQR)	1 (1–3) (*n* = 94)	1 (1–3) (*n* = 101)	0.42
Hunger, median (IQR)	1 (1–2) (*n* = 92)	3 (2–4) (*n* = 104)	<0.0001
Interference with daily activities, median (IQR)	2 (1–2) (*n* = 92)	2 (1–3) (*n* = 104)	0.001
Vomiting post-bowel preparation, *n* (%)	5 (4.7) (*n* = 107)	7 (6.4) (*n* = 110)	0.59

CF, clear fluid; IQR, interquartile range; PEG, polyethylene glycol; PICO, picosalax; SPMC, sodium picosulfate/magnesium citrate; WD, White Diet.

quality or colonoscopy performance compared with a clear fluid diet.[15] Other randomized trials of diet liberalization during bowel preparation suggest that either low-fiber[13] or regular diet[14] the day before colonoscopy with split-dose bowel preparation is associated with improved tolerance and comparable or better colon cleansing compared with a clear fluid diet. In our study, patients taking the White Diet for 2 days reported higher overall satisfaction with the diet and higher satisfaction with the diet compared with any previous colonoscopy (>90% had clear fluid diet at previous colonoscopy). There was also significantly less bloating, weakness, hunger, and interruption to daily activities with the White Diet. Although the duration of the dietary restriction was longer in the White Diet group, our group has previously reported that the daily median energy intake with the White Diet was twice that of a clear fluid diet[15] which may contribute to the improved tolerance compared with a 24-h clear fluid diet. Furthermore, the use of white color as a guide to choose food is a simple strategy which patients found significantly easier to follow and the flexibility of the White Diet allows patients to individualize the diet according to personal dietary preferences. Importantly, patients taking the White Diet reported significantly greater ease in following the diet compared with clear fluids suggesting successful implementation of the diet. Improved patient satisfaction and tolerance during bowel preparation has several potential benefits including increased bowel preparation completion rates which may improve bowel preparation quality and increased likelihood of patients returning for surveillance or screening procedures.

In this study, patients taking the White Diet took a low-volume (two sachets), split-dose Picosalax bowel preparation, which was better tolerated and resulted in non-inferior bowel preparation compared with day-before clear fluids and 1 L PEG and two sachets of SPMC. Low-volume SPMC has been shown to have greater tolerability and equal or greater efficacy compared with sodium phosphate,[22] 2 L PEG and bisacodyl,[5,6] 2 L PEG with ascorbic acid,[23] 3 L of sulfate-free PEG,[24] and 4 L PEG preparations.[25] Non-inferiority of SPMC to PEG has also recently been shown in a meta-analysis.[26] Splitting the dose of either PEG or SPMC is preferred by patients and increases the quality of the bowel preparation compared with day-before regimens.[12,27] A split-dose bowel preparation for all patients or same day preparation for afternoon colonoscopy has been recommended in recent guidelines.[28] Although well tolerated and safe in most, there is a small increased risk of hyponatremia with SPMC in the elderly[29] and, therefore, PEG-based bowel preparation may be more appropriate in these patients.

There are some limitations to our study. We note the low bowel preparation success rates for both the WD/PICO (64.3% per protocol and 57.6% ITT) and CF/PEG + SPMC groups (65.3% per protocol and 61.6% ITT). Bowel preparation success in our study was defined by an Ottawa bowel preparation score ≤ 6 (range: 0–14), which may have been too stringent for determining adequacy of the bowel preparation. Recently, the US Multi-Society Task Force on CRC defined adequate bowel preparation as one that enables the endoscopist to follow the recommended screening and surveillance guidelines and the ability to detect lesions >5 mm in size (target of ≥85%).[30] Alternately, by including patients with risk factors for poor bowel preparation such as diabetes, opioid use, and laxative use (as a marker of constipation),[31] bowel preparation success rates in our study may have been lowered. A limitation of this study was that we compared groups with different dietary regimens (White Diet *vs* clear fluids), bowel preparation types (low-volume Picosalax *vs* combination PEG/SPMC), and bowel preparation dose timing (split-dose *vs* day-before) which makes it difficult to determine which of the study variables resulted in the improved tolerance of the bowel preparation found in the WD/PICO group. A further limitation of our study was that the bowel preparation success rate of 75% used in our sample size calculation was higher than the bowel preparation success rates found in our study which may have resulted in a smaller sample size and therefore reduced the power of our study. Finally, our study was a single-center, non-inferiority controlled trial and not powered to detect a significant difference in bowel preparation quality between groups.

In conclusion, a novel bowel preparation with the White Diet and low-volume, split-dose Picosalax was non-inferior for successful bowel preparation and better tolerated compared with a preparation of clear fluids and day-before combination PEG/SPMC. By utilizing modern bowel preparation strategies prior to colonoscopy such as dietary liberalization with the White Diet, split-dosing, and low-volume regimens, bowel preparations will be better tolerated by patients without compromising cleansing quality.

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