Effectiveness of Naldemedine Compared with Magnesium Oxide in Preventing Opioid-Induced Constipation: A Randomized Controlled Trial

Anna Ozaki, Takaomi Kessoku, Kosuke Tanaka, Atsushi Yamamoto, Kota Takahashi, Yuma Takeda, Yuki Kasai, Michihiro Iwaki, Takashi Kobayashi, Tsutomu Yoshihara, Takayuki Kato, Akihiro Suzuki, Yasushi Honda, Yuji Ogawa, Akiko Fuyuki, Kentaro Imajo, Takuma Higurashi, Masato Yoneda, Masatake Taguri, Hiroto Ishiki, Noritoshi Kobayashi, Satoru Saijo, Yasushi Ichikawa, and Atsushi Nakajima

Abstract: Opioids are used in cancer pain management, however, their continuous use may not be tolerable owing to adverse effects such as constipation, sleepiness, nausea, and respiratory depression. Opioid-induced constipation reduces the quality of life of patients, and osmotic laxatives are conventionally recommended for preventing opioid-induced constipation. Recently, naldemedine, a peripherally acting µ-opioid receptor antagonist, can be used to safely and effectively treat opioid-induced constipation based on its etiological mechanism, without affecting central analgesia. In this study, we compared the effectiveness of magnesium oxide with that of naldemedine in preventing opioid-induced constipation. Naldemedine significantly prevented deterioration in the quality of defecation (the Japanese Patient Assessment of Constipation Quality of Life and complete spontaneous bowel movement) and reduced gastrointestinal adverse effects, mainly nausea, compared with magnesium oxide during 12-week administration.

Simple Summary: Opioids are used in cancer pain management, however, their continuous use may not be tolerable owing to adverse effects such as constipation, sleepiness, nausea, and respiratory depression. Opioid-induced constipation reduces the quality of life of patients, and osmotic laxatives are conventionally recommended for preventing opioid-induced constipation. Recently, naldemedine, a peripherally acting µ-opioid receptor antagonist, can be used to safely and effectively treat opioid-induced constipation based on its etiological mechanism, without affecting central analgesia. In this study, we compared the effectiveness of magnesium oxide with that of naldemedine in preventing opioid-induced constipation. Naldemedine significantly prevented deterioration in the quality of defecation (the Japanese Patient Assessment of Constipation Quality of Life and complete spontaneous bowel movement) and reduced gastrointestinal adverse effects, mainly nausea, compared with magnesium oxide during 12-week administration.
than in the MgO group. Neither significant differences in the change in SBMs between the groups nor serious adverse events/deaths were observed. The CSBM rate was higher in the NAL group than in the MgO group at 2 and 12 weeks. In conclusion, NAL significantly prevented deterioration in constipation-specific QOL and CSBM rate compared with MgO.

**Keywords:** opioid-induced constipation; magnesium oxide; naldemedine; spontaneous bowel movement

1. Introduction

Opioids are used in cancer pain management [1,2], however, their continuous use may not be tolerable owing to adverse effects such as constipation, sleepiness, nausea, and respiratory depression [3–6]. Reportedly, 15–64% of patients receiving strong opioid analgesic treatment experience constipation [7–11], and the cumulative incidence of opioid-induced constipation (OIC) in Japan has been reported to be as high as 79%, which has been observed in patients with breast cancer [12]. Prolonged opioid administration is largely associated with OIC [13] and the prophylactic administration of laxatives is important, as drug tolerance in patients with OIC is low [14]. OIC is worth investigating as the symptoms associated with constipation (abdominal pain, bloating, and appetite loss) may reduce the quality of life (QOL) of these patients.

Conventional OIC treatments include non-drug therapy such as the consumption of a fiber-rich diet and use of medications such as laxatives. In Japan, osmotic laxatives are recommended for OIC treatment [15], and an observational study in Japan revealed that prophylactic magnesium oxide intake at the start of opioid therapy attenuated OIC [16]. Therefore, osmotic laxatives, including magnesium oxide, have been used in Japan for the treatment of OIC caused by opioids that act on µ-receptors in the enteric nerves and impair intestinal motility and secretion [6,17]. Additionally, other osmotic laxatives such as polyethylene glycol are used for treating and as the prophylaxis of OIC in many countries. However, neither diet therapy nor osmotic laxative treatment targets the etiological mechanism of OIC [3,9].

Patients with OIC may feel frustrated, stressed, or anxious because of their dietary restrictions and may feel embarrassed for taking frequent and prolonged bathroom breaks. OIC reduces the QOL of patients and requires preventive treatment. Although there has been progress in research on OIC treatment [9], naldemedine, a peripherally acting µ-opioid receptor antagonist (PAMORA), can be used to safely and effectively treat OIC [18,19] based on its etiological mechanism, without affecting central analgesia [20]. In this study, we compared the effectiveness of magnesium oxide with that of naldemedine in preventing OIC.

2. Materials and Methods

2.1. Study Design

We conducted a single-center, open-label, two-arm, phase II randomized controlled trial between 26 March 2018 and 30 June 2019 in Yokohama City University Hospital. We included 120 adult patients with any type of cancer (aged 20–85 years) who were scheduled to start opioid therapy for cancer pain. The participants were capable of oral intake and providing written consent to participate in the study; they were expected to remain in stable pathological condition during the observation period. Detailed inclusion and exclusion criteria are shown in Supplementary Table S1. The study design is outlined in Figure 1. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Yokohama City University Hospital (approval number: B180301006, approval date: 22 March 2018) prior to the initiation of the study. This trial was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000031891 on 25 March 2018). All patients provided written informed consent. The trial protocol was described according to the standard protocol items: Recommendations for Interventional Trials Patient-Reported Outcome Extension and its
checklists (Supplementary Material File S1) [21]. The results of this trial were reported in conformity with the Consolidated Standards of Reporting Trials 2010 guidelines [22].

Figure 1. Flow chart showing the study outline.

2.2. Randomization and Masking

The patients were randomly allocated (1:1 ratio) using a computer-based system and stratified by age and sex to the magnesium oxide group (MgO group; 500 mg, thrice daily after each meal) or the naldemedine group (NAL group; 0.2 mg, once daily after breakfast), and each drug was administered orally for 12 weeks. Randomization was performed using a computer-generated, centrally administered procedure and a permuted block method. Randomization was conducted independently using a validated allocation system (International University of Health and Welfare Atami Hospital, Japan, performed by T. Kato).

2.3. Endpoints

The summary of endpoints is shown in Supplementary Table S2. The primary endpoint was the change in the Japanese Patient Assessment of Constipation Quality of Life (JPAC-QOL) score from baseline to 2 weeks after treatment initiation. The primary endpoint was calculated from the mean of the difference from baseline at 2 weeks, as opioid-induced constipation develops within 2 weeks of opioid treatment; hence, the primary endpoint was set to 2 weeks. The JPAC-QOL is a reliable and valid psychometric evaluation criterion for patients with functional constipation [23] and comprises 28 questions rated on a five-point adjective score from 0 to 4. A lower the score indicates a higher QOL [24–26].

The secondary endpoints were the change in the JPAC-QOL score from baseline to 12 weeks and the changes in the Patient Assessment of Constipation Symptoms (PAC-SYM) [27]; spontaneous bowel movements (SBMs); Bristol stool form scale (BSFS) [28]; constipation scoring system (CSS) [29]; Rome IV [30]; and short form-36 (SF-36) scores [31] at 2 and 12 weeks after treatment initiation. The changes in complete spontaneous bowel movement (CSBM), JPAC-QOL and JPAC-SYM subscales, and numerical rating score (NRS) for pain were assessed using a post hoc analysis. SBM was defined as the number of defecations not induced by rescue medication. CSBM was defined as the number
of defecations not induced by rescue medication and not accompanied by a sense of incomplete evacuation [32], indicating the patient’s greater QOL at defecation. According to the European Medicines Agency guidelines, patient CSBM is important, as it incorporates spontaneity and completeness [33].

2.4. Statistical Analysis

A retrospective analysis of magnesium oxide/naldemedine in 10 OIC patients in Yokohama City University Hospital showed a mean JPAC-QOL change of $-1.19$ and $-0.76$ in the NAL and MgO groups, respectively. We decided to calculate the appropriate number of patients required for a proper analysis of the variance F-test based on these data. Assuming mean changes in the JPAC-QOL score in the NAL group and the MgO group to be $-1.19$ and $-0.76$, respectively, with a common standard deviation of 0.76, 51 patients were needed in each group to reach 90% statistical power with a two-sided significance level of 5%. To compensate for any dropout, we proposed increasing the number of patients to 60 per group. To reach this number, 120 patients were needed.

The intention-to-treat (ITT) population, which included all patients who underwent randomization, was used to assess the primary efficacy endpoint, which was set as the change in the mean JPAC-QOL score between weeks 0 and 2. The primary efficacy analysis was performed on the ITT population. The primary endpoint was a continuous variable and was performed using the Student’s $t$-test to compare the two groups. Two-tailed $p < 0.05$ indicated statistical significance. Secondary and tertiary endpoints were analyzed similarly. Chi-squared tests were used to assess the categorical variables, such as the frequency of constipation filling the ROME IV criteria and AEs. The intensity of an AE was graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Safety and tolerability analyses were performed on the safety population, which included all patients who received at least one dose of the study drug. JMP software version 11.2.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. This study was overseen by an independent medical monitor (on-site monitoring).

3. Results

3.1. Baseline Characteristics

Of the 166 patients eligible for this study, 120 were included (Figure 1). There was no significant difference in the baseline characteristics of patients in the MgO and NAL groups (Table 1). The MgO group comprised 23 males (38%) and 37 females (62%) (51 ± 9 years old), whereas the NAL group comprised 24 males (40%) and 36 females (60%) (52 ± 9 years old). The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0–2 in 54 patients (90%) in the MgO group and in 52 patients (87%) in the NAL group. None of the patients in either group received chemotherapy within 2 weeks of the baseline. Between 2 and 12 weeks, 27 (45%) patients in the MgO group and 27 (45%) patients in the NAL group received chemotherapy. Moreover, in both the MgO and NAL groups, the use of platinum agents (cisplatin, carboplatin, and oxaliplatin) was 37%; the use of taxane agents (paclitaxel) was 22% and 15%, respectively; the use of anti-metabolite agents (tegafur/gimeracil/oteracil, and fluorouracil) was 37% and 48%, respectively; no irinotecan was used in either group.
Table 1. Demographic and baseline characteristics of modified intention-to-treat populations.

| Characteristic                      | 1500 mg MgO (n = 60) | 0.2 mg NAL (n = 60) |
|-------------------------------------|----------------------|---------------------|
| Age (years)                         | 51 (9)               | 52 (9)              |
| Sex                                 |                      |                     |
| Female                              | 37 (62)              | 36 (60)             |
| Male                                | 23 (38)              | 24 (40)             |
| Body mass index (kg/m²)             | 22 (4)               | 22 (10)             |
| History of abdominal operation      | 33 (55)              | 33 (55)             |
| ECOG PS 0–2                         | 54 (90)              | 52 (87)             |
| Palliative prognosis index ≤ 3.5    | 56 (93)              | 53 (88)             |
| Primary tumor site                  |                      |                     |
| Hepatobiliary and pancreas         | 18 (30)              | 21 (35)             |
| Gastrointestinal tract             | 13 (22)              | 16 (27)             |
| Lung                                | 5 (8)                | 3 (5)               |
| Others                              | 24 (40)              | 20 (33)             |
| Concurrent cancer treatment         |                      |                     |
| Chemotherapy (0–14 days)            | 0                    | 0                   |
| Chemotherapy (15–84 days)           | 27 (45)              | 27 (45)             |
| Chemotherapy type                   |                      |                     |
| Platinum agents                     | 10 (37)              | 10 (37)             |
| Taxane agents                       | 6 (22)               | 4 (15)              |
| Anti-metabolite agents              | 10 (37)              | 13 (48)             |
| Irinotecan                          | 0                    | 0                   |
| Antiemetics during chemotherapy #   | 3 (11)               | 2 (7)               |
| Perioperative                       | 12 (20)              | 12 (20)             |
| Best supportive care                | 9 (15)               | 14 (23)             |
| Others                              | 12 (20)              | 7 (12)              |
| Concomitant medications             |                      |                     |
| Laxative use                        |                      |                     |
| Naïve                               | 38 (63)              | 42 (70)             |
| Regular use (irritant laxative)     | 5 (8)                | 5 (8)               |
| Rescue use (irritant laxative)      | 17 (28)              | 13 (22)             |
| Opioid use at baseline              |                      |                     |
| Strong opioid                       | 27 (45)              | 30 (50)             |
| Weak opioid                         | 33 (55)              | 30 (50)             |
| Mean total daily dose of opioid *   |                      |                     |
| At baseline (mg)                    | 13 (4)               | 13 (4)              |
| At 2 weeks (mg)                     | 14 (4)               | 13 (5)              |
| At 12 weeks (mg)                    | 22 (19)              | 23 (23)             |
| Baseline defecation status          |                      |                     |
| Mean JPAC-QOL                       | 0.9 (0.6)            | 0.9 (0.4)           |
| SBMs per week                       | 4.3 (1.7)            | 4.5 (2.8)           |
| CSBMs per week                      | 3.8 (1.5)            | 3.7 (2.1)           |
| Stool consistency score             | 3.8 (0.7)            | 3.6 (1.9)           |

Data are represented as the mean (SD) or number (%). Age was based on the date of informed consent. Baseline values were based on the last week before the start of drug administration. Stool consistency was assessed according to the Bristol stool form scale scores. * Oral morphine-equivalent. # 5-HT3 receptor antagonists and neurokinin 1 receptor antagonist. Abbreviations: 5-HT3, 5-hydroxytryptamine 3; CSBM, complete spontaneous bowel movement; ECOG PS, Eastern Cooperative Oncology Group performance status; NAL, naldemedine; SBM, spontaneous bowel movement; SD, standard deviation.

Five patients (9%) in the MgO group and five (8%) in the NAL group used regular stimulant laxatives; 17 patients (28%) in the MgO group and 13 (22%) in the NAL group used rescue stimulant laxatives; 38 patients (63%) in the MgO group and 42 (70%) in the NAL group did not use any laxatives. Furthermore, strong opioid use was reported in 45% and 49% of patients in the MgO and NAL groups, respectively. The average oral morphine-equivalent opioid dose in the MgO and NAL groups was 13 mg at baseline, 14 mg and 13 mg at 2 weeks, and 22 mg and 23 mg at 12 weeks.
The patients’ mean JPAC-QOL at baseline in both groups was 0.9, whereas the number of SBMs per week was 4.3 and 4.5 and the number of CSBMs per week was 3.8 and 3.7 in the MgO and NAL groups, respectively. The average stool consistency score based on the BSFS scale was 3.8 in the MgO group and 3.6 in the NAL group at baseline.

3.2. Primary and SecondaryEndpoints

After administration, the change in the overall mean JPAC-QOL from baseline was +0.5 in the MgO group and −0.01 in the NAL group (p < 0.001, lower scores indicate greater QOL) at 2 weeks, and +0.4 in the MgO group and +0.03 in the NAL group (p < 0.001) at 12 weeks (Figure 2A). The change in the overall mean PAC-SYM from baseline was +0.6 in the MgO group and +0.02 in the NAL group (p < 0.001) at 2 weeks, and +0.5 in the MgO group and +0.02 in the NAL group (p < 0.001) at 12 weeks (Figure 2B). There was no difference in the frequency of SBMs between the groups (Figure 3A). However, the post hoc analysis revealed higher mean CSBMs in the NAL group than in the MgO group at both 2 and 12 weeks (0 vs. −0.9, p = 0.01 at 2 weeks and +0.2 vs. −0.7, p = 0.003 at 12 weeks) (Figure 3B). The PAC-QOL subscale (physical discomfort, psychosocial discomfort, and satisfaction) and all mean PAC-SYM subscale (stool symptoms, rectal symptoms, and abdominal symptoms) scores were significantly improved at 2 and 12 weeks (Table 2 and Figure 4A–D). After 2 and 12 weeks of treatment, the number of patients diagnosed with constipation by Rome IV criteria was significantly lower in the NAL group (Table 2). All SF-36 subscales, including the physical, mental, and role component summary, showed no significant differences between the groups at 2 and 12 weeks (Table 2). There was no significant difference in the average time to the first SBM, but the mean time to the first CSBM was significantly shorter in the NAL group at 2 weeks (10.4 h vs. 6.4 h; p < 0.001) and 12 weeks (10.1 h vs. 6.4 h; p < 0.001) (Table 2). No significant change in the NRS was observed at 2 and 12 weeks (Table 2).

Figure 2. (A): Overall Japanese version of Patient Assessment of Constipation Quality of Life (JPAC-QOL) score at baseline and after 2 and 12 weeks of treatment in the magnesium oxide group and naldemedine groups; and (B) overall Patient Assessment of Symptoms (PAC-SYM) score at baseline and after 2 and 12 weeks of treatment in the magnesium oxide group and naldemedine groups.
naldemedine groups; and (B) overall Patient Assessment of Symptoms (PAC-SYM) score at baseline and after 2 and 12 weeks of treatment in the magnesium oxide group and naldemedine groups.

Figure 3. (A) Change in the number of spontaneous bowel movements (SBMs; times/week) from baseline to 2 and 12 weeks (after treatment) in the magnesium oxide group and the naldemedine group; and (B) change in the number of complete spontaneous bowel movements (CSBMs; times/week) from baseline to 2 and 12 weeks (after treatment) in the magnesium oxide group and the naldemedine group.

Table 2. Efficacy in the 2- and 12-week randomized trial.

| Endpoints                  | 2 Weeks               | 12 Weeks              | p-Value   |
|----------------------------|-----------------------|-----------------------|-----------|
| Primary endpoint           |                       |                       |           |
| JPAC-QOL Overall           | 0.5 (0.4)             | −0.01 (0.3)           | <0.001    |
| Secondary endpoints        |                       |                       |           |
| SBM (times/week)           | 0.3 (1.7)             | −0.1 (2.4)            | 0.3       |
| Stool consistency score    | 0.6 (1.1)             | −0.3 (1.1)            | <0.001    |
| PAC-SYM Overall            | 0.6 (0.5)             | 0.02 (0.3)            | <0.001    |
| ROME IV, n (%)             | 33 (55)               | 20 (33)               | 0.02      |
| CSS                        | 0.3 (0.3)             | 0.0 (0.3)             | <0.001    |
| SF-36                      |                       |                       |           |
| Physical component summary | 0 (0)                 | 0.04 (6.6)            | 1.0       |
| Mental component summary   | 0 (0)                 | 1.9 (6.1)             | 0.02      |
| Role component summary     | 0 (0)                 | −1.9 (9.7)            | 0.1       |
| Post hoc analyses          |                       |                       |           |
| CSBM (times/week)          | −0.9 (1.5)            | 0 (2.0)               | 0.01      |
| JPAC-QOL subscale          |                       |                       |           |
| Physical discomfort        | 0.6 (0.9)             | −0.01 (0.6)           | <0.001    |
| Psychosocial discomfort    | 0.6 (0.8)             | −0.01 (0.4)           | <0.001    |
| Worries/concerns           | 0.06 (0.2)            | −0.05 (0.4)           | 0.1       |
| Satisfaction               | 1.0 (0.7)             | 0.07 (0.5)            | <0.001    |
| PAC-SYM subscale           |                       |                       |           |
| Stool symptoms             | 0.3 (0.7)             | −0.1 (0.6)            | <0.001    |
| Rectal symptoms            | 0.7 (0.8)             | 0.1 (0.4)             | <0.001    |
| Abdominal symptoms         | 0.8 (1.0)             | 0.1 (0.4)             | <0.001    |
| Mean time to first SBM (h) | 4.9 (0.8)             | 4.9 (1.0)             | 0.7       |
| Mean time to first CSBM (h) | 10.4 (6.4)            | 6.4 (3.0)             | 0.001     |
| Numerical rating score     | −1.4 (1.8)            | −1.2 (2.8)            | 0.001     |

Data are represented as the mean (SD) or number (%). Abbreviations: CSBM, complete spontaneous bowel movement; CSS, constipation scoring system; NAL, naldemedine; JPAC-QOL, Japanese version of Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; SBM, spontaneous bowel movement; SF-36, short form-36.
Figure 4. (A) Change in the Japanese version of Patient Assessment of Constipation Quality of Life (JPAC-QOL) subscale score at baseline and after 2 weeks of treatment in the magnesium oxide (MgO) group and naldemedine (NAL) groups; (B) change in the JPAC-QOL subscale score at baseline and after 12 weeks of treatment in the MgO group and NAL groups; (C) change in the Patient Assessment of Constipation Symptoms (PAC-SYM) subscale score at baseline and after 2 weeks of treatment in the MgO group and NAL groups; and (D) change in the PAC-SYM subscale score at baseline and after 12 weeks of treatment in the MgO group and NAL groups.

3.3. Safety Outcomes

AEs are listed in Table 3. The rate of treatment-related AEs (TRA) was significantly higher in the MgO group than in the NAL group (MgO; 35% vs. NAL; 18%, \( p = 0.02 \)). TRAEs were observed in 21 patients in the MgO group and in 11 patients in the NAL group. Nausea accounted for the highest proportion of TRAEs in the MgO group at 2 weeks. At 12 weeks, the rate of TRAEs was significantly higher in the MgO group than in the NAL group (MgO; 52% vs. NAL; 27%, \( p = 0.02 \)). TRAEs occurred in 31 patients in the MgO group and in 16 patients in the NAL group. Nausea also accounted for the highest proportion of TRAEs in the MgO group at 12 weeks. No serious AEs or death occurred during the study period.
### Table 3. Adverse events.

| Adverse Events                          | 2 Weeks                          | 12 Weeks                         | p-Value | 2 Weeks                          | 12 Weeks                         | p-Value |
|----------------------------------------|----------------------------------|----------------------------------|---------|----------------------------------|----------------------------------|---------|
|                                        | 1500 mg MgO (n = 60)             | 0.2 mg NAL (n = 60)              |         | 1500 mg MgO (n = 60)             | 0.2 mg NAL (n = 60)              |         |
| Total adverse event                    | 32 (53)                          | 30 (50)                          | 0.02    | 39 (65)                          | 32 (53)                          | 0.01    |
| TRAEs                                  | 21 (35)                          | 11 (18)                          |         | 31 (52)                          | 16 (27)                          |         |
| TRAE leading to discontinuation        | 0                                | 0                                |         | 0                                | 0                                |         |
| Serious AEs                            | 0                                | 0                                |         | 0                                | 0                                |         |
| Serious TRAEs                          | 0                                | 0                                |         | 0                                | 0                                |         |
| Serious TRAE leading to discontinuation| 0                                | 0                                |         | 0                                | 0                                |         |
| Deaths                                 | 0                                | 0                                |         | 0                                | 0                                |         |
| TRAEs                                  | 0                                | 0                                |         | 0                                | 0                                |         |
| Gastrointestinal disorders             |                                  |                                  |         |                                  |                                  |         |
| SOC                                    |                                  |                                  |         |                                  |                                  |         |
| Abdominal pain                         | 4 (7)                            | 3 (5)                            | 0.03    | 20 (33)                          | 7 (12)                           | 0.005   |
| Diarrhea                               | 4 (7)                            | 5 (8)                            |         | 4 (7)                            | 6 (10)                           |         |
| Abdominal distension                   | 1 (0)                            | 0                                |         | 5 (8)                            | 1 (2)                            | 0.06    |
| Nausea                                 | 12 (20)                          | 4 (7)                            |         | 20 (33)                          | 7 (12)                           |         |

Data are represented as n (%). Categorization of adverse drug reactions was based on the Medical Dictionary for Regulatory Activities version 18.0. Abbreviations: NAL, naldemedine; SOC, system organ class; TRAE, treatment-related adverse event.

### 4. Discussion

This proof-of-concept, two-arm, phase II clinical trial demonstrated that the deterioration in JPAC-QOL was significantly lower in the NAL group than in the MgO group after 2 and 12 weeks of drug administration. Therefore, our trial met the primary endpoint. Higher CSBM rates were calculated in the NAL group at 2 and 12 weeks via post hoc analysis. However, no difference in defecation frequency (SBMs) between the MgO and NAL groups at 2 and 12 weeks was observed. Patients in both groups experienced >3 SBMs/week (<3 SBMs/week is one criterion defining constipation in Rome IV).

Several confounding factors were considered for endpoint evaluation, particularly defecation, food intake [34], decreased physical function (frailty) [35], and medication such as opioid [36] and chemotherapy [37], which are associated with gastrointestinal symptoms such as constipation and diarrhea. Opioid-induced constipation is exacerbated as opioid doses increase [36]. However, our results show no significant difference between the groups in terms of oral morphine-equivalent daily dose at baseline and at 2- and 12-weeks post-treatment. Therefore, it is unlikely that the opioids increased the potential risk of OIC in our study.

In addition, the type of chemotherapy [38,39], taxane agents [40], anti-metabolite agents [41], irinotecan [42], and antiemetics (mainly 5-hydroxytryptamine 3 receptor and neurokinin 1 receptor antagonists [43–45]) used for treatment are other confounding factors in constipation and diarrhea. However, as shown in Table 1, no significant differences were observed between the groups, which suggests that the effect of these factors on the primary endpoint is negligible.

PAMORAs, including NAL, are used for OIC treatment and are currently recommended in cases where osmotic or stimulant laxatives are ineffective [46]. However, at present, its long-term effects remain unknown. This study illustrated the efficacy and safety of the prophylactic effect on OIC for up to 12 weeks. Additionally, fewer AEs, especially opioid-induced nausea and vomiting (OINV), were observed in the NAL group at both 2 and 12 weeks. In an animal model, Kanemasa et al. reported the antiemetic properties of naldemedine and its efficacy against OINV [47]. The secondary effects of naldemedine on OINV have been reported by Sato et al., who showed that using naldemedine at an early stage of opioid administration may have secondary benefits in patients with constipation,
such as relief from OINV, in addition to improving OIC [48]. OINV occurs when opioids stimulate the peripheral µ-opioid receptors, thereby altering gastrointestinal motility and function [14], which may be prevented as naldemedine antagonizes these receptors.

This study indicates that magnesium oxide or naldemedine may be used to prevent OIC, although naldemedine significantly prevented deterioration in constipation-specific QOL and CSBM compared with magnesium oxide. One of the advantages of magnesium oxide is that its long-term safety has been empirically established through the conventional use of magnesium oxide for OIC prevention in Japan. Additionally, magnesium oxide is cost-effective, as it costs USD 0.3 (JPY 33.6) per day for a dose of 1500 mg/day whereas naldemedine costs USD 2.6 (JPY 272.1) per day.

There were some limitations to our study. This was a single-center, open-labeled study, and the treatment period (12 weeks) may have been too short to investigate the long-term effects. Therefore, large-scale multicenter blind studies with long-term follow-ups are warranted.

5. Conclusions

When treating OIC in patients with cancer, naldemedine significantly prevented deterioration in constipation-specific QOL and CSBM compared with magnesium oxide. Future studies should evaluate the clinical benefits of naldemedine over magnesium oxide, keeping in mind its cost.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers14092112/s1, Table S1: Patient inclusion and exclusion criteria; Table S2: Study endpoints; File S1: Study protocol. [49,50].

Author Contributions: Conceptualization, A.O., T.K. (Takaomi Kessoku) and A.N.; methodology, H.I. and Y.I.; investigation, K.T. (Kosuke Tanaka), A.Y., K.T. (Kota Takahashi), Y.T., Y.K., M.I. and T.K. (Takashi Kobayashi), T.Y., A.S., Y.H., A.F., Y.O., K.I., T.H., M.Y., N.K. and S.S.; allocation, T.K. (Takayuki Kato); formal analysis, M.T.; writing—original draft preparation, all authors; writing—review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by the Yokohama City University Hospital.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Yokohama City University Hospital (approval number: B180301006; approval date: 22 March 2018) prior to the initiation of the study. This trial was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000031891 on 25 March 2018).

Informed Consent Statement: All patients provided written informed consent.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The skillful technical assistance by Hiroyuki Abe, Kyoko Kato, and Machiko Hiraga, as well as the administrative assistance by Yoshiko Yamasaki, Ayako Ujiie, and Naho Kobayashi are gratefully acknowledged.

Conflicts of Interest: The authors declare no conflict of interests.

References

1. Portenoy, R.K.; Ahmed, E. Principles of Opioid Use in Cancer Pain. J. Clin. Oncol. 2014, 32, 1662–1670. [CrossRef] [PubMed]
2. Caraceni, A.; Hanks, G.; Kaasa, S.; Bennett, M.I.; Brunelli, C.; Cherny, N.; Dale, O.; de Conno, F.; Fallon, M.; Hanna, M.; et al. Use of Opioid Analgesics in the Treatment of Cancer Pain: Evidence-Based Recommendations from the EAPC. Lancet Oncol. 2012, 13, e58–e68. [CrossRef]
3. Poulsen, J.L.; Brock, C.; Olesen, A.E.; Nilsson, M.; Drewes, A.M. Evolving Paradigms in the Treatment of Opioid-Induced Bowel Dysfunction. Ther. Adv. Gastroenterol. 2015, 8, 360–372. [CrossRef] [PubMed]
4. Morlion, B.; 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. 2015, 35, 1–11. [CrossRef]
5. Lazzari, M.; Greco, M.T.; Marcassa, C.; Finocchi, S.; Caldarulo, C.; Corli, O. Efficacy and Tolerability of Oral Oxycodone and Oxycodone/Naloxone Combination in Opioid-Naive Cancer Patients: A Propensity Analysis. *Drug Des. Devel. Ther.* 2015, 9, 5863–5872. [CrossRef]

6. Camilleri, M. Opioid-Induced Constipation: Challenges and Therapeutic Opportunities. *Am. J. Gastroenterol.* 2011, 106, 835–842; quiz 843. [CrossRef]

7. Wirz, S.; Wittmann, M.; Schenk, M.; Schroeck, A.; Schaefer, N.; Mueller, M.; Standop, J.; Kloecker, N.; Nadstawek, J. Gastrointestinal Symptoms under Opioid Therapy: A Prospective Comparison of Oral Sustained-Release Hydromorphone, Transdermal Fentanyl, and Transdermal Buprenorphine. *Eur. J. Pain* 2009, 13, 737–743. [CrossRef]

8. Cook, S.F.; Lanza, L.; Zhou, X.; Sweeney, C.T.; Goss, D.; Hollis, K.; Mangel, A.W.; Fehnel, S.E. Gastrointestinal Side Effects in Chronic Opioid Users: Results from a Population-Based Survey. *Aliment. Pharmacol. Ther.* 2008, 27, 1224–1232. [CrossRef]

9. Bell, T.J.; Panchal, S.J.; Miaskowski, C.; Bolge, S.C.; Milanova, T.; Williamson, R. The Prevalence, Severity, and Impact of Opioid-Induced Bowel Dysfunction: Results of a US and European Patient Survey (PROBE 1). *Pain Med.* 2009, 10, 35–42. [CrossRef]

10. Myotokuri, M.; Nakanishi, A.; Kanematsu, M.; Sakaguchi, N.; Hashimoto, N.; Koyama, F.; Yamaguchi, S.; Ikeda, K.; Konishi, H.; Hirota, Y. Reduction of Opioid Side Effects by Prophylactic Measures of Palliative Care Team May Result in Improved Quality of Life. *J. Palliat. Med.* 2010, 13, 401–406. [CrossRef]

11. Rosti, G.; Gatti, A.; Costantini, A.; Sabato, A.F.; 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.* 2010, 14, 1045–1050. [PubMed]

12. Tokoro, A.; Imai, H.; Fumita, S.; Harada, T.; Noriyuki, T.; Gamoh, M.; Akashi, Y.; Sato, H.; Kizawa, Y. Incidence of Opioid-Induced Constipation in Japanese Patients with Cancer Pain: A Prospective Observational Cohort Study. *Cancer Med.* 2019, 8, 4883–4891. [CrossRef] [PubMed]

13. Tuteja, A.K.; Biskupiak, J.; Stoddard, G.J.; Lipman, A.G. Opioid-Induced Bowel Disorders and Narcotic Bowel Syndrome in Patients with Chronic Non-Cancer Pain. *Neurogastroenterol. Motil.* 2010, 22, 424–430.e96. [CrossRef] [PubMed]

14. Lee, A.A.; Hasler, W.L. Opioids and Gi Motility-Friend or Foe? *Curr. Treat. Options Gastroenterol.* 2016, 14, 478–494. [CrossRef]

15. Japanese Society of Palliative Medicine; Committee on Guidelines. *Guidelines for the Palliation of Gastrointestinal Symptoms in Cancer Patients 2017 Edition*; Published Online; Japanese Society for Palliative Medicine: Osaka, Japan, 2017; p. 32.

16. Ishihara, M.; Ikuse, H.; Matsunaga, H.; Suemaru, K.; Kitaichi, K.; Suesutug, K.; Oishi, R.; Sendo, T.; Araki, H.; Itoh, Y.; et al. A Multi-Institutional Study Analyzing Effect of Prophylactic Medication for Prevention of Opioid-Induced Gastrointestinal Dysfunction. *Clin. J. Pain* 2012, 28, 373–381. [CrossRef]

17. Camilleri, M.; Drossman, D.A.; Becker, G.; Webster, L.R.; Davies, A.N.; Mawe, G.M. Emerging Treatments in Neurogastroenterology: A Multidisciplinary Working Group Consensus Statement on Opioid-Induced Constipation. *Neurogastroenterol. Motil.* 2014, 26, 1386–1395. [CrossRef]

18. Fukumura, K.; Yokota, T.; Baba, Y.; Arjona Ferreira, J.C. Phase 1, Randomized, Double-Blind, Placebo-Controlled Studies on the Safety, Tolerability, and Pharmacokinetics of Naldemedine in Healthy Volunteers. *Clin. Pharmacol. Drug Dev.* 2018, 7, 474–483. [CrossRef]

19. Webster, L.R.; Yamada, T.; Arjona Ferreira, J.C. 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.* 2017, 18, 2350–2360. [CrossRef]

20. Song, X.; Wang, D.; Qu, X.; Dong, N.; Teng, S. A Meta-Analysis of Naldemedine for the Treatment of Opioid-Induced Constipation. *Expert Rev. Clin. Pharmacol.* 2019, 12, 121–128. [CrossRef]

21. Ozaki, A.; Kessoku, T.; Iwaki, M.; Kobayashi, T.; Yoshihara, T.; Kato, T.; Honda, Y.; Ogawa, Y.; Imaio, K.; Higurashi, T.; et al. 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. *Trials* 2020, 21, 453. [CrossRef]

22. Schulz, K.F.; Altman, D.G.; Moher, D.; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. *BMJ* 2010, 340, c332. [CrossRef] [PubMed]

23. Nomura, H.; Agatsuma, T.; Mimura, T. Validity and Reliability of the Japanese Version of the Patient Assessment of Constipation Quality of Life Questionnaire. *J. Gastroenterol.* 2005, 40, 540–551. [CrossRef]

24. Katakami, N.; Harada, T.; Murata, T.; Shinozaki, K.; Tsutsumi, M.; Yokota, T.; Arai, M.; Tada, Y.; Narabayashi, M.; 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.* 2018, 29, 1461–1467. [CrossRef] [PubMed]

25. Nakajima, A.; Seki, M.; Taniguchi, S.; Ohta, A.; Gillberg, P.G.; Mattsson, J.P.; Camilleri, M. Safety and Efficacy of Elobixibat for Chronic Constipation: Results from a Randomised, Double-Blind, Placebo-Controlled, phase 3 Trial and an Open-Label, Single-Arm, phase 3 Trial. *Lancet Gastroenterol. Hepatol.* 2018, 3, 537–547. [CrossRef]

26. Marquis, P.; de la Loge, C.; Dubois, D.; McDermott, A.; Chassany, O. Development and Validation of the Patient Assessment of Constipation Quality of Life Questionnaire. *Scand. J. Gastroenterol.* 2005, 40, 540–551. [CrossRef] [PubMed]
28. Longstreth, G.F.; Thompson, W.G.; Chey, W.D.; Houghton, L.A.; Mearin, F.; Spiller, R.C. Functional Bowel Disorders. *Gastroenterology* 2006, 130, 1480–1491. [CrossRef]

29. Agachan, F.; Chen, T.; Pleifler, J.; Reissman, P.; Wexner, S.D. A Constipation Scoring System to Simplify Evaluation and Management of Constipated Patients. *Dis. Colon Rectum* 1996, 39, 681–685. [CrossRef]

30. Mearin, F.; Lacy, B.E.; Chang, L.; Chey, W.D.; Lembo, A.J.; Simren, M.; Spiller, R. Bowel Disorders. *Gastroenterology* 2016, 150, 1393–1407.e5. [CrossRef]

31. Smith, K.; Hopp, M.; Mundin, G.; Bond, S.; Bailey, P.; Woodward, J.; Palaniappan, K.; Church, A.; Limb, M.; Connor, A. Naloxone as Part of a Prolonged Release Oxycodone/Naloxone Combination Reduces Oxycodone-Induced Slowing of Gastrointestinal Transit in Healthy Volunteers. *Expert Opin. Investig. Drugs* 2011, 20, 427–439. [CrossRef]

32. Smith, P.; Lavery, A.; Turkington, R.C. An Overview of Acute Gastrointestinal Side Effects of Systemic Anti-Cancer Therapy and Their Management. *Best Pract. Res. Clin. Gastroenterol.* 2020, 48–49, 101691. [CrossRef]

33. European Medicines Agency. Guideline on the Evaluation of Medicinal Products for the Treatment of Chronic Constipation (Including Opioid Induced Constipation) and for Bowel Cleansing; European Medicines Agency and Committee for Medicinal Products for Human Use (CHMP): Amsterdam, The Netherlands, 2015.

34. Murakami, K.; Sasakii, S.; Okubo, H.; Takahashi, Y.; Hosoi, Y.; Itabashi, M.; Freshmen in Dietetic Courses Study II Group. Food Intake and Functional Constipation: A Cross-Sectional Study of 3,835 Japanese Women Aged 18–20 Years. *J. Nutr. Sci. Vitaminol.* 2007, 53, 30–36. [CrossRef] [PubMed]

35. Asaoka, D.; Takeda, T.; Inami, Y.; Abe, D.; Shimada, Y.; Matsumoto, K.; Ueyama, H.; Matsumoto, K.; Komori, H.; Akazawa, Y.; et al. The Association Between Frailty and Abdominal Symptoms: A Hospital-Based Cross-Sectional Study. *Intern. Med.* 2020, 59, 1677–1685. [CrossRef] [PubMed]

36. Smith, K.; Hopp, M.; Mundin, G.; Bond, S.; Bailey, P.; Woodward, J.; Palaniappan, K.; Church, A.; Limb, M.; Connor, A. Naloxone as Part of a Prolonged Release Oxycodone/Naloxone Combination Reduces Oxycodone-Induced Slowing of Gastrointestinal Transit in Healthy Volunteers. *Expert Opin. Investig. Drugs* 2011, 20, 427–439. [CrossRef]

37. Smith, P.; Lavery, A.; Turkington, R.C. An Overview of Acute Gastrointestinal Side Effects of Systemic Anti-Cancer Therapy and Their Management. *Best Pract. Res. Clin. Gastroenterol.* 2020, 48–49, 101691. [CrossRef]

38. Asaoka, D.; Takeda, T.; Inami, Y.; Abe, D.; Shimada, Y.; Matsumoto, K.; Ueyama, H.; Matsumoto, K.; Komori, H.; Akazawa, Y.; et al. The Association Between Frailty and Abdominal Symptoms: A Hospital-Based Cross-Sectional Study. *Intern. Med.* 2020, 59, 1677–1685. [CrossRef] [PubMed]

39. Stojanovska, V.; Sakal, S.; Nurgali, K. Platinum-Based Chemotherapy: Gastrointestinal Immuno modulation and Enteric Nervous System Toxicity. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2013, 305, G223–G232. [CrossRef]

40. Narayan, P.; Wahby, S.; Gao, J.J.; Amiri-Kordestani, L.; Ibrahim, A.; Bloomquist, E.; Tang, S.; Xu, Y.; Liu, J.; Fu, W.; et al. FDA Approval Summary: Atezolizumab plus Paclitaxel Protein-Bound for the Treatment of Patients with Advanced or Metastatic TNBC Whose Tumors Express PD-L1. *Clin. Cancer Res.* 2020, 26, 2284–2289. [CrossRef]

41. Hanai, A.; Ishiguro, H.; Sozu, T.; Tsuda, M.; Arai, H.; Mitani, A.; Tsuboyama, T. Effects of a Self-Management Program on Bowel Disorders. *Intern. Med.* 2015, 54, 2473–2482. [CrossRef] [PubMed]

42. Eisentberg, P.; Figueroa-Vadillo, J.; Zamora, R.; Charu, V.; Hajdenberg, J.; Cartmell, A.; Macciocchi, A.; Grunberg, S.; 99-04 endorsement of Emesis. *Am. J. Pharmacol.* 2014, 722, 26–37. [CrossRef]

43. Eisenberg, P.; Figueroa-Vadillo, J.; Zamora, R.; Charu, V.; Hajdenberg, J.; Cartmell, A.; Macciocchi, A.; Grunberg, S.; 99-04 endorsement of Emesis. *Am. J. Pharmacol.* 2014, 722, 26–37. [CrossRef]

44. Tamura, T.; Matsuzaki, T.; Koike, K.; Hasegawa, M.; Suzuki, T. Preventive Effects of Naldemedine, Peripherally Acting NK(1) Receptor Agonists in Prevention of Emesis. *Expert Opin. Investig. Drugs* 2020, 30, 681–685. [CrossRef]

45. Kanemasa, T.; Matsuzaki, T.; Koike, K.; Hasegawa, M.; Suzuki, T. Preventive Effects of Naldemedine, Peripherally Acting Mu-Opioid Receptor Antagonist, on Morphine-Induced Nausea and Vomiting in Ferrets. *Life Sci.* 2020, 257, 118048. [CrossRef] [PubMed]

46. Sato, J.; Tanaka, R.; Ishikawa, H.; Suzuki, T.; Shino, M. A Preliminary Study of the Effect of Naldemedine Tosylate on Opioid-Induced Nausea and Vomiting. *Support Care Cancer* 2020, 28, 1083–1088. [CrossRef]

47. Takeda, T.; Kanemasa, T.; Matsuzaki, T.; Koike, K.; Hasegawa, M.; Suzuki, T. Preventive Effects of Naldemedine, Peripherally Acting NK(1) Receptor Agonists in Prevention of Emesis. *Am. J. Pharmacol.* 2014, 722, 26–37. [CrossRef]

48. Sato, J.; Tanaka, R.; Ishikawa, H.; Suzuki, T.; Shino, M. A Preliminary Study of the Effect of Naldemedine Tosylate on Opioid-Induced Nausea and Vomiting. *Support Care Cancer* 2020, 28, 1083–1088. [CrossRef]

49. Gisondi, P.; Conti, A.; Galdo, G.; Piaserico, S.; de Simone, C.; Girolomoni, G. Ustekinumab does not increase body mass index in patients with chronic plaque psoriasis: A prospective cohort study. *Br. J. Dermatol.* 2013, 168, 1124–1127. [CrossRef]

50. Clinical Guidelines for Cancer Pain Management, 2nd ed.; WHO: Geneva, Switzerland, 2014.