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RESEARCH ARTICLE

Intravenous Fosaprepitant Versus Oral Aprepitant for Children Receiving Highly Emetogenic Chemotherapy: An Investigator-Initiated Randomized, Open-Label, Non-Inferiority Trial

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ABSTRACT

Background: Fosaprepitant is non-inferior to aprepitant in adults receiving highly emetogenic chemotherapy (HEC). We evaluated whether fosaprepitant is non-inferior to aprepitant in children receiving HEC.

Methods: In this open-label, non-inferiority trial, children aged 5–18 years, receiving their first cycle of HEC, were randomized 1:1 to the fosaprepitant or aprepitant group. The fosaprepitant group received a single intravenous dose of 4 mg/kg (max 150 mg). The aprepitant group received oral aprepitant capsules (weight 15 to <30 kg: 80 mg Days 1–3; weight ≥30 kg, or age ≥12 years: 125 mg Day 1, 80 mg Days 2 and 3). Both groups received ondansetron and dexamethasone. The primary outcome was the complete response (CR) rate of vomiting during the acute phase (AP) with a non-inferiority margin of 15%. Secondary outcomes included CR rates in the delayed (DP) and overall phases (OP), grade of vomiting, incidence and severity of nausea, and adverse effects.

Results: A total of 279 children were included in the modified intention-to-treat analysis (fosaprepitant group: 140; aprepitant group: 139). In AP, the difference of CR rate between fosaprepitant [76 (54.3%)] and aprepitant groups [84 (60.4%)] was −6.1% [90% CI: −15.7% to +3.6%], with the lower limit exceeding −15%, failing to establish non-inferiority. The CR rate with fosaprepitant versus aprepitant was 62.1% ($n = 87$) versus 65.5% ($n = 91$) in DP (difference: −3.4%; 90% CI: −12.7% to 6.1%) and 42.9% ($n = 60$) versus 49.6% ($n = 69$) in the OP (difference: −6.7%; 90% CI: −16.5% to 3.1%). Grade of vomiting, incidence and severity of nausea, and adverse effects were similar between the two groups.

Abbreviations: AP, acute phase; CI, confidence interval; CINV, chemotherapy-induced nausea and vomiting; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DP, delayed phase; ECOG PS, Eastern Cooperative Oncology Group performance score; ESAS, Edmonton Symptom Assessment Scale; HEC, highly emetogenic chemotherapy; ITT, intention to treat; MEC, moderately emetogenic chemotherapy; NK1RA, neurokinin-1 receptor antagonist; OP, overall phase.

Azgar Abdul Rasheed, Shuvadeep Ganguly, and Manraj Singh Sra contributed equally to this work.

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Conclusions: Non-inferiority of fosaprepitant compared to aprepitant was not demonstrated in children undergoing their first cycle of HEC.
Trial Registration: Clinical Trials Registry, India (CTRI/2019/05/019082).

1 | Introduction

Chemotherapy-induced nausea and vomiting (CINV) are among the most common and distressing side effects of chemotherapy. In recent years, there have been significant improvements in preventing CINV in both children and adults with the advent of the neurokinin-1 receptor antagonists (NK1RAs) and olanzapine [1]. Antiemetic regimens based on the oral NK1RA aprepitant have been shown to be safe and effective in children receiving highly emetogenic chemotherapy (HEC) and are currently the standard of care [2, 3]. Intravenous fosaprepitant has also been recommended for the pediatric population since the 2020 update of the American Society of Clinical Oncology antiemetic guidelines [4]. The latest clinical practice guidelines by the Pediatric Oncology Group of Ontario also recommend the addition of aprepitant or fosaprepitant to ondansetron and dexamethasone to control acute CINV [5]. However, the guidelines highlight an evidence gap in the optimal dose and dosing frequency of fosaprepitant.

Previously, improvement in complete response (CR) rates in vomiting has been observed in acute and delayed phases of chemotherapy with the addition of fosaprepitant among children receiving moderate or HEC [5–7]. Cross-trial comparisons suggest higher CR rates may be achieved with fosaprepitant compared to aprepitant [2, 3]. The non-inferiority of single-day intravenous fosaprepitant compared to 3-day oral aprepitant has been established in adult patients, but direct comparison among children is lacking [8]. A retrospective study reported comparable outcomes and safety profiles for fosaprepitant and aprepitant in children; however, prospective validation is required [9]. Single-dose intravenous fosaprepitant would offer a convenient alternative to the 3-day oral aprepitant regimen and aid in improving adherence. In countries like India, where the oral aprepitant suspension is unavailable, intravenous fosaprepitant would be a feasible option for young children who struggle to swallow capsules. Additionally, intravenous fosaprepitant may be associated with less CYP3A4 inhibition than oral aprepitant, potentially resulting in fewer drug interactions [10, 11].

In this trial, we aimed to investigate the non-inferiority of fosaprepitant in children receiving HEC, as compared to aprepitant, in combination with ondansetron and dexamethasone, for the prevention of CINV in chemotherapy-naïve pediatric patients (aged 5 to ≤18 years) receiving their first cycle of HEC.

2 | Methods

2.1 | Study Design

This was an investigator-initiated, randomized, open-label, non-inferiority trial, conducted at a tertiary-care hospital in New Delhi, India, from August 2019 to June 2022. This study was approved by the institutional ethics committee of the All India Institute of Medical Sciences, New Delhi (IECGPG-355/29.05.2019). Written informed consent was obtained from the parents or guardians of all patients, and assent was obtained from all children above 6 years of age. The trial was conducted per the Good Clinical Practice guidelines [12]. The trial was registered prospectively with the Clinical Trials Registry, India (CTRI/2019/05/019082). This study followed the CONSORT reporting guideline [13].

2.2 | Eligibility Criteria

Inpatient or ambulatory chemotherapy-naïve children aged 5–18 years, weighing at least 15 kg, with a pathologically confirmed diagnosis of a malignancy, an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0–2, and scheduled to receive their first cycle of HEC, were eligible to be enrolled in the study. A minimum weight of 15 kg was required because aprepitant oral suspension was unavailable, and a capsule-based dosing strategy previously shown to be safe in children weighing ≥15 kg was used [2]. Those with an ECOG PS of 3 were also eligible if the poor PS was attributable to local effects of the disease, such as in osteosarcoma or Ewing sarcoma involving the lower limbs. Only children and guardians who could communicate in either English or Hindi were included. Children experiencing vomiting, retching, or more than mild nausea in the 24 h preceding scheduled chemotherapy were excluded (exclusion criteria detailed in Supporting Material).

2.3 | Randomization and Masking

Eligible patients were allocated 1:1 to either the fosaprepitant or aprepitant groups by permuted block randomization (with varying block sizes of six and eight). As multi-day chemotherapy regimens are a known predictor of poor emesis control, randomization was stratified by single- and multi-day chemotherapy regimens [14]. To ensure allocation concealment, randomization was done by trial personnel not involved in any other aspect of the trial. A study nurse explained the drug administration schedule and distributed the study drugs to the participating children/their parents. The study nurses regularly followed up with the participants to ensure and document adherence to the study drugs. As this was an open-label trial, the study team members responsible for randomization and drug administration, as well as the participating children and their parents, were aware of the allocated treatment groups. However, to minimize bias, the outcome data collection regarding nausea, vomiting, and adverse events was done by a third investigator, who was unaware of the treatment allocations.

2.4 | Study Intervention

Patients in the aprepitant group received oral aprepitant capsules once daily for 3 consecutive days, starting with the first dose an

hour before the initiation of the chemotherapy cycle (Table S1). Children weighing 15 to less than 30 kg received 80 mg on all 3 days, while those weighing ≥30 kg or aged ≥12 years received 125 mg on Day 1 and 80 mg on Days 2 and 3. The 80 mg dosing regimen for children weighing 15 to less than 30 kg was selected due to the unavailability of the oral suspension formulation of aprepitant in India, precluding precise dosing for younger patients. This regimen was adopted from a previous trial that demonstrated a wide safety margin and no serious adverse events due to aprepitant [2]. Patients in the fosaprepitant group received a single dose of intravenous fosaprepitant, infused over 30 min (60 min for children below 12 years) and completed just before the initiation of the chemotherapy cycle. Fosaprepitant was administered through central or peripheral venous lines; however, the route was not recorded. A single intravenous dose of fosaprepitant was chosen for both single- and multi-day chemotherapy based on previous safety and efficacy data for children [6]. Children below 12 years of age received a fosaprepitant dose of 4 mg/kg, up to a maximum of 150 mg, while those aged ≥12 years were given a flat dose of 150 mg. In both groups, patients received dexamethasone (3 mg/m^2 per dose every 6 h) and ondansetron (0.15 mg/kg per dose every 8 h) on chemotherapy infusion days and for 3 days thereafter as per institutional practice [5]. Doses for both were rounded to the nearest 2 mg based on available tablet strength. Both ondansetron and dexamethasone were given intravenously during the day of chemotherapy administrations and orally for evening or night doses during the acute phase and during the remaining 3 days post-chemotherapy. Rescue antiemetics were prescribed for patients with more than two episodes of vomiting in a day and/or severe nausea by a trained healthcare provider. Metoclopramide, with or without promethazine, was used as the first-line rescue antiemetic as per institutional practice. Olanzapine was administered to patients who did not respond to first-line rescue antiemetics. Glenmark Pharmaceuticals Limited provided the study drug fosaprepitant for this study. The company did not participate in the design, conduct, or reporting of this study.

2.5 | Data Collection Procedure

Demographic data and clinical parameters were recorded for all patients. Intravenous fosaprepitant and the first oral dose of aprepitant were administered under supervision. Parents or guardians were responsible for subsequent oral drug administration, with adherence monitored by investigators. Daily follow-ups for patients in both arms, conducted in person or by phone, by the study investigators who collected data on adherence with antiemetic medication (aprepitant, ondansetron, dexamethasone), vomiting, nausea, and other outcomes from the start of the chemotherapy cycle until 120 h after its completion.

In addition, a diary was provided to each patient or guardian to record vomiting, nausea, and treatment-related toxicities (Supporting Material). The recording was done by the parents or guardians themselves, as taught by the study nurse. Diaries were returned after the study period and cross-checked against investigator-collected data. In cases of discrepancies, the higher grade for both nausea or vomiting outcomes or toxicities was considered.

2.6 | Definitions

Nausea was defined as a subjective sensation of unease or discomfort in the stomach with an urge to vomit. Vomiting was defined as the forceful expulsion of one's stomach contents, with distinct vomiting episodes delineated by the absence of emesis or retching for 1 min or more [15]. Retching was defined as involuntary, spasmodic contractions of the abdominal and thoracic musculature [16]. Chemotherapy drugs administered over 1, 2, 3, or 4 consecutive days constituted a chemotherapy cycle. The emetogenicity of the chemotherapy regimens was classified as per the clinical practice guidelines of February 2019 [17].

For the evaluation of CINV, the acute phase was defined as the period starting from the initiation of chemotherapy and extending till 24 h after the completion of the last chemotherapy infusion in that cycle, including the duration of chemotherapy infusion. The delayed phase is defined as 24–120 h after the completion of the chemotherapy cycle. The overall phase thus covered the entire period from the initiation of chemotherapy to 120 h after the completion of chemotherapy.

CR for vomiting was defined as the absence of vomiting and/or retching, and no requirement for rescue antiemetics [15]. Vomiting episodes were graded by investigators as follows: Grade 0: no vomiting; Grade 1 (mild): one to two episodes in 24 h; Grade 2 (moderate): three to five episodes in 24 h; and Grade 3 (severe): six or more episodes in 24 h or requiring hospitalization. The severity of nausea was measured using the Edmonton Symptom Assessment Scale (ESAS), which employs a visual analog scale graded from 0 to 10. ESAS was recorded by parents/guardians as taught by the study nurse, which was followed up and reinforced daily. ESAS scores of 1–3, 4–7, and 8–10 were taken to represent mild, moderate, and severe nausea, respectively [18]. CR for nausea was defined as an ESAS nausea score of 0, indicating the absence of nausea. All toxicities were recorded from the time of receipt of the intervention to 120 h after the completion of the chemotherapy cycle. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

2.7 | Objectives

The primary objective of the study was the comparison of CR rates for vomiting between the two groups in the acute phase. The secondary objectives were the comparison of CR rates for vomiting between the two groups in the delayed and overall phases, nausea severity in either group in all three phases, the need for rescue antiemetics in each group, and the incidence and severity of treatment-related toxicities in either group.

2.8 | Statistical Analyses

Sample size estimation was based on a prior trial comparing ondansetron, dexamethasone, and either oral aprepitant or placebo in pediatric patients receiving HEC [2]. In that study, acute-phase CR for vomiting was 48% with aprepitant versus 12% with placebo ($p < 0.001$), suggesting an improvement of 36% by the addition of a third antiemetic drug. Based on this difference, the acceptable non-inferiority margin was chosen to

be an absolute difference of −15% with fosaprepitant compared to aprepitant [19]. Assuming a one-sided α of 5%, power of 80%, and an expected CR rate of 48% in each group, we estimated a required sample size of 276 patients, with 138 in each group. Accounting for an expected maximum dropout rate of 5%, a total of 290 patients were planned to be enrolled.

Efficacy was analyzed in the modified intention-to-treat (mITT) population, including all randomized patients who received chemotherapy, at least one antiemetic dose, and had ≥1-day post-treatment outcome recorded. Toxicity was assessed by treatment received, regardless of randomization.

An exploratory subgroup analysis was done to look for differences in CR rates with respect to the following factors known to affect CINV incidence: single- versus multi-day chemotherapy regimens, cisplatin-containing versus non-cisplatin regimens, male versus female, and less than 12 versus ≥12 years of age. An exploratory per-protocol efficacy analysis was performed, which included all patients who correctly received the antiemetic regimen they were randomized to, provided they were eligible to be included in the mITT population.

Descriptive statistics were utilized to summarize the demographic data and clinical characteristics of the study population. Continuous variables in the baseline data have been expressed as mean (±standard deviation [SD]), or median (range), and intergroup comparisons have been performed using the unpaired *t*-test or Wilcoxon test. Categorical variables were compared between the two groups using the chi-square test or Fisher's exact test. The two-sided 90% confidence interval (CI) for differences in CR rates between the groups was calculated using the Miettinen–Nurminen method [20]. Non-inferiority was assessed by comparing the lower bound of the two-sided 90% CI, which is equivalent to the lower bound of a one-sided 95% CI, against the prespecified non-inferiority margin. All *p*-values are two-sided with a significance threshold of less than 0.05. All analyses were performed with Stata software, version 15.1 (STATA, College Station, TX).

3 | Results

A total of 279 patients were included in the mITT population, with 139 in the aprepitant group and 140 in the fosaprepitant group (Figure 1). The baseline characteristics of the patients in both groups showed no significant differences (Table 1; Tables S2 and S3). All patients were able to swallow the aprepitant capsules whole. Six patients in the fosaprepitant group (4.3%) and seven patients in the aprepitant group (5%) were not completely compliant with their prescribed antiemetic schedule.

3.1 | Primary Outcome

The CR rates for vomiting in the acute phase was 54.3% (n = 76) in the fosaprepitant group and 60.4% (n = 84) in the aprepitant group, with the difference in CR rate for vomiting between the groups being −6.1% (90% CI: −15.7% to +3.6%) (Table 2). As the lower limit of the one-sided 95% CI exceeded the prespecified non-inferiority margin of −15%, the non-inferiority of fosaprepitant with respect to aprepitant for CR rates for vomiting in the acute phase could not be established (Figure 2A).

3.2 | Secondary Outcomes

The CR rates for vomiting during the delayed phase were 62.1% (n = 87) in the fosaprepitant group and 65.5% (n = 91) in the aprepitant group. During the overall phase, CR rates were 42.9% (n = 60) and 49.6% (n = 69), respectively. The between-group difference in CR rates for vomiting was −3.4% (90% CI: −12.7% to 6.1%) in the delayed phase, and −6.7% (90% CI: −16.5% to 3.1%) in the overall phase (Table 2).

In the acute phase, CR rates for nausea were 38.6% (n = 54) in the fosaprepitant group and 38.8% (n = 54) in the aprepitant group. In the delayed phase, CR rates were 56.4% (n = 74) and 54.0% (n = 75), respectively. During the overall phase, CR rates were 30.7% (n = 43) and 30.9% (n = 43) (Table 2).

Two patients (1.4%) in the aprepitant group had CTCAE Grade III vomiting in the acute phase, compared with none in the fosaprepitant group. One patient (0.7%) in the fosaprepitant group had Grade III vomiting in the delayed phase, with none in the aprepitant group (Table S4). Incidence and severity of nausea did not differ between groups (Table S5). During the acute phase, rescue medication use was similar between the fosaprepitant and aprepitant groups [24.3% (n = 34) vs. 18.0% (n = 25); p = 0.43]. Rescue medication use during the delayed and overall phases was also comparable between groups and is detailed in Table S6.

Subgroup analysis showed no significant difference in CR rates for vomiting across acute, delayed, or overall phases by sex, age group, chemotherapy duration, or cisplatin use (Figure 2). Per-protocol analyses of primary and secondary outcomes are provided in Tables S7 and S8.

3.3 | Adverse Events

There was no statistically significant difference in the spectrum or severity of toxicities between the two groups (Table 3). One patient in the fosaprepitant group experienced a Grade 1 infusion reaction, which was managed with temporary cessation of fosaprepitant and administration of antihistamines. The Grade III adverse event in the fosaprepitant group included constipation (n = 2, 1.4%), decreased appetite (n = 2,1.4%), fatigue (n = 1, 0.7%), and diarrhea (n = 1, 0.7%). In the aprepitant group, Grade III adverse events included diarrhea (n = 4, 2.9%), decreased appetite (n = 1, 0.7%), and fever (n = 1, 0.7%). There were no cases of ifosfamide-encephalopathy in patients receiving ifosfamide. One death occurred in the aprepitant group after the overall phase, attributed to febrile neutropenia and acute gastroenteritis, deemed unrelated to the antiemetic regimens.

4 | Discussion

In this randomized, open-label trial, the non-inferiority of single-day intravenous fosaprepitant to 3-day oral aprepitant

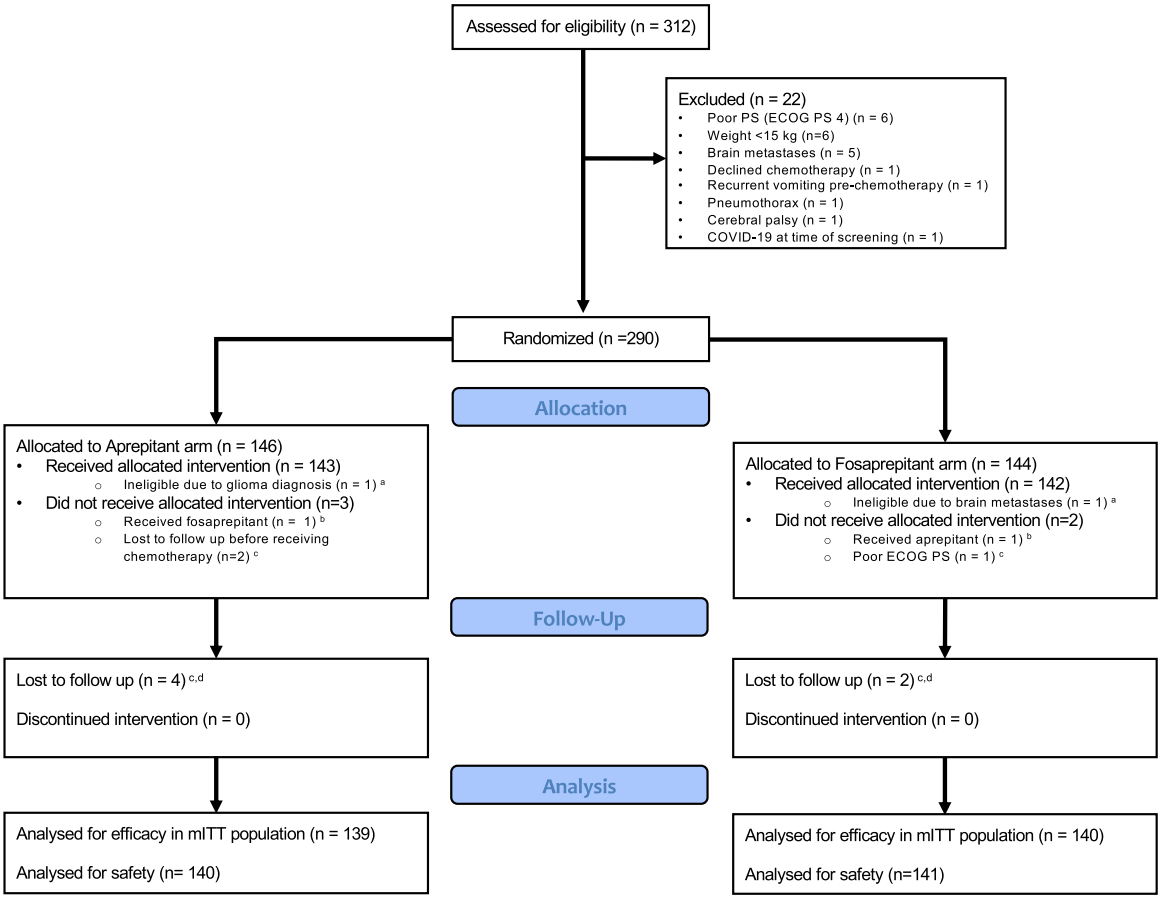

FIGURE 1 | CONSORT diagram for the study. ECOG PS, Eastern Cooperative Oncology Group performance score; mITT, modified intention-to-treat; PP, per protocol. [a]Included in safety analysis and excluded in efficacy analysis. [b]Included in the randomized group for mITT safety and efficacy analysis and excluded from per-protocol efficacy analysis. [c]Excluded in safety and efficacy analysis. [d]Lost to follow-up was defined as patients who received the study drug but did not respond to phone calls for follow-up assessments during the study period. The occurrence of any Grade ≥3 toxicity or death for these patients was confirmed via hospital records and post-study follow-up as available.

for the prevention of CINV among pediatric patients was not demonstrated in terms of CR rates for vomiting during the acute phase. CR rates for vomiting during the delayed and overall phases, as well as CR rates for nausea across all phases, did not differ significantly between groups. The CR rates for vomiting in the fosaprepitant group in this study were lower than those reported in previous studies. In a previous trial, the CR rates were 86% versus 60% (acute), 79% versus 51% (delayed), and 70% versus 41% (overall) for fosaprepitant versus placebo, both combined with ondansetron and dexamethasone, in children receiving moderately emetogenic chemotherapy (MEC) or HEC (all $p < 0.001$) [6]. The inclusion of moderately emetogenic chemotherapy may explain the higher CR rates. In contrast, CR rates in the aprepitant group were consistent with previous reports [2, 3]. In a similar study by Yu et al. among children receiving MEC and HEC, use of single-dose fosaprepitant was associated with superior CR rate in the acute phase compared to oral aprepitant (95% vs. 79%) [21]. However, the study was conducted among children receiving both MEC and HEC with a superiority design, with a limited number of patients. The oral suspension formulation of aprepitant was used in that study, which might have accounted for the observed superiority due to differential bioavailability compared to the capsule formulation used in the current study.

A non-inferiority, randomized, double-blind trial in adult patients showed a difference in CR rate between fosaprepitant and the aprepitant group to be 0.4% (95% CI: 4.1% to 3.3%) in the overall phase and 0.1% (95% CI: 3.5% to 3.7%) in the delayed phase. The study was conducted with a non-inferiority margin of −7%, which was met in the outcome [8]. A key difference between the trials is that the present study included patients receiving both single-day and multi-day chemotherapy regimens, whereas the adult study included only patients on single-day regimens of high-dose cisplatin. Interestingly, subgroup analysis in this study indicates that fosaprepitant is non-inferior to aprepitant for patients receiving single-day chemotherapy regimens, but not for those on multi-day regimens. This suggests that patients undergoing multi-day chemotherapy regimens may require additional doses of intravenous fosaprepitant to achieve adequate control of emesis, as has been observed in recent studies among adults, whereas for single-day chemotherapy regimens, intravenous fosaprepitant may be non-inferior to aprepitant in both adults and children [22].

The most commonly reported adverse effects of all grades were decreased appetite, constipation, and fatigue. Diarrhea was the most common adverse effect of Grade III or higher, occurring in four (2.9%) patients in the aprepitant group and one (0.7%) patient in the fosaprepitant group. The rates of adverse events

TABLE 1 | Baseline characteristics of randomized patients.

Parameter	Allocated to receive aprepitant ($n = 146$)[a]	Allocated to receive fosaprepitant ($n = 144$)[b]	*p*-value
Age, median [range] in years	12.5 [5–18]	13.5 [5–18]	0.07
≤12 years	73 (50)	56 (38.89)	0.07
>12 years	73 (50)	88 (61.11)	
Gender			
Female	56 (38.4)	46 (31.9)	0.31
Male	90 (61.6)	98 (68.1)	
Weight, mean [SD] in kg	37.21 [17]	37.47 [15.3]	0.89
≤30 kg	61 [41.78]	57 [39.58]	0.71
>30 kg	85 [58.22]	87 [60.42]	
Diagnosis			
Osteosarcoma	51 (34.9)	40 (27.7)	0.66
Hodgkin lymphoma	33 (22.6)	35 (24.3)	
Primitive neuroectodermal tumor	33 (22.6)	37 (25.7)	
Rhabdomyosarcoma	8 (5.5)	12 (8.3)	
Others[c]	21 (14.4)	20 (13.9)	
ECOG performance status			
0	4 (2.7)	2 (1.4)	0.52
1	88 (60.3)	88 (61.1)	
2	33 (22.6)	26 (18.1)	
3	21 (14.4)	27 (18.8)	
4	0 (0.0)	1 (0.7)	
Chemotherapy regimen administered			
Cisplatin–Doxorubicin	51 (34.9)	40 (27.8)	0.64
Vincristine–Doxorubicin–Cyclophosphamide	33 (22.6)	38 (26.4)	
Doxorubicin–Bleomycin–Vinblastine–Dacarbazine	33 (22.6)	34 (23.6)	
Vincristine–Actinomycin-D–Cyclophosphamide	8 (5.5)	12 (8.3)	
Others[d]	21 (14.4)	20 (13.9)	
Duration of chemotherapy cycle			
Single-day	83 (56.8)	90 (62.5)	0.39
Multi-day	63 (43.2)	54 (37.5)	

Note: Data are No. (%) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

[a]Total 139 patients were included in the mITT efficacy analysis, and 140 patients in the safety analysis (details in Figure 1).

[b]Total 140 patients included in mITT efficacy analysis and 141 patients in safety analysis (details in Figure 1).

[c]Other diagnoses are listed in Table S2.

[d]Other chemotherapy regimens are listed in Table S3.

in this study were similar to rates reported in a previous meta-analysis [5]. No significant differences in adverse events were observed between the two groups. Infusion site reactions due to fosaprepitant were not specifically monitored and hence may have been missed.

The key strength of this study is that it is the first adequately powered, randomized trial comparing the efficacy and safety of single-day intravenous fosaprepitant versus 3-day oral aprepitant for the prevention of CINV, with the study population being exclusively those receiving their first cycle of HEC. The antiemetic regimens used in this study were standard of care, and single- and multi-day chemotherapy regimens were well represented.

Our study has a few limitations. This study was also not a blinded trial, which might have led to bias in reporting of subjective outcomes like nausea, but efforts were made to avoid investigator

TABLE 2 | Comparison of CR rates for chemotherapy-induced vomiting and nausea between groups.

Outcome	Time period	Fosaprepitant group ($n = 140$)	Aprepitant group ($n = 139$)	p-value	Difference in proportion (fosaprepitant group – aprepitant group)	90% CI of difference
Chemotherapy-induced vomiting	**Acute phase**					
	CR	76 (54.3)	84 (60.4)	0.30	−6.1	−15.7 to +3.6
	No CR	64 (45.7)	55 (39.6)			
	Delayed phase					
	CR	87 (62.1)	91 (65.5)	0.56	−3.4	−12.7 to +6.1
	No CR	53 (37.9)	48 (34.5)			
	Overall phase					
	CR	60 (42.9)	69 (49.6)	0.26	−6.7	−16.5 to +3.1
	No CR	80 (57.1)	70 (50.4)			
Chemotherapy-induced nausea	**Acute phase**					
	CR	54 (38.6)	54 (38.8)	0.96	−0.2	−9.8 to +9.3
	No CR	86 (61.4)	85 (61.2)			
	Delayed phase					
	CR	79 (56.4)	75 (54.0)	0.68	+2.4	−7.3 to +12.2
	No CR	61 (43.6)	64 (46.0)			
	Overall phase					
	CR	43 (30.7)	43 (30.9)	0.97	−0.2	−9.3 to +8.8
	No CR	97 (69.3)	96 (69.1)			

Note: All data are numbers (percentages) unless otherwise noted.
Abbreviations: CI, confidence interval; CR, complete response.

TABLE 3 | Comparison of all grades and Grade ≥3 toxicities between groups.

	All grades				Grade ≥3			
Adverse effect	Fosaprepitant group ($n = 141$)	Aprepitant group ($n = 140$)	Total ($n = 281$)	p-value	Fosaprepitant group ($n = 141$)	Aprepitant group ($n = 140$)	Total ($n = 281$)	p-value
General adverse effects								
Headache	32 (22.7)	26 (18.6)	58 (20.6)	0.39	0 (0)	0 (0)	0 (0)	—
Fatigue	30 (21.3)	31 (22.1)	61 (21.7)	0.86	1 (0.7)	0 (0)	1 (0.36)	>0.9
Abnormal movements	0 (0)	0 (0)	0 (0)	—	0 (0)	0 (0)	0 (0)	—
Decreased appetite	39 (27.7)	47 (33.6)	86 (30.6)	0.28	2 (1.4)	1 (0.7)	3 (1.07)	>0.9
Myalgia	12 (8.5)	12 (8.6)	24 (8.5)	0.99	0 (0)	0 (0)	0 (0)	—
Fever	2 (1.4)	7 (5.0)	9 (3.2)	0.09	0 (0)	1 (0.7)	1 (0.36)	0.50
Gastrointestinal adverse effects								
Abdominal pain	25 (17.7)	32 (22.9)	57 (20.3)	0.29	0 (0)	0 (0)	0 (0)	—
Constipation	33 (23.4)	32 (22.9)	65 (23.1)	0.91	2 (1.4)	0 (0)	2 (0.71)	0.50
Mucositis	10 (7.1)	10 (7.9)	20 (7.1)	0.81	0 (0)	0 (0)	0 (0)	—
Diarrhea	9 (6.4)	16 (11.4)	25 (8.9)	0.14	1 (0.7)	4 (2.9)	5 (1.78)	0.21

Note: All data are numbers (percentages) unless otherwise noted.

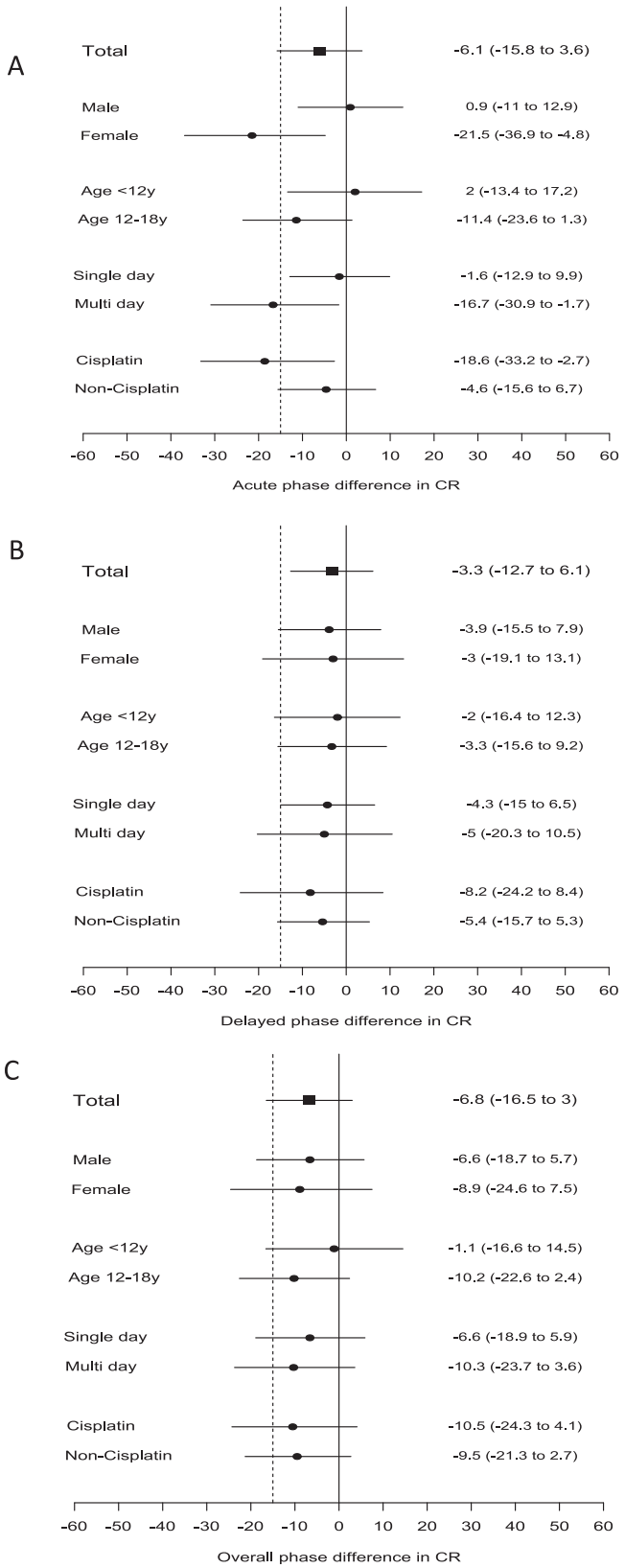

FIGURE 2 | Forest plot showing the difference in complete response rate (90% confidence interval [CI]) between groups in (A) acute phase, (B) delayed phase, and (C) overall study period stratified by subgroups of sex, age, chemotherapy administration duration, and cisplatin-containing regimens. The dashed line indicates the non-inferiority margin of −15%.

bias by ensuring that the investigators evaluating the antiemetic efficacy and toxicities were unaware of the treatment allocations. The ESAS scale, though not validated for nausea assessment in children, was used due to lack of validated tools for Indian children and also due to its prior use in studies at our institute [2, 15]. Nausea and its severity were also assessed by proxy, which might have affected its validity. The validation of the Pediatric Nausea Assessment Tool in the local Hindi language was done during the later course of the study, which will likely be a standard tool for nausea assessment in children in future studies [23].

The fosaprepitant dose used in children under 12 years (4 mg/kg) may have been insufficient, as pharmacokinetic studies suggest that higher doses may be required in this age group because of increased drug clearance related to ontogenetic changes in CYP3A4 metabolism [24]. In addition, the fosaprepitant dose used in children younger than 12 years was lower than the EMA-approved dose [25]. For multi-day chemotherapy regimens, alternate dosing strategies of fosaprepitant need to be explored, such as repeat dosing of fosaprepitant every 48 h or 3-day dosing for intravenous fosaprepitant. Aprepitant dosing in younger or lower weight children also differed from both EMA labeling and the 2017 update of the Pediatric Oncology Group of Ontario guidelines because the oral suspension formulation is unavailable in India [26]. These differences may have influenced efficacy comparisons, particularly in multi-day regimens. However, previous trials using similar dosing strategies have shown adequate control of CINV [2, 15, 27, 28].

In conclusion, the non-inferiority of single-day intravenous fosaprepitant versus 3-day oral aprepitant for the prevention of CINV among 5–18-year-old chemotherapy-naive patients receiving their first cycle of HEC could not be established. Future studies are needed to assess the efficacy of alternate dosing strategies of fosaprepitant for multi-day chemotherapy cycles.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of the study are available from the corresponding author upon reasonable request for any non-commercial use. The data will be readily available from the date of publication with no specified end date.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Documents: 3 (Trial Protocol: S1; CONSORT Checklist: S1; Supporting Information S1). TABLE S1 Antiemetic dosing regimen. TABLE S2 Cancer diagnosis of study participants. TABLE S3 Chemotherapy regimens administered to study participants. TABLE S4 Comparison of severity of vomiting between groups. TABLE S5 Comparison of the severity of nausea between groups. TABLE S6 Rescue medication use in both groups during acute, delayed, and overall periods. TABLE S7 Per-protocol comparison of CR rates for chemotherapy-induced vomiting between groups. TABLE S8 Per-protocol comparison of CR rates for chemotherapy-induced nausea between groups.