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Original Article

Investigating Steroid-associated Peptic Symptoms in Patients With Primary Nephrotic Syndrome

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ABSTRACT

Background and Aim: Nephrotic syndrome is the most common glomerulopathy among children aged 2-10 years old and high doses of corticosteroids are the cornerstone of its management. Whether corticosteroid use induces peptic ulcer disease in these patients remains uncertain. This study explores any relation between steroids and peptic symptoms in these children.

Methods: A total of 100 nephrotic syndrome patients aged 1 to 15 years old treated with oral prednisolone in our Outpatient Department were studied. In this study, we compared nephrotic syndrome patients receiving 2 mg/kg prednisolone daily for 1 month and afterward as every other day until tapering off in about 3-6 months. They were divided into groups. One received aluminum Mg (Al-Mg) or proton pump inhibitors (PPIs) as prophylaxis and the other 50 patients did not receive any prophylaxis. These two groups are investigated for any gastro-intestinal complications. Heartburn, hematochezia, nausea, and dyspepsia are the four complications that were studied. In addition to investigating the relation of each of these complications with prednisolone consumption, we introduced a new variable named digestive complications for patients who have at least one of the above symptoms. Any relationship between steroid consumption and digestive complications and the effect of prophylactic drugs in preventing these complications are investigated

Results: In this study, the data from 100 patients (61 male and 39 female) were analyzed. Accordingly, 46% of the patients consumed 0.5 mg/kg prednisolone every other day and 19% of the patients consumed 2 mg/kg prednisolone daily. In 51% of patients the duration of treatment was more than 6 months and in 19% of cases it was less than a month. Also, among the 68% of the patients who did not take PPIs, none experienced any digestive symptoms, including hematochezia. Among those patients who received prophylactic, PPIs one patient with less than a month of prednisolone taking and one who took prednisolone for more than six months contracted hematochezia. Overall, this study demonstrated no significant relationship between PPI prophylaxis and the occurrence of gastric symptoms. Based on the results, 12 out of 100 patients with heartburn and nausea were investigated and there was no relation between PPI consumption and their symptoms. A total of 80% of patients did not receive Al-Mg and there was no significant relation between Al-Mg consumption and dyspepsia. However, there was a significant relationship between Al-Mg and heartburn (P=0.004). Meanwhile, 50 patients in this study consumed Al-Mg or PPIs and a significant relationship was not observed between utilization of these drugs and hematochezia, melena, and heartburn. On the other hand, there was no relation between heartburn and dyspepsia (P=0.024).

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Conclusion: One-month therapy regimen of 2 mg/kg daily prednisolone and continuation of it until tapering off the steroids causes few gastrointestinal symptoms. The use of PPIs or Al-Mg did not affect the incidence of gastrointestinal symptoms significantly. Accordingly, corticosteroid therapy does not increase peptic ulcers in nephrotic syndrome patients.

Keywords: Nephrotic syndrome, Pediatrics, Peptic ulcer

Introduction

The incidence and prevalence of nephrotic syndrome are 2–7 and 16 in 100000 respectively; accordingly, it is one of the most common renal diseases in children. The most common causes of nephrotic syndrome in children include minimal change, focal segmental glomerulosclerosis, membranous glomerular disease, genetics, following infections or other diseases, drugs, reactions, and rarely neoplasms. It is more prevalent in 1-6-year-old children but may be seen at any age [1].

Patients with nephrotic syndrome are predisposed to multifactorial comorbidities which may be the result of the disease itself or progression of it into chronic kidney disease or the treatment of the underlying disease. The acute complications associated with nephrotic syndrome are well recognized and contribute significantly to its burdens. To improve outcomes in these patients, it is important to understand the full impacts of corticosteroid therapy on patients with nephrotic syndrome [2]. As there is a large waste of proteins in these children, a wide range of biological functions are impaired during the active phase of the disease leading to some different complications. Steroids also induce some complications depending on the dosage and duration of therapy and the patient's condition [3]. Those who have longer duration or more severe proteinuria, such as in focal segmental glomerulosclerosis are at higher risk of systemic problems, including cardiovascular (due to atherosclerosis and thromboembolism), various types of infections, thyroid dysfunction, oral (dental and periodontal) and gastrointestinal (GI) symptoms [4]. The treatment-induced side effects include specific problems, including hypertension, hyperglycemia, diabetes, overweight, obesity, short stature, cataracts, glaucoma, osteoporosis, osteonecrosis, fractures, psychosis, and infections (pneumonia, septicemia and bacteremia, peritonitis, and cellulitis) especially due to systemic steroids [5]. In clinical practice association between corticosteroid use and peptic ulcer has been described as unlikely and the value of anti-ulcer prophylaxis has been questioned due to a low bleeding risk [6]. GI bleeding from peptic ulcer or perforation is the most feared complication of peptic ulcer disease. Those on long-term corticosteroids are associated with considerable morbidity and mortality [7]. Chronic corticosteroid users represent a patient population in whom the balance between the risks and benefits of proton pump inhibitors (PPIs) must be especially balanced. Existing data suggest that corticosteroid users are more likely to receive PPIs than other patients [8]. Corticosteroid users with other risk factors of GI bleeding, including concomitant non-steroidal anti-inflammatory drug therapy are more likely to benefit from PPI drugs [9]. This is designed to evaluate and compare the prevalence of peptic ulcer disease in nephrotic syndrome with and without prophylaxis.

Materials and Methods

In this double-blind prospective study, 100 patients with nephrotic syndrome aged 1 to 15 years old were studied. They were randomly divided into two groups. In 50 patients, Aluminum Mg (Al-Mg) or PPIs were prescribed as prophylaxis and the other 50 patients did not receive any prophylaxis. These two groups were investigated for digestive complications. Prescribed PPIs 1 mg/kg maximum 40 mg daily and Al-Mg 1-5 mL immediately after taking prednisolone. Heartburn, hematochezia, nausea dyspepsia, and GI bleeding were the studied complications. We recorded the use of calcium/vitamin D supplements, anticoagulants (warfarin, heparin and low molecular weight heparin), antiplatelet agents, such as aspirin, clopidogrel, and ticlopidine, thyroid replacement hormone, cardiovascular medications (antihypertensives, rate controlling agents), diuretics and statins and the time of PPIs and prednisolone usage. In addition to investigating the relation of each of these complications with prednisolone consumption, we introduced a new variable named digestive complications for those who have at least one of these complications.

Results

A total of 100 nephrotic syndrome penitents were divided into two groups; one group received PPIs or Al-Mg suspension as prophylaxis and the other did not re-

Table 1. Dosage of prednisolone in nephrotic patients

Dosage	No. (%)
2 mg/kg daily	19(19)
1-1.5 mg/kg every other day	46(46)
<1 mg/kg every other day	35(35)

ceive any prophylaxis. About 17% of patients received prednisolone for 1 month or less, 32% for one to six months, and 51% of patients for longer than 6 months as shown in Table 1. Meanwhile, 61% of patients were male and 39% were female. The age range of patients is shown in Table 2. Recorded GI symptoms include dyspepsia, hematochezia, nausea, vomiting, and abdominal pain. Three patients experienced hematochezia of whom two received PPIs as prophylaxis. Diagnostic endoscopy done of them revealed peptic ulcer disease managed as in other patients. The association between GI symptoms and prophylaxis is shown in Table 3. Prednisolone dosage and duration of treatment did not have any significant relation to GI symptoms. Concomitant medications as risk factors of peptic symptoms were assessed in multivariable models and we observed simultaneous use of antiplatelet medications or non-steroidal anti-inflammatory drugs was associated with more GI symptoms which are independent of the use of prophylaxis (adjusted odd ratio (OR)=1.89, 95% CI, 1.32%, 2.70%).

Discussion

Nephrotic syndrome is one of the most common glomerular diseases in children and in some cases, it causes severe and prolonged proteinuria requiring oral or systemic prednisolone for a long time which is associated with a higher risk of systemic complications. One of the most important problems is GI symptoms, specifically peptic ulcer and GI bleeding leading to discontinuation of prednisolone in severe cases. The role of PIPs in the routine prophylaxis in patients taking steroids is unclear. Although some studies suggest corticosteroids are associated with the development of GI ulcers [10] our analysis did not show any significant increased risk of GI symptoms in nephrotic patients and also prophylactic drugs did not affect GI complications. In this study, GI bleeding occurred in two of the patients who had peptic ulcers in endoscopic investigation and positive helicobacter tests. GI bleeding does not relate to the dosage of prednisolone but is significantly associated with an in-

Table 2. Age distribution of nephrotic patients

Age (y)	No. (%)
1-4	24(24)
4-10	52(52)
10-15	24(24)
Total	100(100)

Table 3. Distribution of peptic symptoms in patients

Variables	No. (%)		
	Peptic Symptom	Peptic Symptom	Total
	Yes	No	
Non-PPI use	16(53.3)	52(74.3)	68(68)
PPI use	14(46.7)	18(25.7)	32(32)
Total	30(100)	70(100)	100(100)

PPI: Proton pump inhibitors.

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creased risk of hospital admission. Most patients admitted due to peritonitis or cellulitis had GI bleeding, which indicates additional factors, such as nephrotic syndrome associated with peritonitis or cellulitis may make some patients more vulnerable to adverse effects of steroids. One possible explanation is that the stress ulcer occurs in some of the admitted patients and another reason may be the simultaneous presence of *Helicobacter pylori*. One of the most commonly used drugs worldwide is PIPs. They are commonly used inappropriately, especially inoutpatient settings and more than one-third of its use is not on a documented basis [11]. Other studies have failed to find any meaningful association (after adjusting confounders factors) [12]. In our study, none of the outpatients experienced peptic ulcers. Accordingly, 2% of our patients who were hospitalized due to cellulitis and peritonitis had peptic ulcers. There is an increased risk of peptic ulcer in oral steroid therapy so concomitant prescribing of PPIs is widely common; however, it is rare (0.4–1.8%) and makes this unjustified [13]. There are a few complications associated with PPI use but they may increase the risk of intestinal infections, fractures, and nutritional problems leading to worse consequences [14]. Enterochromaffin-like cell hyperplasia is reported in patients using steroids for the long term but its importance is not clear right now [15]. Also, hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, toxic epidermal necrolysis, multiorgan failure, and even death are reported in PPI use. Accordingly, inappropriate PPI use on just a theoretical basis is not justified and may be harmful [16]. The general recommendations on the management of patients receiving oral steroids include lowering the steroid dosage to the minimal effective doses fulfilling the recommended therapeutic regimens of the disease (alternating day regimen or circadian rhythm of administration). Also, it is necessary to reduce the dose of the preparation as much as possible until the drug can be withdrawn at all [17].

Conclusion

Although there is a significantly increased risk of GI bleeding in admitted patients under oral steroid therapy there is no similar finding in outpatients. Accordingly, outpatient cases on oral steroids do not require routine PPI prophylaxis.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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