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ORIGINAL PAPER

Neutropaenia following intravenous immunoglobulin therapy in paediatric patients with immune thrombocytopaenia

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ABSTRACT

Introduction: Immune thrombocytopaenia (ITP), previously known as idiopathic thrombocytopaenic purpura, is an acquired autoimmune disorder characterised by immune-mediated platelet destruction. It has been observed that some paediatric patients with ITP treated with intravenous immunoglobulin (IVIG) developed neutropaenia. The aim of the study was to investigate the association between IVIG therapy and neutropaenia in paediatric ITP.
Material and methods: The retrospective cohort study involved 123 children (79 girls, 44 boys) with immune thrombocytopaenia, aged 8.03 ±4.55 (0.8–17.9) years (mean ± standard deviation; range) who underwent IVIG in the Department of Haematology and Paediatric Oncology in Zabrze between April 2014 and December 2021. Correlations between age, sex, weight of patients, total IVIG dose, and neutrophil/platelet counts on administration day and 1, 2, and 3 days after IVIG treatment from official medical records were analysed.
Results: The mean total dose of IVIG was 1.7 ±0.48 g/kg BW. A significant increase in platelet level was observed usually on the first (67.5%) or second (20.3%) day after initial administration of intravenous immunoglobulins. After the course of IVIG, neutropaenia was observed in 50 subjects (40.7%). The neutropaenia occurred mostly (54%) on the first day after administration of IVIG. There was a positive correlation between the onset of neutropaenia and lower age of patients ($p < 0.05$). What is more, the decrease in the neutrophil count was more distinct in the group of subjects with neutropaenia.
Conclusions: Intravenous immunoglobulin therapy in children with ITP can lead to neutropaenia. However, patients benefit noticeably from IVIG therapy, and neutropaenia in this case tends to be a transient, self-limiting condition.

KEY WORDS:
children, intravenous immunoglobulin, immune thrombocytopaenia, IVIG, neutropaenia.

INTRODUCTION

As documented in the literature, around 80–90% of patients experience spontaneous resolution of immune thrombocytopaenia (ITP) within 7–14 days from onset, regardless of the treatment modality employed. Nevertheless, due to the risk of life-threatening bleeding such as intracranial haemorrhage or gastrointestinal bleeding, ITP in paediatric patients with severe thrombocytopaenia or at higher risk of bleeding require pharmacological treatment. According to the study findings (both Polish and international guidelines), the recommended first-line

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treatments for ITP in paediatric patients include intravenous immunoglobulin (IVIG) or corticosteroids [1, 2]. It is crucial to consider not only the benefits but also the drawbacks of each therapy.

When it comes to the corticosteroids, it can be stated that they are effective in a specific percentage of cases (72–80% depending on the drug dosage), but their onset of action is generally slower than IVIG. It is worth noting that corticosteroids can induce numerous side effects, such as mood disorders, reduced activity, sleeping disorders, gastritis, cushingoid obesity, hypertension, hyperglycaemia, cataracts, and osteoporosis [1, 3, 4]. These side effects increase proportionally with the dosage and duration of use, so steroids should be administered for as short a period as possible to achieve a safe platelet count. Corticosteroids continue to be a significant therapeutic choice for treating ITP in children in need of therapy, but without life-threatening bleeding, primarily owing to their low cost, high rates of initial response, universal availability, simplicity of administering treatment, absence of contact with numerous blood contributors, and reasonable short-term tolerability [5]. In many centres bone marrow aspiration is required before starting steroid treatment.

Regarding IVIG therapy, it raises the platelet count in more than 80% of children [1]. The primary advantage of IVIG is its rapid response to treatment, making it the preferred strategy in cases of severe mucosal bleeding. Although the exact pathophysiology of ITP is still not known, it is believed that abnormalities in both humoral and cellular immune systems are involved (Cines and Blanchette, 2002) – IVIG has an effect on both of these immune system elements and is therefore considered to have immunomodulatory properties [6]. However, IVIG therapy has some disadvantages: it is associated with numerous side effects, including mild symptoms such as fever, nausea, vomiting, muscle aches, and allergic reactions, with headache being the most common. Additionally, there are more severe adverse effects, such as the risk of thrombosis and the risk of kidney damage; fortunately, these occur less frequently [1, 4, 7]. Also, it has been observed that some children with ITP treated with IVIG develop neutropaenia [1, 8–11]. In this study, we focused on the issue of neutropaenia induced by the administration of IVIG during the treatment of ITP in children. The purpose of the research was to indicate the presence of neutropaenia and possible predisposing factors in the course of immunoglobulin therapy during the treatment of ITP.

MATERIAL AND METHODS

STUDIED GROUPS

We performed a retrospective study of 123 paediatric patients with ITP who underwent IVIG therapy in the Department of Haematology and Paediatric Oncology in Zabrze, between April 2014 and December 2021. Out of the total, 79 patients were female and 44 were male. Inclusion criteria were the following: age under 18 years, diagnosis of ITP, IVIG therapy, and data completeness (complete blood count on the day of IVIG administration and in 3 consecutive days after treatment). Patients with neutropaenia on admission or with a medical history of cancer and post-transplant immunosuppression treatment were excluded from the study.

LABORATORY TESTS

We obtained clinical data such as: age, sex, weight, height, diagnosed disease, dose and type of treatment, and neutrophil and platelet counts on administration day and 1, 2, and 3 days after treatment from official medical records. When considered necessary, patients were treated with intravenous immunoglobulin. Eighty-two children (63.6%) received Privigen, 33 children (25.6%) received Kiovig, and the others received Gammagard (4.7%), Octagamma (3.1%), IgVena (2.3%), or Flebogamma (0.8%). The mean total dose of IVIG was 1.7 ±0.48 g/kg body weight. We also collected data from the hospitalisation period of each patient with red blood cell count, white blood cell count, platelet levels, haemoglobin, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, and total bilirubin tests.

STATISTICAL ANALYSIS

Statistical analyses were carried out by means of basic descriptive statistics including medians, modal values, means, and standard deviations. Pearson's χ^2 test was used to determine whether there was a statistically significant difference between the expected frequencies. Because the data were not normally distributed, it was decided to use the Mann-Whitney *U* test to compare differences between independent groups. A *p*-value of less than 0.05 was considered as statistically significant. All statistical analyses were made using Statistica software version 10.

ANTHROPOMETRIC MEASUREMENTS

The database also includes information on anthropometric measurements of patients. Height measurements were made with a standardised stadiometer, and weight measurements were performed with digital infant scale or electronic floor scale. Measurement results were rounded to the first decimal place. We did not use body mass index or standardised body mass index, nor did we apply percentile grids in our study. The average weight for females was 25.36 kg, and for males 35.29 kg (median 24 kg). The average height in females was 118.93 cm, and in males 125.62 cm (median 126 cm).

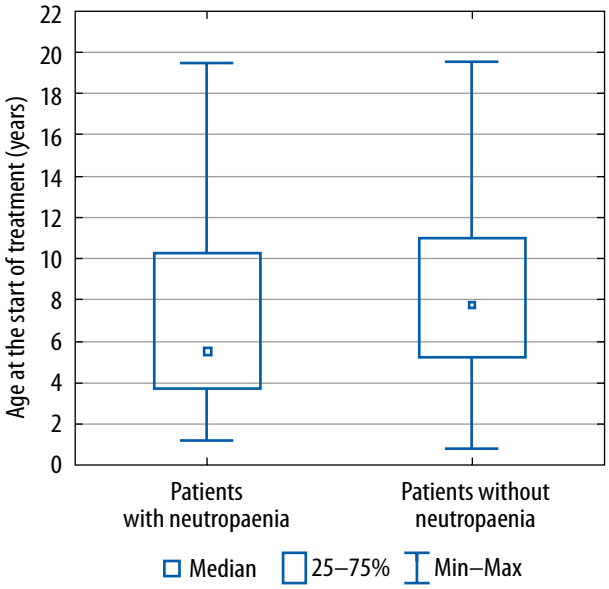

FIGURE 1. Age of patients with neutropaenia after intravenous immunoglobulin (IVIG) administration vs. age of patients without neutropaenia after IVIG administration ($p = 0.04$)

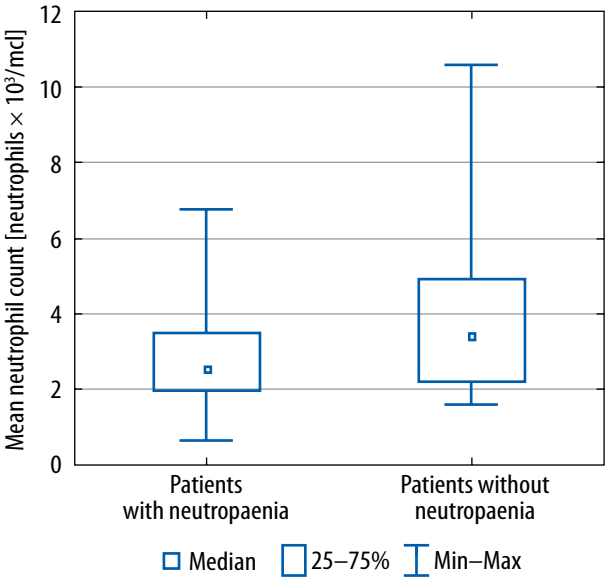

FIGURE 2. Neutrophil count on admission in patients with neutropaenia after intravenous immunoglobulin (IVIG) administration vs. neutrophil count on admission in patients without neutropaenia after IVIG administration ($p = 0.005$)

RESULTS

The retrospective cohort study involved 123 children (79 girls, 44 boys) with ITP. There were 79 female patients and 44 male, with an average patient age of 8.03 ±4.55 years, ranging from 0.8 to 17.9 years. Median platelet count on admission reached 18 ´ 10^9/l. A significant increase in platelet level was observed usually on the first (67.5%) or second (20.3%) day after initial administration of IVIG. Median absolute neutrophil count (ANC) on admission was 3100/mm³. After the course of IVIG, neutropaenia (ANC of < 1500/mm³) was observed in 50 subjects (40.7%); 29 of them (58%) were diagnosed with mild neutropaenia (ANC of 1000–1500/mm³), 14 subjects (28%) with moderate neutropaenia (ANC of 500–1000/mm³), and 7 subjects (14%) with severe neutropaenia (ANC of < 500/mm³). The neutropaenia occurred mostly on the first (54%) and second (22%) day after administration of initial dose of IVIG. It is worth mentioning that neutropaenia was observed in 3 patients at the time of ITP diagnosis, and all of them experienced a significant decrease in neutrophil levels after IVIG administration. None of the subjects had a significant infection during or immediately after the neutropaenic episode. There was a positive correlation between the onset of neutropaenia and lower age of patients ($p = 0.04$) (Figure 1). The pretreatment neutrophil count in a group of children with IVIG-induced neutropaenia (median ANC 2530/mm³) was significantly lower than in the patients without neutropaenia (median ANC 3400/mm³) ($p = 0.005$) (Figure 2). What is more, the decrease in the neutrophil count was more distinct in the group of subjects with neutropaenia (Figure 3). There was no significant correlation between

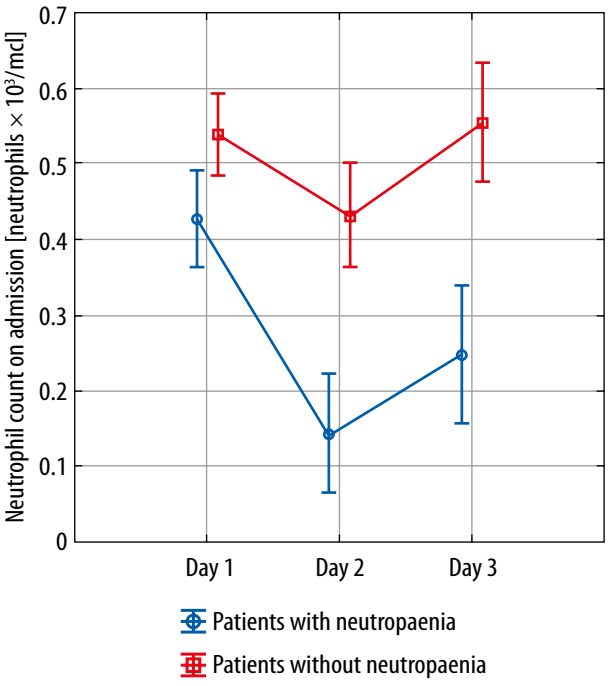

FIGURE 3. Mean neutrophil count in patients with neutropaenia after intravenous immunoglobulin (IVIG) administration vs. in patients without neutropaenia after IVIG administration ($\log_2$ scale) ($p = 0.003$). To illustrate differences between mean neutrophil levels, we decided to convert neutrophil counts into logarithms to obtain a distribution similar to normal. The graph shows that patients with neutropaenia after IVIG therapy initially had lower neutrophil count. What is more, the decline in neutrophil level in that group of patients is much sharper

Day 1 – day of admission to hospital,
Day 2 – first day after intravenous immunoglobulin administration,
Day 3 – second day after intravenous immunoglobulin administration

the occurrence of neutropaenia and gender of the patients, total dose size of IVIG, or platelet count on admission ($p > 0.05$).

DISCUSSION

The aim of our study was to determine the risk of neutropenia during ITP treatment using immunotherapy. When assessing the validity of IVIG therapy, potential benefits and side effects of treatment, individual characteristics, and long-term treatment goals should be taken into account [12]. Intravenous immunoglobulin applies to thrombocytopaenia treatment in children when there is a high risk of serious bleeding and a rapid increase in platelet count is desired, i.e. when the platelet count decreases below 30 ´ 10^9/l, mucosal bleeding occurs, or an invasive procedure causing blood loss is planned [13–15]. The main goals of ITP therapy in children are to prevent the consequences of a drastically reduced platelet count such as bleeding, avoid splenectomy, improve health-related quality of life, and prevent chronic diseases and relapses. Intravenous immunoglobulin therapy is only one of the treatment options, while glucocorticosteroid monotherapy remains the basis of symptomatic treatment [16, 17]. First-line IVIG therapy with concomitant steroids increases platelet count to a safe level faster than glucocorticosteroids alone, especially when a rapid rise in platelet count is desired [18, 19]. This increases the attractiveness of immunoglobulin therapy and encourages its use in patients who have contraindications to glucocorticosteroid therapy and/or the patient's condition requires a rapid increase in platelet count to reduce acute bleeding. According to another study [20] and the results of our database analysis, a significant increase in platelet count is usually (in 67.5% of our patients) observed on the first day (within 24 hours) after IVIG administration. Target platelet count in this case is in the range of ≥ 20–30 ´ 10^9/l, and it is sufficient to stop bleeding or reduce its risk [15]. The presented study shows that the neutropaenia occurred mostly in the first 24 hours and 48 hours after administration of IVIG, whereas in the case of the research by Ansari *et al.* [20] it occurred in the first 72 hours, and when it comes to the study by Berkovitch *et al.* [10], in the first 24 hours. It must be noted that ITP is considered to be a heterogeneous disease. Thus, IVIG may have different effects on different patients, which explains why not all patients respond similarly and different side effects, such as headache, nausea, vomiting, and allergic reactions can occur. Despite that, IVIG therapy is considered to be well tolerated by paediatric patients [6, 19].

Another problem in children with ITP is the possibility of developing chronic ITP, which can have a significant impact on children and their families due to the risk of bleeding, fatigue, parental anxiety, and other problems that can lower health related quality of life. The risk of life-threatening complications in chronic ITP is slight, but clinically significant bleeding occurs in 13–27% of children, which affects frequent parental decisions to limit activity to prevent unwanted injuries [6]. In a systematic review Kochhar *et al.* [17], it was found that IVIG administration is the only modifiable risk factor for the development of chronic ITP (platelet count < 150 × 10^9/l) after 6 months from the onset of first ITP symptoms. When deciding on primary ITP therapy using IVIG, the risk of developing chronic forms should be verified. In a multicentre randomised trial comparing IVIG and non-IVIG therapy of children with immune thrombocytopaenia, primary ITP treatment with IVIG was associated with a reduced tendency to develop chronic ITP, but the endpoint (frequency of chronic ITP) did not differ statistically between these 2 groups [21]. It should also be added that chronic ITP is considered to be a process that worsens by itself (Cines and Blanchette, 2002), and it is hypothesised that IVIG may have a more beneficial effect when given early [6].

If patients are at low risk of bleeding, observation rather than pharmacological treatment is recommended [1], because the introduction of medicines, as well as therapeutic effects, carries the risk of side effects, such as post-IVIG neutropaenia. Nevertheless, our research has not shown that this neutropaenia was associated with a tendency of infection and the decline in immunity in children, which is supported by the fact that inflammatory marker levels were not elevated. Other studies [10, 18, 20] also confirm that neutropaenia appears to be self-limiting and transient, requiring no medical intervention. Therefore, in connection with the above, it can be concluded that the advantages of IVIG therapy outweigh the disadvantages (the benefits outweigh the losses), especially if we have shown that most patients who exhibited neutropaenia were diagnosed with its mild type (58%).

Our study had several strengths. One of the advantages was the fact that it included a high number of patients in comparison to other similar studies. For instance, in the one performed by Ansari *et al.* [20], the research group of comprised 89 patients, and in the study by Berkovitch *et al.* [10] the sample size was 30 patients. What is more, the age range of children in the this research varied similarly to [9, 20], whereas in [10] it was narrower. This study had some limitations: It would be worth adding a control group and conducting the study in other regions of the world to create a meta-analysis in the future. The limitations could also include sources of potential bias or inaccuracy.

CONCLUSIONS

Intravenous immunoglobulin therapy in children with ITP can lead to neutropaenia. Patients get noticeable benefits from IVIG therapy, and neutropaenia in this case tends to be a transient, self-limiting condition. There is

a positive correlation between onset of neutropaenia and lower age of patients or lower pretreatment neutrophil count.

DISCLOSURE

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3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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