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

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

Study protocol

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

Posted Date: August 12th, 2019

DOI: https://doi.org/10.21203/rs.2.12623/v1

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 and naldemedine to determine which is more effective in preventing OIC. Methods: This is a proof of concept, prospective, randomized controlled trial, conducted in Japan in March 2018. Initially, a questionnaire survey will be carried out targeting adult cancer patients who had concomitantly commenced opioid and OIC prevention treatment. Patients will then be randomly allocated into a magnesium oxide (500 mg, tid) group or a naldemedine (0.2 mg, sid) group. 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 25 March 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 may occur at a higher incidence in women and older persons. Long duration of opioid therapy is greatly responsible for opioid-induced constipation (OIC) [12]. Symptoms brought by constipation (stomachache, abdominal fullness, loss of appetite) impairs patients' QOL, thus OIC is a problem worth investigating.

Traditional OIC treatment involves a "non-drug" therapy comprising the consumption of high fiber diets or medications like laxatives. In Japan, the Clinical Guidelines for Gastrointestinal Symptoms in Cancer Patients recommend osmotic laxatives [13]. A Japanese observational study reports that preventive magnesium oxide intake attenuates OIC when patients commence opioid therapy [14]. Thus, osmotic laxatives including magnesium oxide are used as conventional OIC treatment in Japan.

OIC occurs when opioids act on μ-receptors in the intestinal nerves, reducing intestinal motility and intestinal fluid secretion [6,15]. Neither non-drug treatment nor osmotic laxatives 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), such as naldemedine, were shown to treat OIC.

Naldemedine is a novel PAMORA being developed for the treatment of OIC without affecting central analgesia [16] and safety and efficacy of it has been reported to be superior to that of placebos [17,18].

Patients with OIC sometimes feel irritated, stressed, and uneasy 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 the need for preventive treatment. This study will involve a comparative evaluation of conventional magnesium oxide and novel naldemedine with the ultimate aim of identifying a more effective OIC prevention therapy in Japan.

Methods

Trial design

This study is a proof of concept, single institutional, two arm, open-label, phase II, randomized controlled trial , comparing the ability of magnesium oxide (500 mg, tid) and naldemedine (0.2 mg, sid) to prevent OIC, after a 12-week oral administration period. The primary endpoint will be a change in the Japanese version of Patient Assessment of Constipation Quality of Life (JPAC-QOL) score from baseline to 2 weeks into treatment. The study aims at recruiting 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 3 times of points: baseline, 2 weeks after intervention 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 22 March, 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 a qualified Institutional Review Board/Independent Ethics Committee of Yokohama City University prior to subject 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 on a five-point adjectival score

from 1-5, with a lower score indicating a better outcome for QOL [19, 20] and is shown to have acceptable reliability and validity to be used for psychometric evaluation in patients complaining of functional constipation [21].

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), RomeIV, 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 preventive intake of exceeding 1,000 mg/day magnesium oxide was found to be most effective in preventing constipation during oral opioid therapy [22], therefore we chose a magnesium oxide dose of 1,500 mg. Since the only permitted dose of naldemedine in our country is 0.2 mg, we chose this dosage 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 intervention protocols, patients will return the unused tablets at the last visit, and unused tablets will be counted and recorded on the medical records.

Sample size estimation

Our retrospective analysis of magnesium oxide/naldemedine in 10 OIC patients at Yokohama City University Hospital showed a mean JPAC-QOL change of -1.19 in the naldemedine group and -0.76 in the magnesium oxide group. We decided to perform sample size calculation to attain a relevant number for proper analysis of variance F-test based on these data. Assuming mean changes in the JPAC-QOL score in the naldemedine group and magnesium oxide group to be -1.19 and -0.76, respectively, with a common standard deviation of 0.76, 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 to increase the sample size to 60 per group. To reach this sample size, a total of 120 patients in the study are needed.

Eligibility

The study subjects were adult patients (20-85 years of age) with cancer who will commence opioid therapy for cancer pain. The subjects were with no use of laxatives before intervention. When severe OIC that cannot be controlled by magnesium oxide/naldemedine occurs during the intervention, use of senna will be permitted. The inclusion and exclusion criteria are presented in table 2.

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 to receive 1,500 mg magnesium oxide thrice daily, or 0.2 mg naldemedine once daily at the central registration center. Randomization will be carried out 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 by the patient enrolment center. To avoid a large bias, we stratified age (<64, >65) and gender (male, female). Masking is not applicable because this is an open-label study.

Adverse events (AE) monitoring

The investigators must record all 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. AE classified as serious will be recorded on a serious AE reporting tool. The intensity of an AE will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CACTE) version 4.0, which includes the classifications of AE intensity shown in table 3. Any abnormal results related to study drug treatment will be reported weekly until the abnormality is resolved or is otherwise explained.

Criteria for discontinuation

Study treatment will be discontinued when a grade 3 or more severe AE according to the NCI-CACTE version 4.0 appears, when oral compliance is <80%, or when a patient turns out to be ineligible for the trial. Treatment will also cease if the subject requests discontinuation or if continuous medical examination becomes challenging because of patient relocation, change in hospital or business, or discontinuation of the study.

Efficacy evaluation

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

Safety evaluation

AE, dropout ratios, physical examinations are chosen as the safety evaluations of this trial. Physical assessments will be undertaken 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 any subject who receives 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 an intention-to-treat patient population.

For the primary endpoint, one-way analysis of variance across the 2 groups will be performed with calculating the p-value using the Student’s t-test. The paired t-test or Wilcoxon signed-rank test will be performed to compare before and after the intervention within each group. The chi-squared test will be used to assess the frequency of AE. 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.

Trial steering committee and data monitoring committee

The trial steering committee and the independent data monitoring committee 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 do the on-site monitoring and meet 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, monitoring will be done for every 10 patients. 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. There is no contractual agreement regarding investigators' access restrictions on dataset.

Discussion

Patients with OIC report a significantly worse QOL compared with those unaffected [9,21] because of its symptoms like stomachache, abdominal fullness, loss of appetite, but their QOL improves after symptom resolution [23]. JPAC-QOL is a reasonable way to measure the QOL of patients with constipation. We can also assess a decrease in constipation by the number of defecation times using the SBMs score, but evaluating patient comfort solely by this objective index is challenging due to the high inter-individual differences in defecation times. QOL improvement is specifically important in cancer patients. Thus, we chose the change in JPAC-QOL score as the primary endpoint of this study.

In this study, we chose magnesium oxide as control because in Japan, preventive magnesium oxide intake is reported to dampen OIC when patients eventually commence opioid therapy [13], and osmotic laxatives including magnesium oxide are conventionally used to treat OIC. Other laxatives such as senna, lactulose, and sodium picosulfate hydrate are also employed, and are all effective. However, a systematic review by Miles et al indicates no evidence of superiority of one laxative or specific combination of

laxatives for the management of constipation in palliative patients [24]. Similarly, Agra et al 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 [25].

As we conventionally use magnesium oxide for OIC prevention in Japan, its long-term safety is empirically established. Also, magnesium oxide has advantage in terms of medical cost; Magnesium oxide costs 33.6 yen/day (when using 1500mg/day) while naldemedine costs 272.1 yen/day. Naldemedine may have advantage in terms of adherence, since once a day of intake is only required.

A good number of OIC treatment studies exist, with only a few on the use of preventive laxatives against OIC. Further research is therefore encouraged.

Dissemination

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

Trial Status

Protocol version: 1.0, 26 November 2017.

Recruitment began on 22 March, 2018 and it will be completed on 31 December, 2019.

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: the 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 as the committee's approval reference number B180301006. Patient consent to participate in the trial was obtained from all patients. The results of the trial will be informed to participants 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 no external funding and was instead granted from Yokohama City University Hospital.

Author's contributions

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

Acknowledgements

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

References

1 P. Gisondi, A. Conti, G. Galdo, S. Piaserico, C. De Simone, G. Girolomoni. Ustekinumab does not increase body mass index in patients with chronic plaque psoriasis: a prospective cohort study. Br. J. Dermatol. 168 (2013) 1124-1127. doi:10.1111/bjd.12235.

2 A. Caraceni, G. Hanks, S. Kaasa, M.I. Bennett, C. Brunelli, N. Cherny, O. Dale, De F. Conno, M. Fallon, M. Hanna, Haugen, D.F. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 13 (2012) e58-68. doi:10.1016/S1470-2045(12)70040-2.

3 J.L. Poulsen, C. Brock, A.E. Olesen, M. Nilsson, A.M. Drewes. Evolving paradigms in the treatment of opioid-induced bowel dysfunction. Therap. Adv. Gastroenterol. 8 (2015) 360-372. doi:10.1177/1756283X15589526.

4 B. Morlion, Clemens, K.E., Dunlop, W. Quality of life and healthcare resource in patients receiving opioids for chronic pain: a review of the place of oxycodone/naloxone. Clin. Drug. Investig. 35 (2015) 1-11. doi:10.1007/s40261-014-0254-6.

5 M. Lazzari, M.T. Greco, C. Marcassa, S. Finocchi, C. Caldarulo, Corli, O. Efficacy and tolerability of oral oxycodone and oxycodone/naloxone combination in opioid-naive cancer patients: a propensity analysis. Drug. Des. Devel. Ther. 9 (2015) 5863-5872. doi:10.2147/DDDT.S92998.

6 Camilleri, M. Opioid-induced constipation: challenges and therapeutic opportunities. Am. J. Gastroenterol. 106 (2011) 835-842. doi:10.1038/ajg.2011.30.

7 S. Wirz, M. Wittmann, M. Schenk, A. Schroeck, N. Schaefer, M. Mueller, J. Standop, N. Kloecker, J. Nadstawek. Gastrointestinal symptoms under opioid therapy: a prospective comparison of oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine. Eur. J. Pain 13 (2009) 737–743. doi: 10.1016/j.ejpain.2008.09.005.

8 S.F. Cook, L. Lanza, X. Zhou, C.T. Sweeney, D. Goss, K. Hollis, A.W. Mangel, Fehnel, S.E. Gastrointestinal side effects in chronic opioid users: results from a population-based survey. Aliment Pharmacol Ther 27 (2008) 1224–1232. doi: 10.1111/j.1365-2036.2008.03689.x.

9 T.J. Bell, S.J. Panchal, C. Miaskowski, S.C. Bolge, T. Milanova, Williamson, R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). Pain Med. 10 (2009) 35–42. doi: 10.1111/j.1526-4637.2008.00495.x

10 M. Yotoku, A. Nakanishi, M. Kanematsu, N. Sakaguchi, N. Hashimoto, F. Koyama, S. Yamaguchi, K. Ikeda, Konishi, H. and Hirotani, Y. Reduction of opioid side effects by prophylactic measures of palliative care team may result in improved quality of life. J. Palliat. Med. 13 (2010) 401–406, doi: 10.1089/jpm.2009.0355.

11 G. Rosti, A. Gatti, A. Costantini, A.F. Sabato, Zucco, F. Opioid-related bowel dysfunction: prevalence and identification of predictive factors in a large sample of Italian patients on chronic treatment. Eur. Rev. Med. Pharmacol. Sci. 14 (2010) 1045–1050.

12 A.K. Tuteja, J. Biskupiak, G.J. Stoddard, Lipman, A.G. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. Newrogastroenterol. Motil. 22 (2010) 424-430. doi: 10.1111/j.1365-2982.2009.01458.x.

13 Clinical Guidelines for Gastrointestinal Symptoms in Cancer Patients ver. 2017

14 M. Ishihara, H. Ikesue, H. Matsunaga, K. Suemaru, K. Kitaichi, K. Suetsugu, R. Oishi, T. Sendo, H. Araki, Itoh, Y. Japanese study group for the relief of opioid-induced gastrointestinal dysfunction. A multi-institutional study analyzing effect of prophylactic medication for prevention of opioid-induced gastrointestinal dysfunction. Clin J Pain 28 (2012) 373-81. doi: 10.1097/ajp.0b013e318237d626.

15 M. Camilleri, D.A. Drossman, G. Becker, L.R. Webster, A.N. Davies, Mawe, G.M. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol. Motil. 26 (2014) 1386-1395. doi:10.1111/nmo.12417.

16 Song. X, Wang. D, Qu. X, Dong. N, Teng. S. A meta-analysis of naldemedine for the treatment of opioid-iduced constipation. Expert Rev Clin Pharmacol. 12 (2019) 121-128. doi: 10.1080/17512433.2019.1570845.

17 K. Fukumura, T. Yokota, Y. Baba, J.C. Arjona Ferreira. Phase 1, Randomized, double-blind, placebo-controlled studies on the safety, tolerability, and pharmacokinetics of naldemedine in healthy volunteers.

Clin. Pharmacol. Drug. Dev. 7 (2017) 474-483. doi:10.1002/cpdd.387.

18 L.R. Webster, T. Yamada, J.C. Arjona Ferreira. A phase 2b, randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of naldemedine for the treatment of opioid-induced constipation in patients with chronic noncancer pain. Pain Med. 18 (2017) 2350-2360. doi:10.1093/pm/pnw325.

19 N. Katakami, T. Harada, T. Murata, K. Shinozaki, M. Tsutsumi, T. Yokota, M. Arai, Y. Tada, M. Narabayashi, Boku, N. Randomized phase III and extension studies: efficacy and impacts on quality of life of naldemedine in subjects with opioid-induced constipation and cancer. Ann. Oncol. 29 (2018) 1461-1467. doi: 10.1093/annonc/mdy118.

20 A. Nakajima, et al. Safety and efficacy of elobixibat for chronic constipation: results from a randomized, double-blinded, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial. Lancet Gastroenterol Hepatol. 3 (2018) 537-547. doi: 10.1016/S2468-1253

21 Mokhtare, M. et al. Reliability and validity of the Persian version of patient assessment of constipation- quality of life (JPAC-QOL) questionnaire. Gastroenterol Hepatol Bed Bench. 10 (2017) 289-294.

22 Ishihara, M. et al. A multi-institutional study analyzing effect of prophylactic medication for prevention of opioid-induced gastrointestinal dysfunction. Clin J Pain 28 (2012) 373-381. doi: 10.1097/ajp.0b013e318237d626.

23 A.J. Hatswell, Vegter, S. Measuring quality of life in opioid-induced constipation: mapping EQ-5D-3 L and JPAC-QOL. Health Econ. Rev. 6 (2016) 14-…. doi: 10.1186/s13561-016-0091-9

24 C.L. Miles, D. Fellowes, Goodman, M.L. and Wilkinson, S. Laxatives for the management of constipation in palliative patients. Cochrane Database Syst. Rev. 4 (2006) CD003448. doi: 10.1002/14651858.cd003448.

25 Y. Agra, SacristáA. n, GonzáM. lez, M. Ferrari, PortuguéA. s, Calvo, M.J. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. J. Pain Symptom Manage. 15 (1998) 1-7. doi: 10.1016/S0885-3924(97)00276-5.

Table 1

Table 1

Study endpoints

Primary endpoint

Change in JPAC-QOL from baseline at 2 weeks

Key secondary endpoints

Change in SBMs from baseline at 2 and 12 weeks

Other secondary endpoints

Change in JPAC-QOL from baseline at 12 weeks
Change in PAC-SYM from baseline at 2 and 12 weeks
Change in CSS from baseline at 2 and 12 weeks
Change in RomeIV from baseline at 2 and 12 weeks
Change in BSFS from baseline at 2 and 12 weeks
Change in SF-36 from baseline at 2 and 12 weeks

Safety endpoint

Assessment of adverse events that appeared from the first day to 28 days after treatment

Figures

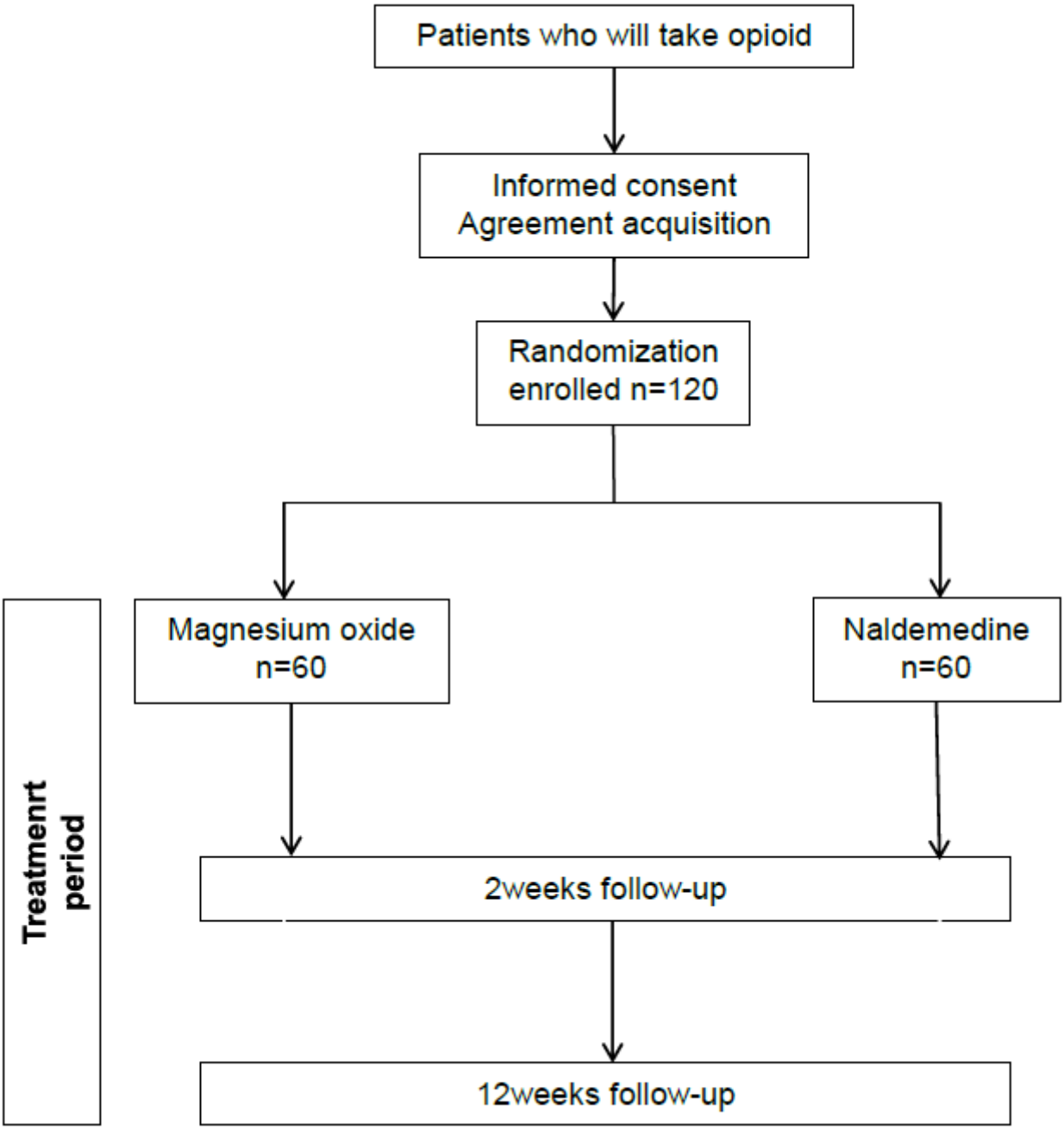

Figure 1

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

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.pdf