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A Comparative Study of Ondansetron and Palonosetron for Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Modified Radical Mastectomy

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ABSTRACT

Introduction: PONV is the most distressing complication of anesthesia and surgery. PONV occurs in about 30% of all surgical patients and in 70-80% of high risk patients. Several receptors like dopaminergic, cholinergic, histaminic and serotonergic are involved in pathophysiology of vomiting. Among them selective 5-HT3 receptor antagonist like palonosetron is now a 1st line of option because of its effectiveness and general lack of adverse reactions.

Aim: To compare the efficacy, duration of action and side effects of palonosetron and ondansetron as a prophylactic regimens for prevention of PONV in patients undergoing MRM under general anesthesia.

Materials and methods: After obtaining institutional review board approval and written informed consent 100 adult patients of ASA grade I and II undergoing modified radical mastectomy were randomly divided into two different groups (50 patients in each group).

Group P: Palonosteron 0.075 mg (prior to induction). Group O: Ondansetron 8 mg (prior to induction).

All patients were assessed for the incidence of nausea, retching, vomiting, total PONV, complete response, requirement of rescue antiemetic and presence of adverse effects from 0-24 h at 3 h interval.

Results: The incidence of Nausea, retching and vomiting was lower in the palonosetron group compared to ondansetron group during all study period however this difference was not statistically significant ($P>0.05$). However the incidence of total PONV was significantly less in group P than group O during 0-24 h with $P<0.05$. Complete response was significantly more in the palonosetron group (60%) compared with the ondansetron group (26%) ($P<0.05$). 16 patients in group O required rescue anti-emetics as compared to 6 patients in group P during 0-24 h time interval and the difference was statistically significant ($P<0.05$). Incidence of adverse effects was comparable and no significant difference was observed between two groups with P value>0.05.

Conclusion: Palonosetron is more effective in preventing PONV with fewer requirements of recue antiemetic in comparison to ondansetron in patients undergoing MRM under GA.

Keywords: Palonosetron, Ondansetron, Postoperative nausea and vomiting, Modified radical mastectomy

INTRODUCTION

Post-operative nausea and vomiting (PONV), defined as nausea and or vomiting occurring within 24 h after surgery [1-4]. It is described as "The big little problem" and from the patients perspective, PONV is the most distressing complication of anesthesia and surgery [5]. Patients reports that avoidance of PONV is of greater concern than avoidance of postoperative pain [6,7].

PONV not only causes pain, but also leads to dehydration, anxiety, acid base and electrolyte imbalance and wound dehiscence [8]. Hence PONV represents a major challenge in the practice of modern anesthesia. PONV occurs in about 30% of all surgical patients and in 70-80% of high risk patients [9,10].

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The genesis of PONV is multifactorial and result from activation of 4 vomiting centers: the vestibular system, the CTZ, the GI vagal system, and the cortical center and is influenced by patient, surgery and anesthesia related factors. Several receptors like dopaminergic, cholinergic, histaminic and serotonergic are involved in pathophysiology of vomiting [1]. Among them selective 5-HT3 receptor antagonist is now a 1st line of option because of its effectiveness and general lack of adverse reactions [11,12].

Palonosetron is a newer 5-HT3 receptor antagonist approved by USFDA for prevention of PONV in 2008 [13]. Its unique pharmacodynamics mechanism of allosteric binding and positive co-operativity trigger internalization, result in persistent inhibition and long duration of action [14].

The present prospective randomized study was aimed to compare the efficacy, duration of action, and side effects of palonosetron and ondansetron as prophylactic regimens for prevention of PONV in patients undergoing MRM under general anesthesia.

AIMS AND OBJECTIVE

Primary

To compare the efficacy of IV palonosetron with IV ondansetron in preventing PONV during 1st 24 h following MRM.

Secondary

- To compare the need for rescue antiemetic in both the groups.
- To compare the side effects of study drugs in both the groups.

MATERIALS AND METHODS

Selection of patients

100 adult patients ranging from 18 years to 60 years undergoing modified radical mastectomy were selected for the study. Only patients belonging to ASA I and ASA II were selected for study. Patients were assessed adequately in the pre-operative period. Thorough history and clinical examination, investigations were conducted and analyzed.

Exclusion criteria

- History of motion sickness and previous history of PONV.
- Full stomach.
- Gastro esophageal reflux disease.
- Pregnant and menstruating women.
- Those who had taken antiemetic medication within 24 h.
- Known history of allergy to any study drug.

Method

After obtaining institutional review board approval, written informed consent was obtained from 100 adult patients undergoing modified radical mastectomy and were randomly divided into two different groups (50 patients in each group).

Group P: Palonosteron 0.075 mg (prior to induction). Group O: Ondansetron 8 mg (prior to induction).

Patients were kept nil by mouth for at least 8 h before surgery. Patients were pre-medicated with Tab. Lorazepam night before surgery. Anesthetic techniques were identical in all patients. Anesthesia was induced with IV Inj. Glycopyrrolate (4 mcg/kg), Inj. Thiopentone Sodium (5-7 mg/kg), Inj. Fentanyl (1-2 mcg/kg). Tracheal intubation was facilitated with IV Inj. Vecuronium Bromide (0.1 mg/kg) and with cuffed endotracheal tube of appropriate size. Anesthesia was maintained with O_2 (50%) + N_2O (50%) + Sevoflurane (0.4% to 1.0%). Muscle relaxation was provided by Inj. Vecuronium Bromide (0.1 mg/kg) IV. Ventilation was controlled and adjusted to maintain an end tidal concentration of CO_2 between 30 and 40 mm of Hg.

Intra operatively patients were monitored with pulse oximetry, ECG, non-invasive blood pressure measurement and end tidal CO_2 concentration.

All patients were reversed at the end of surgery with inj. glycopyrrolate and Inj. neostigmine and extubated after return of pharyngeal and laryngeal reflexes.

Postoperative assessment: All patients were assessed for the incidence of nausea, retching, vomiting, total PONV, complete response, requirement of rescue antiemetic and presence of adverse effects from 0-24 h at 3 h interval.

Rescue antiemetic: Inj. Metoclopramide 10 mg IV was given on patient demand or 2 or more episodes nausea, vomiting or retching was recorded.

Postoperative pain assessment: At the surgical site was assessed by using VAS scale (0-No Pain to 10 Most Severe Pain).

Analgesic: All the patients were given diclofenac sodium 1.5 mg/kg intramuscularly (max. 75 mg) as analgesic at 8 hourly intervals after surgery or earlier if they demanded pain relief.

STATISTICAL ANALYSIS

Data were analyzed using computer statistical software system Graph Pad. Categorical variables between the study groups were assessed by Z-test. Similarly, comparisons among two groups involving quantitative variables were assessed by the Student's t-test. Differences between groups were declared as statistically significant at $P<0.05$.

OBSERVATION AND RESULTS

The following observation and results were noted in a comparative study between ondansetron and palonosetron to prevent post-operative nausea and vomiting in 100 patients undergoing modified radical mastectomy.

Table 1. Demographic data.

Variables	Group O (n=50)	Group P (n=50)	P-value
Age (years)	46.22 ± 8.73	45.32 ± 8.82	0.6092
Sex (F/M)	49/1	50/0	-
Weight (kg)	55.12 ± 9.59	56.28 ± 8.24	0.5180
ASA Grade I/II	42/8	41/9	-
Duration of surgery	69.1 ± 14.37	70 ± 19.35	0.7923
HR	79.46 ± 8.03	79.92 ± 8.88	0.7864

There was no significant difference between two study groups in terms of patients demography and baseline hemodynamic data (P>0.05) **(Table 1)**.

Table 2. No. of Pts (%) with nausea, retching, vomiting and total PONV at 3 h interval post operatively up to 24 h.

	Group O (n=50)	Group P (n=50)	P-Value
0-3 h			
Nausea	9 (18%)	4 (8%)	0.136
Retching	5 (10%)	3 (6%)	0.459
Vomiting	4 (8%)	02 (4%)	0.400
Total PONV	18 (36%)	9 (18%)	0.042
3-6 h			
Nausea	6 (12%)	2 (4%)	0.141
Retching	4 (8%)	2 (4%)	0.400
Vomiting	3 (6%)	1 (2%)	0.307
Total PONV	13 (26%)	5 (10%)	0.037
6-9 h			
Nausea	4 (8%)	1 (2%)	0.167
Retching	5 (10%)	2 (4%)	0.238
Vomiting	1 (2%)	0 (0%)	0.312
Total PONV	10 (20%)	3 (6%)	0.037
9-12 h			
Nausea	3 (6%)	2 (4%)	0.645
Retching	3 (6%)	0 (0%)	0.078
Vomiting	2 (4%)	0 (0%)	0.152
Total PONV	8 (16%)	2 (4%)	0.045
12-24 h			
Nausea	3 (6%)	1 (2%)	0.307
Retching	4 (8%)	0 (0%)	0.041
Vomiting	0 (0%)	0 (0%)	0
Total PONV	7 (14%)	1 (2%)	0.027

The incidence of Nausea, retching and vomiting was lower in the palonosetron group compared to ondansetron group during all study period (P>0.05). But this difference was not statistically significant. However the incidence of total PONV was significantly less in group P than group O during 0-24 h with P<0.05 **(Table 2)**.

Table 3. Incidence of post-operative nausea and vomiting in 24 h.

Incidence of nausea and vomiting in 24 h	GroupO(n=50)	GroupP(n=50)	P value
Incidence of nausea in 24 h	25 (50%)	10 (20%)	0.001
Incidence of vomiting in 24 h	10 (20%)	3 (6%)	0.037

In group O, 50% patients while in group P, 20% of patients experienced nausea during 24 h postoperatively and this difference was statistically significant (P<0.05). Also incidence of vomiting in 24 h postoperatively was significantly less in palonosetron group (6%) compared to ondansetron group (20%) (P<0.05) **(Table 3)**.

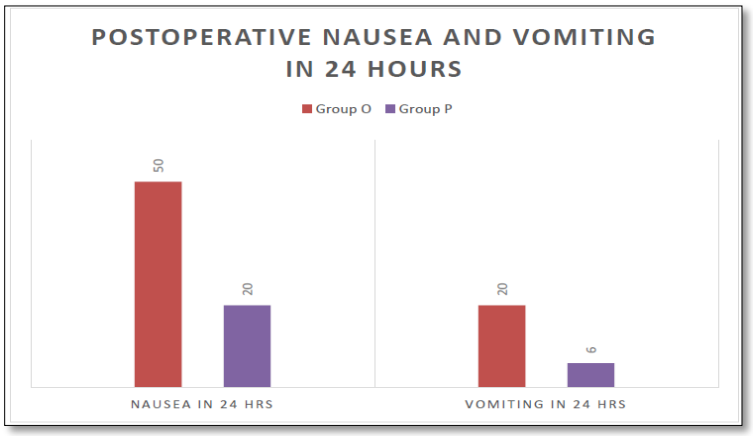

Figure 1. Incidences of nausea and vomiting in 24 h.

Table4. Incidenceof completeresponseandneedforrescueanti-emetics.

	Group O (n=50)	Group P (n=50)	P value
Complete Response	13 (26%)	30 (60%)	0.0005
Rescue Anti-emetics	16 (32%)	6 (12%)	0.0157

Complete response was significantly more in the palonosetron group (60%) compared with the ondansetron group (26%) (P<0.05). 16 patients in group O required rescue anti-emetics as compared to 6 patients in group P during 0-24 h time interval and the difference was statistically significant (P<0.05) **(Table 4 and Figure 1)**.

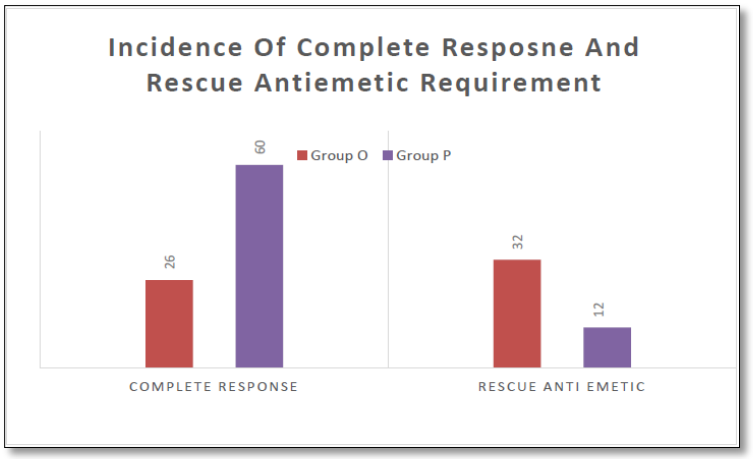

Figure 2. Incidences of complete response and rescue anti-emetic requirement.

Table 5. Heart rate and mean arterial pressure.

	Group O	Group P	P value
0-3 h			
HR	77 ± 6.39	78.12 ± 6.12	0.372
MAP	90.02 ± 7.1	89.96 ± 7.9	0.968
3-6 h			
HR	79.24 ± 5.90	80.16 ± 5.32	0.414
MAP	92.69 ± 6.39	93.09 ± 6.4	0.755
6-9 h			
HR	82.2 ± 7.88	80.76 ± 7.65	0.356
MAP	94.90 ± 4.92	94.26 ± 6.1	0.565
9-12 h			
HR	82.52 ± 5.41	82.24 ± 6.90	0.821
12-24 h			
HR	84.08 ± 6.15	83.2 ± 7.55	0.524
MAP	94.22 ± 6.72	94.58 ± 5.74	0.773

The Heart rate and mean arterial pressure between the study groups had no significant difference during 0-24 h postoperatively with P>0.05 **(Table 5 and Figure 2)**.

Table 6. Incidence of adverse effects.

	Group O	Group P	P value
Headache	3 (6%)	4 (8%)	0.696
Dizziness	4 (8%)	2 (4%)	0.400
Drowsiness	1 (2%)	2 (4%)	0.555
Constipation	1 (2%)	0 (0%)	0.312

Incidence of adverse effects was comparable and no significant difference was observed between two groups with P value>0.05 **(Table 6 and Figure 3)**.

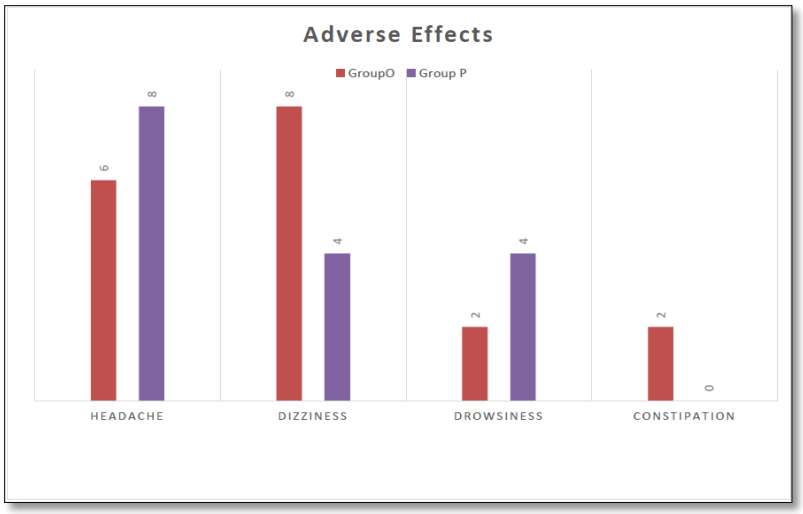

Figure 3. Incidences of adverse effects between two groups.

DISCUSSION

Post-operative nausea and vomiting is most common and distressing complication after surgery and anesthesia. PONV not only causes pain but also leads to anxiety, dehydration, electrolyte and acid-base imbalances, aspiration pneumonia and wound dehiscence [8]. It is a leading cause of delayed postoperative recovery and discharge.

The genesis of PONV is multifactorial involving operative, anesthetic and patient specific factors. Apfel et al. [15] stated that female, a history of PONV or motion sickness, nonsmoker and postoperative opioid use were the more important risk factors and each additional risk factor increased the PONV incidence rate to 21, 39, 61 and 79%. Several receptors like dopaminergic, serotonergic, cholinergic and histaminic are involved in the pathophysiology of vomiting. The use of anti-emetics, either alone or in combination remains the mainstay of PONV management. Drugs used include anti-cholinergic, dopamine antagonists, anti-histaminic, steroids and selective 5-HT3 receptors antagonists. Among them serotonergic receptor antagonists are 1st line drug of PONV prophylaxis because of its effectiveness, more safety and favorable side effects [11,12].

In 1990s 5-HT3 receptor antagonists was heralded as the major advance in prophylaxis against PONV and are routinely used now a days to prevent PONV as they lack major adverse effects [16-18.] Ondansetron, granisetron, dolasetron, topisetron and palonosetron are currently available 5-HT3 receptor antagonists [17].

Ondansetron, selective 5-HT3 receptor antagonists is considered as the first 5-HT3 receptor antagonists highly effective antiemetic that has been used for both prevention and treatment of PONV [19]. Its antiemetic effect is stronger than its anti-nausea effect. It has a short half-life of 3-5 h [20]. It's being routinely used either alone or in combination with other drugs in day care surgeries for PONV prophylaxis because of its lower cost.

Palonosetron is a new, potent 2nd generation 5-HT3receptor antagonists with unique structural, pharmacological and clinical characteristics. Its allosteric binding creates a conformational change in serotonin receptor so that serotonin binding is indirectly inhibited [21]. Consequently, palonosetron has higher affinity with 5-HT3 receptors, which ultimately leads to greater potency and longer duration of (20%) action of 40 h in comparison with standard 5-HT3 antagonists [10,22].

Our study was done to compare the efficacy of palonosetron 0.075 mg and ondansetron 8 mg for prevention of PONV in patients undergoing MRM under general anesthesia. Study drug was administered prior to induction of anesthesia based on the hypothesis that greater antiemetic effect of drugs is seen if we block the CTZ before the arrival of emetic stimuli associated with anesthesia and surgery.

Honkavaara et al. [23] in their study concludes that ondansetron 8 mg was not superior to 4 mg in preventing PONV and the need for rescue antiemetic. In our study we selected ondansetron 8 mg on the basis of Paventi et al. [24] dose ranging study of ondansetron in which they concluded that single dose of ondansetron 8 mg was more effective than ondansetron 4 mg and is the minimum effective dose in the prevention of PONV. A study done by Tramer et al. [25] also in view of that ondansetron 8 mg is the optimal dose for the prevention of PONV.

Candiotti et al. [26] evaluated the three different single IV doses of palonosetron (0.025 mg, 0.05 mg and 0.075 mg) compared with placebo for the prevention of PONV in patients at risk for nausea and or vomiting. They observed a linear trend in efficacy with increasing doses, with the highest dose (0.075 mg) of palonosetron demonstrating a statistically significant effect compared with placebo over

the first 24 h. In addition Kovac et al. [27] also in his study compared palonosetron in doses of 0.025 mg, 0.05 mg and 0.075 mg. They found that lower doses were not as effective as palonosteron 0.075 mg, which significantly reduced the severity of nausea and delayed the time to emesis. US FDA also approved 0.075 mg as the minimum effective dose of palonosetron for PONV prophylaxis [26,28]. Therefore we chose palonosetron 0.075 mg in our study.

We did not include a control group receiving placebo as Aspinall and Goodman [29] have suggested that if effective drugs are available, placebo controlled trials maybe unethical.

In the present study both the groups were comparable with respect to age, sex, body weight and mean duration of surgical procedure **(Table 1)** with no statistical difference between two groups (P>0.05).

No major hemodynamic changes were observed in either group. Our observations were similar to the previous studies [30-32].

In our study, incidence of nausea, retching, vomiting and total PONV were observed during 0-3, 3-6, 6-9, 9-12 and 12 -24 h time interval postoperatively. We found that the incidence of nausea was 18% in group O and 8% in group P at 0-3 h. While during 3-6 h, it was 12% and 4% in group O and group P, respectively. At 6-9 h group O had 8% while group P had 2% of nausea. During 9-12 h it was 6% in group O compared to 4% in group P and at12-24 h 6% and 2% in group O and group P, respectively. While comparing incidence of vomiting, during 0-3 h it was 8% in group O while it was 4% in group P, at 3-6 h we found 6% and 2% as incidence of vomiting in group O and group P, respectively. During 6-9 h it was 2% in group O and 0% in group P, while at 9-12 h we found it was 4% and 0% in group O and group P and during 12-24 h both group O and P had 0% vomiting. While comparing the incidence of retching during 0-24 h it was found to be less in palonosetron group than ondansetron group. From the above findings it was clear that incidence of nausea, retching and vomiting was less in the palonosteron group during all the time periods compared to ondansetron group. Though the incidence was lower in the palonosetron group than ondansetron group, they were not statistically significant (P>0.05).

This is in accordance with Patel et al. [33] study, where they found the incidence of nausea during 0-2 (5.71% vs. 14.29%), 2-6 (5.71% vs. 14.29%) and 6-12 (0% vs. 8.57%) hours and the incidence of vomiting during 0-2 (2.86% vs. 11.43%), 2-6 (0% vs. 2.86%) and 6-12 (2.86% vs. 2.86%) hours' time interval was less in the palonosetron group than ondansetron group but this difference was not statistically significant. Similar results were observed in Ahmed et al. [34] study where they studied the incidence of PONV in patients who were given either palonosteron or ondanserton for prophylaxis of PONV in middle ear surgery. They found incidence of nausea and vomiting was lower in palonosetron group as compared to ondansetron group but was not significantly different between the two groups.

In our study we found the overall incidence of nausea during 24 h time interval postoperatively was 50% in group O compared to 20% in group P and the difference was statistically significant with P=0.001. And the overall incidence of vomiting during 24 h postoperatively was 20% in ondansetron group and 6% in palonosteron group which was statistically significant (P=0.037). Bajwa et al. [35] found significantly higher incidence of nausea and vomiting (20% and 13.33%) in ondansetron group during 0-72 h in comparison to 6.67% and 3.33% in palonosteron group respectively (P<0.05). Similarly Taninder Singh et al. [36] found that the overall incidence of post-operative nausea in 24 h was 56.66% in patients among ondansetron group and 30% in patients of palonosetron group with statistically significant difference (p=0.037) between the two and the overall incidence of vomiting during 24 h was 20% in ondansetron group and 3.33% in palonosetron group (P=0.044). In the study conducted by Sarvesh et al. [37] the incidence of nausea during 0-24 h was 26.6% in ondansetron group and 8.9% in palonosetron group with significant difference between two (P=0.0005) and the incidence of vomiting during 24 h study period was 21.8% and 4% in group ondansetron and palonosetron, respectively, which was statistically significant with P value of 0.0001.

In case of breakthrough PONV, according to Guidelines from the Society for ambulatory anesthesia (SAMBA) it has been recommended that when PONV occurs after antiemetic prophylaxis, rescue drug used should be from a different class than one used for prophylaxis [42]. Candiotti et al. [43] in their study concluded that patients who failed ondansetron prophylaxis did not have a significant response to the same class of drug. In Bhalla et al. [44] study, the rescue antiemetic used was Inj. dexamethasone 8 mg IV as it has been recommended that patients should receive a rescue antiemetic drug from a different class of anti-emetics than one used for prophylaxis. They found that the need for rescue anti-emetics was significantly higher in patients receiving ondansetron (32%) as compared to palanosetron (16%). Based on the above results we used Inj. Metoclorpamide 10 mg as a rescue anti-emetics in our study if 2 or more episodes of vomiting occurs or on patient demand. In study conducted by Patel et al. [33], 5.71% of patients in palonosetron group and 23.53% patients in ondansetron group required rescue anti-emetic and this difference was statistically significant. Also in Singh et al (2014)[45] the need for rescue antiemetic was significantly more in ondansetron group (23.53%) than in the palonosetron group (5.71%). In our study patient requiring rescue anti-emetic was 32% in group O, while 12% in group P (P=0.0157) with statistically significant difference between the two and it was comparable to the above study findings.

In our study adverse effects with single IV dose of palonosetron and ondansetron were not clinically serious and there were no significant difference in the incidence of headache, dizziness or drowsiness between two groups. In the study done by Kim et al. [46] they did not find any significant difference in the incidence of side effects among two groups. Also in the study done by Laha et al. [30], Ahmed et al. [34] and Patel [33] found no significant differences in the side effect profile between the two groups confirming our findings.

CONCLUSION

In conclusion, the results of the present study clearly conveys that the palonosetron hydrochloride is more effective in preventing PONV with less requirement of recue anti-emetics in comparison to ondansetron hydrochloride in patients undergoing MRM under GA.

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