Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: http://dx.doi.org/10.18203/2319-2003.ijbcp20150388

Research Article

# Occurrences of thrombocytopenia with valproic acid used for psychiatric indication

**Jharna Sahu[1], Rajesh Hishikar[2], Manoj Kumar Sahu[3], Presenjit Raut[1], Augustin Kumar Bharti[2]*, Suraj Agrawal[2]**

[1]Department of Pharmacology, Late Shree Lakhiram Agrawal Memorial Government Medical College, Raigarh, Chhattisgarh, India, [2]Department of Pharmacology, Pt. Jawahar Lal Nehru Memorial Medical College & Dr. Bhim Rao Ambedkar Memorial Hospital, Raipur, Chhattisgarh, India, [3]Department of Psychiatry, Pt. Jawahar Lal Nehru Memorial Medical College & Dr. Bhim Rao Ambedkar Memorial Hospital, Raipur, Chhattisgarh, India

**Received:** 27 June 2015
**Revised:** 06 July 2015
**Accepted:** 18 July 2015

***Correspondence to:**
Augustin Kumar Bharti,
Email: akrbharti@gmail.com



## ABSTRACT

**Background:** The main aim of this study is to find out the effect of valproic acid on platelet count and to know the possible risk factors for thrombocytopenia in patients taking valproate (VPA).
**Methods:** On 72 patients having psychiatric indication, a longitudinal observational study was designed and conducted from February 2012 to July 2013 at Department of Psychiatry (out-patient department) of Pt. Jawahar Lal Nehru Memorial Medical College and Dr. Bhim Rao Ambedkar Memorial Hospital, Jail Road, Raipur, Chhattisgarh. Platelet count was monitored and determined using an automatic coulter analyzer. The patients were followed up to 6 months. Statistical tool standard deviation ± was used for statistical analysis. $p<0.05$ is considered as statistically significant.
**Results:** Total percentage of thrombocytopenia was found to be 12.5%; among that males constitute 9.8% and females 19.04%. The maximum number of cases falls in the age group between 51 and 60 years (55.5%). The major diagnostic group was reported to be consisted of mania (40.4%), followed by resistant cases of schizophrenia (25%) and then bipolar affective disorder (23.6%). The study indicated that maximum patients suffered from mild thrombocytopenia (11.1%) and (1.4%) patients have moderate thrombocytopenia. The mean time from exposure to VPA therapy to the first episode of thrombocytopenia was reported 92 days.
**Conclusions:** Our findings underlined the importance of monitoring platelet counts in patients treated with VPA. This monitoring should be continued indefinitely on monthly basis. The studies indicate that the demands of more vigilant monitoring of patients should occur in age of 50-60 years, and result of entire studies indicates that females were found to be subjected to incidences of thrombocytopenia especially.

**Keywords:** Thrombocytopenia, Valproate, Bipolar affective disorder, Schizophrenia

## INTRODUCTION

The therapeutic effects of valproate (VPA) therapy in psychiatric conditions are most substantially recognized in bipolar disorder. VPA shows the most promising efficiency in treating mood as well as anxiety disorders, with possible efficiency in the treatment of agitation and impulsive aggression and less convincing therapeutic response in treating psychosis, alcohol withdrawal, or dependence.[1]

There have been wide-ranging reports of thrombocytopenia and other forms of platelet dysfunction as side effect of VPA

therapy are noted, but exact incidence is not known.[2] No reports have specifically described on increased, occurrence of thrombocytopenia associated with VPA use in patient well defined. Thrombocytopenia has been reported in 6-33% of adult patients with epilepsy taking VPA, but a lowering of platelet count was noted in almost all patients that appeared to be dose related.[3]

Thrombocytopenia is one of the most common side effects associated with VPA therapy, with incidence ranging from 1% to 30%.[4,5] It is mild to transient in most cases which usually resolves spontaneously on dosage reduction or withdrawal of the drug.[6,7] Available reports showed that thrombocytopenia associated with VPA therapy has been reported to resolve without interruption of VPA treatment[8] and has also been reported to endure over time or to have an erratic course.[5] Reports on the use of VPA with psychiatric patients have described a drop in platelet count without thrombocytopenia or with a minimal incidence of thrombocytopenia[9,10] without any associated adverse clinical events related to this findings.[11] The study shows the effect of valproic acid on platelet count in patients receiving VPA therapy in psychiatry out-patient department (OPD) for bipolar disorders, mania, mood disorders, etc. The dose related and usage of high doses could be considered possible risk factors for thrombocytopenia in patients taking VPA therapy.

## METHODS

### *Study design*

Our longitudinal observational study was designed and conducted from February 2012 to July 2013 at Department of Psychiatry OPD of Pt. Jawahar Lal Nehru Memorial Medical College and Dr. Bhim Rao Ambedkar Memorial Hospital, Jail Road, Raipur, Chhattisgarh. Consecutive patients meeting inclusion and exclusion criteria were enrolled in the study. The study had clearance from Institutional Ethical Committee. Informed Consent was taken from all the patients involved in the study after proper counseling and acceptances. The study was conducted for a period of 1½ year. One year was used for the enrollment and 6 months for follow-up of patients.

Selection of study population was done on following inclusion and exclusion criteria.

### *Inclusion criteria*

1. Sex - Male/female
2. Age - >18 years
3. New subject on VPA treatment for at least 1-month duration were considered.

### *Exclusion criteria*

1. Patient on concomitant drug with known hematological side effect
2. Patient with medical illness having hematological consequence
3. Patient having history of treatment with VPA or other drug known to cause thrombocytopenia.

### *Investigational plan (Method adopted for platelet count)*

1. Study was performed on a single peripheral venous blood sample drawn from the antecubital vein without vein occlusion and transferred into glass container containing 3.8% trisodium citrate and was stored at 37°C and test was performed randomly
2. The platelet count was determined using an automatic coulter analyzer (An apparatus for cell counting)
3. After baseline platelet count of patients under VPA treatment, their platelet count was performed during regular monthly follow-up for 6 months.

### *Sample size*

Total 100 patients were enrolled, of which, only n=72 patients came for regular follow-up.

### *Tools and statistics*

Descriptive statistics (mean and standard deviation as appropriate) were computed for the study sample. $\chi^2$ test and Z test were used for statistical analysis. $p<0.05$ is considered significant.

## RESULTS

The total of 100 patients was enrolled, of which, 72 came for regular follow-up. Results are represented. Figure 1 shows results of 5 male patients developed thrombocytopenia, so the percentage of thrombocytopenia in male is 9.8%. The total number of females registered was found to be 21 and 4 females developed thrombocytopenia. So the percentage of thrombocytopenia in female is 19.04%. Total percentage of thrombocytopenia is 12.5% percentage among 72 patients.

Figure 2a and b shows the percentage and number of patient with age-wise distribution of thrombocytopenia attending psychiatric OPD taking VPA therapy. The number of cases in the age group – 21-30 years is 37.5%, followed by 31-40 years 23.6%. Patients developing thrombocytopenia in age group 41-50 years were 22.1% and 51-60 years was 55.5%. Totally, 9 patients had been reported thrombocytopenia.

Figure 3 shows the mean platelet count variation over baseline and after VPA exposure from 1 to 6 months of total 72 patients. The downfall of mean platelets counts from baseline after VPA exposure over 1-6 months period noted. Although the fall in mean platelet count is not in the range

of thrombocytopenia, definitely there is fall in mean platelet count from baseline. Maximum fall in mean platelet count from baseline is seen on 5th month that is 2,30,000 (µl). This decrease in platelet count is also statistically significant after 3 months having $p<0.05$ that is: 3 months $p=0.0172$, 4 months $p=0.0016$, 5 months $p=0.0117$, 6 months $p=0.0164$.

Figure 4 shows a frequency distribution of patient in different range of platelet count during six months of VPA therapy (platelets count in µl).

Figure 5 shows the number of patients with thrombocytopenia with different dose of valproic acid and is statistically significant. 750-1000 mg shows significant age-dependent incidences of lower platelets counts.

## DISCUSSION

Thrombocytopenia is one of the most common side effects associated with VPA therapy; however, the exact mechanism of VPA associated thrombocytopenia is unclear. This study was done in a tertiary care referral hospital in OPD patients. Totally, 100 patients were registered, over a period of 1½ year (between Feburary-2012 and July-2013) but only 72 came for regular follow-up. The percentage of thrombocytopenia in this study was found to be 12.5%. In previous study, the reported frequency of VPA-induced thrombocytopenia has varied greatly and ranged from 0% to 32%.[7,10,12-19] The strength of our study is that we conducted a longitudinal observational study in which the sequential assessment of platelets counts was done monthly to analyze the effect of VPA on platelet count.

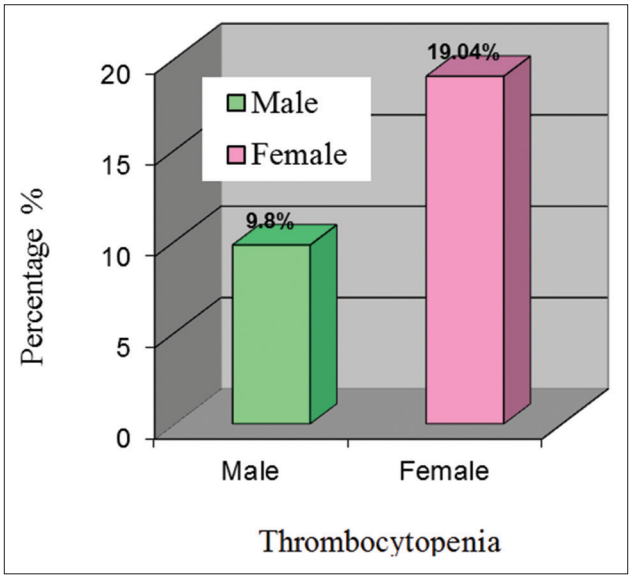


**Figure 1: Percentage of thrombocytopenia in patient taking valproate therapy.**

In our study, the mean time from VPA therapy exposure to the first observed episode of thrombocytopenia was 92 days (ranged 30-180 days). It is likely that the true onset was sooner but was first observed at 92 days.

Previous studies have indicated that the interval between the initiation of VPA treatment and platelet counts is variable among patients who develop thrombocytopenia, ranging from 8 days to 16 months.[6,16]

In females, the results of our present study shows the percentage of thrombocytopenia is reported 19.04% and in males 9.8%. The underlying mechanism for gender difference in platelets counts is unclear; it could be that the immune system of women is more adept in generating a VPA-induced thrombocytopenia or those women are more susceptible to VPA-induced bone marrow suppression. Thrombocytopenia occurs in different mechanism. Although some drugs causes the bone marrow suppression or pressuring the megakaryocyte in producing thrombocytopenia,[4,20] higher percentage of thrombocytopenia was seen in age group of 51-60 years, it was 55.6% and in age group 41-50 years, it was 22.2%. There have been several studies assessing the incidence of thrombocytopenia who received VPA. The two studies have been published that attempt to identify the prevalence of this blood dyscrasia in the psychiatric population.[10,19,21]

Some authors have seen that VPA-induced thrombocytopenia is dose-related, and usage of high doses can be considered as a potential risk factor.[22,23]

It has also been reported that the VPA-induced thrombocytopenia resolves without interruption of VPA

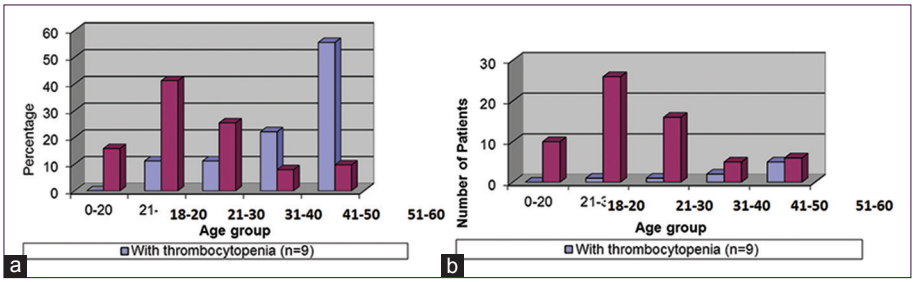


**Figure 2: (a) Percentage of patient with age-wise distribution of thrombocytopenia attending psychiatric out-patient department taking valproate therapy, (b) Number of patient with age-wise distribution of thrombocytopenia attending psychiatric out-patient department taking valproate therapy.**

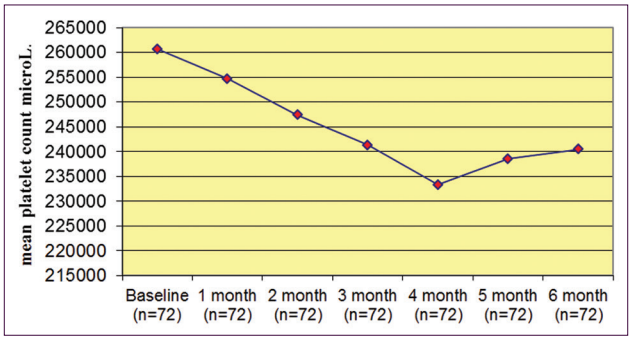


**Figure 3: Mean platelet count variation over baseline and after valproic acid exposure from 1 to 6 month of total 72 patients.**

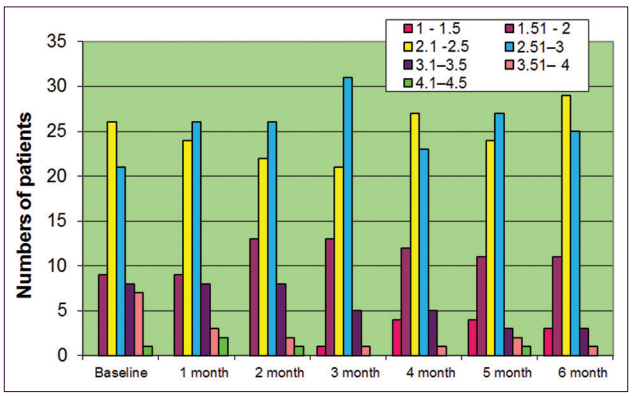


**Figure 4: A frequency distribution of patient in different range of platelet count during 6 months of valproate therapy (platelets count in µL).**

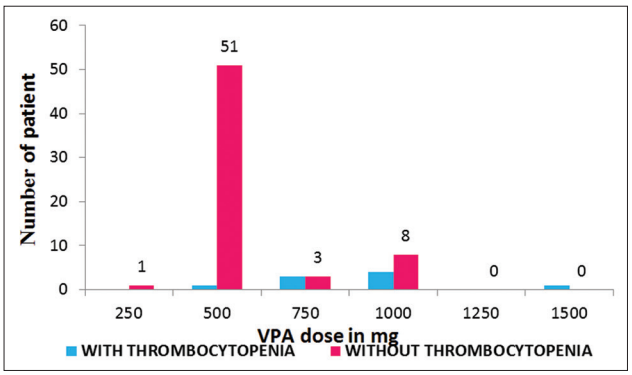


**Figure 5: The number of patients with thrombocytopenia with different dose of valproic acid and is statistically significant.**

treatment that means thrombocytopenia is transient and shows self-resolving phenomena (increase in platelet count) which may predict that there is some hidden mediator for that transient recovery from thrombocytopenia in some subjects during the course of the study.[24,25] So future researches should be required for this phenomenon.

In our investigation, all the patients had VPA dose in range of 250-1500 mg, and they developed thrombocytopenia that may be due to one possible route VPA inhibits the platelet arachidonate cascade with a mechanism similar to aspirin.[26,27] Another interesting hypothesis is that hypersensitivity to VPA may lead to the development of drug-induced platelet antibodies and, consequently, thrombocytopenia and alteration of the bleeding time: drug-induced platelet antibodies usually belong to the immunoglobulin G (IgG) class, but occasionally IgM and/or IgA antibodies may be present.[28,29]

The limitations of this study were the relatively small number of subjects and lack of control group. Despite these limitations, our evidence shows that thrombocytopenia does occur in psychiatric patients taking VPA and suggests that elderly patients and females patients are more susceptible to these effects.

## CONCLUSION

We state that our findings underlined the importance of strict monitoring platelet counts in patients treated with VPA therapy, as advised in the product label, before the onset and during the therapy. This monitoring should be continued indefinitely at least on a monthly basis. More vigilant monitoring of platelet should occur in the higher age group and in females. However, the discontinuation of the drug is not necessary when the platelet count is within the reference range (>1.5 lakh µL) because these alterations have little clinical importance. Most of the time, thrombocytopenia is mild and transient that resolve spontaneously.

## ACKNOWLEDGMENTS

We would like to thank the faculty members and the technicians of Pharmacology, Biochemistry and Psychiatry Department for their full support, suggestive criticism and effortless contribution in making this work successful.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Eliopoulos H. Thrombocytopenia Coincident With Depakote Therapy. Abbott Park, III, Abbott Pharmaceutical Products Division, Professional Information and Product Safety; 1993.
2. Neophytides AN, Nutt JG, Lodish JR. Thrombocytopenia associated with sodium valproate treatment. Ann Neurol. 1979;5(4):389-90.
3. Covanis A, Gupta AK, Jeavons PM. Sodium valproate: monotherapy and polytherapy. Epilepsia. 1982;23(6):693-720.
4. Smith FR, Boots M. Sodium valproate and bone marrow suppression. Ann Neurol. 1980;8(2):197-9.
5. May RB, Sunder TR. Hematologic manifestations of long-term valproate therapy. Epilepsia. 1993;34(6):1098-101.
6. Delgado MR, Riela AR, Mills J, Browne R, Roach ES.

Thrombocytopenia secondary to high valproate levels in children with epilepsy. J Child Neurol. 1994;9(3):311-4.
7. Winfield DA, Benton P, Espir ML, Arthur LJ. Sodium valproate and thrombocytopenia. Br Med J. 1976;2(6042):981.
8. Eastham RD, Jancar J. Sodium valproate and platelet counts. Br Med J. 1980;280(6208):186.
9. Calabrese JR, Markovitz PJ, Kimmel SE, Wagner SC. Spectrum of efficacy of valproate in 78 rapid-cycling bipolar patients. J Clin Psychopharmacol. 1992;12 1 Suppl:53S-6.
10. Tohen M, Castillo J, Baldessarini RJ, Zarate C Jr, Kando JC. Blood dyscrasias with carbamazepine and valproate: a pharmacoepidemiological study of 2,228 patients at risk. Am J Psychiatry. 1995;152(3):413-8.
11. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. JAMA. 1994;271(12):918-24.
12. Richardson SG, Fletcher DJ, Jeavons PM, Stuart J. Sodium valproate and platelet function. Br Med J. 1976;1:221-2.
13. von Voss H, Petrich C, Karch D, Schulz HU, Göbel U. Letter: sodium valproate and platelet function. Br Med J. 1976;2(6028):179.
14. Coulter DL, Wu H, Allen RJ. Valproic acid therapy in childhood epilepsy. JAMA. 1980;244(8):785-8.
15. Loiseau P. Sodium valproate, platelet dysfunction, and bleeding. Epilepsia. 1981;22(2):141-6.
16. Barr RD, Copeland SA, Stockwell ML, Morris N, Kelton JC. Valproic acid and immune thrombocytopenia. Arch Dis Child. 1982;57(9):681-4.
17. Ganick DJ, Sunder T, Finley JL. Severe hematologic toxicity of valproic acid. A report of four patients. Am J Pediatr Hematol Oncol. 1990;12(1):80-5.
18. Anderson GD, Lin YX, Berge C, Ojemann GA. Absence of bleeding complications in patients undergoing cortical surgery while receiving valproate treatment. J Neurosurg. 1997;87(2):252-6.
19. Conley EL, Coley KC, Pollock BG, Dapos SV, Maxwell R, Branch RA. Prevalence and risk of thrombocytopenia with valproic acid: experience at a psychiatric teaching hospital. Pharmacotherapy. 2001;21(11):1325-30.
20. Bharti AK. Incidences of thrombocytopenia in psychiatric population taking valproic acid: Demand's clarification and attention. Int J Pharm Sci Rev Res. 2014;27(1):332-5.
21. Trannel TJ, Ahmed I, Goebert D. Occurrence of thrombocytopenia in psychiatric patients taking valproate. Am J Psychiatry. 2001;158(1):128-30.
22. Fawcett RG. Dose-related thrombocytopenia and macrocytic anemia associated with valproate use in bipolar disorder. J Clin Psychiatry. 1997;58(3):125.
23. Kaufman KR, Gerner R. Dose-dependent valproic acid thrombocytopenia in bipolar disorder. Ann Clin Psychiatry. 1998;10(1):35-7.
24. Hoffman LM. Sodium valproate and thrombocytopenia. Can Med Assoc J. 1982;126(4):358-9.
25. Vasudev K, Goswami U, Kohli K. Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. Psychopharmacology (Berl). 2000;150(1):15-23.
26. Kis B, Szupera Z, Mezei Z, Gecse A, Telegdy G, Vécsei L. Valproate treatment and platelet function: the role of arachidonate metabolites. Epilepsia. 1999;40(3):307-10.
27. Szupera Z, Mezei Z, Kis B, Gecse A, Vécsei L, Telegdy G. The effects of valproate on the arachidonic acid metabolism of rat brain micro vessels and of platelets. Eur J Pharmacol. 2000;387(2):205-10.
28. Chong BH. Drug-induced immune thrombocytopenia. Platelets 1991;2(4):173-81.
29. Rizvi MA, Shah SR, Raskob GE, George JN. Drug-induced thrombocytopenia. Curr Opin Hematol. 1999;6(5):349-53.

**Cite this article as:** Sahu J, Hishikar R, Sahu MK, Raut P, Bharti AK, Agrawal S. Occurrences of thrombocytopenia with valproic acid used for psychiatric indication. Int J Basic Clin Pharmacol 2015;4:765-9.