A randomised trial of topical polaprezinc to prevent oral mucositis in patients undergoing haematopoietic stem cell transplantation (ToPaZ Study)

Midori Nakagaki (midori.nakagaki@health.qld.gov.au)
Royal Brisbane and Women's Hospital
Glen A Kennedy
Royal Brisbane and Women's Hospital
Nicole C Gavin
Queensland University of Technology
Jason Butler
Royal Brisbane and Women's Hospital
Alexandra Clavarino
University of Queensland
Karen Whitfield
University of Queensland

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Abstract

Purpose

Oral mucositis (OM) is a common complication in haematopoietic stem cell transplantation (HSCT). Polaprezinc, an anti-ulcer drug, has been shown to be effective to prevent OM in several studies when administered topically and systemically. This study aimed to evaluate the effectiveness of topical polaprezinc in patients undergoing HSCT.

Methods

This was an open-label randomised clinical trial comparing polaprezinc and sodium bicarbonate mouthwashes for the prevention of severe OM in HSCT patients. Adult patients who received conditioning regimens at moderate to high risk of developing OM were included. The primary endpoint was the incidence of severe (WHO grade 3–4) OM. The secondary endpoints included duration of grade 3–4 OM, incidence and duration of Grade 2–4 OM, patient-reported pain and functional limitations.

Results

In total, 108 patients (55 test arm, 53 control arm) were randomised. There was no difference in the incidence of grade 3 to 4 OM (35% test arm versus 36% control arm). The secondary endpoints were not significantly different. In both arms, patients reported more throat pain compared to mouth pain.

Conclusions

Topical polaprezinc had no effect in prevention of OM in HSCT patients. Further research is required to evaluate the effects of systemic polaprezinc. The OM assessment tool needs to be reviewed as throat mucositis was a main issue in this study.

Trial registration

ACTRN12320001188921

Introduction

Oral mucositis (OM) is a common early complication in haematopoietic stem cell transplantation (HSCT). Patients with OM can suffer from pain, decreased function, emotional distress, insomnia, infection, decreased oral intake and malnutrition (1). OM also has economic implications due to prolonged hospital

stay, the need for additional support including antimicrobials, the use of Total Parenteral Nutrition (TPN) and Patient Controlled Analgesia (PCA) (1).

Despite a large number of clinical trials and available guidelines, effective interventions for the prevention and treatment of OM are limited. Palifermin is the only drug approved for the prevention of OM in HSCT patients. More interventions that are effective and safe in HSCT patients, preferably with easy access and low cost are needed to alleviate patient symptoms and enhance clinical outcomes.

Polaprezinc, also called zinc-L-carnosine, is a chelated and polymerised compound containing L-carnosine and zinc, and is licensed in Japan for the treatment of peptic ulcers (2, 3). It appears that the anti-ulcer effects are mainly due to zinc ion and thought to be a direct local effect (4, 5). The slow dissociation rate of polaprezinc in the stomach prolongs the local effects and L-carnosine increases the affinity to the ulcers (4, 6). Animal studies suggest that polaprezinc has anti-inflammatory action through suppressing inflammatory cytokines (7–9), in addition to ulcer healing and repair effects through its antioxidants action and stimulation of growth factors (7, 9, 10). Furthermore, polaprezinc enhances mucosal protection (7, 8). These animal studies also demonstrated clinical effectiveness of polaprezinc against ethanol-induced and indomethacin-induced gastric ulcers (7, 11). For OM, animal model showed polaprezinc enhanced healing of fluorouracil-induced and acetic acid-induced OM in hamsters (12, 13).

Polaprezinc has been consistently reported to be effective for the prevention or treatment of OM in small clinical studies in cancer patients (14–19). It has been exclusively studied in Japan for the prevention and treatment of OM. The majority of these studies are retrospective cohort studies and study patients and control patients were treated at different time periods. There have been three RCTs, of which two are in HSCT patients (16, 17, 19). There have been numerous methodological issues associated with these studies, including small sample sizes (17, 19), use of the chi-square test in small samples (17), and administration of polaprezinc to the control arm as a treatment (16). Polaprezinc has been used as a mouthwash or lozenges in the studies, which implies topical administration (14–23). However, it was also ingested in most studies except a few cohort studies (20, 22).

The effectiveness of polaprezinc has not been proven in a good quality prospective RCT, and if effective, it is not clear whether the effects are due to topical or systemic actions. As the number of published studies increases, it is important to conduct larger high quality studies, preferably outside of Japan, before recommending polaprezinc to the wider community.

Therefore, this study aimed to evaluate the efficacy of topical polaprezinc to prevent OM in non-Japanese patient population who undergo HSCT. To maximise the quality of the study, the accuracy of OM assessment was evaluated at the study site, and education was provided to the nursing evaluators before commencement of this study (24). The incidence of OM in different regimens was also evaluated at the study site to determine inclusion criteria and stratification strategy (25).

Methods

Study design

This was a single centre phase II randomised open label parallel study to evaluate the efficacy of topical polaprezinc in the prevention of oral mucositis in an HSCT setting. Patients were admitted as inpatients to the Bone Marrow Transplant Unit in an Australian tertiary hospital.

Patients

The inclusion criteria were patients who underwent allogeneic or autologous HSCT after moderate to high risk conditioning regimens (i.e. myeloablative cyclophosphamide/ TBI, myeloablative fludarabine/TBI, reduced intensity fludarabine /melphalan, carmustine/ cytarabine/ etoposide/ melphalan: BEAM autologous and high dose melphalan autologous), who were 18 years and over and had freely provided informed consent to participate in the study. Patients were excluded if they were allergic to any of the study interventions, if they had oral mucositis prior to HSCT, if they had HSCT regimens not listed in the inclusion criteria, if they were planned to be transferred or discharged early after HSCT or if they required an interpreter for daily assessment.

Randomisation

The randomisation function of REDCap (Research Electronic Data Capture) was used to randomise patients. REDCap is a secure, web-based software platform designed to support data capture for research studies, hosted by the study hospital (26, 27). An allocation table was generated and uploaded to REDCap using the Robust Randomisation App (28): https://clinicalresearch-apps.com/RRApp.html. To minimise allocation bias, a stratified permuted block randomisation technique was chosen, and allocation sequence was concealed. Patients were randomised (1:1) to either the control arm (Sodium bicarbonate mouthwash) or the study arm (polaprezinc mouthwash). Randomisation was stratified according to the conditioning regimens.

Study treatment

Patients who were randomised to the control arm received standard care - normal saline (N/S) mouthwash 10mL then sodium bicarbonate mouthwash 10mL four times a day. Patients who were randomised to the study arm received N/S mouthwash10mL then polaprezinc mouthwash 5mL four times a day. Sodium bicarbonate (1%) mouthwash was provided as a commercial product. Polaprezinc (0.375 W/V%: 18.75mg/5mL) mouthwash was compounded by the research pharmacist, using water for irrigation and polaprezinc (PepZin GI®) manufactured by Hamari Chemicals, Ltd. The compounded mouthwash presented as 5mL suspension in a single use syringe, and patients were instructed to shake well before use. Patients were instructed to use N/S mouthwash followed by sodium bicarbonate or polaprezinc mouthwash four times a day after each meal and at bedtime. They were advised to rinse with the mouthwash for 30 seconds then spit out the contents. All patients, including patients in the control arm were instructed not to eat or drink for one hour after the mouthwash. Treatment with the mouthwashes was commenced on hospital admission (before or during conditioning) and continued

until study completion for the patient, which was neutrophil recovery (> $0.5x10^9$/L) with grade 0–1 OM or hospital discharge.

All patients who received high dose melphalan as a part of their conditioning regimen routinely used 2-hour cryotherapy. All other supportive medicines including antiemetics, anti-infectives and a proton pump inhibitor were given according to the unit guidelines. All allogeneic patients received immunosuppressants and ursodeoxycholic acid as standard of care. These allogeneic patients also had nasogastric (NG) tube from day + 1 post HSCT, and enteral feed was given according to patient's oral intake. For patients who refused or failed NG tube insertion or dislodged NG tube, TPN was used when oral intake dropped to less than 50% of daily requirement. All patients received vitamin and mineral supplements, that contained the daily requirement of zinc.

OM assessment

Oral Mucositis was assessed by ward nurses once daily using the standardised oral assessment sheet (Appendix 1). This was created by combining institutional assessment sheet and a published tool by Quinn et al (29). Oral intake and pain were recorded based on patients' reports. Then nurses assessed ulceration and erythema in the patient's oral cavity. Finally, they determined OM grade each day according to the WHO scale (grade 0: none, grade 1: soreness +/- erythema, grade 2: ulcers, able to eat solid, grade 3: ulcers, liquid diet only, grade 4: ulcers, no alimentation). Prior to the study, an oral assessment manual was created, and nurses underwent training to ensure accuracy of assessment. Oral assessment was continued from admission until hospital discharge or complete healing of OM, whichever occurred earlier.

Patients were asked to use a Patient Daily Self-Assessment to score mouth/ throat pain and associated limitations of swallowing, eating, drinking, talking and sleeping (Appendix 2). This was a modified Oral Mucositis Daily Questionnaire (OMDQ) (30). The OMDQ is a validated tool, however for our specific purpose a question about overall health and two questions about diarrhoea were removed due to limited relevance to the study. There were two questions asking about "overall mouth and throat pain" (10 points and 5 points). The 5 point question was removed due to duplication. The OMDQ asked about overall "mouth and throat" pain. We added "mouth only pain" and "throat only pain" to differentiate these 2 locations.

Other assessment

Patients' demographics, including age, gender, conditioning regimen, disease, weight, height, body surface area (BSA) and body mass index (BMI) were collected from the medical record. The use of PCA and its duration were collected from the medication chart. The use of PCA indicates severe and/ or consistent pain not controlled by PRN opioids administered by nurses. Enteral nutrition at a rate of 50mL/hour or above, and TPN use and duration were recorded from the medication chart and medical notes. These interventions indicate that the patients' oral intake dropped below 50% of daily requirement. Any acute adverse reactions were collected using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 .

Study endpoints

The primary endpoint of the study was incidence of grade 3–4 OM. The secondary endpoints included duration of WHO grade 3–4 OM, incidence and duration of WHO grade 2–4 OM, patient reported mouth and throat pain and functional difficulties, the use of NG feed/TPN and the use of PCA.

Data analysis

Based on the published data (14–18) and local data (25), a sample size of 108 (54 participants per arm) was calculated assuming that grade 3–4 OM will be reduced from 47–20%. The calculation used 80% power and two-sided significance level of 5%.

OM data and uses of PCA and feed were analysed per intention to treat. All WHO grading was reviewed against observations (i.e. oral intake, ulceration, mouth pain). For patient-reported pain score and functional limitations (e.g. swallowing), the Area Under the Curve (AUC) was calculated as outlined by Spielberger et al (31). Data from patients who completed at least 70% of self-assessments was included. If any data was missing, the average value of immediately prior and post missing data was used. The incidence of grade 3–4 and grade 2–4 OM, PCA and nutrition supplement use were analysed using the Fisher's Exact test. Duration of grade 3–4 and grade 2–4 OM, patient-reported outcomes were compared using the Mann-Whitney U test. Comparison of throat and mouth pain was analysed with the Wilcoxon Signed-Ranks test.

Ethical consideration and registry

This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was obtained from the Institutional Human Research Ethics Committee. Informed consent was obtained from all individual participants included in the study. This trial was registered to the Australian New Zealand Clinical Trials Registry (ANZCTR). Registration number is ACTRN12320001188921

Results

Patients

Between February 2021 and July 2022, 171 patients were assessed for eligibility. Of these, 63 patients were not included (33 declined, 20 met exclusion criteria, 3 HSCTs were cancelled, 7 were unable to be recruited or start due to researcher's absence). In total,108 patients were randomised and started the allocated mouthwashes (Fig. 1). Baseline characteristics and treatment were similar, and are shown in Table 1.

Table 1
Baseline characteristics and treatment

	Sodium bicarbonate arm N = 53	Polaprezinc arm N = 55
Gender: Female (%)	19 (36%)	24 (44%)
Age: Median (range)	58 (20–70)	56 (21–72)
Diagnosis		
AML	16 (30%)	16 (29%)
ALL	10 (19%)	5 (9%)
Lymphoma	6 (11%)	10 (18%)
Myeloma	10 (19%)	11 (20%)
MDS	6 (11%)	9 (16%)
Other	5 (9%)	4 (7%)
Regimen		
CyTBI allo	10 (19%)	11 (20%)
FluMel allo	27 (51%)	26 (47%)
FluTBI haplo	2 (4%)	3 (5%)
BEAM auto	4 (7%)	4 (7%)
HDM auto	10 (19%)	11 (20%)
BMI: Median	29	27

Incidence and duration of OM

Table 2 shows the incidence and duration of OM and the use of PCA and nutrition supplement, either TPN or NG feed 50mL/ hour or higher. Polaprezinc had no beneficial effect in any of the outcomes. While the incidence of grade 3–4 OM was the same, the incidence of grade 2–4 OM, duration of grade 3–4 and 2–4 OM were all insignificantly higher in polaprezinc arm.

Table 2
Incidence and duration of OM and the use of PCA and nutrition supplements

Variables	Sodium bicarb (N = 53)	Polaprezinc (N = 55)	p-values
Incidence of grade 3–4 OM (%)	19 (36%)	19 (35%)	$p = 1$
Duration of grade 3–4 OM (median duration among patient who had grade 3–4 OM)	5 days	6.5 days	$p = 0.42$
Incidence of grade 2–4 OM (%)	33 (62%)	40 (72%)	$p = 0.31$
Duration of grade 2–4 OM (median duration among patient who had grade 2–4 OM)	5 days	7 days	$p = 0.53$
Use of PCA (%)	16 (30%)	20 (36%)	$p = 0.54$
Use of nutrition supplement (%)	32 (60%)	35 (64%)	$p = 0.84$

Patient-reported outcomes

In control and study arms, 45/53 (85%) and 46/55 (84%) patients completed the self-assessment. Table 3 shows the median AUCs of pain score and functional limitation scores. Patients in polaprezinc arm reported higher mouth and throat pain, but not significantly. There were no differences in the limitations of swallowing, eating, drinking, talking and sleeping between the arms.

When comparing patient-reported mouth pain versus throat pain, throat pain was significantly higher in both study arms (Sodium bicarbonate arm: p = 0.0001, Polaprezinc arm: p = 0.0002)

Table 3
Patient-reported outcomes

Variables	Sodium bicarb (N = 45)	Polaprezinc (N = 46)	p-values
Self-assessment completed (%)	N = 45 (85%)	N = 46 (84%)	
Mouth and throat soreness (median AUC)	36.25	41.875	$p = 0.289$
Mouth soreness (median AUC)	10	25.75	$p = 0.09$
Throat soreness (median AUC)	31	44	$p = 0.25$
Swallowing (median AUC)	18	17.5	$p = 0.52$
Eating (median AUC)	17.5	20.5	$p = 0.60$
Drinking (median AUC)	14	14	$p = 0.75$
Talking (median AUC)	5	8.5	$p = 0.50$
Sleeping (median AUC)	3	3.5	$p = 0.81$

Safety

Table 4 shows adverse reaction in study patients. Data was collected through patient interview and review of medical records (N = 49 and 48 in each arm). These adverse reactions were unlikely to be caused by the mouthwashes. There were no differences in adverse reactions between the sodium bicarbonate group and the polaprezinc group. One patient developed a mild adverse reaction possibly from polaprezinc mouth wash. The reaction was a subjective sensation of tongue tightness and was reported to the institutional ethics committee.

Table 4
Adverse reactions

	Sodium bicarbonate arm N = 49		Polaprezinc arm N = 48	
	All grade	≥Grade 3	All grade	≥Grade 3
Diarrhoea	31 (63%)	5 (10%)	26 (54%)	5 (10%)
Constipation	20 (41%)	0 (0%)	13 (27%)	0 (0%)
Nausea	39 (80%)	9 (18%)	39 (81%)	6 (13%)
Vomiting	18 (37%)	1 (2%)	18 (38%)	1 (2%)
Fevers	40 (82%)	0 (0%)	39 (81%)	0 (0%)
Rash	18 (37%)	2 (4%)	18 (38%)	1 (2%)
Irritation	6 (12%)	0 (0%)	7 (15%)	1 (2%)

Discussion

Unlike previously published studies, our study demonstrated no benefit of topical polaprezinc compared to a bland mouthwash (sodium bicarbonate). The results showed equal incidence of grade 3–4 OM between test arm and control arm, and insignificantly higher incidence of grade 2–4 OM and longer duration of grade 2–4 and 3–4 OM in the polaprezinc arm. Patient-reported pain scores were also insignificantly higher in the polaprezinc arm.

There are only two studies that have evaluated topical effects of polaprezinc (20, 22), and in all other studies polaprezinc was ingested after topical use. These two studies were both conducted in head and neck cancer patients receiving chemoradiation and were retrospective cohort studies where patients in two cohorts were treated at the different time periods. Topical polaprezinc has never been evaluated in any prospective studies as a prevention of OM. There are six studies evaluating the effects of topical and systemic polaprezinc in HSCT patients (14–18, 21), including two RCTs (16, 17). All studies used mouthwash or lozenges and demonstrated preventative effects of polaprezinc, although the studies had quality issues.

The assumption of topical effects of polaprezinc was derived from animal data showing adherence of polaprezinc to the gastric ulcer sites (4, 6), and also from clinical data using polaprezinc enemas and ointments (32, 33). However, in our study, polaprezinc mouth wash did not show any benefits. Polaprezinc is a chelated substance, which is insoluble in the mouth but soluble in the stomach due to the acidic condition. Polaprezinc may have a topical anti-ulcer effect only in acidic conditions where it is slowly broken down into L-carnosine and zinc at the ulcer sites.

If polaprezinc is effective for the prevention of OM, it is likely to be through systemic effects. One study demonstrated zinc deficiency to be a risk factor of severe OM (34). In the relatively large RCT by Kitagawa et al, polaprezinc reduced the incidence of grade 2–4 OM. If zinc deficiency is relatively common in Japan, the positive effects of polaprezinc in Japanese studies can be explained as a simple zinc supplement. In our study, patients' serum zinc levels were not measured, however, all patients received zinc supplementation either thorough multivitamin and mineral tablets or through their feeds. Therefore, additional zinc supplement is unlikely to be beneficial.

Another possible mechanism is that the anti-ulcer effects of polaprezinc in the gastrointestinal tract may affect the OM through reduction of systemic inflammation. Polaprezinc may also affect gut microbiome, as suggested by multiple studies demonstrating its effects on helicobacter pylori eradication (35–37). Currently, there is no strong evidence that gut microbiome affects oral microbiome or OM. However, this area is of great interest among mucositis researchers (38).

Our mouthwash formulation was also different from previous studies. In the published studies, mouthwash contained sodium alginate or other thickeners to enhance retention to oral mucosa, or lozenges were used. We used a simple polaprezinc suspension as a mouthwash. Given that there was insignificant inferiority in some of the outcomes with polaprezinc, it is unlikely the results would be reversed when adding thickeners or using lozenges.

To the best of our knowledge, this is the largest RCT testing polaprezinc, and the only study using topical only application in HSCT patients. We stratified randomisation so that the conditioning regimens between the arms were almost the same, which previous studies have not performed.

Our study had some limitations. Most importantly, it was an open-label study. Due to the insoluble nature of polaprezinc and the need to shake the mouthwash before use, a double-blind trial was impossible. As patients and assessors were both aware of the mouthwashes used, there were risks of bias. Particularly, grade 3–4 OM (primary outcome) was determined by the patient's ability to eat, and this may have affected the results if patients believed they were using a "new good mouthwash". This may explain more patients in polaprezinc arm remained grade 2 while they reported higher pain scores. A further limitation was OM assessment. We used the WHO scale, in which ulceration and ability to eat are the primary drivers to determine OM grades. However, from our results, patients reported more throat pain compared to mouth pain. There were also patients who had minimal oral pain but considerable throat pain that interfered with their oral intake. The WHO scale can potentially underscore these cases due to absence of oral ulcers. It is often impossible to objectively assess a patient's' throat and therefore, clinically patient-reported outcomes may be more important.

In conclusion, our study showed that topical polaprezinc has no effect in preventing OM in HSCT patients. Large high-quality studies are required to confirm the effectiveness of systemic polaprezinc. In addition, the choice of OM assessment tools should be carefully considered in future studies.

Declarations

Acknowledgement

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Midori Nakagaki. Sample size calculation and statistics were supported by Jason Butler. The first draft of the manuscript was written by Midori Nakagaki and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

All authors have no conflicts of interest.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was obtained from the Royal Brisbane & Women's Hospital Human Research Ethics Committee (HREC/2020/QRBW/60530) and the University of Queensland's Human Research Ethics Committee (2020001484 / HREC/2020/QRBW/60530). Informed consent was obtained from all individual participants included in the study. This trial was registered to the Australian New Zealand Clinical Trials Registry (ANZCTR). Registration number is ACTRN12320001188921.

Availability of data and material

All data is available on request.

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Figures

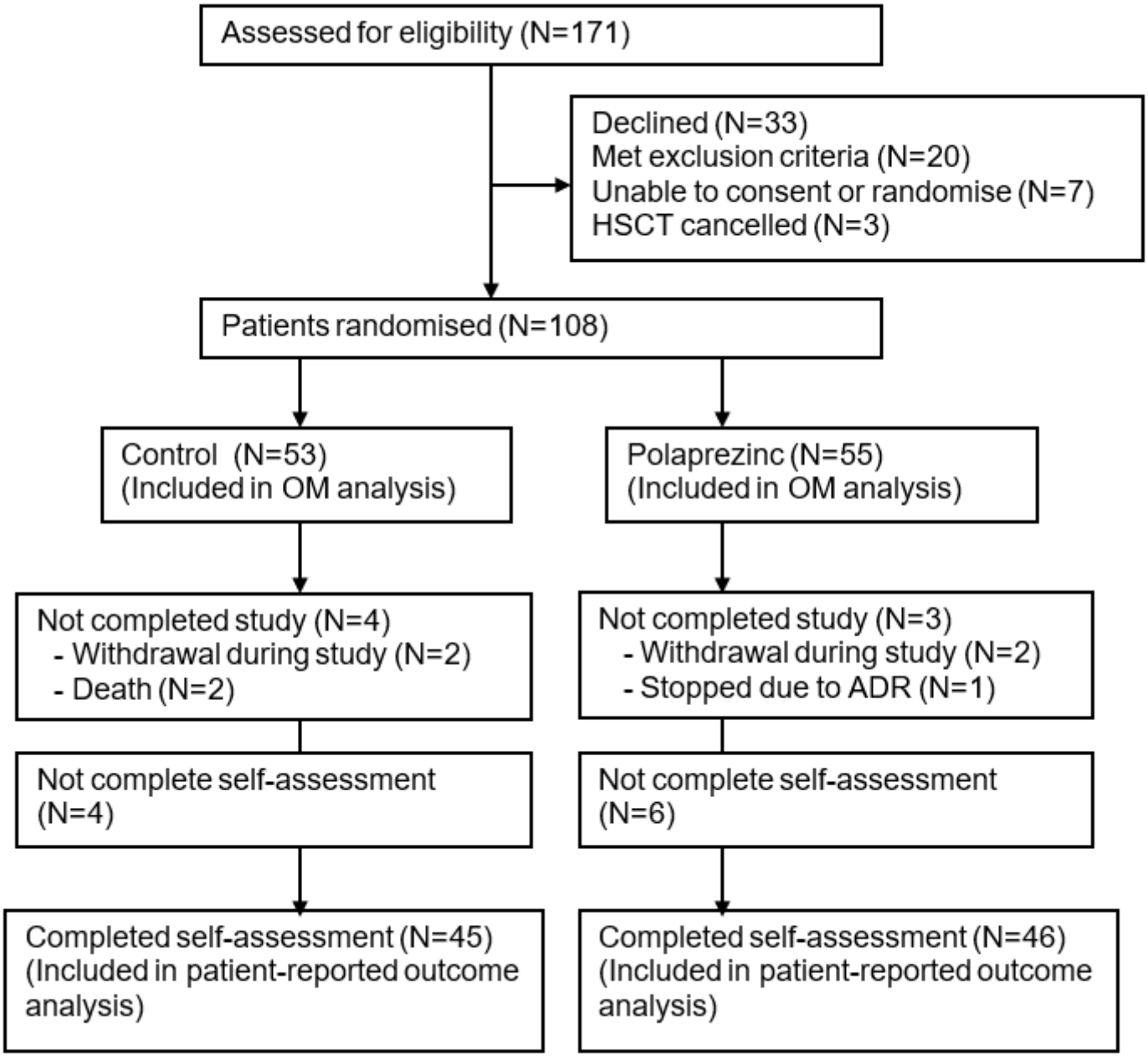

Figure 1

Patient flowchart

Supplementary Files

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