Original Article *Iran J Ped Hematol Oncol. 2019, Vol 9.No 1, 9-16*

Antibiotic induced hemolytic anemia and thrombocytopenia among pediatric patients admitted to intensive care unit

Hassan Taherahmadi MD[1], Ali Reza Moradabadi MSc[2], Ali Arjomand shabestari MD[1], Javad Nazari MD[1], Manijeh Kahbazi MD[1,2,*]

1. Department of pediatrics, School of Medicine, Arak University of Medical Sciences, Arak, Iran
2. Infectious Diseases Research Center (IDRC), Arak University of Medical Sciences, Arak, Iran
*Corresponding author: Dr Manijeh Kahbazi, MD, Department of pediatrics, School of Medicine, Arak University of Medical Sciences, Arak, Iran. Email: dr.kahbazi@arakmu.ac.ir

Received: 10 June 2018 **Accepted:** 05 October 2018

Abstract

Background: Drug induced hemolytic anemia and thrombocytopenia (DIHA and DIT) are common drug adverse effects of antibiotics in patients admitted to hospital. This reaction is important in patients who have a chronic disease especially in pediatrics. In this study, possible hemolytic anemia was investigated before and after the antibiotics administration.

Materials and Methods: A total of 835 children were investigated in this retrospective study. The laboratory tests were performed before and at least one week after antibiotics administration. The red blood cell (RBC), platelet (plt), hematocrit (Hct), and hemoglobin (Hb) were measured.

Results: With respect to age, 76.11% of studied patients were under 6 years old. The others were between 6-10 years (mean 5.38 years). The two tailed T tests results on the patients' information showed a difference between RBC, platelet, hematocrit, and hemoglobin values before and after antibiotics administration to the point where the RBC mean counts before and after administration were 4.53 to 3.82 *1012/L, respectively. These changes for plt, Hb, and Hct were 323.5 to 232.5 *109/L, 13.61 to 11.46 mg/dL, and 40.83 to 34.38 %, respectively. The p-values were 0.000025, 0.000051, 0.000061, and 0.000032 for RBC, platelet, hematocrit, and hemoglobin; respectively. This finding confirmed that antibiotics administration can decrease the platelets and RBC count. The antibiotics used in the children were ceftriaxone (38.2%), clindamycin (23.3%), Clarithromycin (19.6%), and acyclovir (12.1%); respectively. The dose of the ceftriaxone varied from 50 mg/kg to 70 mg/kg in shigelloses and pneumonia, respectively. Additionally, clindamycin, clarithromycin, and acyclovir were prescribed for 10 mg/kg, 5-10, and 10 mg/kg per day; respectively.

Conclusion: This study showed that antibiotics administration had adverse effects and should be considered when they are prescribed to children with chronic diseases. The physicians should be awarded about proper dosing to decrease adverse effects.

Keywords: Anti-Bacterial Agents, Drug-Related Side Effects, Adverse Reactions, Hemolytic Anemia, Pediatric, Thrombocytopenia

[DOI: 10.18502/ijpho.v9i1.291]

Introduction

Drug-induced hemolytic anemia (DIHA) and drug-induced thrombocytopenia (DIT) are common clinical disorders in patients who are admitted to hospital and take antibiotics. Neonatal thrombocytopenia (platelets <150×109/litter) is one of the most common hematological abnormalities in neonates occurring in 1 to 2% of healthy term neonates, which is 18% to 35% among sick children (1). Among the children admitted to neonatal intensive care units (NICUs), the platelet count drop below 150 ×109/L (under the reference range) occurred one in every four children, and count drop below 50 × 109/L (sever thrombocytopenia.) occurred one in every twenty (2). Early onset thrombocytopenia is usually related with pregnancy complications such as HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), intrauterine growth restriction, maternal diabetes, or drug use (1). The antibiotic-related adverse events are the major effects in the admitted patients (3, 4). The main effect of taking

antibiotics is thrombocytopenia and hemolytic anemia (5). Severe thrombocytopenia (platelet count under 50 000/μL) may lead to serious complications in patients with neoplasms (6). In addition, the hemolytic anemia can affect kidney, heart, lung, and other vital organs (6, 7). In case of patients with DIT, decrease in platelet count results from decreased platelet production and increased platelet destruction. In addition these results can also occur in DIHA (3, 8). In most of the cases, the applied drugs are antibiotics. Other drugs include Iimmunosuppressive and chemotherapeutic agents which can be cytotoxic and are typically dose-dependent and affect all cell lines (6). In contrast, DIT and DIHA involve antibody-mediated cell destruction in phagocytic organ like spleen liver, etc. This condition leads to isolated thrombocytopenia, anemia or both without leucopenia (9–11). One of the popular mechanisms occurs when drug-dependent antibodies bind to the platelet membrane glycoproteins and activate platelet consumption signaling. In the DIHA, the drug binds to the membrane protein in red blood cell. As a result, the immune system recognizes this new epitope and produces antibody to remove the new epitope (12–15). The other mechanism is mediated by complement immune system. This mechanism is run by activating the complement system as a result of autoantibodies produced against the antigens on the anti-erythrocyte surface, overwhelming the protection of cell surface complement regulators, which also leads to hemolytic anemia (16). One of the important mechanisms is caused by the impaired hematopoiesis and bone marrow suppression. This effect starts with thrombocytopenia, continues with leukopenia and ends with pancytopenia. This adverse drug effect is very important in patients with susceptibility to infection and bleeding disorders (17, 18). Several other mechanisms are offered for DIHA and DIT.

Some of the hemolysis is related to the enzyme in red blood cell (RBC). This category is Hereditary Nonspherocytic Hemolytic Anemia (HNSHA) arising from change in enzyme activity. Enzymes involved in antioxidant defense system such as catalase, glutathione reductase, and glutathione peroxidase are cleared from the cell as a result of defense against oxidants produced in antibiotics metabolism (19). In addition, antibiotics may cause anemia and thrombocytopenia by making a toxic condition in the patient (20).

In several works, adverse drug-related events have been demonstrated from which the antibiotics are majorly included (21–23). The most frequent antibiotic used in hospital are β- lactams which have common and predicable adverse events, like nausea or vomiting, diarrhea, abdominal pain, and headaches (24). However, the DIHA and DIT are not predictable and can deteriorate the patient's conditions. Drugs such as quinidine/quinine, salicylates, sulphamethoxazole/trimethoprim, aspirin, vancomycin, and clopidogrel ,as DIHA and DIT inducing drugs (25–27), are mostly antibiotics.

Here, we described the frequency of DIHA, DIT or both in the patient admitted to the pediatric intensive care unit (PICU) and received antibiotic. We studied the hematology indices and found the frequency of this condition in these patients.

Materials and Methods

A total of 835 patients entered in this retrospective study who were admitted to Amir Kabir Hospital during September to March 2017. This study was approved in the Ethics Committee of Arak University of Medical Sciences (IR.ARAKMU.REC.1396.280). Most of the patients were under 6 years old (about 76.16%), and others were under 10 years old (mean= 5.38 years), the boys and girls were 56.89% and 43.11%, respectively.

[DOI: 10.18502/ijpho.v9i1.291]

The informed parental consent of agreement was signed by parents.

All patients received antibiotics. The most frequent antibiotics used in the ward are summarized in Table I. Ceftriaxone is the most frequent antibiotics prescribed in about 38.2% of patients used in shigelloses, pneumonias, and Urinary Tract Infections (UTI) by 50mg/kg and 70 mg/kg, respectively. The other antibiotics and antiviral drugs are clindamycin (23.3%), clarithromycin (19.6%) and acyclovir (12.1%) prescribed for 10, 5-10 and 10 mg/kg every day, respectively. All patients entered in the study received antibiotics and also had two CBC tets. Complete blood count (CBC) was requested twice; first, when the child entered the hospital and second, after receiving antibiotics. The anemia and Thrombocytopenia were based on the decrease in plt and RBC counts in the normal range. In case of children with anemia and Thrombocytopenia out of normal range, they were treated by the physician. However, this study concerned about the change in the range and warned the physician in case of low plt and RBC count before antibiotic administration. During hematologic investigation, we compared the platelet count with the first laboratory report on day of admission and the second plt count after antibiotic administration (at least one week after the first report). In addition, to increase sensitivity of RBC and platelet counts, the lower count limit for anemia and thrombocytopenia was not set. We used the comparison between the RBC and plt counts on day of antibiotics admission and the counts after one week following hospital admission . T test was used to determine the correlation between the investigated results before and after antibiotics receiving.

Results

Laboratory test was performed before and at least one week after antibiotics administration. In all cases, we found second laboratory finding by about 1 week after the first laboratory finding. The RBC paired mean count in T test showed singificant difference between two sets of data (P value< was 0.0001). The difference between the mean of each group was 0.71 and the R2 was 0.765 (Figure 1).

The platelet counts before and after administration showed a difference of 90 counts per liter in the mean counts. Additionally, paired two-tailed T test showed p value fell into less than 0.05 (Figure 1). The paired two-tailed T-test results are shown in Table II. The other parameters in anemia are hemoglobin and hematocrit. These parameters are related to RBC count and decrease in anemia. The relation between this parameter and other red blood cells indices shows hemolytic anemia (28).

The hematocrit (Hct) and hemoglobin (Hb) contents were compared on the first day of admitting and after one week of receiving antibiotics and significant difference was observed ((p-value= 0.000061 vs. p-value= 0.000032, respectively). The summarized data are shown in Figure 1 and Table II. In addition, the RBC mean count before and after administration were 4.53 to 3.82 *1012/L, respectively. This change for the platelet (plt), Hb and Hct were 323.5 to 232.5 *109/L, 13.61 to 11.46 mg/dL and 40.83 to 34.38 %, respectively.

[DOI: 10.18502/ijpho.v9i1.291]

Table I: The frequency of antibiotics used in the PICU

Antibiotic	Frequency of use	dose
ceftriaxone	38.2%	50 mg/ kg in shigelloses
		70 mg/kg in pneumonia
clindamycin	23.3%	10 mg/kg every day
Clarithromycin	19.6%	5-10 mg/kg every day
acyclovir	12.1%	10 mg/kg every day
others	6.8%	----------

Table II: Paired t test analysis table

Reported item	Platelet count	RBC count	Hct	Hb
P value	P<0.0001	P<0.0001	P<0.0001	P<0.0001
P value summary	0.000025	0.000051	0.000061	0.000032
Are means significant different? (P < 0.05)	Yes	Yes	Yes	Yes
One- or two-tailed P value?	Two-tailed	Two-tailed	Two-tailed	Two-tailed
t, df	t=30 df=110	t=11.14 df=112	t=7.580 df=224	"t=7.580 df=224"
Mean of differences	91.49 ± 14.54	0.7159 ± 0.09445	6.443 ± 0.8501	2.148 ± 0.2834
95% confidence interval	62.98 to 120.0	0.5885 to 0.8433	4.777 to 8.110	1.592 to 2.703
R squared	0.9	0.5257	0.2041	0.2041

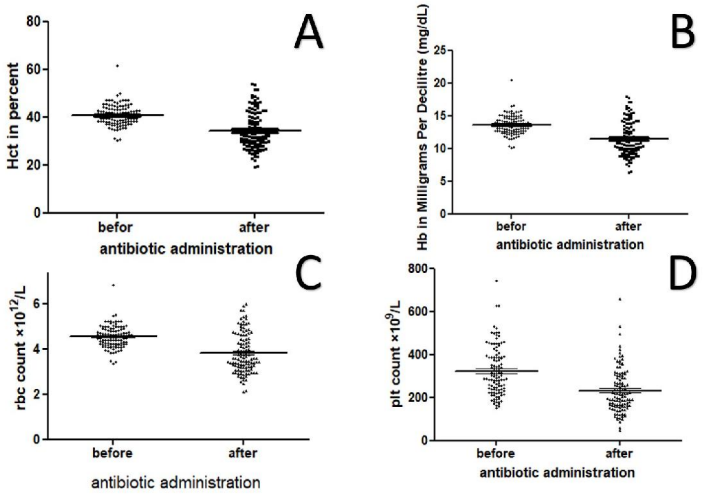

Figure 1. the difference between RBC count, plt count, hematocrit, and hemoglobin mean before and after antibiotics administration, A) hematocrit in percent B) hemoglobin in gram per deciliter C) RBC count D plt count

[DOI: 10.18502/ijpho.v9i1.291]

Discussion

DIHA and DIT are rare conditions in patients consuming antibiotics but it is caused by a broad spectrum of antibiotics and it can be life-threating especially in pediatric cases (29). DIIHA usually begins 1 to 2 weeks after receiving drugs, and terminates after these toxic chemicals removal (30). This threat is more important when the child has other serious conditions such as chronic disease (31). Based on the Naranjo algorithm, we can score the patient for estimating the probability of adverse drug reactions. Naranjo et al., have used 10 parameters to find this effect. They investigated children, who had decrease in RBC count, plt count, Hct and Hb, and they found a count increase after stopping the antibiotics (32). Finding the difference between the admitted patients in ICU before and after antibiotics administrations confirmed that most of this effect was caused by the antibiotic administration. The paired T test showed difference in RBC count, Plt counts, hematocrit, and hemoglobin means 0.71×1012 /L, 91.49×109/L , 6.44%, and 2.14 g/dl; respectively. This finding showed that the hemolytic anemia and thrombocytopenia were induced by antibiotics. The relation between RBC count, Hct, and Hb showed a mild microcytic anemia. In a study by Konstantinos et al, the β-lactams were associated with adverse events but these events were mild under proper dosing and could be controlled in admitted patients (24). Eslami Z et al., investigated thrombocytopenia and associated factors in neonates admitted to NICU (1). They showed thrombocytopenia in 350 neonates who were admitted to NICU. In other words,28.5% had thrombocytopenic from which 75.3% were primary and 24.7% were delayed. Moreover, they found that thrombocytopenia was associated with sepsis, intrauterine growth retardation sepsis, asphyxia, gestational diabetes mellitus, maternal hypertension, and prematurity. This finding is in line with our study results on thrombocytopenia in pediatric patient admitted to NICU. The antibiotics can induce hemolysis and platelet destruction. Also, toxic situation, especially infection in pediatric and adult ages, can induce anemia and thrombocytopenia. Behnaz F et al in a study investigated hematologic manifestations of brucellosis in 238 patients diagnosed with brucellosis and showed that thrombocytopenia (Platelet < 150.000/ mm3) in (24/200) 12% and pancytopenia in (3/200) 1.5%of patients were present (20). This finding confirmed that the toxic situation and chronic infection can cause pancytopenia. In addition, this finding matched our study as the toxic situation and the antibiotic administration can enhance their damaging effect and but include a synergetic effect. This study showed the mild DIHA and DIT form in patients who received antibiotics, which was evident as a result of difference between the mean RBC count, Plt count, hemoglobin, and hematocrit before and after antibiotics administration. Due to administration of different drugs, the mechanism of the hemolysis is not clear but in most patients whose third laboratory test result was used(after complete treatment and stoping administration of antibiotic) the RBC count, plt count, hemoglobin, and hematocrit increased to normal range. Enoli De Silva et al., in a study showed that the drug can affect platelet production called “drugs induced mylosuppression. The other mechanism which is suggested for DIT is destruction of the platelets in the peripheral blood called “drug- induced platelet destruction.” Both mechanisms caused thrombocytopenia and in case of severity it can be life-threatening, causing internal bleeding. The main drugs which have this effect are heparin and antibiotics (33). Heparin is administrated in patients which have thrombotic problem, but antibiotics are administrating broad spectrum of patients with variety of diseases. The heparin induces platelet

[DOI: 10.18502/ijpho.v9i1.291]

destruction in the peripheral blood but antibiotics also affect megakaryocyte and platelet production. The latter is the effect of antibiotics administration in the first week and it has more severe response to platelet destruction by immune system in peripheral blood(34). This effect leads to impaired hematopoiesis, pancytopenia, and a higher susceptibility to infections (35). The other adverse effect of antibiotics is the platelet function. Matthew et al. in a case study reported the Piperacillin–tazobactam as an antibiotic which can affect the platelet function leading to patient to bleeding (36).

Conclusion

Contrary to prior studies, no risk of In this study, we found the thrombocytopenia as an adverse drug effect, occurring in pediatric ward. Therefore, it is recommended to consider thrombocytopenia in children with chronic diseases, especially in anemic or thrombocytopenic children. Physicians should consider these effects when patients have borderline platelet and RBC counts.

Acknowledgment

The authors would like to thank all staff of Amir Kabir hospital in Arak University of Medical Sciences and the physicians who helped us collect the sample. We are also thankful of the nurse and laboratory professions who contributed us in collecting the laboratory reports of the patients.

Conflict of interest

Authors declared no conflict of interst.

References

1. Mohammad Pour N, Eslami Z, Lookzadeh M, Noorishadkam M, Hashemi A, Ghilian R, et al. Thrombocytopenia and Associated Factors in Neonates Admitted to NICU during Years 2010_2011. IJPHO 2013;3(1):28-24.
2. Vincent J-L, Castro P, Hunt BJ, Jörres A, Praga M, Rojas-Suarez J. Thrombocytopenia in the ICU: disseminated intravascular coagulation and thrombotic microangiopathies—what intensivists need to know. BioMed Central 2018. 1-9.
3. Williamson DR, Lesur O, Tétrault J-P, Pilon D. Drug-induced thrombocytopenia in the critically ill: a case-control study. Ann Pharmacother 2014;48(6):697-704.
4. Arndt PA, Leger RM, Garratty G. Serologic characteristics of ceftriaxone antibodies in 25 patients with drug-induced immune hemolytic anemia (CME). Transfusion 2012;52(3):602-612.
5. Garratty G, Arndt P. Drugs that have been shown to cause drug-induced immune hemolytic anemia or positive direct antiglobulin tests: some interesting findings since 2007. Immunohematology 2014;30(2):66-79.
6. Moradabadi AR, Farsinejad AR, Fatemi A. Modified PCR-RFLP for detection of JAK2V617F mutation in patients with myeloproliferative neoplasm. Sci J Iran Blood Transfus Organ 2017, 14(4): 289-294
7. Sim D, Yu J, Jeong J, Koh YI. Ciprofloxacin-induced immune-mediated thrombocytopenia: No cross-reactivity with gemifloxacin. J Clin Pharm Ther 2018;43(1):134-136.
8. Sukhal S, Gupta S. Drug-induced immune haemolytic anaemia caused by levofloxacin. Singapore Med J 2014;55(8):e136-e142.
9. Shander A, Javidroozi M, Ashton E. Drug-induced anemia and other red cell disorders: a guide in the age of polypharmacy. Curr Clin Pharmacol 2011;6(4):295-303.
10. Wright DE, Rosovsky RP, Platt MY. Case 36-2013: A 38-Year-Old Woman with Anemia and Thrombocytopenia. N Engl J Med 2013;369(21):2032-2043.
11. Basseri RJ, Schmidt MT, Basseri B. Autoimmune hemolytic anemia in

[DOI: 10.18502/ijpho.v9i1.291]

treatment-naive chronic hepatitis C infection: a case report and review of literature. J Clin Gastroenterol Hepatol 2010;3(5):237-242.
12. Shrimali J, Patel H, Gumber M, Kute V, Shah P, Vanikar A, et al. Ceftriaxone induced immune hemolytic anemia with disseminated intravascular coagulation. Indian J Crit Care Med 2013;17(6):394-397.
13. Chapin J, Terry HS, Kleinert D, Laurence J. The role of complement activation in thrombosis and hemolytic anemias. Transfus Sci 2016;54(2):191-198.
14. Khosravi A, Yáñez A, Price JG, Chow A, Merad M, Goodridge HS, et al. Gut microbiota promote hematopoiesis to control bacterial infection. Cell host & microbe 2014;15(3):374-381.
15. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366(20):1881-1890.
16. Tahmasebi L, Haghpanah S, Rezaei N, Karimi M. Red Cell Enzymopathies in Patients with Hemolytic Anemia in Southern Iran: Case Series. IJPHO 2016;6(4): 3-7.
17. Behnaz F, Mohammadzadeh M. Hematologic manifestations of brucellosis. IJPHO2011;1(3):90-93.
18. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study II. N Engl J Med 1991;324(6):377-384.
19. Morimoto T, Sakuma M, Matsui K, Kuramoto N, Toshiro J, Murakami J, et al. Incidence of adverse drug events and medication errors in Japan: the JADE study. J Gen Intern Med 2011;26(2):148-153.
20. Scripcaru G, Mateus C, Nunes C. Adverse drug events—Analysis of a decade. A Portuguese case-study, from 2004 to 2013 using hospital database. PloS one 2017;12(6):e0178626.
21. Vardakas KZ, Kalimeris GD, Triarides NA, Falagas ME. An update on adverse drug reactions related to β-lactam antibiotics. Expert Opin Drug Saf 2018;17(5):499-508.
22. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost 2009;7(6):911-918.
23. Arnold D, Kukaswadia S, Nazi I, Esmail A, Dewar L, Smith J, et al. A systematic evaluation of laboratory testing for drug-induced immune thrombocytopenia. J Thromb Haemost 2013;11(1):169-176.
24. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med 2007;357(6):580-587.
25. Barcellini W, Fattizzo B. Autoimmune hemolytic anemia-progress in emerging treatment options. Expert Opin Orphan Drugs 2018;6(4):273-282.
26. Garratty G. Immune hemolytic anemia caused by drugs. Expert Opin Drug Saf 2012;11(4):635-642.
27. Pacifici GM. Clinical Pharmacology of the Antimalarial Quinine in Children. Int J Pediatr 2018;6(4):7451-7465.
28. De Silva E, Kim H. Drug-induced thrombocytopenia: Focus on platelet apoptosis. Chem Biol Interact 2018;1-9.
29. Patil A, Khillan V, Thakur M, Kale P, Bihari C. Antimicrobial-Induced Cytopenia and Bone Marrow Hypocellularity in Patients with Cirrhosis. Bone Marrow Res 2018;2018:6-11.
30. Garratty G. Immune hemolytic anemia caused by drugs. Expert Opin Drug Saf 2012;11(4):635–42
31. Luzzatto L, Arese P. Favism and glucose-6-phosphate dehydrogenase deficiency. N Engl J Med 2018;378(1):60-71.
32. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981.30(2):239–45.

[DOI: 10.18502/ijpho.v9i1.291]

33. De Silva E, Kim H. Drug-induced thrombocytopenia: Focus on platelet apoptosis. Chem Biol Interact 2018;284:1–11.
34. Patil A, Khillan V, Thakur M, Kale P, Bihari C. Antimicrobial-Induced Cytopenia and Bone Marrow Hypocellularity in Patients with Cirrhosis. Bone Marrow Res 2018;2018:1–6.
35. Ianiro G, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. Gut 2016;65(11):1906-1915.
36. Bower M, Borders C, Schnure A, Groysman L, Tran M-H. Platelet Dysfunction and Intracerebral Hemorrhage in a Patient Treated with Empiric Piperacillin–Tazobactam in the Neurocritical Care Unit. World Neurosurg 2018;114:204-210.

[DOI: 10.18502/ijpho.v9i1.291]