Comparing the effectiveness of magnesium oxide and naldemedine in preventing opioid-induced constipation: A proof of concept, single institutional, two arm, open-label, phase II, randomized controlled trial: the MAGNET study

Anna Ozaki
Yokohama City University Hospital
Takaomi Kessoku
Yokohama City University Hospital
Michihiro Iwaki
Yokohama City University Hospital
Takashi Kobayashi
Yokohama City University Hospital
Tsutomu Yoshihara
Yokohama City University Hospital
Takayuki Kato
Yokohama City University Hospital
Yasushi Honda
Yokohama City University Hospital
Yuji Ogawa
Yokohama City University Hospital
Kento Imajo
Yokohama City University Hospital
Takuma Higurashi
Yokohama City University Hospital
Masato Yoneda
Yokohama City University Hospital
Masataka Taguri
Yokohama City University Hospital
Takeharu Yamanaka
Yokohama City University Hospital
Hiroto Ishiki
National Cancer Center Hospital

Noritoshi Kobayashi
Yokohama City University Hospital
Satoru Saito
Yokohama City University Hospital
Yasushi Ichikawa
Yokohama City University Hospital
Atsushi Nakajima (✉ nakajima-tky@umin.ac.jp)
Yokohama City University Hospital

Study protocol

Keywords: opioid-induced constipation, magnesium oxide, naldemedine, randomized controlled trial.

Posted Date: February 19th, 2020

DOI: https://doi.org/10.21203/rs.2.12623/v2

Version of Record: A version of this preprint was published at Trials on June 1st, 2020. See the published version at https://doi.org/10.1186/s13063-020-04385-0.

Abstract

Background: Patients taking opioids are known to develop opioid-induced constipation (OIC), which reduces their quality of life (QOL). The aim of this study is to compare magnesium oxide to naldemedine and determine which is more effective in preventing OIC.

Methods: This is a proof of concept, prospective, randomized controlled trial, that commenced in Japan in March 2018. Initially, a questionnaire-based survey will be conducted targeting adult cancer patients who had concomitantly commenced opioid and OIC prevention treatment. Patients will then be randomly allocated to magnesium oxide (500 mg, thrice daily) or naldemedine (0.2 mg, once daily) groups. Each drug will be orally administrated for 12 weeks. The primary endpoint is defined as any improvement in the Japanese version of Patient Assessment of Constipation Quality of Life (JPAC-QOL) scores from the baseline to 2 weeks of treatment.

Discussion : The primary endpoint is changes in the JPAC-QOL scores from the baseline to 2 weeks of intervention. The key secondary endpoint will be changes in spontaneous bowel movements (SBMs) at 2 and 12 weeks of intervention. This study will determine whether magnesium oxide or naldemedine is more effective for the prevention of OIC.

Trial registration: This trial is registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000031891). Registered March 25, 2018, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000036408.

Background

Opioids are used for cancer pain management [1,2]; however, there are challenges associated with continuous opioid therapy owing to complications such as nausea, constipation, sleepiness, and respiratory depression [3–6]. Constipation develops in 15-64% of patients receiving strong opioid analgesics [7–11] and chronic constipation may occur at a higher incidence in women (men:women, 1:2.2) and older persons [12]. In patients with various cancers in Japan, the cumulative incidence of opioid-induced constipation (OIC) is lung, 48%; pancreatic, 53%; colon, 60%; breast, 79%; stomach, 71%; esophageal, 60%, prostate, 50%; bladder, 50%; and others, 59% [13]. Long duration of opioid therapy is largely responsible for OIC [14] and drug tolerance against OIC is rarely established, so preventive administration of laxatives is important [15].

Symptoms of constipation (abdominal pain, fullness and loss of appetite) impair patients' QOL; thus, OIC is a problem worth investigating. Traditional OIC treatment involves "non-drug" therapy comprising consumption of high-fiber diets or administration of medications such as laxatives. In Japan, the Clinical Guidelines for Gastrointestinal Symptoms in Cancer Patients recommend osmotic laxatives [16]. A Japanese observational study reported that preventive magnesium oxide intake attenuated OIC when patients commenced opioid therapy [17]. Thus, osmotic laxatives including magnesium oxide are a conventional OIC treatment in Japan. OIC occurs when opioids act on μ-receptors on intestinal nerves,

reducing intestinal motility and fluid secretion [6,18]. Both non-drug treatments and osmotic laxatives do not target the underlying mechanism of OIC [3,9].

Over the years, little progress has been made in OIC treatment research [9]. Recently, peripherally acting μ-opioid receptor antagonists (PAMORAs) were shown to be effective in treating OIC. Naldemedine is a novel PAMORA being developed for the treatment of OIC without affecting central analgesia [19]. Furthermore, the safety and efficacy of it has been reported to be superior to that of placebos [20,21]. Patients with OIC sometimes feel irritated, stressed, and uncomfortable because of their restricted diet, or they are ashamed of their frequent and long bathroom breaks, especially during social activities. Constipation impairs patient's QOL, hence there is a need for preventive treatment. This study will compare magnesium oxide to naldemedine and determine which is more effective in preventing OIC.

Methods

Trial design

This study is a proof of concept, single institutional, two arm, open-label, phase II, randomized controlled trial, comparing the effectiveness of MAGnesium oxide (500 mg, thrice daily) and NaldEmedine (0.2 mg, once daily) to prevent opioid-induced consTipation for 12 weeks (MAGNET study). The primary endpoint will be a change in the Japanese version of the Patient Assessment of Constipation Quality of Life (JPAC-QOL) score from baseline to 2 weeks into treatment. The study aims to recruit 120 adult patients with cancer from the Yokohama City University Hospital cohort.

A flow chart of the study is shown in fig. 1. Evaluations will be performed at three time points: baseline and 2 and 12 weeks after intervention, as shown in fig. 2.

Ethical issues

The study will be performed in accordance with the Declaration of Helsinki and the Japanese ethical guidelines for clinical research. The protocol was approved by the Ethics Committee of Yokohama City University Hospital on March 22, 2018. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)-patient reported outcome (PRO) Extension and its checklists were followed in preparing the protocol. This trial is registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000031891. All participants will be required to provide written informed consent. The protocol and any information supplied to gain informed consent were approved by the qualified Institutional Review Board/Independent Ethics Committee of Yokohama City University prior to patient enrolment. The participant personal information will be maintained in a separate locked cabinet and password-protected hard drive at the institution. Records will be retained for 5 years after study completion and then destroyed by the data center.

Study endpoints

The expected endpoints are indicated in table 1. The primary endpoint is the change of JPAC-QOL from baseline to 2 weeks with magnesium oxide vs naldemedine intervention. JPAC-QOL consists of 28 questions assessed using a five-point adjectival score from 1–5, with a lower score indicating a better outcome for QOL (table 2) [22–24] and is shown to have acceptable reliability and validity to be used for psychometric evaluation in patients complaining of functional constipation [25].

The secondary endpoints include the change of baseline JPAC-QOL scores at 12 weeks, and change in Patient Assessment of Constipation-Symptoms (PAC-SYM), constipation scoring system (CSS), Rome IV, Bristol Stool Form Scale (BSFS), spontaneous bowel movements (SBMs), and short form-36 (SF-36) at 2 and 12 weeks after commencing the intervention.

Dosing rationale

A Japanese multi-institutional retrospective study reported that prophylactic intake of 1,000 to < 2,000 mg/day magnesium oxide was significantly effective in preventing constipation during oral opioid therapy [26], therefore, we chose a dose of 1,500 mg (the median effective dose). Since the only permitted dose of naldemedine in Japan is 0.2 mg, we chose this dose for this trial.

Drug supply

Both the doctor and patient will be aware of the treatment allocation. The doctor will prescribe magnesium oxide 1,500 mg/day or naldemedine 0.2 mg/day according to the drug name provided by the patient enrolment center. To improve adherence to interventional protocols, patients will be required to return the unused tablets at the last visit, which will be counted and recorded in the medical records.

Sample size estimation

Our retrospective analysis of magnesium oxide/naldemedine in 10 OIC patients at Yokohama City University Hospital showed mean JPAC-QOL changes of -1.19 and -0.76 in the naldemedine and magnesium oxide groups, respectively. We decided to calculate the sample size required to conduct a proper analysis of variance F-test based on these data. Assuming mean changes in the JPAC-QOL score in the naldemedine and magnesium oxide groups would be -1.19 and -0.76, respectively, with a common standard deviation of 0.76, we determined that 51 patients are needed in each group to reach 90% statistical power with a two-sided significance level of 5%. To compensate for any dropout, we proposed a sample size increase to 60 per group. To reach this sample size, a total of 120 patients will be needed in the study.

Eligibility

The target study subjects are adult patients (20–85 years of age) with cancer who will commence opioid therapy for cancer pain. There is no distinction in the type and location of cancer. Type, dose, or frequency of opioid medication will not be restricted in this study. Eligible subjects will be required not to have used laxatives before the study intervention. If severe OIC that cannot be controlled by magnesium oxide or naldemedine occurs during the intervention, the use of senna will be permitted. The inclusion and exclusion criteria are presented in table 3.

Randomization and masking

Eligible patients satisfying the screening inclusion and exclusion criteria will be invited to participate in the study by the investigators. Patients will be randomly assigned (1:1) to receive 500 mg magnesium oxide thrice daily or 0.2 mg naldemedine once daily at the central registration center. Randomization will be performed after the patient has signed the informed consent form. The principal investigator or co-investigator will be notified of the patient ID number and drug name by fax from the patient enrolment center. To avoid a large bias, we will stratify patients by age (<65 or $\geq$65) and sex (male or female) using a computer-generated administered procedure with a permuted-block method at an independent institution. Masking of patients and physicians is not applicable because this is an open label study, but the independent outcome evaluator will be masked to treatment assignments.

Adverse event (AE) monitoring

The investigators will be required to record all adverse events (AE) that occur during the study in the medical records, including information about onset and end date (if applicable), AE severity and seriousness, the investigator's opinion of the association with magnesium oxide or naldemedine treatment, action taken regarding magnesium oxide or naldemedine usage and AE treatment, cause of event (if known), and information regarding the resolution or outcome. AEs classified as serious will be recorded using a serious AE reporting tool. The intensity of an AE will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0, which includes the classifications of AE intensity shown in table 4. Any abnormal results related to study drug treatment will be reported weekly until the abnormality is resolved or otherwise explained.

Criteria for discontinuation

Study treatment will be discontinued when a ≥ grade 3 severe AE according to the NCI-CTCAE version 4.0 occurs, oral compliance is < 80%, or a patient is found to be ineligible for the trial. Treatment will also discontinue if requested by a patient or if continuous medical examination becomes challenging because of patient relocation, change in hospital or business, or discontinuation of the study.

Definition of protocol deviations

Protocol deviations are defined as follows:

1. Dropout before randomization: patients who were not randomized after informed consent.
2. Screen failure: patients who do not meet the inclusion Criteria or met the exclusion criteria.
3. Patients who were not treated: patients who did not receive the study drugs
4. Fulfilment of criteria for discontinuation: patients who met the criteria described in “Criteria for discontinuation” but did not discontinue the study treatment or who did not meet the criteria but discontinued the study treatment during the observation period.
5. Non-adherence to dosage regimen: patients with any deviation from the protocol relating to the dosage regimen
6. Violation of concomitant medications/therapy requirement: patients who had concomitant medications (therapy) that were prohibited in the protocol.
7. Violation of the methods or timing of observations, tests, or assessments requirement: patients with any deviation from the protocol relating to the methods or timing of observation, test, or assessment.

Efficacy evaluation

JPAC-QOL (the primary endpoint) score will be calculated as the mean of difference from baseline at 2 weeks. The secondary efficacy endpoints will be calculated as the mean of difference from baseline at 2 or 12 weeks.

Safety evaluation

AEs, dropout ratios, and physical examinations are the chosen safety evaluations of this trial. Physical assessments will be performed and analyzed using standard procedures in Yokohama City University. Dropout will be defined as an oral compliance < 80%.

Statistical hypothesis

The full analysis set is defined as all patients who receive any amount of the study medication with initial information on the primary endpoint. The full analysis set will be the primary analysis set for efficacy to use as intention-to-treat patient population. For the primary endpoint, a one-way analysis of variance will be performed between the two groups to calculate the p-value using the Student's *t*-test. The p-value will be significant at a two-sided significant level of 5% and both the p-value and confidence intervals will be used to determine the statistical significance of our results. The paired *t*-test or Wilcoxon signed-rank test will be performed for within group comparisons before and after the intervention. The chi-squared test will be used to assess the frequency of AEs. while the treatment compliance rate will be calculated and compared using Fisher's exact test. The JMP version 11.2.0 software (SAS Institute, Cary, NC, USA) will be used for all statistical analyses. Complete case analysis based on likelihood will be used for the primary analysis or a multiple imputation method will be also used to handle missing data as a sensitivity analysis.

Trial steering and data monitoring committees

The trial steering and independent data monitoring committees will be located at the Department of Biostatistics, Yokohama City University School of Medicine and Yokohama City University Center for Novel and Exploratory Clinical Trials. The management team will conduct the on-site monitoring and meet with the facility person in charge when necessary. Any visit to the facility will be reported in the monitoring report.

In principle, the first patient will be monitored continuously throughout the trial and if there is no problem, every 10 patient will be monitored. To confirm that necessary documents are stored properly, on-site monitoring will be performed appropriately and if there are any problems, corrective action will be taken. The result will be recorded in the monitoring report.

The data monitoring committee will have access to the final trial dataset and there is no contractual agreement regarding investigators' access restrictions to the dataset.

Discussion

Patients with OIC report a significantly worse QOL than those who are unaffected by OIC [9,21] because of associate symptoms such as abdominal pain, fullness and loss of appetite, but their QOL improves after symptom resolution [23]. JPAC-QOL is a reliable method for measuring the QOL of patients with constipation. A decrease in constipation can also be determined by the number of times a patient defecates using the SBM score, but evaluating patient comfort solely using this objective index is challenging because of the high inter-individual differences in defecation times. QOL improvement is particularly important in cancer patients and, thus, we chose change in JPAC-QOL score as the primary endpoint of this study.

In this study, we chose magnesium oxide as the control because in Japan, its preventive intake is reported to dampen OIC when patients eventually commence opioid therapy [16], and osmotic laxatives including magnesium oxide are conventionally used to treat OIC. Other laxatives such as senna, lactulose, and sodium picosulfate hydrate are also used and are all effective. However, a systematic review by Miles et al. [28] indicates no evidence of superiority of one laxative or specific combination of laxatives for the management of constipation in palliative patients. Similarly, Agra et al [29] reported no difference in the effects of senna and lactulose after observing the subjective index for over 72 hours, and the number of days with defecation throughout the study.

Magnesium oxide is conventionally used for OIC prevention in Japan and, therefore, its long-term safety is empirically established. In addition, magnesium oxide has advantages in terms of medical cost at 33.6 yen/day (1500 mg/day) over naldemedine, which costs 272.1 yen/day. Naldemedine may have the advantage of adherence with a once daily required intake.

A good number of OIC treatment studies exist, with only a few on the use of preventive laxatives against OIC. Additionally, some limitations to our study are the 1) single center and 2) open label design, and 3) a potentially short treatment period (12 weeks). The rationale for conducting this trial as an open label is 1) This trial compares two drugs, which are already on the market and used in clinical practice, 2) Both agents compared in this trial are active drugs, 3) The double-dummy method is required for blinding, and the logistics for using that method in a study such as placebo manufacturing costs, drug management, and dispensing are challenging and 4) This is an exploratory study. We have considered the need to blind the next phase using the double dummy method. Further research is encouraged.

Dissemination

The results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at conferences. Authorship will be ascribed in accordance with the International Committee of Medical Journal Editors guidelines.

Trial Status

Protocol version: 1.0, November 26, 2017.

Recruitment began on March 22, 2018 and it is ongoing on February 10, 2020.

List Of Abbreviations

OIC: opioid-induced constipation, PAMORAs: peripherally acting μ-opioid receptor antagonists, JPAC-QOL: the Japanese version of patient assessment of constipation quality of life, PAC-SYM: patient assessment of constipation symptom, CSS: constipation scoring system, BSFS: Bristol stool form scale, SBMs: spontaneous bowel movements, SF-36: short form-36.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Ethics Committee of Yokohama City University Hospital (Approval reference number: B180301006). Informed consent to participate in the trial was obtained from all patients, who will be informed of the trial results by the investigators.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This trial was conducted with funding granted by Yokohama City University Hospital and no external funding was used.

Authors' contributions

AO, T. Kessoku, and AN conceived the study. T. Yamanaka, HI, and YI conducted the feasibility phase work. Recruitment of patients and follow-up will be performed by MI, T. Kobayashi, T. Yoshihara, YH, YO, KI, TH, MY, NK, and SS. Allocation will be performed by T. Kato and data will be analyzed by MT. All authors contributed to writing the manuscript and read and approved the final version.

Acknowledgements

This work was supported in part by the palliative care team at Yokohama City University.

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Tables

Please see the supplementary files section to access the tables.

Figures

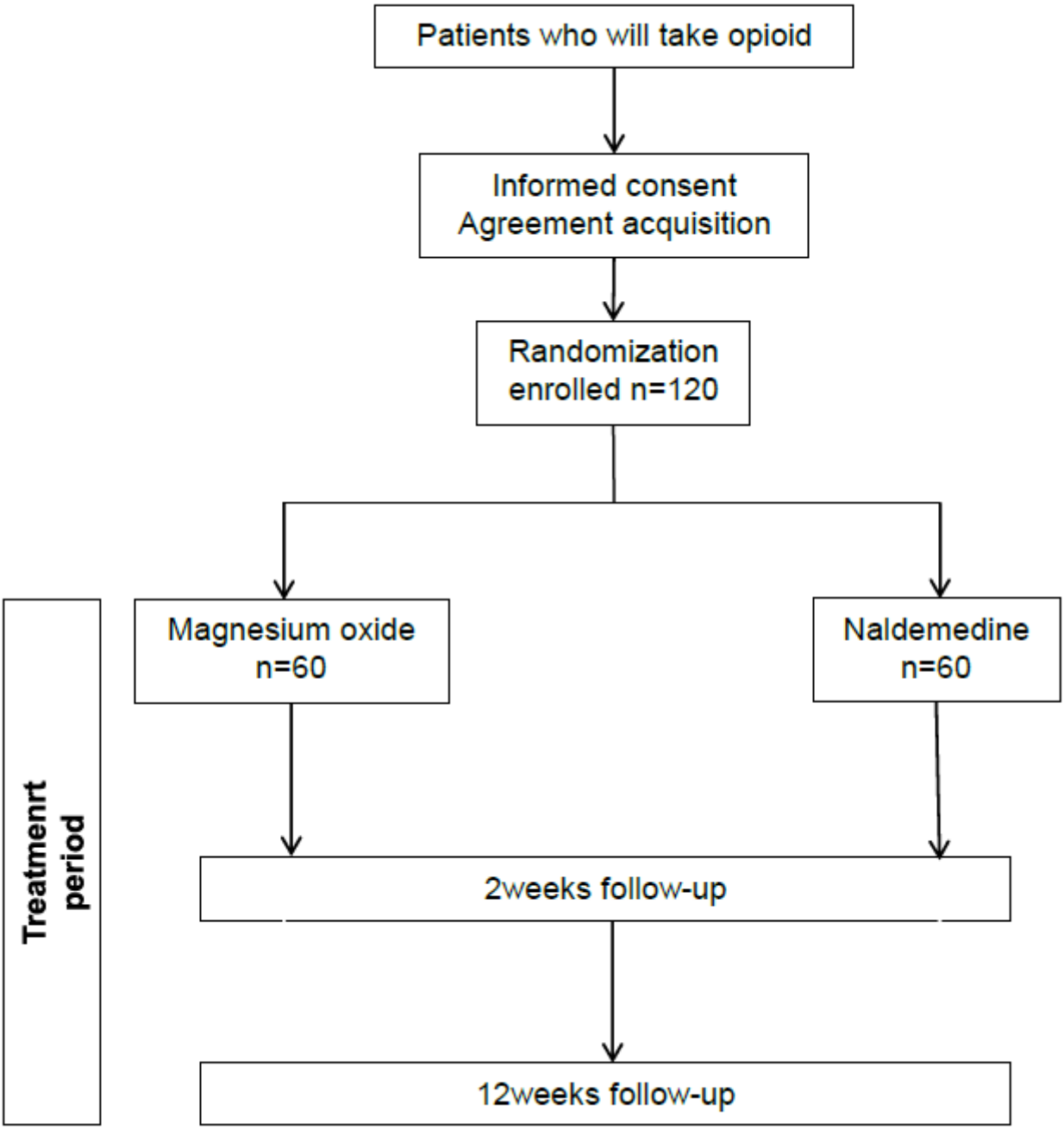

Figure 1

Study flow chart.

	Before enrolment	treatment period					
Week	4weeks before enrolment (baseline)	2	4	6	8	10	12
Patients' background	◎						
Physical examination	◎	◎	○	○	○	○	◎
Symptoms (adverse events)	◎	◎	○	○	○	○	◎
JPAC-QOL	◎	◎					◎
PAC-SYM	◎	◎					◎
CSS	◎	◎					◎
RomeIV	◎	◎					◎
BSFS	◎	◎					◎
SBMs	◎	◎					◎
SF-36	◎	◎					◎

Figure 2

Study schedule All objectives will be compared between magnesium oxide and naldemedine. JPAC-QOL: the Japanese version of patient assessment of constipation quality of life, PAC-SYM: the patient assessment of constipation symptom, CSS: constipation scoring system, BSFS: Bristol stool form scale, SBMs: spontaneous bowel movements, SF-36: short form-36.

Supplementary Files

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