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Comparison of Upper Gastrointestinal Toxicity of Enteric-Coated Prednisolone Versus Non-Enteric-Coated Prednisolone Among Patients Managed at the Rheumatology Department

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ABSTRACT

***Objective*:** To compare the upper gastrointestinal toxicity of enteric-coated Prednisolone versus non-enteric-coated Prednisolone among patients managed at the rheumatology department.

Study Design: Cross-sectional study.

***Place and Duration of Study*:** Rheumatology Department, Pak Emirates Military Hospital Rawalpindi, from May 2019 to Mar 2020.

***Methodology*:** Patients of any rheumatological or immune-based condition who were taking Prednisolone for more than three months were included in the study. Stool for occult was performed for all the patients from the laboratory of their hospital, and patients with the presence of melena were classed as having upper gastrointestinal toxicity.

***Results*:** Mean age of the study participants was 43.64±2.74 years, 43(17.2%) patients had the presence of upper gastrointestinal toxicity, while 207(82.8%) did not show the presence of upper gastrointestinal toxicity. Pearson chi-square test revealed that advancing age and use of non-enteric coated Prednisolone had a statistically significant association with upper gastrointestinal toxicity among the patients suffering from any rheumatological condition managed with Prednisolone (p-value <0.05).

Conclusion: Upper gastrointestinal toxicity emerged as a common finding among the patients managed in the rheumatology department with Prednisolone for various immune-based disorders. The use of non-enteric coated tablets and advancing age emerged as strong predictors for upper gastrointestinal toxicity among the study participants.

Keywords: Enteric-coated, Prednisolone, Upper GI toxicity.

How to Cite This Article: *Malik MS, Fakhr A, Hakim F, Amer A. Comparison of Upper Gastrointestinal Toxicity of Enteric-Coated Prednisolone Versus Non-Enteric-Coated Prednisolone Among Patients Managed at the Rheumatology Department. Pak Armed Forces Med J 2023; 73(3): 629-632. DOI: https://doi.org/10.51253/pafmj.v73i3.4631*

INTRODUCTION

Multiple management techniques have been used to manage these immune-based disorders for the long and short term.[1,2] Oral steroids are usually recommended for the short term, but still, they are a mainstay of treatment even for long-term management of such patients due to multiple reasons.[3] Long-term steroid therapy, especially via the oral route, has many adverse effects that need to be explained to the patients prior to the commencement of the treatment.[4,5]

Multiple strategies have been used by clinicians to prevent or manage the gastropathy-related symptoms experienced by patients using Prednisolone or other steroids for the long term.[6] The use of enteric-coated tablets has been one of these popular strategies. Hulme *et al*. concluded that the absorption of the enteric-coated preparation is delayed, and the peak plasma concentration is much lower than that attained using the same dose of the uncoated material.[7] This has implications in producing the desired & the adverse effects.[8,9]

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Received: 26 Jun 2020; revision received: 08 Dec 2021; accepted: 14 Jan 2022

Epidemiological statistics show that steroids have been used frequently to manage various immunological and rheumatological diseases in our setup.[10] Due to side effects, many clinicians prescribe proton pump inhibitors or enteric-coated tablets to avoid the chances of gastrointestinal side effects. However, being a developing country with a limited health budget, we need to examine whether these expensive interventions help achieve what clinicians want and patients require or if it is just a myth. Therefore, we planned this study to compare the upper gastrointestinal toxicity of enteric-coated Prednisolone and non-enteric-coated Prednisolone among patients managed at the rheumatology department in our hospital.

METHODOLOGY

The cross-sectional study was conducted at Rheumatology Department, Pak Emirates Military Hospital Rawalpindi, from May 2019 to March 2020. Permission from the Hospital Ethics Committee (Letter number A/124 EC/159/2020) was sought prior to the commencement of the study. The sample size was calculated using the WHO sample size calculator keeping the population prevalence of GI toxicity with Prednisolone

as 82%.[11] Non probability consecutive sampling technique was used to gather the required sample size for this study.

Inclusion Criteria: Patients who were put on long-term (>3 months) Prednisolone therapy by a consultant rheumatologist for any immune-based or rheumatological condition aged 15 and 60 years were included in the study.

Exclusion Criteria: Patients who were using other medications along with Prednisolone and had a clear risk for gastropathy, or those having peptic ulcer disease prior to using Prednisolone, were excluded from the study. Patients with comorbid malignant disease of any type were also excluded at the start of the study. Patients who were using any kind of illicit or psychoactive substance were also not included in the study. Patients with any bleeding disorder due to any cause were also excluded from the study. Patients with any fresh bleed on stool tests indicative of lower GI bleed were also excluded from the study.

All the patients signed the informed consent form before enrolling in the study. The stool was collected in a dry, clean container. An applicator stick was applied to a small stool inside the testing card, typically in a box labelled "A." The applicator stick was then used to obtain a second sample from a different part of the stool, which is also placed inside the testing card, typically in a box labelled "B." The testing card was then stored at room temperature, away from heat and light, until transported to the appropriate laboratory. The chemistry behind testing involves a catalysed reaction. The heme occult testing card had an Alpha guaiaconic acid (guaiac) impregnated paper. A hydrogen peroxide reagent was then added to the paper. If heme was present in the stool sample, hydrogen peroxide oxidises the Alpha guaiaconic acid to a blue-coloured quinone. The blue colour would signify a positive test result and indicate the presence of GI bleed.[12]

Prednisolone (may be enteric coated or non-enteric coated as decided mutually by the patient and treating consultant taking into account all the factors and affordability) was usually received by the study participants in a standard dose of at least 5 mg or equivalent for ≥ 3 months before 9 am, and they were not prescribed and proton pump inhibitors or H-2 receptor blockers for prophylaxis against GI toxicity.[13]

Statistical analysis was performed by using SPSS 23.0. Frequency and percentage were calculated for the qualitative variables. Mean, and standard deviation were calculated for the patients' age and duration of Prednisolone therapy. Pearson chi-square test was used to see the association. The *p*-value ≤0.05 was considered significant for this study.

RESULTS

Two hundred and fifty patients of any rheumatological or immune-based disorder who had been using Prednisolone orally for more than three months were recruited in the analysis after inclusion and exclusion criteria were applied. The mean age of the study participants was 37.41±5.72 years (Table-I).

Table-I: Characteristics of Patients Included in the Study (n=250)

Study Parameters	n(%)
Age (years)	
Mean±SD	43.64±2.74 years
Range (min-max)	15 years-57years
Mean duration of Prednisolone use (months)	15.6±7.254 months
Gender	
Male	83(33.8%)
Female	167(66.2%)
Presence of GI Toxicity	
No	207(82.8%)
Yes	43(17.2%)
Enteric Coated Tablet Use	
No	127(50.8%)
Yes	123(49.2%)

The mean duration of prednisolone use among the study participants was 15.6±7.254 months. 207 (82.8%) patients had no sign of GI toxicity, while 43(17.2%) were positive on stool for occult blood showing signs of GI toxicity. As shown in Table II,

Table II: Relationship of Various Factors with the Gastrointestinal Toxicity among the Target Population (n=250)

Socio-Demographic Factors	No GI Toxicity	Presence of GI Toxicity	*p*-value
Age			
<40 years	138(66.7%)	18(41.8%)	0.003
>40 years	69(33.3%)	25(58.2%)	
Gender			
Female	137(66.2%)	30(69.7%)	0.648
Male	70(33.8%)	18(30.3%)	
Duration of Prednisolone Use			
<12 months	89(42.9%)	16(37.2%)	0.482
>12 months	118(57.1%)	27(62.8%)	
Use of Enteric Coated Tablet			
No	93(44.9%)	34(79.1%)	<0.001
Yes	114(55.1%)	09(20.9%)	

The Pearson chi-square test revealed that advancing age (*p*-value-0.003) and use of non-enteric coated tablets (*p*-value <0.001) had a statistically significant association with the presence of GI toxicity among the patients suffering from rheumatological conditions

managed with long term Prednisolone. In contrast, gender (*p*-value-0.648) and duration of Prednisolone (*p*-value-0.642) use had no statistically significant relationship with the presence of GI toxicity.

DISCUSSION

The use of non-enteric coated tablets was significantly related to GI toxicity in our study participants. Adequate knowledge of adverse effects is necessary for clinicians to prescribe any medications. However, it gets more important when drugs are prescribed for the long-term management of any clinical condition. Steroids, in this aspect, have been considered notorious drugs that many clinicians from various specialities prescribe. However, patients usually get lost in follow-up and develop complications or side effects. A study by Farooqi *et al*. conducted in 1997 concluded that 40% of their patients were on steroids. In some cases, the underlying illness was non-responsive to steroids. More than 60% of the patients with RA were using steroids as well, and that too in a bizarre manner. Most of the prescriptions were made by non-rheumatology doctors. More than 35% of patients had adverse effects related to steroids.[14] García Rodríguez *et al*. studied the concept of upper GI bleeding with common drugs notorious for this purpose. They concluded that oral steroids or Aspirin increase the risk of UGI bleeding by around two times while NSAIDs increase to 4 times.[15] Our findings were consistent with what they described.

Zhang *et al*. studied enteric-coated tablets and compared them with regular tablets in terms of efficacy, which are the main aim of any therapy, and concluded that due to pharmacokinetic reasons and delayed absorption enteric, coated tablets could not achieve the desired response among the patients of adrenal insufficiency.[16] Abajo *et al*. published a study to look for the effect of enteric coating and various other factors on the GI toxicity precipitated by Aspirin. They concluded that low-dose Aspirin increases the risk of upper GI bleeding in the general population twofold, and its coating does not modify the effect. Concomitant use of low-dose Aspirin and NSAIDs at high doses put patients at a specially high risk of upper GI bleed.[17] Though we chose Prednisolone for our study, and that may be the reason for the difference in results as GI bleed was significantly less in patients using enteric coated tablets in our study population as compared to those using non-enteric coated tablets. Porter *et al*. discussed various types of coating and the purpose it serves. One of the main aspects they mentioned was preventing gastric irritation that ultimately leads to gastric toxicity.[18] Our findings supported their point of view as enteric-coated tablets were significantly less associated with GI toxicity in our target population.

GI toxicity should be remembered as an important adverse effect of patients using steroids for rheumatologically conditions. Therefore, using enteric-coated tablets may be encouraged to prevent this adverse effect.

LIMITATIONS OF STUDY

Many confounding factors were not considered, possibly related to GI bleeding among these patients. Therefore, the role of enteric-coated tablets in preventing GI bleed could not be evaluated with precision. For generating accurate and generalisable results, large studies with a better study design may be conducted in future, making our results a baseline.

CONCLUSION

Upper gastrointestinal toxicity emerged as a common finding among the patients managed in the rheumatology department with Prednisolone for various immune-based disorders. In addition, using non-enteric coated tablets and advancing age emerged as strong predictors for upper gastrointestinal toxicity among the study participants.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MSM: Data acquisition, data analysis, drafting the manuscript, approval of the final version to be published.

AF & FH: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

AA: Critical review, concept drafting the manuscript, interpretation of data approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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