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Original Research Article

Comparative efficacy of diclofenac sodium gel and urea cream in preventing capecitabine-induced hand-foot syndrome: a randomized interventional study

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ABSTRACT

Background: The oral prodrug of 5-fluorouracil, capecitabine, is frequently used to treat breast and colorectal malignancies. The effectiveness of therapy is compromised by hand-foot syndrome (HFS), a typical dose-limiting hazard that frequently requires dose adjustments. Topical agents such as diclofenac sodium gel and urea cream have shown promise as prophylactic options for managing HFS. To compare the efficacy of diclofenac sodium gel and urea cream in preventing capecitabine-induced HFS.

Methods: This randomized, open-label, double-arm interventional study included 100 adult patients with breast or gastrointestinal malignancies receiving capecitabine chemotherapy. Arm A (diclofenac sodium gel) and Arm B (urea cream) were the two groups into which participants were randomly assigned. According to the Common Terminology Criteria for Adverse Events (CTCAE v5.0), the main goal was to prevent grade 2 or above HFS during a 12-week period. HFS severity, modifications in capecitabine dosage and therapy discontinuations were secondary outcomes. Both descriptive and inferential techniques were used in the statistical analysis.

Results: HFS developed in 48% of participants, with no significant difference between the diclofenac arm (26 participants) and the urea arm (22 participants) (p=0.42). Grade 1 HFS was most prevalent (41%), while grades 2 and 3 were infrequent (6%). Treatment interruptions due to HFS occurred in 6% of participants and capecitabine dose modifications were required in 5%, with no significant differences between the two arms. Both interventions demonstrated comparable efficacy in HFS prevention.

Conclusions: Diclofenac sodium gel and urea cream are equally effective in preventing capecitabine-induced HFS, reducing its severity and maintaining treatment adherence.

Keywords: Capecitabine, Diclofenac sodium gel, Hand-foot syndrome, Urea cream

INTRODUCTION

Colorectal and breast cancers are among the many tumors that can be effectively treated with capecitabine, an oral prodrug of 5-fluorouracil. Its mechanism of selective activation in tumour tissues via thymidine phosphorylase has revolutionized cancer therapy by minimizing systemic exposure to the active drug.[1] However, dose-dependent toxicities, such as diarrhoea and HFS, pose significant challenges to its clinical utility. HFS, also termed palmoplantar erythrodysesthesia, is characterized by erythema, edema and painful dysesthesia of the palms and soles, often leading to dose modifications or treatment discontinuation, thereby impacting therapeutic efficacy and patient quality of life.[2]

Capecitabine-induced HFS occurs in 50% to 60% of instances, with 20% to 30% of cases found to be severe.[3] Several pathophysiological mechanisms, such as the upregulation of cyclooxygenase (COX)-2, have been

hypothesized, suggesting the potential role of COX-2 inhibitors like celecoxib in mitigating this adverse effect. However, concerns regarding cardiotoxicity limit their widespread adoption. Alternative strategies, including the use of topical agents like diclofenac gel and urea cream, have shown promise in reducing HFS severity without systemic side effects. Recent studies, such as those by Santosh et al and Hofheinz et al, highlight their prophylactic efficacy.[4,5]

Given the need for effective and patient-friendly interventions, this research aims to compare the efficacy of diclofenac sodium gel and urea cream in preventing capecitabine-induced HFS. By addressing this critical gap, the findings of this research could significantly enhance the management of capecitabine toxicity, ensuring better adherence to therapy and improved patient outcomes.

METHODS

Patients from Government Stanley Medical College in Chennai, India, from October 2023 to September 2024, who were 18 years of age or older and receiving capecitabine chemotherapy for breast or gastrointestinal cancers were included in this study. Eligible participants had an ECOG performance status of 0 to 2 and met specific haematological parameters, including a haemoglobin level of at least 10.0 g/dl, a leukocyte count of at least 3,000/µl and a platelet count of at least 100,000/µl.

Patients did not have unresolved toxicities from prior chemotherapy or radiotherapy. Dermatological conditions that could interfere with the evaluation of HFS, as well as recent exposure to chemotherapy or radiotherapy within four weeks prior to the study, were exclusionary. Before the trial started, the patients' written informed consent was obtained.

Trial design and objectives

The purpose of this randomized, open-label, double-arm interventional trial was to compare the effectiveness of urea cream and diclofenac sodium gel in reducing HFS brought on by capecitabine. Evaluating the prevention of grade 2 or above HFS during the 12-weeks treatment period was the study's primary goal. Secondary objectives included evaluating the time to the development of HFS of any grade, assessing the time to capecitabine dose modification or interruption due to HFS.

Treatment regimens

One of two treatment arms was assigned to each participant at random. For 12 weeks, patients in Arm A received capecitabine and 1% diclofenac sodium gel, which they administered twice daily in 1 g dosages to the palms and soles. Arm B involved capecitabine combined with 12% urea cream, similarly applied twice daily to the same areas and for the same duration. The study protocol prohibited the use of any additional skin care products on the hands or feet during the treatment period and participants were instructed to reapply the study product after washing their hands. Randomization was conducted using a simple randomization technique, ensuring equal allocation between the two arms.

Statistical methods

The sample size for this study was calculated using GPower software, accounting for an estimated effect size of 55%, a study power of 90% and an alpha error of 5%. A total of 100 participants, 50 in each arm, were recruited to account for a 10% attrition rate.

Data collected during the study were entered into Microsoft Excel and analyzed using SPSS v27.0. Baseline demographics and clinical characteristics were summarized using descriptive statistics, while comparative analyses assessed differences in outcomes between the two arms. A p value of less than 0.05 was considered statistically significant and 95% confidence intervals were reported in every analysis.

RESULTS

The study included a total of 100 participants, of whom 54% were female and 46% were male. The majority of participants had a performance status of PS 1 (72%), followed by PS 2 (24%) and PS 3 (4%). Regarding the type of malignancy, 75% of participants were diagnosed with gastrointestinal (GIT) cancers, while 25% had breast cancer.

The stage of malignancy varied among the participants, with 15% at stage 2, 44% at Stage 3 and 41% at Stage 4 (Table 1). The age distribution of study participants showed a mean age of 56 years and a median age of 55 years in the diclofenac arm, while the urea arm had a slightly lower mean age of 53 years.

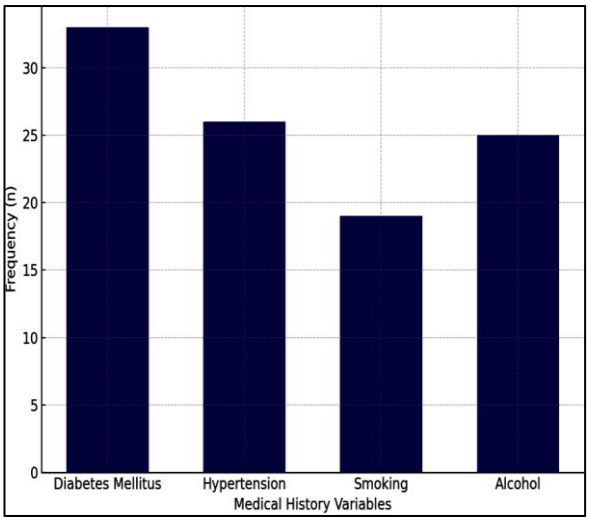

Figure 1: Medical history of study participants.

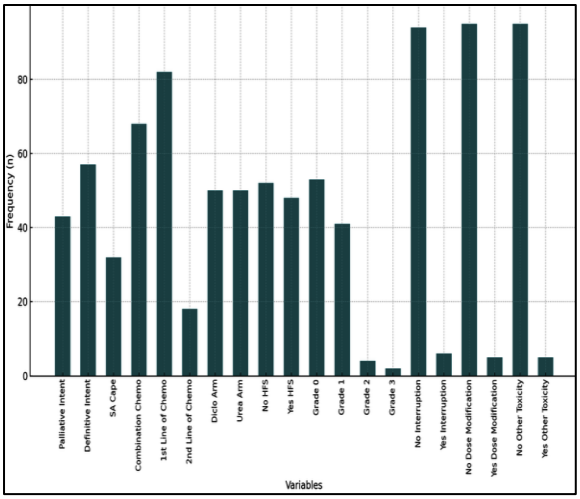

Figure 2: Frequency distribution of other variables.

The medical history of the study participants revealed that 33% had diabetes mellitus, while 67% did not. Hypertension was present in 26% of participants, with the remaining 74% being free from the condition. Regarding smoking habits, 19% of participants reported being smokers, whereas 81% were non-smokers. Additionally, 25% of the participants consumed alcohol, while 75% abstained (Figure 1). Capecitabine was prescribed with palliative intent for 43% and definitive intent for 57%. Single-agent capecitabine (SA Cape) was used in 32%, while 68% received it as part of combination chemotherapy.

Most participants (82%) were on their first line of chemotherapy, with the remaining 18% on the second line. Participants were equally distributed between the diclofenac (50%) and urea (50%) arms. Hand-foot syndrome (HFS) occurred in 48% of participants, with 41% experiencing grade 1, 4% grade 2 and 2% grade 3. HFS developed during the second cycle in 17%, the third cycle in 10% and the fourth cycle in 18%, while 55% did not develop HFS. Treatment interruption due to HFS was rare (6%), as was capecitabine dose modification (5%) and interruption due to other toxicities (5%) (Figure 2). The comparative analysis between the Diclofenac (Diclo) and Urea arms revealed no statistically significant differences in most variables, including gender, performance status, hypertension, smoking, alcohol consumption, type and stage of malignancy ($p>0.05$). However, diabetes mellitus was significantly more prevalent in the Diclo arm ($p=0.04$), single-agent capecitabine usage was higher in the Diclo arm ($p=0.02$) and first-line chemotherapy was more frequent in the Urea arm ($p<0.01$) (Table 2).

Table 3 shows comparative analysis between the diclofenac (Diclo) and urea arms revealed no statistically significant differences in the occurrence of hand-foot syndrome (HFS). HFS occurred in 26 participants in the Diclo arm and 22 participants in the Urea arm ($p=0.27$).

Regarding the severity of HFS, grade 0 (no HFS) was the most common, observed in 25 participants in the diclo arm and 28 participants in the urea arm. Grade 1 HFS was the most frequent among those who developed HFS, with 21 cases in the Diclo arm and 20 in the urea arm. Grades 2 and 3 HFS were rare, with only 2 cases of grade 2 in each arm and 2 cases of grade 3 observed prominently in the Diclo arm.

The time to HFS development was also similar between the two arms, with most cases occurring during the second, third or fourth cycle of treatment ($p=0.24$). Dose modifications of tablet capecitabine due to HFS were infrequent, affecting 3 participants in the Diclo arm and 2 in the Urea arm ($p=0.50$). Treatment interruptions due to HFS were similarly rare, with 4 participants in the diclo arm and 2 in the urea arm experiencing interruptions ($p=0.33$). interruptions due to other toxicities occurred in 3 participants in the diclo arm and 2 in the urea arm ($p=0.50$).

Table 1: Demographic characteristics of study participants.

Variable	Category	Frequency (N)	(%)
Gender	Female	54	54
	Male	46	46
	Total	100	100
Performance status	PS 1	72	72
	PS 2	24	24
	PS 3	4	4
	Total	100	100
Type of malignancy	Breast	25	25
	GIT	75	75
	Total	100	100
Stage of malignancy	Stage 2	15	15
	Stage 3	44	44
	Stage 4	41	41
	Total	100	100

Table 2: Comparative analysis of study variables between diclofenac (diclo) arm and urea arm.

Variable	Category	Diclo arm (N)	Urea arm (N)	Total (N)	P value
Gender	Female	28	26	54	0.42
	Male	22	24	46	
Performance status	PS 1	36	36	72	0.55
	PS 2	13	11	24	
	PS 3	1	3	4	
Diabetes mellitus	No	29	38	67	0.04
	Yes	21	12	33	
Hypertension	No	35	39	74	0.24
	Yes	15	11	26	
Smoking	No	39	42	81	0.30
	Yes	11	8	19	
Alcohol	No	37	38	75	0.50
	Yes	13	12	25	
Type of malignancy	Breast	13	12	25	0.50
	GIT	37	38	75	
Stage of malignancy	Stage 2	5	10	15	0.35
	Stage 3	24	20	44	
	Stage 4	21	20	41	
Capecitabine intent	Palliative	22	21	43	0.50
	Definitive	28	29	57	
Cape SA/combination chemo	SA Cape	21	11	32	0.02
	Combination Chemo	29	39	68	
Line of chemotherapy	1st Line	36	46	82	0.00
	2nd Line	14	4	18	

Table 3: Comparative analysis of HFS and treatment-related outcomes between diclofenac and urea arms.

Variable	Category	Diclo arm (N)	Urea arm (N)	Total (N)	P value
Hand-foot syndrome (HFS)	No	24	28	52	0.27
	Yes	26	22	48	
Grade of HFS	Grade 0	25	28	53	0.53
	Grade 1	21	20	41	
	Grade 2	2	2	4	
	Grade 3	2	0	2	
Time to HFS development	No HFS	25	30	55	0.24
	2nd Cycle	8	9	17	
	3rd Cycle	8	2	10	
	4th Cycle	9	9	18	
Treatment interruption due to HFS	No	46	48	94	0.33
	Yes	4	2	6	
Capecitabine dose modification	No	47	48	95	0.50
	Yes	3	2	5	
Interruption due to other toxicity	No	47	48	95	0.50
	Yes	3	2	5	

DISCUSSION

HFS remains a significant dose-limiting toxicity of capecitabine, impacting patient quality of life and treatment adherence. The current study compared the efficacy of topical diclofenac sodium gel and urea cream in preventing HFS, finding no statistically significant differences in the occurrence of HFS, treatment interruptions or dose modifications between the two arms. These findings align with previous evidence but also contribute new insights into managing capecitabine-induced toxicities. The findings align with the research conducted by Santhosh et al, (D-TORCH Trial), which showed that topical diclofenac was effective in limiting

dose decreases of capecitabine and dramatically lowering grade 2 or higher HFS.[4]

Only 3.8% of the diclofenac group experienced grade 2 or higher HFS in their research, but 15.0% of the placebo group did (p=0.003). Similarly, diclofenac gel decreased grade 2 or higher HFS to 3.6%, compared to 19.2% in the placebo arm (p=0.01), according to the subgroup analysis of capecitabine monotherapy in the same study. Although the current study did not include a placebo group, the comparable reduction in HFS grades in the diclofenac arm reinforces its prophylactic efficacy.

However, a trial by Hofheinz et al, indicated that urea cream was better at preventing HFS during the first six weeks of treatment than an antioxidant-rich ointment (p=0.02).[5] In the present study, the efficacy of urea cream was comparable to diclofenac gel, with 48% of participants developing HFS in both groups. This highlights that while urea cream is effective in reducing skin toxicities, its advantage over diclofenac may depend on the specific patient population and treatment setting. The combination of aloe Vera gel and urea cream, studied by Wanichtanom et al, also showed promise in reducing the severity of HFS, with a lower incidence of grade 2-3 HFS in the combination group (13.3% vs 35.5%, p=0.045).[6]

However, the lack of a significant difference in quality-of-life measures between the groups raises questions about the long-term benefits of such combinations. The systematic review by Elif et al, emphasizes the importance of early recognition and prophylaxis for HFS, recommending systemic or topical interventions.[7] The findings of this review corroborate the use of non-invasive, patient-friendly strategies like topical diclofenac and urea cream as demonstrated in the present study.

The current study's strengths include its randomized design and sufficient sample size allowing for a reliable comparison between diclofenac gel and urea cream. However, the lack of a placebo group limits the ability to assess their absolute efficacy. Additionally, the study duration may have precluded the evaluation of long-term outcomes beyond 12 weeks.

CONCLUSION

This randomized study demonstrated that both diclofenac sodium gel and urea cream are effective and comparable in preventing capecitabine-induced hand-foot syndrome (HFS). No statistically significant differences were observed between the two treatment arms in terms of HFS occurrence, severity, treatment interruptions or capecitabine dose modifications. While the findings suggest that both interventions are viable options for managing HFS, the choice between them can be guided by patient preference, accessibility and tolerance.

The study emphasizes the importance of proactive, patient-friendly interventions to minimize HFS, ensuring better treatment adherence and improved quality of life. Further research, including placebo-controlled trials and longer follow-ups, is warranted to establish the long-term efficacy and optimal use of these interventions.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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