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ORIGINAL CONTRIBUTIONS

Improving Nausea and Vomiting Post-Elipse Balloon: a Novel Single-Dose Regimen of 300 mg Netupitant/0.5 mg Palonosetron Hydrochloride

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Abstract

Background Post intragastric balloon placement symptoms like nausea and vomiting have been the major cause of a high rate of early removal. Common therapy with ondansetron alone, or in combination, with prokinetic agents have been shown to have very little or no effect. Recently, an improved therapy based on aprepitant and ondansetron combination showed a significant improvement in symptoms management. Lack of aprepitant availability in several countries and patients difficulties to follow the right prescription convinced us to explore other pharmacological options.

Objective Evaluate safety and efficacy of a netupitant and palonosetron-combined drug and to reduce and control post Elipse® placement symptoms

Methods Between January and March 2018, 30 patients (9 male, 21 female), (mean weight 97.8 and mean BMI 34.7), underwent Elispe® placements, at 550 ml volume, in an outpatient fashion. All patients received a single pill 300 mg netupitant/0.5 mg palonosetron 6 h prior to placement. All patients received ondansetron 4 mg prescription to be taken as needed. A daily VAS score to report intensity of nausea, vomit, cramps, gastric pain, satiety for the first week post-placement was completed.

Results 4/30 (13%) reported vomiting on days 1, 2, and 3; 9/30 (30%) reported nausea higher than score 4 on days 1, 2, and 3; 8/30 (26.6%) reported gastric pain higher than score 4 on days 1, 2, and 3.

Conclusion In our experience, the use of a single-pill netupitant/palonosetron resulted to be very easy to administer and effective in reducing vomit, nausea, and gastric pain in 87%, 70%, and 73.4% patients respectively, ameliorating the post Elipse™ placements symptoms safely.

Keywords Weight loss · Obesity · Intra-gastric balloon · Intra-gastric balloon drug therapy · Overweight · Elispe balloon · Anti-emetic drug · Balloon side effects · Nausea · Vomiting

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Introduction

Intragastric balloon (IGB), a temporary weight loss device, has been shown to be safe and effective in the management of overweight and obese patients in several studies [1, 2]. In combination with lifestyle intervention, it has been shown to reduce weight in obese patients before bariatric surgery or in patients who do not qualify for surgery or refuse it [1, 3]. A new swallowable intragastric balloon, Elipse™, has emerged as a nonsurgical/non-endoscopic option to treat obesity [4]. Nausea and vomiting are common and distressing side effects during the first week post IGB placement [5]. Different antiemetic drug regimens have been used to manage these symptoms. The first therapy used with ondansetron or other serotonin 5-HT3 receptor antagonists, in combination with prokinetic agents such as metoclopramide or domperidone, were not very effective [6]. In the last 3 years, an antiemetic drug used for chemotherapy, aprepitant, in combination with ondansetron, has been adopted to control nausea and vomiting post IGB placement. Compared to the previous treatments, this antiemetic regimen has been much more effective in preventing vomiting but less in preventing nausea [7]. Due to the multiple-dose use of aprepitant and also the fact that it is not widely available, we evaluated a new therapy for use with IGBs. Netupitant/palonosetron hydrochloride is a fixed combination drug indicated to prevent nausea and vomiting associated with cancer chemotherapy. In the first studies, it was shown to be a safe and effective drug in reducing both nausea and vomiting [8–10]. The aim of our study was to verify the effectiveness and safety of this drug in association with a low dose of ondansetron in the management of post-placement side effects (nausea and vomiting) in patients with the Elipse™ balloon.

Patient and Method

The Elipse™ System: The Elipse™ balloon (Allurion Technologies, Natick, MA-USA) is enclosed in a capsule and is swallowed and then filled with 550 ml of liquid through a thin catheter attached to the balloon. Placement is performed in a 20-min outpatient visit without endoscopy or sedation. The correct position of the balloon is checked using an abdominal x-ray, and after filling, the catheter is removed. A stylet to stiffen the catheter can be used in case of difficulty in swallowing. The Elipse self-empties via a valve that opens at 4 months, allowing the empty balloon to pass naturally.

300 mg Netupitant/0.5 mg Palonosetron Hydrochloride Mechanism of Action

Netupitant/palonosetron hydrochloride is a fixed combination of netupitant, a substance P/neurokinin 1 (NK1) receptor antagonist, and palonosetron, a serotonin-3 (5-HT_3) receptor antagonist. It is indicated to prevent acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy [11]. Netupitant has a mean plasma half-life of approximately 80 h and has shown a 92.5% NK_1 receptor occupancy at 6 h, with 76% occupancy at 96 h. Oral palonosetron has a mean plasma half-life of approximately 48 h [12].

Study Design and Patients

This was a multicenter clinical trial conducted in overweight and obese patients from January 2018 until August 2018. Four international centers were involved in the study (Table 4). The study analyzed the first week after Elipse (TM) balloon placement. Inclusion criteria were age between 18 and 65 years, body mass index (BMI) greater than 27 kg/m^2 and less than 45 kg/m^2 with previous failed dietary treatments. Patients excluded from the study were pregnant women and patients with history of any abdominal surgery with the following exceptions: diagnostic laparoscopy, laparoscopic appendectomy, open appendectomy with lower right abdominal incision, and laparoscopic cholecystectomy. Also contraindicated were patients with clinical history of perforated appendix or those who had three or more cesarean sections, patients with swallowing problems, patients with previous intestinal obstruction, those with inflammatory bowel disease, GI cancer and GI bleeding, severe coagulopathy, and severe psychological or eating disorders.

Intervention

After establishing eligibility, 78 patients (24 M, 54 F,), with mean weight and BMI respectively of 92.4 Kg and 33.7 Kg/m^2, underwent Elipse intragastric balloon placement. Prior to placement, a detailed medical obesity history, nutritional behavior history, anthropometric evaluation (height, weight, BMI), and routine blood test were performed. All patients received only one (1) 300 mg netupitant/0.5 mg palonosetron pill 3 h before placement and 70/78 patients (90%) added ondansetron 4 mg every 8 h for 3 days starting after placement.

Trial Assessments and Safety Evaluations

For the first week, starting from the day of placement, patients completed a visual analogue scale (VAS) (score

Table 1 Demographic

	78 patients (24 M, 54 F)
Mean weight	92.4 Kg ± 8.1
Mean BMI	33.7 ± 2.4

Table 2 Symptom intensity score by visual analog scale (VAS), mean ± SD

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Nausea	5.9 ± 3.8	5.3 ± 3.7	3.8 ± 2.9	2.2 ± 2.2	1.1 ± 2.2	0.3 ± 0.5
Satiety	7.8 ± 1.3	7.6 ± 1.8	7.5 ± 1.9	7.9 ± 0.9	7.9 ± 1	7.8 ± 1
Vomiting	2.6 ± 4	2.3 ± 3.6	1.8 ± 2.6	1.2 ± 2.1	0.6 ± 2.3	0.0 ± 0.0
Cramps	4.9 ± 2.9	4.8 ± 2.7	3.7 ± 2.3	2.2 ± 2.2	1.4 ± 2.2	0.7 ± 1.1
Regurgitation	4.4 ± 3.1	3.9 ± 2.9	2.6 ± 3	2.3 ± 2.4	0.9 ± 1.3	0.7 ± 0.9
Abdominal pain	5.3 ± 2.9	5 ± 2.7	3.6 ± 2.2	3 ± 2.4	1.6 ± 2.2	0.8 ± 1.5
Heaviness	4.9 ± 3.1	4.6 ± 2,8	3.3 ± 2,1	2.5 ± 2,9	2.1 ± 1,9	1.8 ± 2.4
Drinking difficulty	5.7 ± 1.4	4.8 ± 1.4	3.6 ± 1.5	2.5 ± 1.3	1.8 ± 1.8	0.8 ± 1.2
Eating difficulty	0.0 ± 0.0	0.1 ± 0.3	0.3 ± 0.8	0.2 ± 0.8	0.2 ± 0.8	0.2 ± 0.4

Day 1 is day of placement, days 2, 3, 4, 5, and 6 are from Elipse placement

was from 0 to 10 points, with 10 being most severe) in order to evaluate the intensity of the post-placement side effects (nausea and vomiting, satiety, epigastric pain, gastric heaviness, regurgitation, difficulty in eating liquids and solids). Patients were provided with written informed consent. Safety was monitored throughout the trial by reporting all adverse events and serious adverse events. The safety assessment included checking vital signs, physical examination, and evaluation of laboratory values. In addition, the patients received a diary to record all medication intake.

Statistical Analysis

Results were expressed by mean, standard deviation, min, max, and range.

Results

Patients Seventy-eight patients underwent Elipse treatment and received as a single pill 300 mg netupitant/0.5 mg palonosetron hydrochloride. Eight (10.2%) patients did not need to add ondansetron, while the remaining ones added 4 mg every 8 h for 3 days starting immediately after placement. Every patient was able to complete the study.

Anthropometric Parameters

At baseline, there were 78 patients, 54 females (69.2%) and 24 males (30.8%). The mean weight was 92.4 ± 8.1 kg, mean BMI was 33.7 ± 2.4 kg/m^2 (Table 1). All patients demonstrated good compliance to nutritional recommendations and all lost weight during the first week of treatment.

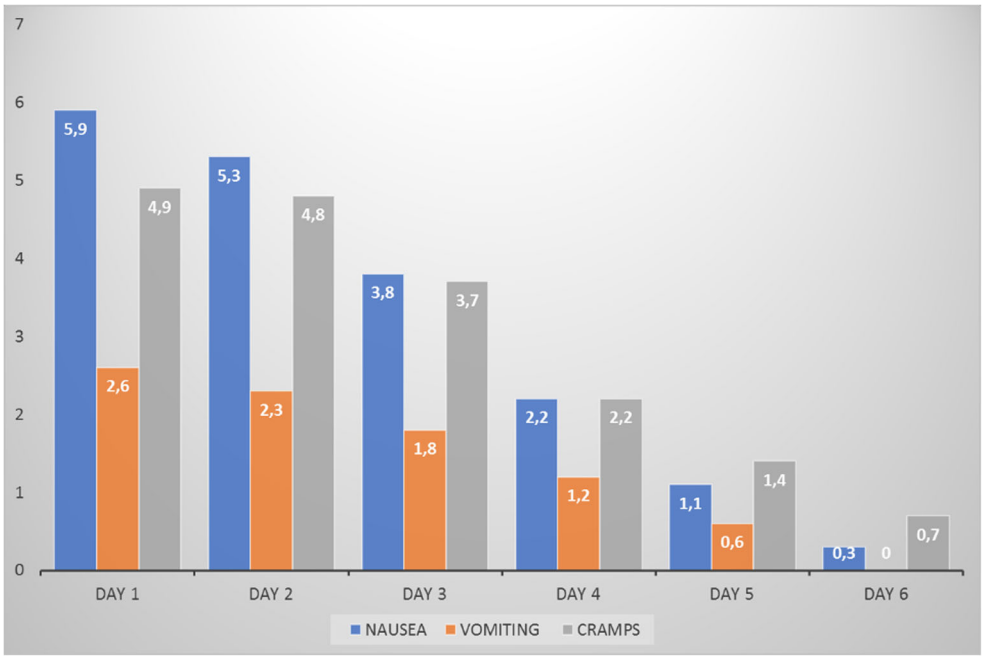

Fig. 1 Trend of intensity for nausea, vomiting, and cramps in the first week post placement

Table 3 Percentage of symptomatic patients

	Day 1	Day 2	Day 3	Day 6
Nausea	82%	82%	20%	1%
Vomiting	35%	35%	2%	0%
Cramps	100%	100%	4%	3%

Outcome

Symptom assessment score was measured by visual analog scale (VAS), mean ± SD (Table 2). Netupitant/palonosetron hydrochloride as antiemetic drug in patients receiving Elipse™ balloon, resulted in scores for level of vomiting and nausea of only 2.6 ± 4 and 5.9 ± 3.8 on the day of placement. By day 6 after placement, this had decreased to 0 and 0.3 ± 0.5 respectively. Eighty-two percent of patients had nausea, and 35% had vomiting on day 1 or day 2 after Elipse placement. Scores for level of abdominal cramps were 4.9 ± 2.9 on the day of placement. During the next days, these progressively decreased down to 0.7 ± 1.1 on day 6 after placement. (Fig. 1). Mild abdominal cramps occurred in 100% of patients in the first 2 days. By day 3 following placement, nausea and vomiting occurred in 20% and 2% of patients respectively and abdominal cramps in 4% of patients. By day 6 after placement, vomiting had completely resolved. Nausea and cramps persisted in 1% and 3% of total patients (Table 3).

Safety

No serious adverse events were observed during treatment. One patient had early gastric dilatation that resolved by switching the diet from a solid to a liquid diet for 2 days. The resolution of gastric dilation was checked by an abdominal x-ray. 18/78 patients (23%) patients had constipation due to the low caloric solid food intake during the first days of treatment, and it resolved with the increase of water and fiber in the diet. 24/78 patients (18.7%) reported tiredness during the first 2 days (Table 4).

Discussion

Nausea and vomiting are common side effects post IGB placement, and they are the major cause for the high rate of hospital readmissions and early balloon removal [13]. Management of these symptoms is crucial in order to improve the success of intra-gastric balloon treatment. Several studies have shown greater effectiveness in reducing vomiting using a combination treatment of aprepitant and ondansetron in post-Elipse-placement patients [4, 14, 15]. The previous therapy that used ondansetron alone, all patients presented with very high levels of vomiting and nausea during the first week after placement of IGBs [6]. Subsequently, with the addition of midazolam, the incidence of nausea and vomiting during the first 24-h post IGB insertion significantly decreased [16]. Recently, Machytka et al. showed that the percentage of vomiting in patients receiving Elipse balloons was dramatically reduced using a combination of ondansetron and aprepitant compared to patients treated with ondansetron or aprepitant alone. In the ondansetron only and aprepitant only treated group, 100% and 85.5% of patients vomited respectively. However, in the group treated with a combination of the two medications, only 41% vomited. However, these studies did not report the same results for nausea although it did appear to have been reduced. Furthermore, the lack of aprepitant availability in several countries and patients' poor compliance in following the correct prescription (125 mg on day before deployment, 80 mg daily for next 2 days), motivated us to explore other pharmacological options. Three hundred milligrams of netupitant/0.5 mg palonosetron hydrochloride is a fixed combination medication indicated for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy. The longer half-life of netupitant, 80 h, in comparison to the 9–13 h of aprepitant, suggested a better efficacy of netupitant/palonosetron hydrochloride in terms of decreasing both nausea and vomiting [12]. This consideration allowed us to reduce the dose of ondasentron from 8 mg (as used in the previous pharmacological treatment in association with aprepitant) to 4 mg. In our study, all patients received a single 300 mg netupitant/0.5 mg palonosetron pill 3 h before placement, and 70 patients (89.8%) were also administered ondansetron 4 mg every 8 h for 3 days starting immediately after placement. This resulted in an improvements in nausea and vomiting (only 35% of patients had any vomiting in the first 2 days of treatment and the mean level of nausea was 5.9). Improvements were also reflected in the patients' pain sensation. In fact, we recorded a very low score of abdominal cramps (4.9 on day 1 and 4.8 at day 2) and consequently much better tolerance of the Elipse balloon. The significantly

Table 4 Centers involved in the study

Department	Institute	City
"Elipse Weight management center"	Nuova Villa Claudia	Roma (Italy)
"Emergency and Metabolic Surgery"	Pineta Grande Hospital	Caserta (Italy)
"Surgical Division"	BR Medical Suites	Healthcare City, Dubai (UAE)
"Bariatric Center"	Al Zahra Hospital	Dubai (UAE)

improved tolerance resulted in no balloons having to be removed. Five days post Elipse placement, one patient developed uncontrolled vomiting and was diagnosed with gastric dilation. The patient was switched from a solid to a liquid diet for 2 days. A subsequent abdominal x-ray revealed resolution of the gastric dilation in 2 days. The patient then went back to a solid diet without further issues. There were no other serious adverse events. A few patients reported constipation and tiredness, most likely attributed to the decreased food intake and change in diet. However, the possibility that the medication may have contributed could not be ruled out.

Conclusions

The current protocol appears safe and resulted in a symptom rate lower than that reported in other studies using a different protocol. The single pill netupitant/palonosetron was very easy to administer and well tolerated by the patients. Further studies will confirm the results from our experience, and to assess the role of netupitant/palonosetron hydrochloride as a tool to control nausea and vomiting in patients with the Elipse™ and other intragastric balloons.

Compliance with Ethical Standards

Conflict of Interest Roberta Ienca and Cristiano Giardiello are consultants for Allurion; Faruq Badiuddin is an advisor for Allurion. The authors declare that there are no other conflicts of interest for this study.

Ethical Approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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