Asia-Pacific Journal of Science and Technology :Volume :27 .Issue :01 .Article ID :.APST-27-01-07. Research Article

APST

Asia-Pacific Journal of Science and Technology

https//:www.tci-thaijo.org/index.php/APST/index

Published by the Research and Graduate Studies,
Khon Kaen University, Thailand

Dexamethasone and clinical outcomes in malignant intestinal obstruction: A retrospective cohort study

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Received 21 October 2020
Revised 7 April 2021
Accepted 26 April 2021

Abstract

The benefit of glucocorticoids is still inconclusive although many guidelines recommend using glucocorticoids in malignant intestinal obstruction. This study aimed to identify the efficacy of dexamethasone for clinical outcomes in malignant intestinal obstruction in a tertiary care hospital by retrospective cohort study. One hundred and forty-two patients were admitted for malignant intestinal obstruction, from January 2013 to July 2018, diagnosed by signs and symptoms, confirmed by radiologic imaging, and consequently investigated. The primary outcome was the change of vomiting at day four while the secondary outcome focused on the change of other clinical events at day four. Mean changes, 95% CIs, and comparison tests, were used to analyze. Dexamethasone users' group was found to be associated with a higher mean change number of vomiting at day four [-3.0 (-4.3, -1.6) vs -1.0 (-1.3, -0.6), $p<0.05$] and a higher mean change of pain scores at day four [-5.4 (-6.2, -4.5) vs -1.8 (-2.3, -1.2), $p<0.05$]. Moreover, dexamethasone users' group was proven to have a higher proportion of improved vomiting (80.8% vs 33.9%, $p<0.05$), a higher proportion of improved ability to pass stool (88.5% vs 35.7%, $p<0.05$), a higher proportion of improved abdominal pain at day four (96.2% vs 61.8%, $p<0.05$). In patients with malignant intestinal obstruction, dexamethasone was found to be associated with a higher mean change number of vomiting at day four, and a higher proportion of improved clinical outcomes at day four. Our investigation established the possible benefits of dexamethasone in malignant intestinal obstruction.

Keywords: Malignant intestinal obstruction, Dexamethasone, Clinical outcomes

1. Introduction

Malignant intestinal obstruction is found in 3% to 15% of overall cancers [1]. The incidence is even higher with 20% to 50% in ovarian cancer and 10% to 29% in colorectal cancer [2]. This condition leads to distress due to its symptoms include nausea, vomiting, loss of appetite, constipation, and abdominal pain [2]. The treatment options comprise pharmacological and surgical treatment [3]. As a pharmacological choice, antiemetics and anticholinergics showed benefits in malignant intestinal obstruction [4]. However, the benefit of glucocorticoids is still inconclusive although many guidelines recommend using glucocorticoids in malignant intestinal obstruction [3-7].

The trials supported limited efficacy. Conclusions were based on very small sample size [8-10]. For instance, a randomized-placebo controlled trial in the UK found that the resolution rate of malignant intestinal obstruction by intravenous dexamethasone was similar in 35 patients with advanced intra-abdominal cancer [8]. However, a randomized-placebo controlled trial from France found that intravenous methylprednisolone reduced the stress symptoms of malignant intestinal obstruction in 52 patients with advanced cancer [9]. Moreover, a conclusion from a systematic review of the previous two studies indicated that the resolution rate was similar in glucocorticoids compared to placebo in malignant intestinal obstruction [10]. Therefore, we conducted this

study to identify the efficacy of dexamethasone for clinical outcomes in malignant intestinal obstruction at our institute.

2. Materials and methods

2.1 Study design

We carried out a retrospective cohort study using data from our institute's tertiary hospital database, from January 2013 to July 2018. The medical records included demographic data, diagnosis, clinical outcomes, prescribed drugs, and adverse events coded according to the international classification of diseases, 10th revision [11]. All data from the medical records were de-identified, and therefore informed consent was not required. For the accuracy and completeness of the data, methods of verification were performed.

2.2 Study participants and criteria for inclusion and exclusion

Inclusion criteria were (1) patients were diagnosed with cancer and admitted in the hospital, (2) an intestinal obstruction was diagnosed by signs and symptoms, e.g., nausea, vomiting, abdominal pain, and (3) an intestinal obstruction was confirmed by radiologic imaging. We excluded those who underwent surgery to resolve intestinal obstruction and discharged within the first four days of admission or died during this period.

2.3 Dexamethasone user

We classified a "dexamethasone user" as anyone who received dexamethasone 8-24 mg/day intravenously for at least three consecutive days after admission.

2.4 Outcomes

The primary outcome was the change of vomiting at day four while the secondary outcome focused on the change of other clinical events at day four, including vomiting, ability to pass stool, abdominal pain, intra-hospital death, and adverse events. Outcomes ought to be measured at day five [8] or day four [9] similar to the previous published papers, however we chose to measure at day four because a shorter duration of dexamethasone was used. We labelled "improved vomiting" as $\geq$ 1 less in numbers of vomiting, "improved ability to pass stool" as $\geq$ 1 more in numbers of defecation, "improved abdominal pain" as $\geq$ 1 less in numeric pain score. The pain was evaluated via a numeric rating scale. The rationale was that the condition of "$\geq$ 1 less or more" is the minimal substantial improvement in the clinical outcomes judged by a patient. However, the mean changes of each of those clinical outcomes were additionally analysed and their details presented.

2.5 Statistical analysis

Categorical data were presented with numbers, percentages and were analyzed with Fisher's exact test or chi-squared test. Continuous data were presented with means $\pm$ standard deviations, medians (range), and frequency. The comparisons between the two groups were analyzed using independent t-test or Mann-Whitney U test. The data were analyzed using Stata version 10.1 and a $p<0.05$ was considered as statistically significant.

3. Results

3.1 Patients

From January 2013 to July 2018, we diagnosed 467 patients with malignant intestinal obstruction. Two hundred twelve underwent surgery within four days while 113 were discharged within four days, and 142 met the inclusion criteria. Twenty-six were exposed to dexamethasone while 116 had no exposure. (Figure 1).

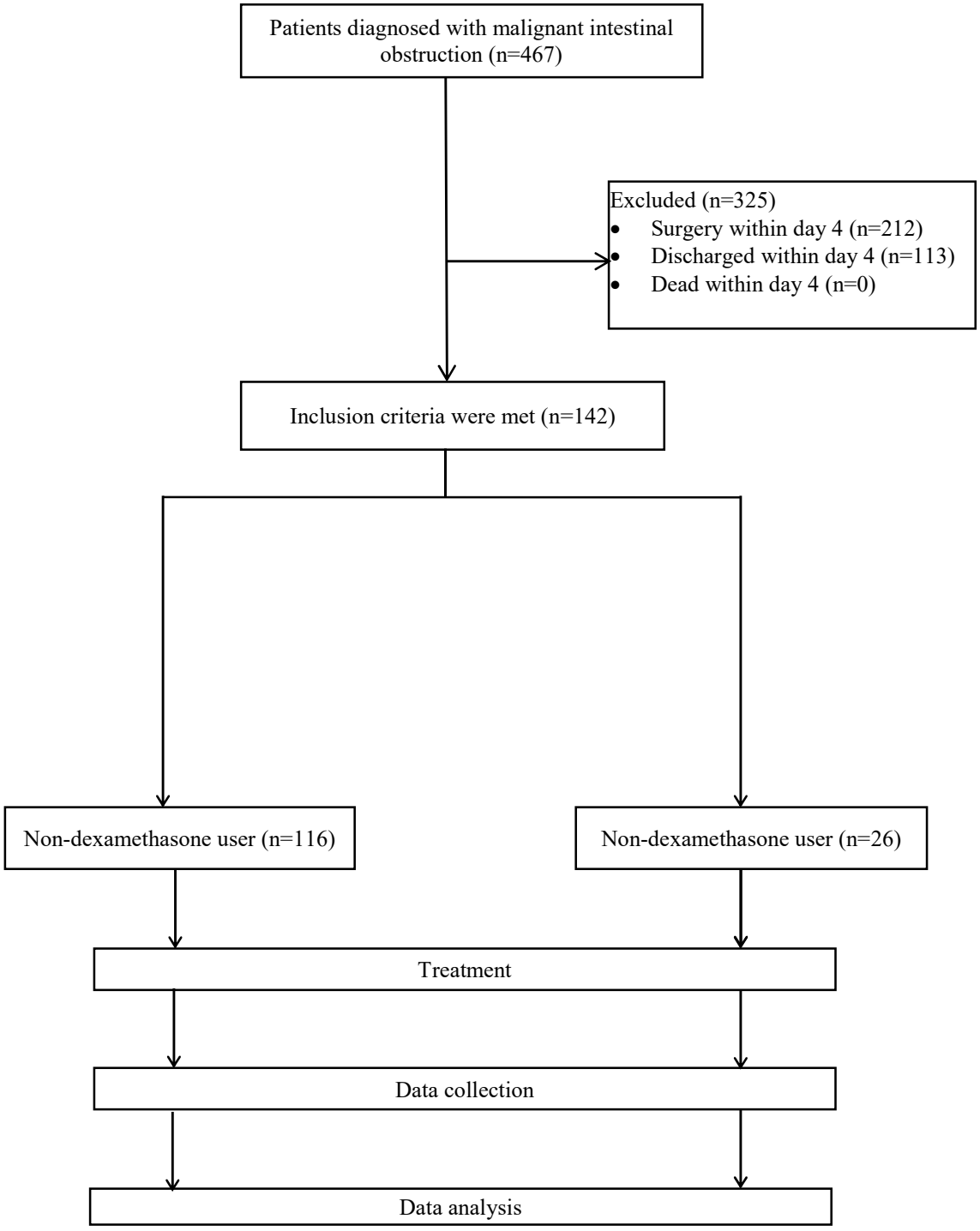

Figure 1 Patients flow diagram.

Itemization of the different characteristics between the two groups including sex, age, type of cancer, previous cancer treatment, number of vomiting at day zero, pain score at day zero, and medication has been created (Table 1). Since this was a retrospective cohort study, differences between the two groups were unavoidable such as in female proportion, years of age, baseline vomiting number and pain score, proportions of colon and stomach cancers, proportions of surgery and chemotherapy, proportions of morphine, ondansetron, hyoscine, and bisacodyl use (p<0.05). Results in almost all of these categories were found to be higher or more in the dexamethasone users, with exception for the years of age, colon cancer, and bisacodyl use.

Table 1 Characteristics of the study patients*

Characteristics	Non-dexamethasone users (n=116)	Dexamethasone users (n=26)	*p*-value
Female–no. (%)	60 (51.7)	22 (84.6)	<0.05
Age–yr	59.9 ±12.8	48.1±9.5	<0.05
BMI–kg/m^2	20.5±3.8	21.7±3.7	0.38
Duration of diagnosed cancer–month			
Median (range)	2 (0.03-144)	6 (0.03-60)	0.08
Symptom Duration–day			
Median (range)	3 (1-90)	3 (1-30)	0.960
Numbers of vomiting at day zero			
Median (range)	1 (0 - 14)	3 (0 - 10)	<0.05
Pain score at day zero	4.6±2.6	6.4±2.7	<0.05
Diagnosis of cancer–no. (%)			
Anus	2 (1.7)	0	>0.99
Bile duct	1 (0.9)	0	>0.99
Cervix	3 (2.6)	2 (7.7)	0.28
Colon	47 (40.5)	5 (19.2)	<0.05
Endometrium	3 (2.6)	1 (3.9)	0.56
Fallopian tube	1 (0.9)	0	>0.99
Germ cell tumor	0	1 (3.9)	0.18
Kidney	1 (0.9)	0	>0.99
Lymphoma	3 (2.6)	1 (3.9)	0.56
Nerve sheath	1 (0.9)	0	>0.99
Ovary	14 (12.1)	6 (23.1)	0.21
Prostate	2 (1.7)	0	>0.99
Rectum	33 (28.5)	6 (23.1)	0.64
Small intestine	1 (0.9)	0	>0.99
Stomach	0	3 (11.5)	<0.05
Unknown primary	0	1 (3.9)	0.18
Urinary bladder	4 (3.5)	0	>0.99
Previous cancer treatment–no. (%)			
Surgery	82 (70.1)	24 (92.3)	<0.05
Chemotherapy	55 (47.4)	23 (88.5)	<0.05
Radiotherapy	16 (13.8)	5 (19.2)	0.54
Comorbidities–no. (%)			
Diabetic mellitus	12 (10.3)	1 (3.9)	0.46
Hypertension	16 (13.8)	3 (11.5)	>0.99
Chronic kidney disease	6 (5.2)	0	0.59
Medication use–no. (%)			
Morphine	28 (24.1)	12 (46.2)	<0.05
Ondansetron	0	7 (26.9)	<0.05
Hyoscine	4 (3.5)	6 (23.1)	<0.05
Bisacodyl	50 (43.1)	2 (7.7)	<0.05
Unison enema	37 (31.9)	5 (19.2)	0.24
Metoclopramide	31 (26.7)	8 (30.8)	0.68
Lactulose	6 (5.2)	0	0.59
Milk of magnesia	18 (15.5)	5 (19.2)	0.77
Mist carminative	3 (2.6)	3 (11.5)	0.08
Sennosides	11 (9.5)	2 (7.7)	>0.99
Nasogastric tube	109 (94.0)	23 (88.5)	0.39

*Plus–minus values are means ± SD.

3.2 Outcomes

Our primary outcome was the change of vomiting at day four. Dexamethasone users group was found to be associated with a higher mean change number of vomiting at 4 [-3.0 (-4.3, -1.6) vs -1.0 (-1.3, -0.6), $p<0.05$] (Figure 2 and Table 2) and a higher mean change of pain score at 4 [-5.4 (-6.2, -4.5) vs -1.8 (-2.3, -1.2), $p<0.05$] (Figure 3 and Table 2).

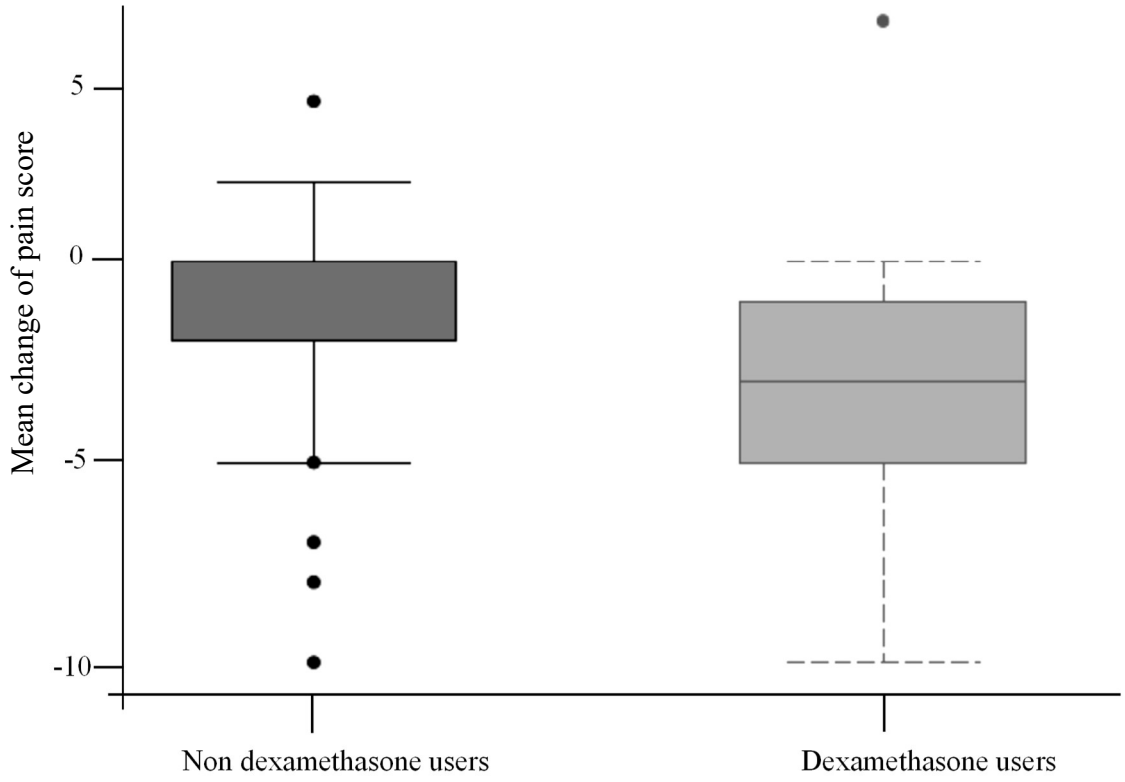

Figure 2 The change of numbers of vomiting at day four**.**

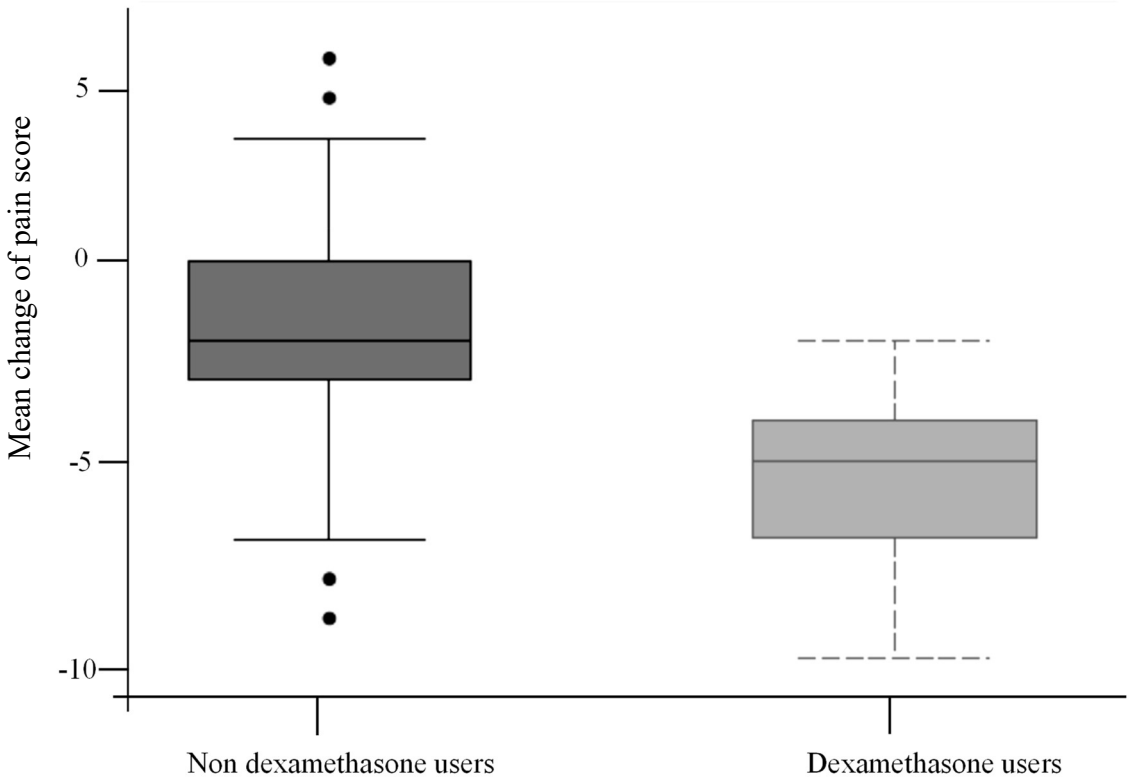

Figure 3 The change of pain score at day four.

Table 2 Changes of clinical outcomes between day four and day zero*.

Clinical outcomes	*Non-dexamethasone users* Mean (95% CI)	*Dexamethasone users* Mean (95% CI)	*Mean difference* Mean (95% CI)	*p-value*
Number of vomiting	(n=106)	(n=26)		
	-1.0 (-1.3, -0.6)	-3.0 (-4.3, -1.6)	-2.0 (-3.0, -1.0)	<0.05
Pain score	(n=92)	(n=26)		
	-1.8 (-2.3, -1.2)	-5.4 (-6.2, -4.5)	-3.6 (-4.8, -2.4)	<0.05

*Analyzed using independent sample t-test.

Moreover, dexamethasone users group have a higher proportion of improved vomiting (80.8% vs 33.9%, $p<0.05$), a higher proportion of improved ability to pass stool (88.5% vs 35.7%, $p<0.05$), and a higher proportion of improved abdominal pain at day four (96.2% vs 61.8%, $p<0.05$) (Table 3).

Table 3 Clinical outcomes at day four*.

Clinical outcomes	*Non-dexamethasone users* (n=116)	*Dexamethasone user*s (n=26)	*p-value*
Improved vomiting at day Four-no. (%)	39 (33.9)	21 (80.8)	<0.05
Improved ability to pass stool at day four-no. (%)	41 (35.7)	23 (88.5)	<0.05
Improved abdominal pain at day four-no. (%)	68 (61.8)	25 (96.2)	<0.05

*Analyzed using Chi-squared test**.**

There was no difference in adverse events between the two groups. Four deaths were found in the non-dexamethasone users group, three due to severe pneumonia and one due to complications of colonic obstruction. There was also one death in the dexamethasone users group due to severe pneumonia (Table 4).

Table 4 Adverse effects*.

Adverse effects	*Non-dexamethasone users* (n=116)	*Dexamethasone user*s (n=26)	*p-value*
Agitation-no. (%)	8 (6.9)	1 (3.9)	>0.999
Candidiasis-no. (%)	0	0	NA
Polyuria-no. (%)	0	0	NA
Intra-hospital death-no. (%)	4 (3.5)	1 (3.9)	>0.999

*Analyzed using Fisher's exact test.

4. Discussion

This study showed the association between dexamethasone users and a higher mean change number of vomiting at day four, a higher mean change of pain scores at day four, and higher proportions of improved clinical outcomes at day four, such as vomiting, ability to pass stool, and abdominal pain. Our results confirmed a possible beneficial effect of dexamethasone in malignant intestinal obstruction [9].

In some newly diagnosed colonic cancer cases in which dexamethasone was occasionally used, patients had a high chance to undergo surgery for the first time after the fourth day of admission. Therefore, non-dexamethasone users group had a higher proportion of aging patients, a higher proportion of patients with colonic cancer, and a lesser proportion of patients with previous treatment. In the dexamethasone users group, there were higher numbers of vomiting and higher numbers of pain scores at day zero. These were considered to be from either a higher proportion of chemotherapy or the different severities of the disease.

Due to the nature of a retrospective cohort study, differences between the two groups were expected. Although many baseline characteristics were found to be higher or more in dexamethasone users, those that might affect outcomes (baseline vomiting number and pain score) were not in favour of this group. Higher values were found in either of them among dexamethasone users but could have produced more significant outcomes compared with non-users.

The higher numbers of vomiting and pain scores lead to a higher proportion of morphine and antiemetic drugs. A higher proportion of female patients in the dexamethasone users group might be from higher proportion of ovarian cancer in this group. Dexamethasone was found to be safe in malignant intestinal obstruction patients since the adverse effects were no different between the two groups. However, there were nine patients with agitation but these might be due to other causes that had not been investigated in our study.

Our study also showed a beneficial effect of dexamethasone for improved clinical outcomes in malignant intestinal obstruction. Our findings were supported by a trial from France, reporting that intravenous methylprednisolone relieved the obstructive symptoms in 52 patients with a nasogastric tube in inoperable intestinal obstruction in terminal cancer [9].

Conversely, a study from the United Kingdom reported that intravenous dexamethasone had a similar resolution rate of malignant intestinal obstruction with placebo in 35 patients with advanced intra-abdominal cancer [8]. This inconsistency might be from the outcomes measurement method. Hardy et al. [8] assessed only the resolution of obstruction while clinical outcomes were not evaluated, while this study appraised the effect of intravenous dexamethasone for many clinical outcomes in malignant intestinal obstruction.

Although this study has some strength as mentioned above, it also had some limitations. Firstly, it was retrospective, and missing data were inevitable. However, the missing data were kept minimal and all data were verified before data entry. The measurement of abdominal pain score might be interfered by the pain of other sites. Other confounding variables influenced by differences in patient characteristics such as sex, age, type of cancer, previous cancer treatment, and medication, might also interfere with the outcome.

5. Conclusion

In this study, dexamethasone was found to be associated with a higher mean change number of vomiting at day four, and a higher proportion of improved clinical outcomes at day four. Our investigation established the possible benefits of dexamethasone in malignant intestinal obstruction. A larger cohort study or a randomized-controlled trial should be performed to evaluate the effects of dexamethasone on clinical outcomes in malignant intestinal obstruction.

6. Ethical approval

The study was approved by the Institutional Review Board of Khon Kaen Hospital (Reference Number: KEXP62005).

7. Acknowledgements

Authors received a non-specific funding for this study from Department of Social Medicine, Khon Kaen Hospital. The authors thank (a) all participants and personnel participating in this study (b) Department of Social Medicine, Khon Kaen Hospital, Muang, Khon Kaen, Thailand in granting and permission to do this study and (c) Mr. Dirk Krapf for the English editing of the manuscript.

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