ORIGINAL

Neurokinin-1 receptor antagonism, aprepitant, effectively diminishes post-operative nausea and vomiting while increasing analgesic tolerance in laparoscopic gynecological procedures

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Abstract : *Purpose* : Post-operative nausea and vomiting (PONV) remains the most frequently reported patient complaint after anesthesia. Aprepitant is the first neurokinin-1(NK1) receptor antagonism available for use as an antiemetic. We investigated whether aprepitant can effectively decrease PONV in patients undergoing laparoscopic gynecological surgery. *Methods* : Sixty four patients receiving general anesthesia for laparoscopic gynecological surgery were randomly assigned to either receive a preoperative dose of 80 mg aprepitant or no drug. Efficacy was assessed in 2 and 24 hours after surgery. Primary and secondary endpoints were analyzed for the time intervals 0-2 hours (acute phase) and 2-24 hours (delayed phase). Vomiting, nausea, use of rescue anti-emetic, and visual analog scale (VAS) were assessed. Nausea was assessed on a 4-point scale, from 0 to 3. *Results* : Sixty patients participated in the study. At acute phase, PONV was present in both control and NK1 group and were 63% and 43% respectively. The severity of nausea was much less in the NK1 group. PONV prevalence at delayed phase was present in control but absent in NK1 group 27% vs. 0%, respectively. The amount of pain medication used by patients in the NK1 group was significantly less for diclofenac and pentazocine suggesting increase pain tolerance. *Conclusions* : Neurokinin-1 receptor antagonism effectively lowered PONV increased pain tolerance, and expedited recovery in patients undergoing laparoscopic gynecological surgery. J. Med. Invest. 58 : 246-251, August, 2011

Keywords **:** *neurokinin-1 receptor, post-operative nausea and vomiting, aprepitant, laparoscopic gynecological surgery*

INTRODUCTION

Nausea and vomiting is one of the most frequently reported patient complaints following anesthesia (1, 2). This phenomenon, known as post-operative nausea and vomiting (PONV) is of greater concern to patients than postoperative pain (3). PONV occurs in approximately 30% of all patients undergoing generalized anesthesia (4). PONV can result in several post-surgical complications including discomfort or pain, fluid and electrolyte imbalances, surgical wound dehiscence, hemorrhage, and aspiration pneumonia (4). PONV has four main risk factors including : female gender, history of PONV

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or motion sickness, nonsmoking, and the use of postoperative opioids (5). Interestingly, laparoscopic gynecological procedures have nearly an 80% incidence of PONV (6). Although the exact reasoning is unknown it has been suggested that in addition to the female gender risk factor that the increased intra-abdominal pressure used during laparoscopic procedures may be partly responsible for this dramatic increase in PONV (7).

Primary control of nausea and vomiting arises from the "central pattern generator for vomiting," located in the medulla oblongata (8). There are five primary afferent pathways involved in stimulating vomiting : the chemoreceptor triggering zone, the vagal mucosal pathway in the gastrointestinal system, neuronal pathways from the vestibular system, reflex afferent pathways from the cerebral cortex, and midbrain afferents. Stimulation of one of these afferent pathways can activate the sensation of vomiting *via* cholinergic (muscarinic), dopaminergic, histaminergic, or serotonergic receptors (8).

Traditionally, the most common anti-emetics used to treat PONV include serotonin 5-hydroxytryptamine type 3 antagonists such as ondansetron, corticosteroids, like dexamethasone, or droperidol, which is a neuroleptic. However, these anti-emetics are not completely reliable and only reduce the incidence of PONV by ~26% (5).

Neurokinin-1 (NK1) receptors are found in gastrointenstinal vagal afferents and within the central nervous system vomiting reflex pathways. NK1 receptors are activated by Substance P, which is a regulatory peptide and preferred endogenous ligand (9). NK1 receptor antagonism acts both at the peripheral and central levels and has been shown to decrease PONV when administered preoperatively for non-laparoscopic procedures (10, 11). However, incidence of PONV is significantly lower in non-laparoscopic procedures. As a result, we investigated whether NK1 antagonism can effectively diminish PONV in patients undergoing laparoscopic gynecological surgery.

METHODS

Data were collected at Tokushima University Hospital (Tokushima, Japan) and the study protocol was approved by the Human Research Ethics Committee of the University of Tokushima. Sixty four female patients between the ages of 20-70 years old, ASA physical state of I-II, who were undergoing elective laparoscopic gynecologic surgical procedures with general anesthesia were enrolled. Exclusion criteria included : obesity (BMI >33), pregnancy, steroid use, abnormal liver or renal function, and neuronal disease. All patients gave written informed consent. All patients were questioned about previous PONV, motion sickness, state of menstrural cycle, and smoking state and history. Patients were randomized into two groups : NK1 group which received an oral NK1 antagonist, aprepitant at 80 mg, and a control that did not receive any anti-emetic.

Aprepitant was administered 180 mins before induction of anesthesia. Premedication were not received and standard monitoring were used, including electrocardiography, noninvasive blood pressure, pulse oximetry, and capnography. Induction and neuromuscular blockade was accomplished with 0.3-0.5 μg/kg/min remifentanil, 4 mg/kg thiamylal, and 0.8 mg/kg rocuronium intravenously. Anesthesia was maintained with 0.2-0.3 μg/kg/min remifentanil and 1.0 minimum alveolar anesthetic concentration sevoflurane. Rocuronium were injected 0.2 mg/kg every 45-60 mins.

Laparoscopies were performed with CO_2 insufflation to a pneumoperitoneal pressure of 8 mmHg. Neostigmine 1.0 mg and atropine 0.5 mg were used for reversal and 1.0 mg/kg flurbiprofen axetil was administered 15-30 mins before the end of surgery. Nitrous oxide and morphine were not a used during the procedure. Patients requiring postoperative rescue antiemetics, were administered metoclopramide, analgesic adjuncts 25 mg diclofenac sodium SUP, or 15 mg pentazocine i.v. The types of analgesic adjuncts were chosen by the gynecologist.

Efficacy was assessed in 2 and 24 hours after surgery. Primary and secondary endpoints were analyzed for the time intervals 0-2 hours (acute phase) and 2-24 hours (delayed phase). The extent of nausea was assessed by 4-point scale, which patients rated nausea from 0 to 3 (0 : no nausea, 1 : mild nausea, 2 : moderate nausea, and 3 : severe nausea) as well as vomiting. Patient pain was recorded with the visual analog scale (VAS) and patient analgesic demand was also recorded.

STATISTICS

All results were analyzed with Graphpad Prism 5.0 software (La Jolla, CA) and are expressed as mean ± SD. The means of each group were analyzed by unpaired student's t-test. Contingency tables

were analyzed with Fisher's exact tests. Statistical significance was set at $P < 0.05$ for all tests.

RESULTS

Sixty four total patients were enrolled, but only 60 patients participated in the study. Four patients withdrew due to either changes in the surgical procedure from laparoscopic to laparotomy, changes in anesthesia to propofol, and one patient decided not to receive aprepitant after enrolling.

Thirty patients were in each group and the mean ages for the control group and NK1 group were insignificant at 38 and 35 years, respectively. There were no significance between patient height or weight and both groups had relatively similar ASA physical states and risk factors for PONV (Table 1). Furthermore, patients in both groups had similar menstrual cycle phases. All patients tolerated aprepitant without any adverse effects.

Surgical/anesthetic values throughout the procedure also remained insignificant between control and NK1 groups (Table 2). Duration of anesthesia, length of procedure, patient blood loss, and infused fluid volume were all similar. Additionally, similar doses of remifentanil and rocuronium were used in both groups.

PONV incidence at acute phase was present in both control and NK1 groups and was 63% and 43%, respectively. However, nausea, vomiting, and the use of a rescue anti-emetic were less in the NK1 group all though no significance was observed (Table 3). Furthermore, the severity of nausea was

Table 1. Patients Demographics

	Control group	NK1 group
Patients	n=30	n=30
Age, yr (mean ± SD)	38 ± 13	35 ± 11
Height, cm (mean ± SD)	157 ± 5	159 ± 6
Weight, kg (mean ± SD)	53 ± 7	54 ± 8
ASA Physical state I/II, (n)	21/9	24/6
Risk factor		
Tobacco use (n)	4	6
History of motion sickness/PONV (n)	14	13
Phase of menstrual cycle (n)		
Follicular	13	15
Luteal	12	13
Postmenopause	5	2

Data are presented as number of patients or mean ± SD.

Table 2. Surgery/anesthesia values

	Control group	NK1 group
Duration of anesthesia, min	180 ± 59	173 ± 45
Duration of surgery, min	130 ± 52	125 ± 43
Anesthetics (mean ± SD)		
Remifentanil, mg	3.1 ± 2.0	2.6 ± 1.1
Rocuronium, mg	52.8 ± 11.9	56.3 ± 12.5
Type of surgery (n)		
Ovarian cystectomy/tumorectomy	24	21
Adhesiolysis	1	4
Myomectomy	3	1
Laparoscopic assisted vaginal hysterectomy	1	3
Salpingostomy	1	1
Temperature, ˚C (mean ± SD)	36.5 ± 0.4	36.6 ± 0.4
Blood loss, ml (mean ± SD)	25 ± 52	39 ± 67
Fluid volume, ml (mean ± SD)	1114 ± 318	1051 ± 247

Data are presented as number of patients or mean ± SD.

Table 3. Postoperative nausea and vomiting

	Control group	NK1 group
Acute phase (0-2 hours)		
Postoperative nausea and/or vomiting	19	13
Nausea	19	12
Low nausea severity (nausea score=0 or 1)	17	25 *
Vomiting (no. of episodes/no. of patients)	9/4	1/1
Rescue Anti-emetic	6	1
Delayed phase (2-24 hours)		
Postoperative nausea and/or vomiting	8	0 *
Nausea	8	0 *
Low nausea severity (nausea score=0 or 1)	28	30
Vomiting (no. of episodes/no. of patients)	3/2	0/0
Rescue Anti-emetic	3	0

Data are presented as absolute values. *$P<0.05$ vs. Control group. Nausea scores were assessed by patients rated nausea from 0 (no nausea) to 3 (severe nausea).

significantly less in the NK1 group with the majority of scores less than 1 (Table 3 and Figure 1).

At delayed phase PONV was present in the control group, but was absent in the NK1 group (27% and 0%, respectively). Furthermore, vomiting, and the use of a rescue anti-emetic were less in the NK1 group (Table 3). Nausea intensity was significantly less prevalent/absent in the NK1 group whereas the control group still had patients in all nausea scores (Figure 2).

VAS pain scales were not significantly different at acute or delayed phase. However, the amount of pain medication required by patients was significantly less for diclofenac and pentazocine in the NK1 group suggesting greater pain tolerance or less physical pain (Table 4).

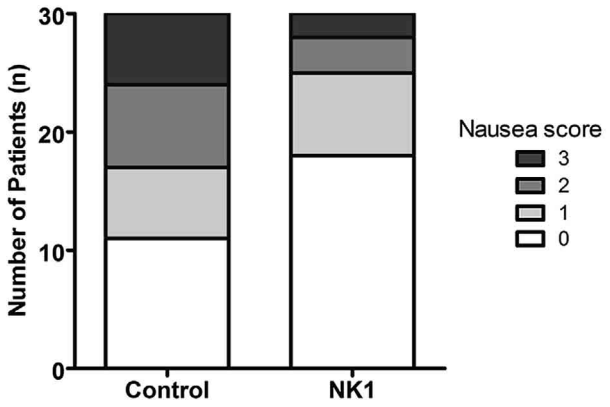

Figure 1. Patient nausea level between 0-2 hours. The severity of nausea was recorded using the following scale : nausea score : 0=no nausea ; 1=mild nausea ; 2=moderate nausea ; 3=severe nausea.

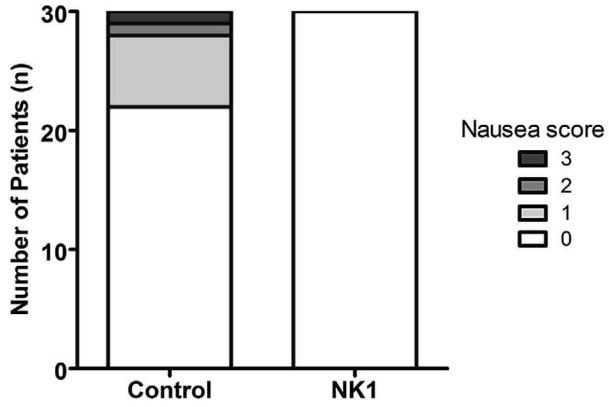

Figure 2. Patient nausea level between 2-24 hours. The severity of nausea was recorded using the following scale : nausea score : 0=no nausea ; 1=mild nausea ; 2=moderate nausea ; 3=severe nausea.

Table 4. Postoperative pain data

	Control group	NK1 group
VAS Pain scale (mean± SD)		
Acute phase (0-2 hours)	6.0± 2.4	5.4± 2.5
Delayed phase (2-24 hours)	3.7± 2.5	3.0± 2.1
Postoperative medication, mg (mean± SD)		
Diclofenac	20.8± 18.7	10.4± 13.2 *
Pentazocine	7.0± 8.1	3.0± 6.1 *

VAS=visual analog scale (0=no pain to 10=the worst pain imaginable).
*$P<0.05$ vs. Control group.

DISCUSSION

These results show that NK1 receptor blockade *via*, aprepitant can effectively decrease PONV in laparoscopic gynecological procedures. Furthermore, these results suggest that NK1 blockade can hasten recovery from PONV as well as decrease the amount of pain medication required following surgery. These results suggest that NK1 blockade may be advantageous in suppressing PONV and may be beneficial if administered prior to these type of procedures.

Aprepitant has traditionally been used in the treatment of cancer chemotherapy induced nausea and vomiting (12). Recently, aprepitant has also been shown to be highly efficient in treating PONV. In clinical trials, aprepitant was shown to be even more efficacious than traditional medications such as ondansetron (10, 11). However, these trials mainly investigated non-laparoscopic procedures, which have a significantly lower incidence of PONV. Furthermore, these trials did not investigate the effect of NK1 antagonism on post-operative pain, which has been effective in animal models, but has been difficult to translate into humans (13). Aprepitant has been shown to be ineffective in healthy human models for electrical hyperalgesia (14). In our results VAS pain scores were not significant between NK1 and control groups, however, we found that the total amount of pain medication administered was significantly decreased in NK1 groups for diclofenac and pentazocine suggesting an increased pain tolerance and decreased need for analgesia.

Substance P (SP) is one of neurotransmitters found in both the central and peripheral nervous systems, and it is known that after binding to the NK1 receptors, SP regulates many biological functions in the central nervous system such as emotional behavior, stress, depression, and anxiety (14). SP has been also implicated in inflammation and pain (8). By contrast, it is known that NK1 receptor antagonists specifically inhibit these biological functions mediated by SP after binding to NK1 receptors in animal tests (13, 14). However, NK1 receptor antagonists failed to efficacy in clinical trials in humans (13, 14). In our study, aprepitant was significantly decreased the amount of postoperative analgesic rescue adjuncts. This is shown NK1 receptor antagonists might be effective analgesics in humans.

Control patients only had a 63% incidence for PONV which is much lower than the previously reported 80% (6). Furthermore, aprepitant was only effective in about 60% of patients at acute phase but by delayed phase was effective in all of the patients. Interestingly, at delayed phase roughly 73% of control patients were also symptom-free suggesting that PONV quickly resolves without intervention in our patient population. Diemunsch *et al* (10) stated that a 40 mg dose was effective in 64% of their patients, but their results may have overestimated the effect of aprepitant as they did not have a control group that did not receive any medication. Our current results also suggest that aprepitant may also hasten the recovery from PONV as all patients in the NK1 group were symptom free by 24 hours.

Aprepitant can have serious side effects as it is non-selective in NK1 receptor blockade. These effects can include asthma, anxiety, arthritis, migraine, schizophrenia, glaucoma, neural injury and stroke (8). Furthermore, a potential side effect of aprepitant is nausea and vomiting. Although vomiting in the NK1 group was a result from PONV or from the aprepitant itself.

There are some limitations in our results. Use of flurbiprofen axetil cause nausea and vomiting in approximately 0.5-5%, it may be effective for PONV. However, patients in both groups were administered flurbiprofen axetil, it was not detected an effect of flurbiprofen axetil for PONV.

For postoperative rescue antiemetics, patients were administered pentazocine. Pentazocine occurred nausea and vomiting itself. Compared with other opioids, nausea and vomiting associated with pentazocine was generally tolerated.

In conclusion, our study investigated the use of aprepitant in PONV laparoscopic gynecological procedures. Our results, suggest that aprepitant can effectively lower PONV and also hasten recovery. Furthermore, our data suggests that aprepitant may have partial analgesic effects by increasing pain tolerance as pain medication doses were significantly lower in NK1 treated groups.

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