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Recommended Citation

Shah, A. A., Syed, A. A., Zafar, S. B., Awan, S. (2019). The use of folic acid in dengue: Has it any value?. *Tropical Doctor*, 49(2), 85-87.

Available at: https://ecommons.aku.edu/pakistan_fhs_mc_med_intern_med/129

The use of folic acid in dengue: has it any value?

Folic acid in dengue

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Key Words: Dengue; Folic acid; Thrombocytopenia

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Abstract

Folic acid is used in dengue patients. Our study aims to compare the duration of recovery of thrombocytopenia in patients with dengue infection who received folic acid and those who did not. We retrospectively reviewed the medical records of adult patients admitted over six years with a diagnosis of dengue. Of 2,216 patients, 1464 fulfilled the inclusion criteria. Group A were those patients who received folic acid and group B were those who

did not. 1322 (90.3%) patients received folic acid. Mean time period required for platelets to double the nadir was 1.7 (\pm 2.2) days days in both groups A and B (p value 0.89). In conclusion, there is no significant difference in the recovery of thrombocytopenia in patients with dengue fever who received folic and those who did not receive folic acid.

Introduction

South Asia has been declared as an endemic area of dengue infection by the World Health Organization (WHO). Pakistan has been hit by several dengue epidemics since 1994 and now is an endemic area.⁽¹⁾ Despite being a growing threat to almost whole world there is still no specific treatment for dengue infection, and treatment largely remains supportive. Several specific treatments have been tried in patients with no robust data to suggest any therapeutic options as standard. Such include steroids,⁽²⁾ calcium and vitamin D supplements, ⁽³⁾ papaya leaves extract, ⁽⁴⁾ chloroquine, ⁽⁵⁾ immunoglobulin,⁽⁶⁾ folic acid ^(7, 8) and so on. Many of these treatment regimens focus on rapid improvement of thrombocytopenia.

Folic acid is frequently used without any scientific basis.⁽⁷⁾ Up to 30% of paediatric patients with dengue infection received folic acid in addition to other supportive measures in a typical Indian study.⁽⁸⁾ The rationale for folic acid use in dengue is not clear. It may be prescribed because of its low cost, its few adverse effects and its role as a haematinic. Interestingly, one study ⁽⁹⁾ showed that the replication of dengue viruses inhibited by methotrexate was restored by folinic acid, a natural folate. Hence it is possible that folic acid may actually be deleterious in dengue!

Materials and methods

This study was conducted at the Department of Medicine of the Aga Khan University Hospital Karachi, Pakistan, which is a 700 bed tertiary care academic medical institute

receiving patients not only from Karachi, which is the most populous city of Pakistan with an estimated population in excess of 20 million, but also from rest of the country.

Ethical approval was obtained for the study from the institutional Ethical Review Committee (4095-Med-ERC-16).

Our primary objective was to determine the duration of recovery of thrombocytopenia in patients with dengue infection who received and did not receive folic acid during hospitalization. The secondary objectives were to compare the mortality, ICU stay, length of stay, and creatinine among patients with dengue infection between the two groups. We reviewed the medical records of all patients over 16 years of age admitted in the department of Medicine at our hospital from 1st June 2007 to 31st December 2013 with a diagnosis of dengue infection who had evidence of doubling of platelets from an earlier nadir. All patients who had received platelet transfusion were excluded from the study. A case of dengue fever was defined as a patient admitted with fever who had a positive dengue IgM antibody or dengue antigen test. The lowest platelet count after admission was recorded. Subsequent platelet counts double the nadir were also recorded during the hospital stay, as were creatinine levels at the time of admission and discharge, and the length of hospital stay. Group A were those patients who received folic acid and group B were those who did not.

Data regarding frequency of deaths and ICU stay were also collected and compared between the two groups and compared. P values <0.05 were deemed significant. Fisher's exact T test and Mann-Whitney *U* test were used to compute P values. All analyses were conducted by using the Statistical Package for Social Science SPSS 19.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.).

Results

Medical records of 2,216 adult patients who were admitted in our hospital with a diagnosis of dengue infection from 1st June 2007 to 31st December 2013 were analysed. 1464 fulfilled our inclusion criteria. Their mean age was 36.6 (\pm 15.0) years. The mean lowest platelet count was 35.5 (\pm 13.2) $\times 10^9/L$. The mean doubled platelet count from nadir was 81.3 (\pm 35.2) $\times 10^9/L$. The dose of folic acid received by each patient was 5mg per day (Table 1).

Out of the 1464 patients, 1322 (90.3%) received folic acid. The mean time period required for platelets to double the nadir was 1.7 (\pm 2.2) days and 1.7 (\pm 2.2) days, respectively, in groups A and B ($P = 0.89$) (Table 2). Only 11 patients required ICU admission and all of them belonged to group A ($P = 0.99$). Similarly, there were only two patients who died and both were of group A ($P = 0.99$).

The mean creatinine at admission was 107.9 (\pm 31.7) and 105 (\pm 31.1) $\mu\text{mol/L}$ in group A and B respectively ($P = 0.30$), and at discharge 107 (\pm 31.5) $\mu\text{mol/L}$ and 105.9 (\pm 35) $\mu\text{mol/L}$, respectively ($P = 0.69$).

Data extracted are shown in Tables 1 & 2.

Table 1. Baseline characteristics of study population (n=1464)

Mean age	36.5 ± 15.0 years
Mean lowest platelet count	35.5 ± 13.2 x 10 ⁹ /L
Mean doubled platelet count from nadir	81.3 ± 35.2 x 10 ⁹ /L
Mean platelet doubling time	1.7 ± 2.2 days
Dose of folic acid received by each patient	5 mg per day
Mean length of hospital stay (days)	3.4 ± 3.9
Mean creatinine at admission (µmol/L)	107.5 ± 31.6
Mean creatinine at discharge (µmol/L)	106.8 ± 31.8

Table 2. Frequency and comparison of doubling time of platelets from nadir, creatinine, length of stay, ICU admission and mortality status in group A (dengue patients who received folic acid) and B (dengue patients who did not receive folic acid) (n=1464)

	Group A	Group B	<i>p</i> value
Mean age (years)	36.6 ± 14.9	35.9 ± 15.4	0.38
Mean lowest platelet count (x 10 ⁹ /L)	35.7 ± 13.3	34.5 ± 12.6	0.37
Mean doubled platelet count from nadir (x 10 ⁹ /L)	81.5 ± 35.3	79.5 ± 33.7	0.52
Mean Platelets doubling time from nadir (days)	1.7 ± 2.2	1.7 ± 2.2	0.89*
Mortality			
Yes	2 (0.15%)	0 (0%)	0.99**
No	1320 (99.84%)	142 (100%)	
ICU admission (no. of patients)			
Yes	11 (0.83%)	0 (0%)	0.99**
No	1311 (99.16%)	142 (100%)	

Mean length of hospital stay (days)	3.4 ± 3.9	3.6 ± 3.9	0.75*
Mean creatinine at admission (μmol/L)	107.8 ± 31.7	105 ± 31.1	0.30
Mean creatinine at discharge (μmol/L)	107 ± 31.5	105.8 ± 35	0.69

*Mann-Whitney *U* test

**Fisher's Exact test

Discussion

Our study showed that there was no significant difference in the duration of recovery of thrombocytopenia whether folic acid was taken or not. There was likewise no significant difference in length of hospital stay.

There is no specific treatment available for dengue fever and good supportive treatment is the mainstay of management,⁽¹⁰⁾ but the use of several drugs has been proposed.²⁻⁶⁾ Trials in vitro including anti-TNF antibodies,⁽¹¹⁾ celgosivir and ribavirin (antiviral agents),^(12, 13) have been undertaken without conclusive success.

Thrombocytopenia, being the most important manifestation of dengue, has been the target of most of these studies. Use of folic acid, despite the absence of scientific justification, is virtually ubiquitous.^(7, 8)

Conclusion

To the best of our knowledge, ours is the first of its kind assessing the effects of folic acid supplementation on several outcomes of dengue. This study presents only retrospective data, and we compared the doubling time from a nadir value of platelets rather than absolute values as a marker of recovery of thrombocytopenia. There is a need for prospective controlled studies to compare the effects of folic acid on both the recovery of thrombocytopenia and other parameters in patients with dengue. However, it seems that there is no significant value in the use of folic acid regarding recovery of thrombocytopenia in dengue.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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