

Prophylactic Effect of oral Methylnaltroxane on Post Hysterectomy Bowel Motility: A Pilot Study

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Article Info

 [10.30699/jogcr.7.2.83](https://doi.org/10.30699/jogcr.7.2.83)

Received: 2021/06/14;
Accepted: 2021/07/22;
Published Online: 25 Oct 2021;

Use your device to scan and read the article online



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ABSTRACT

Background & Objective: Opioids that are used during anesthesia may prolongate intestinal peristalsis. This study aimed to examine the effect of oral methylnaltrexone (OMNTX) on ileus after hysterectomy.

Materials & Methods: This study was performed as a randomized, double-blind screening for elective abdominal hysterectomy at Alzahra Hospital in Rasht, Iran; 33 patients were assigned to the OMNTX group (25 mg) and 33 to the placebo group using the random block method. Patients were asked and recorded about gas passing, constipation, vomiting, itching, and urinary retention.

Results: There was a significant difference in the meantime of initiation of intestinal sound ($P=0.039$) and constipation ($P=0.62$) between the two groups. There was a positive correlation coefficient in the placebo group ($P=0.02$) between the hours of surgery and the time of initiation of bowel movements after the surgery, but there was not in the OMNTX group ($P=0.0001$). The mean onset of bowel sounds after the surgery was not related to age ($P=0.599$) and the duration of surgery significantly ($P=0.926$).

Conclusion: It is possible that OMNTX before the surgery can trigger bowel sounds sooner after the surgery and prevent ileus.

Keywords: Bowel motility, Methylnaltroxane, Opioid, Patients



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Introduction

Hysterectomy is one of the most common professional surgeries all over the world (1). After this surgery, many patients experience disruption of bowel movements to some degree (2). Several factors can postpone the gut transient time postoperatively (3), among them is opioid, which is the oldest herbal remedy traditionally used as an analgesic and sedative substance during anesthesia (4). Opioids have many side effects, such as prolongation of intestinal peristalsis, delayed bowel sounds, and constipation (5). Opioid receptor antagonists have proved to be effective in managing postoperative ileus (6). It has been illustrated that methylnaltrexone (MNTX) is an opioid antagonist (as a first quaternary ammonium opioid antagonist) that cannot cross the blood-brain barrier (BBB). It has fewer peripheral gut side effects with preserving analgesia (7). In 1999, Yuan *et al.* reported

that intravenous MNTX could reverse constipation, which is one of the opioid side effects in patients with methadone maintenance programs (8). In 2008, MNTX bromide (Relistor, Salix Pharmaceuticals) was approved by the US Food and Drug Administration (FDA). They concluded that MNTX did not inhibit central analgesic effects or precipitating opioid withdrawal (9).

Also, MNTX was approved by FDA as a subcutaneous and oral formulation (10). Return of bowel sounds leads to faster defecation, postsurgical pain improvement, and faster ambulation; thus, due to the availability, low side effects, and low cost, we decided to conduct this study to identify how this remedy could be effective in faster bowel movement; constipation, nausea, vomiting and urinary retention

reduction. The remedy will also bring more patient comfort, shorter hospitalization and less expenses. Regarding a safer and more convenient way of oral medication, we evaluated the efficacy of OMNTX on post-hysterectomy bowel motility in this study.

Materials and Methods

This study was performed as a double-blind, randomized controlled trial (with ethics committee number 1900136005 and IRCT registration number IRCT201104121946N8) on 35 to 55 women who were candidates for non-obstetrical elective abdominal hysterectomy. After obtaining informed consent, 66 patients were randomized in blocks of four and randomly divided into two groups of 33 subjects. Researchers were not aware of the prescribed drug.

After recording the baseline information in the research form, all patients underwent general anesthesia with the same drugs for induction and maintenance of anesthesia, and all of them were operated by the same surgeon (MMG). The first group was given one tablet of 25 mg OMNTX (Alhavi Company, Iran) with a glass of water 2 h before the operation, and the second group was given a placebo similar to OMNTX tablets in terms of size, shape, and color (Iran Pharmaceutical Company, Iran).

After preparing patients for surgery and connecting them to cardiac monitors, their oxygen level was measured by pulse oximetry, their blood pressure was taken, and adequate oxygen administration was done. Before the induction of anesthesia, fentanyl (1 g/kg), midazolam (0.05 mg/kg), lidocaine (1 mg/kg), atracurium (0.05 mg/kg), and ketamine (2 mg/kg) were administered; then, patients were ventilated with 100% oxygen and were intubated after 3 min. Maintenance of anesthesia was the same in all patients and consisted of O₂ (50%) + N₂O (50%) + isoflurane (0.75%-1%), and, if necessary, fentanyl (0.5 mg/kg), ketamine (0.5 mg/kg), and atracurium (0.5 mg/kg) were given again.

From the time of preparation of patients for the induction of anesthesia and during the operation until discharge from recovery and delivery to the surgical department, their cardiovascular and respiratory systems were monitored continuously. After the complete stabilization of vital signs, patients were transferred to the surgical ward.

After the surgery, bowel sounds were checked every 1 h (from 12 to 24 h for 3-5 min) to increase the accuracy. The patient was asked about gas excretion and constipation. Symptom indexes for nausea or vomiting were precisely recorded, and urinary retention was assessed after urinary catheter removal.

Considering the pain, the patient was administered in 3 doses or more of a 2 mL pethidine ampoule containing 100 mg of the active substance intramuscularly every 4 h.

The inclusion criteria were as follows:

1. Women between the ages of 35 and 55 years old (with ASA class I, II);
2. Absence of predisposing diseases for nausea and vomiting after surgery, such as peptic ulcer disease, gastritis, or the use of chemotherapy drugs;
3. No history of chronic constipation, irritable bowel disease (IBD), and irritable bowel syndrome (IBS);
4. No history of drug allergy to naltrexone, other drugs, and foods, as well as no history of seasonal allergies, other allergies, and asthma;
5. No history of kidney disease;
6. No history of liver disease, especially hepatitis;
7. No history of drug abuse (tramadol, morphine), as well as alcohol abuse;
8. No history of psychotic drug use or painkillers containing codeine or propoxyphene/clonidine/disulfiram/laxatives/immunosuppressive drugs/thyroxin;
9. No history of laparotomy two or more than two times;
10. No history of lung diseases that lead to cough and sputum after surgery; and
11. No history of organ transplantation.

The exclusion criteria were as follows:

1. Operation lasting longer than 2 h;
2. Existence of other surgical procedures along with hysterectomy; and
3. Occurrence of complications of surgery or anesthesia during the operation.

Statistical Analysis

In accordance with the frequency of constipation, mentioned in Yuan et al. article (11), approximately 33 samples were obtained from each group.

Data analysis was performed using SPSS 16 (SPSS Inc., Chicago, Ill., USA). Age, operation duration, and bowel sounds initiation were assessed using the *t* test. The chi-square test was used to compare the frequency of side effects. The Pearson correlation test was used for the duration of surgery and the time of bowel movements. The value of 0.05 or less was considered significant.

Results

In the present study, 66 patients were entered based on the inclusion criteria. Subjects were randomly assigned to two groups of 33 subjects.

There was no statistically significant difference between the average age in the two groups ($P=0.599$).

In the placebo group, the youngest person was 41 years old, and the oldest person was 54 years old. Further, in the OMNTX group, the youngest person was 39 years old, and the oldest person was 55 years old.

Using the *t*-test, it was found that there was no statistically significant difference between the mean duration of hysterectomy in both groups ($P=0.926$).

Moreover, using the *t* test, a statistically significant difference was found between the mean time of bowel sounds initiation in both groups ($P=0.039$), see [Table 1](#).

Table 1. The comparison of mean age, operation duration, and the onset of initiation of bowel sounds in the two groups

Variable	OMNTX (n=33) Mean±SD	Placebo (n=33) Mean±SD	P-value
Age (year)	46.81±4.25	47.33±3.64	0.599
Operation duration (min)	111±0.25	110±0.27	0.926
Bowel Sounds Initiation(hour)	6.69±1.75	7.87±2.5	0.039

t-test

The Chi-square test showed that there was no statistically significant difference between postoperative vomiting in both groups ($P=0.62$).

The Chi-square statistical test showed that there was no statistically significant relationship between postoperative itching in both groups ($P=0.492$).

Our results demonstrated that the prevalence of postoperative itching in the placebo group was 50% slightly, 0% more, 50% very, and 0% a lot. Further, it was shown 0% in the OMNTX group. However, the performance and measurement of tests were not possible because of the small sample size.

Using the Chi-square statistical test, it was found that there was a statistically significant relationship between postoperative constipation in both groups ($P=0.011$).

Using the chi-square statistical test, there was no statistically significant relationship between postoperative urinary retention in the two groups ($P=0.502$).

Using the chi-square statistical test, there was no statistically significant relationship between the presence of side effects (including vomiting, itching, constipation, and urinary retention after the surgery) in both groups ($P=0.999$).

The frequency distribution of the number of side effects (including vomiting, itching, constipation, and

urinary retention) in the OMNTX group was as follows: 39.4% had no side effects, 54.6% had one side effect, 3% had two side effects, and 3% had three side effects. In the placebo group, 39.4% had no side effects, 36.4% had one side effect, 21.2% had two side effects, and 3% had three side effects. Using the chi-square statistical test, we found no statistically significant relationship between the number of side effects after the surgery in both groups ($P=0.127$), see [Table 2](#).

Also, in our study, by using the Pearson correlation coefficient, it was found that subjects generally showed a positive correlation between the duration of surgery and the time of bowel movements ($P=0.0001$). There was a correlation between the increase and decrease in the length of the operation time, as well as between later or earlier onset of bowel movements ($P=0.0001$).

In the placebo group, there was a positive correlation between the duration of surgery and the time of onset of bowel movements ($P=0.02$). The increase in the length of the operation was associated with later onset of bowel movements. However, in the OMNTX group, there was no correlation between the duration of surgery and the time of onset of bowel movements ($P=0.0001$). The increase in the length of the operation was not correlated with later onset of bowel movements ([Table 3](#)).

Table 2. The frequency of post-operative side effects in the two groups

	OMNTX N (%)	Placebo N (%)	P-value
Vomiting	20 (60.6%)	17 (51.5%)	0.62
Itching	0 (0%)	2 (6.1%)	0.492
Constipation	2 (6.1%)	10 (30.3%)	0.011
Urinary retention	1 (3%)	0 (%)	0.502
Side effects	20 (60.6%)	20 (60.6%)	0.999

Chi-square

In this study, the mean time of onset of intestinal sounds in the placebo group was 7.68 ± 2.6 h in the age group of less than 50 years old and 8.09 ± 2.38 h in the age group of more than 50 years old. In the OMNTX group, it was 6.75 ± 1.72 h in the age group of less than 50 years old and 6.55 ± 1.94 h in the age group of more than 50 years old. Using the *t* test, we found no statistically significant difference between the mean time of onset of intestinal sounds in women under 50 years of age in both groups ($P=0.165$). Also, the difference was not seen for the age of 50 within the two groups ($P=0.138$).

Regarding the mean time of onset of bowel sounds in subjects, when the duration of surgery in the placebo

group was less than 2 h, the average time of onset of bowel sounds was 6.4 ± 2.41 h, which reached 8.43 ± 2.33 h in surgeries lasting up to 2 h.

However, in the OMNTX group, the mean onset of bowel sounds in operations lasting less than 2 h was 4.8 ± 0.63 h, which reached 7.51 ± 1.41 h in operations lasting up to 2 h ($P=0.058$).

Using the *t* test, no statistically significant difference was found between the two groups regarding the mean time of onset of bowel sounds in operations lasting less than 2 h or those lasting up to 2 h ($P=0.058$ and $P=0.17$).

Table 3. Correlation between the duration of surgery and the time of bowel movements

Bowel movements initiation Operation duration	OMNTX	Placebo	Total
Pearson Correlation	0.639	0.403	0.472
P-value	0.0001	0.020	0.0001
Correlation	positive	positive	positive

Discussion

After hysterectomy, which is one of the most common surgeries (12), many patients experience bowel ileus to some degree (13).

Opioids are the oldest herbal remedies traditionally used as analgesic, sedative, and anti-diarrheal substances. Opioids have many side effects, such as prolongation of intestinal peristalsis, delayed hearing of intestinal sounds, and constipation, which is one of the most common and problematic side effects of narcotics (5).

However, MNTX (the fourth derivative of naltrexone) can prevent or treat the environmental side effects of narcotics by maintaining the central analgesia of narcotics and their environmental effects (14).

Our results indicated that prophylactic OMNTX expedited bowel motility and reduced constipation after abdominal hysterectomy.

As MNTX is a drug that has more polarity and lower fat solubility than naltrexone, this selective antagonism of opioid μ -receptors can prevent or eliminate the effects of opioids in the gut without affecting the therapeutic function of drugs in the central nervous system (15).

In our study, consistent with Kraft *et al.* (16), Thomas *et al.* (17), Abarca *et al.* (9), Neetyes *et al.* (7), Yuan *et al.* (15), MNTX expedited gut motility and transit.

Regarding constipation, our results were consistent with Neefyes *et al.* (7), Yuan *et al.* (15), Thomas *et al.* (17), Greenwood *et al.* (18), and Holzer *et al.* (4) and in contrast with Patel *et al.* article (19).

In Yuan's *et al.* article, low-dose intravenous MNTX effectively reversed delay in gut transit time and methadone-induced constipation (8).

In Yuan's *et al.* article study, low-dose enteric-coated MNTX reversed morphine-induced changes in gut transit (20).

Portenoy compared the effect of subcutaneous MNTX and placebo on constipation and showed that it preserved the effect of opioids and blocked their peripheral activity (3).

Abraca concluded that OMNTX could be safely used in opioid-induced constipation management that is consistent with our results (9).

Kraft showed that the OMNTX group had a short ileus period, and MNTX reduced hospitalization (one day) (16).

Patel found no evidence to support the use of OMNTX in opioid-induced constipation treatment in critically ill patients (19).

The results of the present study indicated that postoperative vomiting in the case and control groups was not statistically significant, in contrast with Thomas's study (17).

We performed and compared statistical calculations on cases with vomiting and found no statistically significant difference between the two groups; also, there was no significant difference in the distribution of itching between the two groups. It is in line with Holzer's results (4).

Another result of our study was that with increasing or decreasing the length of the surgery, bowel movements occurred sooner or later. Thus, it seems that there was a positive correlation coefficient between operation duration and bowel movement initiation in the receiving group ($P=0.0001$).

There was no correlation between the duration of the surgery and the time of bowel movements in the OMNTX group.

In fact, OMNTX and its effects on the onset of bowel movements can counteract the negative effects of prolongation of surgery. There is no similar study in this regard.

Our study indicated that the rate of bowel sounds was faster in the case group than in the control group. Also, it was shown that MNTX was effective on the onset of bowel sounds with the removal of meddling factors. There was no difference according to age and duration of the surgery.

In the present study, the use of OMTNX resulted in beneficial effects because it reduced the side effects of opioids.

With maintaining the analgesic effects of opioids, rapid return of bowel sounds, faster defecation, faster

recovery from surgery, low cost, and the ability of patients to get out of bed (reducing the risk of embolisms), we recommend OMNTX before surgery.

Therefore, it seems that OMNTX could bring more comfort and reduced hospitalization and costs. However, further studies with a larger sample size are needed in this area to get more comprehensive results.

Conclusion

It seems, usage of preoperative OMNTX can trigger bowel sounds and prevent ileus.

Acknowledgments

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Conflict of Interest

The authors declared no conflicts of interest.

Funding

The finance of the recent study has been supported by Vice-Chancellorship of Research and Technology, Guilan University of Medical Science, Rasht, Iran.

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How to Cite This Article:

Mansour Ghanaei M, Ebadollahi Nodeh E, Asghari Ghalebini S M, Sharami S H, Haryalchi K. Prophylactic Effect of Oral Methylnaltrexone on Post Hysterectomy Bowel Motility: A Pilot Study. *J Obstet Gynecol Cancer Res*. 2022; 7(2):83-88.

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