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Effect of Ondansetron alone or in Combination with Dehydrobenzperidole and Dexamethasone on Discharge Time Following Gynecological Laparoscopy

Hanne Ulka Petersen, Claus Hemmingsen*

Department of Anaesthesiology, Frederiksberg Hospital, Copenhagen, Denmark

Abstract We aimed to examine a possible accelerated discharge time after gynecological laparoscopy when treated with a combination of ondansetron, dehydrobenzperidole and dexamethasone as compared to ondansetron alone. Sixty ASA 1-2 women were included in this prospective double-blind study and were randomised to either peroperative ondansetron 4 mg, dehydrobenzperidole 0.625 mg and dexamethasone 8 mg or to ondansetron 4 mg only. General anaesthesia was induced by fentanyl, propofol, mivacurium and maintained by sevoflurane in 50% oxygen. Patients were tracheal intubated and had a orogastric tube during the laparoscopy. The neuromuscular block was allowed to wear of without the use of neostigmine. In case of postoperative nausea and vomiting in the ondansetron only group, escape medication with dehydrobenzperidole and dexamethasone was given. The discharge criteria at the day surgery unit were fulfilled at 7h 45min (range 3h 10min - 24h 16min) after the end of surgery in the women treated with ondansetron only, but was accelerated to 5h 11min (range 3h 9min – 21h 8min) in the women having peroperative treatment with both ondansetron, dehydrobenzperidole and dexamethasone ($p<0.01$). Postoperative nausea and vomiting was evident in 4% at arrival at day surgery recovery after treatment with the triple combination, but in 16% in the patients treated with ondansetron alone ($p<0.01$). In conclusion, peroperative treatment with a combination of ondansetron, dehydrobenzperidole and dexamethasone allows a significantly accelerated discharge time after gynecological laparoscopy and causes a significantly reduced incidence of nausea and vomiting.

Keywords Gynecological Laparoscopy, Discharge Time, Postoperative, Nausea and Vomiting, Ondansetron, Dehydrobenzperidole, Dexamethsone

1. Introduction

Postoperative nausea and vomiting (PONV) are common complications after gynecological laparoscopy and in the absence of prophylactic antiemetics the incidence has been described up to 75% even with the use of modern anesthetics. Numerous studies have shown that the administration of prophylactic antiemetics, either alone or in combination, can reduce this incidence significantly [1].

In a study of patient attitudes regarding surgery, vomiting, nausea, and pain were ranked as three of the primary outcomes that patients found equally least desirable [2].

Because of cost-saving potential and the convenience for the patients, gynecological laparoscopy is routinely performed in day surgery. PONV however, remains a major problem and has been found to reduce patient satisfaction in this setting. Since the causes of PONV are multifactorial, with at least four different neurotransmitter systems implicated in the etiology, no single antiemetic drug possesses the ability to prevent PONV in all patient populations [1]. The specific delay in discharge time caused by PONV after gynaecological laparoscopy and its dependency upon various anti-emetic regimes remains unclear [3].

Aim of the present study was therefore to examine a possible accelerated discharge time after gynecological laparoscopy when treating patients with a combination of ondansetron, dehydrobenzperidole and dexamethasone as compared to ondansetron alone. Our theoretical null hypothesis was that there was no difference in discharge time depending upon mono or triple anti-emetic medication.

2. Methods

Sixty ASA 1-2 female patients, ages 18 – 70 years, were enrolled in this prospective double-blind study and were randomised to either peroperative ondansetron 4 mg, dehydrobenzperidole 0.625 mg and dexamethasone 8 mg or to ondansetron 4 mg only. The study was performed in the elective day surgery center at Frederiksberg Hospital, Copenhagen. The protocol was approved by The Danish Medicines Agency and by the local Ethics Committee, all

* Corresponding author:
clhe@dadlnet.dk (Claus Hemmingsen)
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patients received oral and written information, and gave informed consent prior to participation.

Patients experiencing wonted nausea and vomiting, having a BMI>35, scored to ASA-group 3 or higher, being pregnant or lactating, being planned for admission, or being allergic to the medications used were excluded from participating in the study.

General anaesthesia was induced by fentanyl, propofol, mivacurium and maintained by sevoflurane in 50% oxygen. Patients were tracheal intubated and had a orogastric tube during the laparoscopy. The neuromuscular block was monitored by Train-of-Four stimulation and was allowed to wear off without the use of neostigmine. Postoperative pain was treated with a standard regime of oxycodone and ibuprofen. The anti-emetic medication was administered intravenously in a double-blinded fashion immediately after the induction of anesthesia. The personnel at the awakening, at the recovery room and at day surgery were blinded to the anti-emetic used. The intravenous fluid administration consisted of 1000 ml of isotonic saline.

The level of nausea and vomiting was scored immediately after awakening in the operating theatre and then every 15 minutes in the recovery room and in day surgery. Nausea was scored by using the scoring shown in table 1, and in case of any level of postoperative nausea and vomiting in the ondansetron only group, escape medication with dehydrobenzperidole 0.625 mg and dexamethasone 8 mg was administered. Pain after arrival at recovery or day surgery was treated with oxycodon 2.5 – 10 mg.

Home readiness in the day surgery was evaluated at 15-minutes intervals by using a postanesthesia scoring system shown in table 2, the maximum score being required for discharge, and time to discharge ready was recorded for all patients.

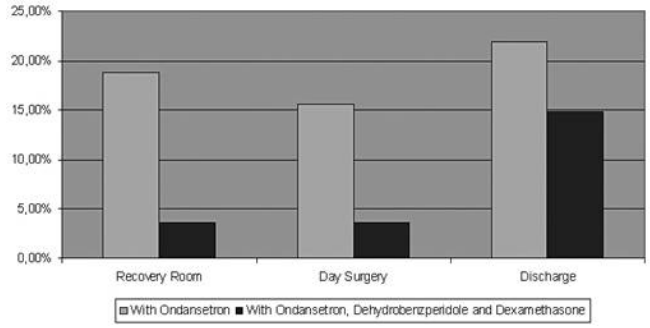

Figure 1. Incidence of nausea and vomiting

Our day surgery unit closes at 1800 hours and patients not fulfilling discharge criteria at this time were admitted for observation at the surgical ward. The frequency of admittance of patients to the surgical ward was registered.

The sample seize was calculated on the basis of a pilot investigation, and we determined that 30 patients per group would be sufficient to demonstrate a reduction of PONV by 20% with a power of 0.8 and risk of type 2 fault < 0.05.

The duration of anesthesia and the time to discharge were not normally distributed and data were therefore logarithmically transformed before analysis. Data are presented as medians (interquartile range), groups were compared by analysis of variance, and $p<0.05$ was considered significant. No correction for multiple comparisons was made, but to exclude a possible effect of surgery time, we added a matched-pairs analysis.

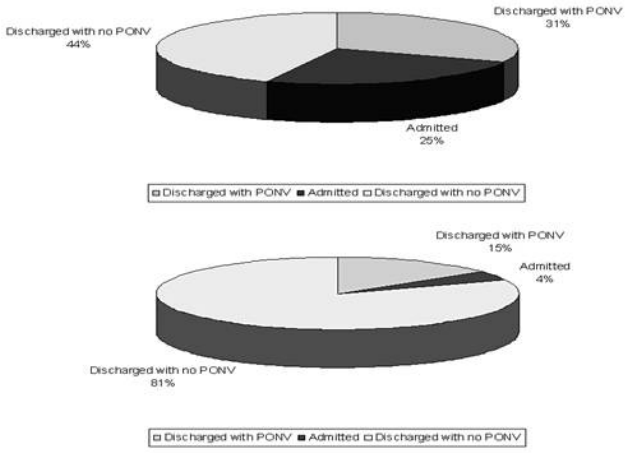

Figure 2. Status at discharge

3. Results

The discharge criteria at the day surgery unit were fulfilled at 451 min (interquartile rage 244,411) after the end of surgery in the women treated with ondansetron only, but was accelerated to 319 min (217,309) in the women having peroperative treatment with both ondansetron, dehydrobenzperidole and dexamethasone ($p<0.05$)(Table 3 and Fig 1).

The two groups spent an equal amount of time in the recovery room (97 vs. 90 min), whereas patients receiving monotherapy spent 361 min (139,337) in the day surgery compared to 218 min (136,220) for the triple-therapy group ($p<0.05$)

All patients presenting PONV in the ondansetron only group (56%) were supplied with dehydrobenzperidole and dexamethasone.

Postoperative nausea and vomiting was evident in 4% at arrival at day surgery recovery after treatment with the triple combination, but in 16% in the patients treated with ondansetron alone ($p<0.01$) (Fig 2).

At the time of discharge from hospital, 31% in the ondansetron only group had light PONV, and 25% were admitted for further observation at the surgical ward. In the triple treatment group, 15% had light PONV ($p<0.05$) and 4% were admitted for the surgical ward ($p<0.05$).

4. Discussion

Despite numerous publications and guidelines, PONV is still the most common reason for poor patient satisfaction in the postoperative period. The effect of various regimes against PONV has been thoroughly described in several

previous studies. The present study adds information on the effect on discharge time in a day surgery unit with rigid criteria of discharge. Our data shows that treatment with a combination of ondansetron, dehydrobenzperidole and dexamethasone accellerates discharge after gynecological laparoscopy in addition to reducing the incidence of PONV.

Further, our data shows that the triple treatment minimizes the frequency of patients needing a discharge time longer than 400 min. This reduces the amount of patients needing admission to a surgical ward due to their recovery exceeding opening hours of day surgery from 25 to 4%.

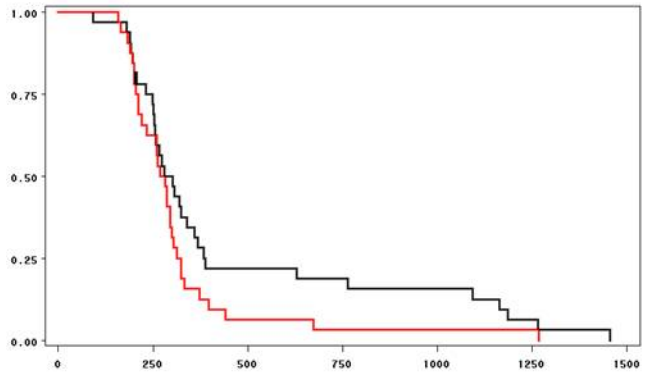

Figure 3. Kaplan-Meier survival curves showing time of discharge (minutes) in Ondansetron alone (black) and combination group (red)

The use of a combination of anti-emetics with different mechanisms of action is a beneficial option for the prevention and treatment of PONV. Dehydrobenzperidole (DHB, droperidole), a major tranquilizer with predominantly dopamine 2 receptor antagonist effect on the chemoreceptor triggerzone of the medulla, has a long history of efficient use against PONV and has often been tested in combination with other anti-emetics for treating PONV [4,5].

The routine use of DHB has been questioned by a FDA "black box warning" in 2002 due to its possible prolonging effect on the QTc-interval [6,7]. This warning has since caused an intense debate in the anesthesiological community, latest by a series of publications in the May 2008 issue of Anesthesia and Analgesia [8,9,10]. At present, FDA maintains its warning against the use of DHB, but in the present study, in accordance with several recent studies on the subject [11], we saw no cardiogenic side-effects in any of the included patients.

Dexamethasone exerts its anti-emetic effect by ativating the glucocorticoid receptors in the bilateral nucleus tractus solitarii of the medulla [12]. Combining dexamethasone with ondansetron increases efficacy [5,13], as ondansetron is most effective against early vomiting, whereas dexamethasone is effective against both early and late (2–24 h) nausea and vomiting, its late efficacy being pronounced[14].

The optimum prophylactic dose of ondansetron alone appears to be 4–8 mg [13, 15]. Dexamethasone 8–10 mg is widely used but smaller doses are effective for ambulatory laparoscopic surgery and 2.5 mg may be the minimum effective dose after major gynaecological surgery [16].

For simplicity, the anti-emetic drugs were administered immediately after induction of anesthesia. It has previously been established, that ondansetron is more effective when administered at the end of anesthesia, whereas the reverse appears true for dexamethasone [17,18], so an alternative timing schedule may possibly have changed outcomes.

We did not observe any incidents or adverse events attributable to any of the anti-emetic drugs. Both ondansetron and dexamethasone present very favorable side effect profiles after single-dose administration[19]. Theoretically, dexamethasone will suppress adrenal function, but the clinical implication of this in the perioperative setting has been minimal in numerous studies. Specifically, wound infection rates were not increased in a high-risk surgical population exposed to dexamethasone 4 mg intraoperatively [20].

In the absence of a placebo control group, the baseline risk of PONV without prophylaxis is unknown in our study population, but according to Apfel et al [21] it could be predicted to be in the area of 60% after inhaled anesthesia without prophylactic antiemetic therapy.

Table 1. Time related outcome in minutes presented as median (interquartile range)

variable	Ondansetron alone	Ondansetron plus Dexamethasone and Droperidole
Surgical duration (min)	24 (14-49)	20 (12-44)
Anaesthesia Duration (min)	55 (44-110)	58 (38-61)
Time in recovery (min)	84 (68-112)	81 (65-101)
Time in day surgery (min)	230 (139-337)	185 (136-220)
Time from end of surgery to discharge (min)	305 (244-411)	281 (217-309)

In the present study, mean time from surgery to discharge was accelerated from 451 min to 319 min. This is in accordance with several previous studies, but differs markedly from to recent studies, where discharge time was reduced to 216 - 240 min [22,23] . In these studies, anesthesia was provided with fentanyl and propofol, laryngeal mask was used in the majority of cases, ropivacain was instilled into the pelvic peritoneal cavity by the gynaecologist, and in the study of White and Black even a large proportion of included cases were having a hysteroscopy only.

In conclusion, peroperative treatment with a combination of ondansetron, dehydrobenzperidole and dexamethasone allows a significantly accelerated discharge time after gynecological laparoscopy and causes a significantly reduced incidence of nausea and vomiting.

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