Original Article

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Comparing the Efficacy of Palonosetron versus Ondansetron in the Prevention of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients; A Randomized Controlled Trial

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ABSTRACT

Objectives: To compare the efficacy of Palonosetron and Ondansetron as premedication in the prevention of early and delayed chemotherapy-induced nausea and vomiting (CINV) in pediatric patients with cancer receiving moderately or highly emetogenic chemotherapy.

Methodology: This randomized controlled trial study was conducted at the Oncology Department of Children's Hospital, PIMS Islamabad, on patients aged 6 months to 12 years undergoing chemotherapy. Patients were divided in 2 groups by stratified random sampling and random allocation. Patients in Group 1 received a single intravenous dose of 20 microgram/kg Palonosetron and dexamethasone before chemotherapy, while Group 2 received intravenous Ondansetron 8 hourly along with dexamethasone. Nausea and vomiting severity were assessed from 0–120-hour interval using the CTCAE V 5.0 grading system. Data analysis was performed using SPSS version 23, employing chi-square and Fisher exact tests to compare outcomes between the two groups.

Result: 218 pediatric oncology patients were included who received moderate or high intensity chemotherapy with the mean age of 5.25 ± 2.96 years. The majority of the participants were male (58.7%). The most common diagnosis was Wilms tumor (37.6%), followed by acute lymphoblastic leukemia (21.1%) and Ewing sarcoma (9.6%). Complete response to antiemetics was significantly more in Group 1 as compared to group 2, on day 1 and 2 with p value of 0.004 and 0.001 respectively. Grade of vomiting was significantly less on day in Group 1 study participants.

Conclusion: Pediatric oncology patient receiving moderately or highly emetogenic chemotherapy showed effective response to palonosetron as compared to ondansetron in prevention and control of early and delayed chemotherapy induced nausea and vomiting.

Key Words: Chemotherapy-induced nausea and vomiting, pediatric oncology, Palonosetron, ondansetron.

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Introduction

Chemotherapy administration in patients with oncological diseases is commonly associated with Chemotherapy–induced nausea and vomiting CINV.[1] This sole side effect of chemotherapy can result in poor compliance of patients to this life saving treatment. Targeted antiemetics can cover CINV and can directly improve patient compliance, quality of life and disease outcome.[2,3, 4]

Chemotherapy induced emesis can be classified into anticipatory, acute and delayed emesis based upon significant nausea or vomiting during previous cycles, occurring within or after 24 hours of chemotherapy

administration respectively. [5] The various antiemetic protocols developed are based upon severity of chemotherapy induced emesis. Low adherence to antiemetic prophylaxis has seen in clinical practice and despite much progress in the development of various antiemetic protocols CINV remains a significant side effect of chemotherapy.[6]

Chemotherapeutic agents are categorized into three types based upon anticipated severity risk of causing emesis. These include highly emetogenic with >90% risk, moderately emetogenic with risk between 30 to 90% and low or minimally emetogenic with <30% risk of emesis.[7] There are various drugs used to prevent CINV, common being 5-hydroxytryptamine receptor antagonists (5 HT-3), neurokinin 1 receptor antagonist (NK-1), and glucocorticoids (especially dexamethasone) which can be used alone or in combination.[8]

The commonly used 1st generation 5-HT-3 includes Ondansetron and Grenesteron. Despite some pharmacological differences between these drugs, almost same efficacy has been noted and depending upon the availability they can be used interchangeably at equipotent doses.[9] A more potent and selective 2nd generation 5-HT-3 antagonist Palonosetron is also available in Pakistan. The extended elimination half-life of Palonosetron makes is a preferred choice over other drugs of 5-HT-3 family.[10,11, 12]

This research compares the efficacy and cost effectiveness of Palonosetron and Ondansetron as premedication in the prevention of early and delayed chemotherapy-induced nausea and vomiting in pediatric patients with cancer receiving moderately or highly emetogenic chemotherapy.

This study aims to determine whether palonosetron is more effective than ondansetron in preventing CINV in pediatric patients with cancer. The results of this trial could potentially lead to improved treatment options and better management of CINV in pediatric patients undergoing chemotherapy.

Methodology

A randomized controlled trial was conducted at the Oncology Department of Children's Hospital, PIMS Islamabad for a duration of six months. Stratified random sampling technique was adopted for high and moderately emetogenic chemotherapeutic agents to counter selection bias. Using the envelop method of randomization, patients were equally (1:1) divided into two groups. i.e. group 1 and group 2, receiving Palonosetron and Ondansetron respectively. Double-blinded data collection procedure was adopted. Sample size of 218 in both groups with ratio of 1:1 was calculated by WHO sample size calculator with assumption of the outcome in group 1 and 2 as 0.722 and 0.5 respectively at the confidence level of 0.95 and the power of 0.9. Patients (6 months- 12 years age) getting chemotherapy that could cause vomiting was included in the study, whereas patients with abnormal heart rhythm, low-risk chemotherapy, vomiting from other causes, taking anti-vomiting drugs before the study, or Acute lymphoblastic leukemia in maintenance phase were excluded from the study. Patients were included in the study after written informed consent from parents. Study was approved by hospital ethical committee.

Group 1 received an intravenous single dose of 20 microgram/kg (max 1.5mg) Palonosetron and 0.2 mg/kg dexamethasone half an hour before chemotherapy and group 2 received 0.15 mg/kg (max 16mg) intravenous Ondansetron along with dexamethasone half hour before chemotherapy and then repeat 8 hourly. A single Palonosetron dose per chemotherapy cycle was given to each patient regardless the regimen was a single day or multiple days, however, Ondansetron was given in three doses on day 1 / daily as per protocol. Severity of nausea and vomiting measured daily for the 0–120 h interval according to the grading system in CTCAE V 5.0.[13]

Complete response is the absence or mild vomiting and nausea due to chemotherapy, and if both vomiting and nausea are grade 0 or grade 1 controlled by rescue medication. No response is either vomiting or nausea is grade 1 and not controlled by rescue medication, or both vomiting and nausea are higher than grade 1.

Data from both groups was collected by using a specialized proforma. Data was analyzed using the SPSS version 23. Categorical variables are presented as frequencies and percentages while continuous data variables are expressed as mean and standard deviation. The Chi-square test and Fisher exact test are utilized to compare outcome variables among two groups.

Results

Study was conducted on 218 pediatric oncology patients who received moderate or high intensity chemotherapy with the mean age of 5.25± 2.96 years. The majority of the participants were male (58.7%). The most common diagnosis was Wilms tumor (37.6%), followed by acute lymphoblastic leukemia (21.1%) and Ewing sarcoma (9.6%). The other diagnoses included various sarcomas, lymphomas, germ cell tumors, neuroblastoma, Langerhans

Table I: Complete response to anti emetic (Vomiting).

	Group 1		Group 2		p-value
	Yes	No	Yes	No	
Day 1	86 (78.9%)	23 (21.1%)	74(67.9%)	35 (32.1%)	0.046*
Day 2	106 (97.2%)	3(2.7%)	85 (77.9%)	24 (22.0%)	0.001*
Day 3	103 (94.4%)	6 (5.5%)	105 (96.3%)	4 (3.66%)	0.374
Day 4	109 (100%)	0	109 (100%)	0	
Day 5	109 (100%)	0	109 (100%)	0	

Table II: Complete response to antiemetics (Nausea).

	Group 1		Group 2		p-value
	Yes	No	Yes	No	
Day 1	93 (85.3%)	16 (14.6%)	91 (83.4%)	18 (16.5%)	0.42
Day 2	97 (88.9%)	12 (11%)	92 (84.4%)	17 (15.5%)	0.425
Day 3	106 (97.2%)	3 (2.7%)	105 (96.3%)	4 (3.6%)	0.5
Day 4	109 (100%)	0	109 (100%)	0	
Day 5	109 (100%)	0	109 (100%)	0	

Table III Vomiting Grade.

	Group 1	Group 2	p-value
Day 1	Grade 0- 56 (51.4%) Grade 1- 30 (27.5%) Grade 2- 15 (13.8%) Grade 3- 8 (7.3%) Grade 4- 0 (0%)	Grade 0- 49 (45.0%) Grade 1- 25 (22.9%) Grade 2- 18 (16.5%) Grade 3- 14 (12.8%) Grade 4 – 3 (2.8%)	0.235
Day 2	Grade 0- 64 (58.7%) Grade 1-42 (38.5%) Grade 2- 0 (0%) Grade 3- 3 (2.8%)	Grade 0 – 73 (67%) Grade 1 – 12 (11%) Grade 2 – 21 (19.3%) Grade 3 – 3 (2.8%)	0.001*
Day 3	Grade 0- 85 (78%) Grade 1- 18 (16.5%) Grade 2- 6 (5.5%)	Grade 0- 94 (86.2%) Grade 1- 11 (10.1%) Grade 2- 4 (3.7%)	0.271
Day 4	Grade 0- 109 (!00%) Grade 1- 0 (0%)	Grade 0 – 106 (97.25%) Grade 1 – 3 (2.8%)	0.123
Day 5	Grade 0- 103 (94.5%) Grade 1- 6 (5.5%)	Grade 0- 109 (100%)	0.015*

Table IV: Nausea Grade.

Day 1	Grade 0- 64 (58.7%) Grade 1- 29 (26.6%) Grade 2- 9 (8.3%) Grade 3- 7 (6.4%)	Grade 0- 48 (44%) Grade 1- 43 (39.4%) Grade 2- 18 (16.5%) Grade 3- 0 (0%)	0.001*
Day 2	Grade 0- 65 (59.6%) Grade 1- 32 (29.4%) Grade 2- 12 (11%) Grade 3- 0 (0%)	Grade 0 – 65 (59.6%) Grade 1- 27 (24.8%) Grade 2- 13 (11.9%) Grade 3- 4 (1.8%)	0.249
Day 3	Grade 0 - 88 (80.7%) Grade 1 - 18 (16.5%) Grade 2 – 3 (2.8%)	Grade 0- 81 (74.3%) Grade 1- 24 (22%) Grade 2- 4 (3.7%)	0.527
Day 4	Grade 0- 93 (85.3%) Grade 1- 16 (14.7%)	Grade 0 – 96 (88.1%) Grade 1 -13 (11.9%)	0.345
Day 5	Grade 0 – 104 (95.4%) Grade 1- 5 (4.6%)	Grade 0 – 102 (93.6%) Grade 1- 7 (6.4%)	0.384

cell histiocytosis, and acute myeloid leukemia with Down syndrome. Complete response to antiemetics was significantly more in Group 1 as compared to group 2, on day 1 and 2 with p-value of 0.004 and 0.001 respectively. The grade of vomiting was significantly less (P-value 0.001) on day 2 in Group 1 study participants.

Discussion

CINV is clinically important side effect in Pediatric population undergoing chemotherapy, therefore prophylaxis is recommended in guidelines. Several areas in the central nervous system, peripheral nervous system, and gastrointestinal system are involved in the pathophysiology of CINV. The chemoreceptor trigger

zone constitutes of three areas in the brain stem, the Central Pattern Generator (vomiting center), Nucleus Tractus Solitarius, and Area Postrema. It lies outside the blood-brain barrier and is therefore vulnerable to emetic stimuli carried either in blood or CSF. An emetic response can be triggered by a peripheral pathway or a central pathway. The peripheral pathway involves 5HT-3 receptors in the intestinal tract and is associated with acute emesis. Meanwhile, the central pathway involves NK-1 and substance P and is mainly associated with delayed emesis. The objective of antiemetic therapy is the complete prevention of CINV, and this should be achievable in the majority of patients receiving chemotherapy even with highly emetogenic agents.

First-generation 5-HT3 receptor antagonists can prevent acute CINV in 50% to 70% of the cases, whereas their action as single agent in preventing delayed CINV is not widely established. A significant number of patients who receive these agents continue to experience nausea and vomiting after receiving moderately or highly emetogenic chemotherapy. A randomized control trial on pediatric oncology patients showed overall comparable efficacy and safety of Long acting 2nd generation 5-HT3 antagonist palonosetron and ondansetron, however palonosetron was more effective in prevention of delayed CINV and was more cost effective.[14,15]

Over the 5-day period, complete response to the administered antiemetic drug was observed after administration of antiemetics with chemotherapy in both groups. This shows that a single dose of Palonosetron administrated daily is equally effective in controlling and preventing CINV in the long run as 3 doses of Ondansetron administered 8-hourly. However, day-by-day analysis of CINV after administration of emetic drug shows a consistently higher number of patients in group 1 reporting absence of nausea and vomiting than group 2 each day. Hence speaking to the relative efficacy of Palonosetron to Ondansetron in CINV prevention, with a higher rate of absence of nausea and vomiting in group 1 compared to group 2.

In terms of cost-effectiveness of either drug, it is important to note that cost of the drug alone does not determine cost-effectiveness. While Palonosetron costs PKR 542 per vial compared to PKR 100 for Ondansetron, the overall cost to the patient of anti-emetic treatment is determined by cost and required dosage in congruency. The required dosage of the anti-emetic drug is calculated based on patient's age, weight, overall health profile, and the type of chemotherapy regime they will be undergoing. Previous studies examining this question with patients undergoing moderate to high and highly emetogenic chemotherapy agreed that despite the obvious cost difference, all things considered Palonosetron proved to be comparatively more cost-effective than Ondansetron. A study conducted in 2009 quoted 50% cost saved per cycle with Palonosetron.[16] While the percentage of cost-saved is subject to the cost of either drug in the country, evidence suggests that Palonosetron is a more cost-effective option for preventing and controlling CINV.

In addition to CINV, delayed CINV is also a source of constant discomfort for patients receiving chemotherapy. Consequently, the required frequency of administration of anti-emetic drug to generate a complete anti-emetic response both during and after a chemotherapy session is an important factor contributing to adherence to the treatment plan. Results of the current study show that a single dose of Palonosetron administered before chemotherapy controls and prevents CINV longer than a single dose of Ondansetron. From a healthcare giver's perspective, administration of a single-dose drug is resource-efficient and allows for better management in busy Oncology centers. From a patient's perspective, increased convenience owning to single-dose regime eases compliance to the treatment plan. Similarly, mode of administration – oral vs intravenous – may also impact compliance to treatment. Previous studies on the safety of oral and intravenous Palonosetron show that the drug is safe and well received in both forms.[17] Future studies into the efficacy of oral Palonosetron vs. intravenous Palonosetron and the impact of mode of administration on the willingness to comply to treatment can help healthcare givers further improve patient experience.

In summary, the study's results, when compared with previous literature, reinforce the potential of Palonosetron as a superior choice for preventing both acute and delayed CINV in pediatric patients undergoing chemotherapy. These findings contribute to the growing body of evidence supporting the effectiveness of second-generation 5-HT3 receptor antagonists, guiding future research and clinical practice in the realm of pediatric oncology.

Conclusion

Pediatric oncology patient receiving moderately or highly emetogenic chemotherapy showed effective response to palonosetron as compared to ondansetron in prevention and control of early and delayed chemotherapy induced nausea and vomiting.

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References

1. Carnio S, Galetta D, Scotti V, Cortinovis DL, Antonuzzo A, Pisconti S, Rossi A, et al. Chemotherapy-induced nausea and vomiting (CINV) in patients with advanced lung cancer during the first-line treatment: assessment by physicians, nurses, and patients from an Italian multicenter survey. Support Care Cancer. 2018 Jun;26(6):1841-1849. https://doi.org/10.1007/s00520-017-4004-1
2. Aapro M, Ruffo P, Panteri R, Costa S, Piovesana V. Oncologist perspectives on chemotherapy-induced nausea and vomiting (CINV) management and outcomes: A quantitative market research-based survey. Cancer Rep (Hoboken). 2018 Dec;1(4):e1127. https://doi.org/10.1002/cnr2.1127
3. Mellin C, Lexa M, Leak Bryant A, Mason S, Mayer DK. Antiemetic Guidelines: Using Education to Improve Adherence and Reduce Incidence of CINV in Patients Receiving Highly Emetogenic Chemotherapy. Clin J Oncol Nurs. 2018 ;22(3):297-303. https://doi.org/10.1188/18.CJON.297-303
4. Roeland EJ, Ruddy KJ, LeBlanc TW, Nipp RD, Binder G, Sebastiani S, Potluri R, Schmerold L, Papademetriou E, Schwartzberg L, Navari RM. What the HEC? Clinician Adherence to Evidence-Based Antiemetic Prophylaxis for Highly Emetogenic Chemotherapy. J Natl Compr Canc Netw. 2020 Jun;18(6):676-681. https://doi.org/10.6004/jnccn.2019.7526
5. Ruggiero A, Rizzo D, Catalano M, Coccia P, Triarico S, Attinà G. Acute chemotherapy-induced nausea and vomiting in children with cancer: Still waiting for a common consensus on treatment. J Int Med Res. 2018;46(6):2149-2156. https://doi.org/10.1177/0300060518765324
6. Aapro M, Scotté F, Escobar Y, Celio L,Berman R, Franceschetti A, Bell D, et al. Practice Patterns for Prevention of Chemotherapy-Induced Nausea and Vomiting and Antiemetic Guideline Adherence Based on Real-World Prescribing Data, The Oncologist. 2021 Jun; 26(6);1073-e1082. https://doi.org/10.1002/onco.13716
7. Paw Cho Sing E, Robinson PD, Flank J, et al. Classification of the acute emetogenicity of chemotherapy in pediatric patients: A clinical practice guideline [published correction appears in Pediatr Blood Cancer. 2021 May;68(5):e28990]. Pediatr Blood Cancer. 2019;66(5):e27646. doi:10.1002/pbc.27646 https://doi.org/10.1002/pbc.27646
8. Karthaus M, Schiel X, Ruhlmann CH, Celio L. Neurokinin-1 receptor antagonists: review of their role for the prevention of chemotherapy-induced nausea and vomiting in adults. Expert Rev Clin Pharmacol. 2019;12(7):661-680. https://doi.org/10.1080/17512433.2019.1621162
9. Bansal R, Agrawal S, Kohli S, Das K. Clinician preference and comparison of the efficacy of ondansetron, granisetron, and palonosetron in preventing chemotherapy-induced nausea and vomiting among children receiving moderate or highly emetogenic chemotherapy. Pediatr Hematol Oncol J. 2023;8(3):200-204. https://doi.org/10.1016/j.phoj.2023.08.006
10. Cabanillas Stanchi KM, Ebinger M, Hartmann U, et al. Efficacy, Safety And Feasibility Of Antiemetic Prophylaxis With Fosaprepitant, Granisetron And Dexamethasone In Pediatric Patients With Hemato-Oncological Malignancies. Drug Des Devel Ther. 2019;13:3439-3451. Published 2019 https://doi.org/10.2147/DDDT.S214264
11. Hsu, YC., Chen, CY., Tam, KW. et al. Effectiveness of palonosetron versus granisetron in preventing chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis. Eur J Clin Pharmacol .2021;77, 1597–1609. https://doi.org/10.1007/s00228-021-03157-2.
12. Jain S, Kapoor G, Koneru S, Vishwakarma G. A randomized, open-label non-inferiority study to compare palonosetron and ondansetron for prevention of acute chemotherapy-induced vomiting in children with cancer receiving moderate or high emetogenic chemotherapy. Support Care Cancer.2018;26(9):3091-7. https://doi.org/10.1007/s00520-018-4158-5
13. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [Internet]. Bethesda, MD: National Cancer Institute; 2017 [cited 2023 Oct 30]. Available from: Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov).
14. Kovács G, Wachtel AE, Basharova EV, Spinelli T, Nicolas P, Kabickova E. Palonosetron versus ondansetron for prevention of chemotherapy-induced nausea and vomiting in paediatric patients with cancer receiving moderately or highly emetogenic chemotherapy: a randomised, phase 3, double-blind, double-dummy, non-inferiority study. Lancet Oncol.2016;17(4):483-492. https://doi.org/10.1016/S1470-2045(15)00584-7
15. Chaudhary NK, John RR, Boddu D, Mahasampath G, Nesadeepam N, Mathew LG. Palonosetron is a Better Choice Compared With Ondansetron for the Prevention of Chemotherapy-induced Nausea and Vomiting (CINV) in a Resource-limited Pediatric Oncology Center: Results From a Randomized Control Trial. J Pediatr Hematol Oncol. 2019 May;41(4):294-297. https://doi.org/10.1097/MPH.0000000000001357
16. Bernardo G, Palumbo R, Frascaroli M, Bernardo A, Losurdo A, Poggi G, Teragni C, Et al. Palonosetron compared to ondansetron in the prevention of chemotherapy-induced nausea and vomiting: Activity, safety, and cost-effectiveness evaluation. J Clin Oncol. 2009;27(15 Suppl):e20573. https://doi.org/10.1200/jco.2009.27.15_suppl.e20573
17. Chen R, Wang H, Zhong W, Chessari S, Lanzarotti C, Bernareggi A, Hu P. Pharmacokinetics and safety evaluation of oral Palonosetron in Chinese healthy volunteers: A phase 1, open-label, randomized, cross-over study. Eur J Pharm Sci.2021;160:105752. https://doi.org/10.1016/j.ejps.2021.105752