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Neutropenia Following Intravenous Immunoglobulin Therapy in Pediatric Patients with Idiopathic Thrombocytopenic Purpura

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Abstract

Background: Children with idiopathic thrombocytopenic purpura who are treated with intravenous immunoglobulin therapy might experience a decline in their absolute neutrophil count. The aim of this study was to investigate the incidence of neutropenia following intravenous immunoglobulin therapy in children with idiopathic thrombocytopenic purpura undergoing intravenous immunoglobulin therapy.

Patients and Methods: This was a retrospective cross sectional study. Patients with idiopathic thrombocytopenic purpura admitted to Ali-Asghar hospital from October 2003 to June 2010 with no immunosuppressive diseases negative coombs test and no sign of other infections before the admission entered the study and their neutrophil count before the intravenous immunoglobulin therapy, and in days1, 2, and 3 after the initiation of therapy was recorded.

Results: From eighty nine patients 51 patients (57.3%) were male and 38 patients (42.7%) were female. Neutropenia was seen in 13 patients (14.6%) after treatment, but there was no statically significant difference between the mean absolute neutrophil count before and 1, 2, and 3 days after the start of the treatment (P=0.922).

Conclusion: Intravenous immunoglobulin can lead to neutropenia in a few number of patients which is transient and self limited and most patients get benefits from intravenous immunoglobulin therapy as induced platelets count.

Keywords: Neutropenia, idiopathic thrombocytopenic purpura, intravenous immunoglobulin .

Introduction

Idiopathic Thrombocytopenic Purpura (ITP) is caused by auto antibodies against platelet membrane antigens (Glycoprotein IIB/IIIA) [1, 2], causes trapping of platelets in reticuloendothelial system and lead to thrombocytopenia and an increased risk of bleeding. Patients may exhibit symptoms such as petechiae, ecchymosis, or mucosal bleeding and typically present after a viral illness such as pharyngitis, or after vaccinations. As there is no definitive diagnostic test for ITP, it is a diagnosis of exclusion [1]. ITP is a self-limiting condition, spontaneously remitting in 80% to 90% of patients regardless of the treatment used; whereas most sources point to the risk of serious bleeding, such as intracranial hemorrhage or gastrointestinal bleeding, as the reason for ITP treatment in children [3]. Pharmacologic treatment, including steroids, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin (WinRho), provide a faster rise in platelet count than observation alone [2, 4, 5], however they may cause significant side effects. Clinically, it has been observed that some children with ITP have exhibited a significant decrease in their Absolute Neutrophil Count (ANC) following the IVIG treatment [3, 6, 7, 8, 9].

The aim of the present study was to further investigate the association between IVIG therapy and neutropenia in pediatric ITP patients in Iran.

Patients and Methods

This retrospective cross-sectional study was performed on all 89 ITP patients aged 1 to18 years who underwent IVIG therapy in Ali-Asghar children's hospital, Tehran, Iran, from October 2003 to June 2010. Patients included in this study had available complete and differential blood count

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immediately before, and 1, 2, and 3 days after treatment. They were also without neutropenia; immune compromising diseases like HIV, SLE, Evans syndrome; positive coombs test; or other infections before the admission; and also did not have a history of spelenectomy. The diagnosis of ITP in all patients was based on clinical manifestation of petechiae and purpura and evidence of isolated thrombocytopenia on peripheral blood smear as well as increased megakaryocyte count in bone marrow. Each patient was included only once in the study, even if the patient had been hospitalized more than once. During hospital admission, patients were treated with a standard protocol consisting of the IV administration of immunoglobulin (in a standardized dosage of 1g/kg / day, 2days). Prior to the beginning of the study, patients were fully informed of the conduct and consequences of the study and signed a consent form. This study was conducted after approval by institutional review board and ethics committee and was in accordance with the ethical principles described in the declaration of Helsinki.

Demographic and clinical data such as: age; sex; acute or chronic disease; clinical presentation and neutrophil and platelet counts before and 1, 2, 3 days after treatment were obtained from reviews of personal and official medical documents for all patients.

Statistical assessment was carried out by means of the Chi-Square, repeated measures ANOVA, independent-samples T- test, and a p of <0.05 was considered to be statistically significant. The results were analyzed using SPSS software version 16.

Results

From 89 ITP patients 51 patients (57.3%) were male and 38 patients (42.7%) were female with the mean age of 47.1 months (SD=54.6) ranging from 1 to 216 months. Seventy seven patients (86.5%) had acute ITP and 12 patients (13.5%) had the chronic form of the disease. The mean platelet count changed from 24602±32364 before treatment to 41456±57349 one day after the start of the treatment (Table 1).

The absolute neutrophil count (ANC) before the therapy ranged from 1600 to 13000 per µL with the mean of 4752±2641 per µL (Table 2). The mean ANC 24 hours after treatment with IVIG was 4772±3314 per µL (neutrophil count reduction was observed in 48 patient and increase in 41 patients). This number reached 4847±3725 per µL (neutrophil count reduction was observed in 51 and increase in 38 patients) 48 hours and got to 4725±3631per µL (neutrophil count reduction in 52 and increase in 37 patients) 72 hours after treatment (Table 2, Figure 1).

No significant difference was found between the mean ANC before the initiation of the treatment and 24, 48 and 72 hours after the start of IVIG therapy (P=0.922). Neutropenia (ANC of <1500/mm3) was observed in 13 patients (14.6%) during the first 72 hours of the treatment. Frequency of neutropenia had no statistical relation with the

Table 1: Pre and post intravenous immunoglobulin treatment platelet counts among patients.

	Min	Max	Mean ± SD
Pretreatment platelet count	2000	171000	24602±32364
Platelet count 24h after treatment	5000	348000	41456±57349
Platelet count 48h after treatment	5700	318000	73285±72879
Platelet count 72h after treatment	8700	620000	173731±120990

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type of ITP (acute or chronic) (P=0.824) and also sex (P=0.738).

Discussion

IVIG is one of the common treatments for ITP although complications like neutropenia have been reported in some studies. Use of IVIG has been reported to induce neutrophil apoptosis and degranulation in vitro [10]. For example in a study performed by Niebanck et al. [6], on 104 ITP patients, the mean ANC had a 1404±1982/µl decrease after IVIG therapy and 21% of the patients showed ANC <1500. In another study by Berkovitch et al. [1], on 14 patients with ITP, neutropenia was seen in 5 patients (36%) during 24 hours after the first course of IVIG therapy which resolved spontaneously without any complication on day 2 and authors concluded that neutropenia following IVIG therapy is not uncommon but is self limited and transient.

Another study by Veys et al.[9] on 48 patients with ITP, showed decreased ANC on day 3 and 4 compared to pretreatment levels although it got to normal levels on day 7 and authors concluded that in the absence of infection neutropenia has the least clinical importance and not only neutropenia is not considered as this therapy's complication but also a decrease in the phagocytic capacity of IgG coated neutrophils may help in increasing the platelet count. Moreover in a differently designed study, Sugita et al.[8] included 49 patients with ITP from whom 9 patients did not get any treatment as controls.

Among 40 remained patients, 22 (55%) who did not have fever showed significant reduction in ANC on day 2 that resolved until the last day of therapy and this reduction showed a significant difference between patients under IVIG therapy and controls. Interestingly patients with fever had increase in their ANC. Similarly in our study ANC increased in some patients and decreased in others but,

Table 2: Pre and post intravenous immunoglobulin treatment absolute neutrophil counts among patients according to the sex.

Sex		n	Mean ± SD	Total Mean ± SD
Male	**Pretreatment ANC**	51	4598±2789	4752±2641
Female		38	4960±2450	
Male	**ANC 24 hours after treatment**	51	4543±3229	4772±3314
Female		38	5079±3445	
Male	**ANC 48 hours after treatment**	51	4550±3245	4847±3725
Female		38	5247±4300	
Male	**ANC 72 hours after treatment**	51	4515±3566	4725±3631
Female		38	5007±3746	

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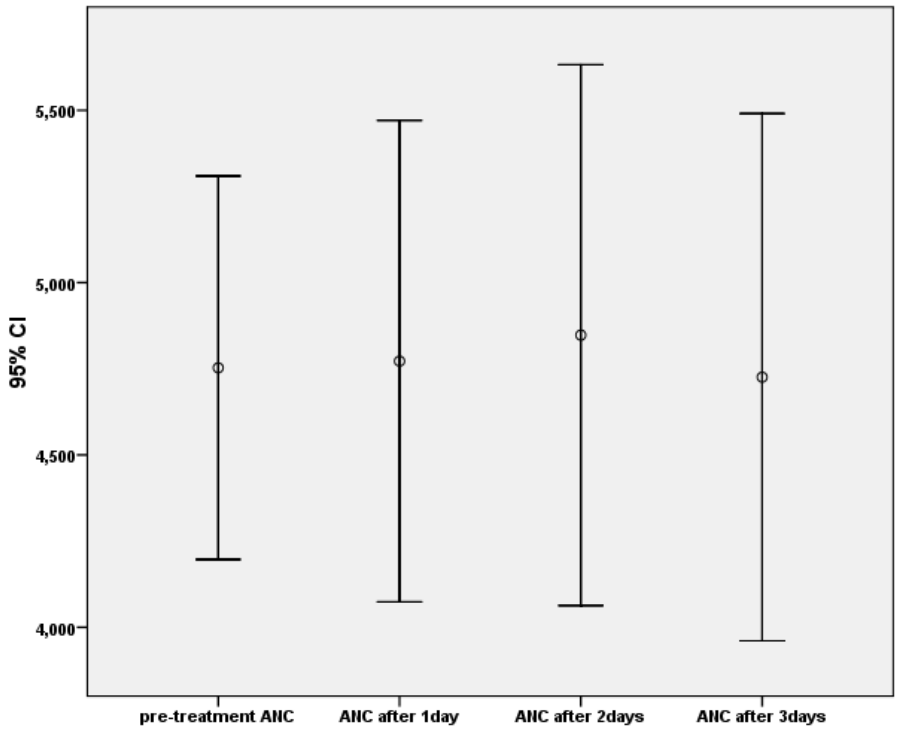


Figure1: Average absolute neutrophil count (per µL) in 3 days after intravenous

reduction was seen in more patients. In contrast to all previous studies, our patients showed an increase of mean ANC, 1 and 2 days after the initiation of therapy and a sudden decrease on day 3, although this pattern was not seen in the male group and also the mean ANC did not show a significant difference across the treatment period. In addition we reported a relatively low incidence of 14.6% neutropenia among our patients.

One of the positive points of our study was its high sample size in comparison to similar

studies and its negative points were the absence of long term follow up to assess the improvement of neutropenia and probability of infections as well as the lack of a control group.

Conclusion

Intravenous immunoglobulin can lead to neutropenia in a few number of patients which is transient and self limited and most patients get benefits from intravenous immunoglobulin therapy as induced platelets count.

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