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General Medicine

EXPLORATORY STUDY TO EVALUATE COAGULATION ABNORMALITIES IN MALARIA PATIENTS AND THEIR RELATIONSHIP IN THE OUTCOME OF THE DISEASE

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ABSTRACT **Background:-** Malaria is an important endemic disease in India and many tropical countries. It's a parasitic infection that leads to acute life threatening disease and poses a significant global health threat. It is estimated that about 250 million people are at risk of contracting malaria annually. It has been observed that malaria induces coagulation abnormalities which needs further evaluation. Our study deals with coagulation abnormalities in malaria and their relationship to outcome of the disease. **Methods:-** The study was carried out in a large teaching hospital in Mumbai over a period of 1 year. 74 patients were included in this study All the patients were from medical intensive care unit. Peripheral smear for malarial parasite was done on admission and blood samples collected for parasitic index and coagulation abnormalities in form of thrombocytopenia, prothrombin time (PT) / international normalized ratio (PT/INR), partial thromboplastin time (PTT) test, serum fibrinogen and fibrinogen degradation product (FDP). Other symptoms were also noted for evaluation. **Result:-** Maximum number of the patients were young adult males. Malena was the most common presenting symptom. Maximum number of patients had coagulation abnormalities. High parasitic index was associated with morbidity and mortality. P. falciparum was associated more with the coagulation abnormalities. Patients with severe coagulation abnormalities in form of DIC had the worst prognosis. Artesunate with doxycycline and blood and blood products helped in improving the outcome of the patients. **Conclusion:-** We could conclude that maximum number of patients had coagulation abnormalities and P. falciparum patients had more risk of developing coagulation abnormalities. Outcome worsened with the increasing severity of coagulation abnormality with Artesunate with doxycycline and blood and blood products improving the outcome of the patient.

KEYWORDS : Malaria, coagulation abnormalities, artesunate, doxycycline

INTRODUCTION

Malaria is the most important parasitic disease of a man. It is a protozoan disease transmitted by the bite of infected female Anopheles mosquito. Its transmission is in 103 countries affecting more than 250 million people and causing between 6 1 and 7 lac deaths each year. The disease is far from being solved and the health problem presented by the infection world wide are probably greater today than what it was yesterday.

Malaria is endemic in tropics and has always posed a major health problem. The nomination of malaria as a preeminent tropical disease is thus well deserved and the problem of treatment and control today are more complex and intractable than ever before.

Malaria is a disease which when severe affects almost all the organ systems be it kidneys, brain, heart, lungs, liver, hematological either in form of coagulopathy or hemolysis or other complications. Coagulation abnormality is one of the severe complications which needs further evaluation.

Our study deals with the changes in the blood coagulation system that occur in malaria, their various complications, their treatment either in form of drugs or in form of blood and blood products and their relationship to the outcome of the disease.

AIMS AND OBJECTIVES

1. To study demography of coagulation abnormality in malaria.
2. To study the clinical spectrum of coagulation in malaria.
3. To study the biochemistry of coagulation abnormality in malaria.
4. To study the effect of various drugs on the outcome in patients with coagulation abnormalities in malaria.
5. To study the effect of blood and blood products on the outcome in patients with coagulation abnormalities in malaria.
6. To study the relationship between the severity of coagulation abnormality and the mortality in patients with coagulation abnormalities in malaria.

MATERIAL AND METHODS

The aims and objectives of the study were to study demography of coagulation abnormality and clinical spectrum of coagulation in malaria, to study the biochemistry of coagulation abnormality, to study the effect of various drugs on the outcome in patients with coagulation abnormalities in malaria, to study the effect of blood and blood products on the outcome in patients with coagulation abnormalities in malaria and to study the relationship between the severity of coagulation abnormality and the mortality in patients with coagulation abnormalities in malaria.

This study was carried out in a large teaching hospital in Mumbai. The study was conducted over a period of one year and from May 2021 to May 2022 and data from 74 patients were included in this study. All patients studies were from the medical intensive care unit and were followed up during the hospital stay. Peripheral smear were done on admission and multiple (3 to 4) sample from capillary or venous blood were studied for parasitic index and the type of parasite were studies every 3rd day till disappearance of parasite. All patients were treated with either IV artesunate alone or in combination with oral doxycycline (both for 5 days). According to coagulation abnormality, patient received blood and blood products in form of fresh whole blood, platelet concentrate, fresh frozen plasma either alone or in combination with each other. Some patients did not receive any blood or blood products.

Inclusion Criteria -

Male and female patients with 1. with Smear smear positivity for malarial parasite were included in this study irrespective of age.
Patients with any of the following 2. coagulation abnormality in form of any one of the following:including

a. Thrombocytopenia- (Platelet count<1.5 lacs.),
b. Prothrombin Time (INR)>1.2,
c. Partial partial thromboplastin time > 35 seconds, .
d. Serum fibrinogen<200 mg/dl and
e. Iincreased serum fibrin degradation product. were included in this study

Whereas Exclusion Criteria Includedpatients with smear negative and clinically suspected malaria patients without coagulation abnormality in the above form. Were excluded from this study.

Ethics committee permission was taken before the start of the study.

OBSERVATIONS AND RESULTS

Our study population consisted of 74 patients, admitted in the MICU who were recruited with the convenient sampling method. according

to their order of admission into the MICU of the hospital. Once they satisfied the inclusion and exclusion criteria data collection was proceeded with and relevant investigations were done.

Our observations from the study are described below-

Patients age ranged from 12 years and above. They were divided in 3 groups as given in Table I. Maximum patients (56.8%) in this study belong to the age group 56.8% patients were aged between 12 to 30 years.

1)Table – I : Age wise distribution

Age in Years	Number	Percentage
12 - 30	42	56.8
31-50	29	39.2
>50	3	4.1

- 56.8% patients were aged between 12 to 30 years.

2)Table – II: Symptom wise distribution

Symptom	Number	Percentage (%)
Epistaxis	8	10.8
Hematuria	8	10.8
Hematemesis	10	13.5
Hemoptysis	14	18.9
Malena	26	35.13
Rash	14	18.9
Generalised bleeding	10	13.5

Table II gives the distribution based on symptoms, other than the common malaria symptoms of fever, chill and rigors. Maximum number of patients (35.13%) had malena as a presenting symptom

3)Table – III : Sign wise distribution

Sign	Number	Percentage (%)
Subconjunctival haemorrhage	24	32.4
Purpura	19	25.7
Echymosis	16	21.6
Bleeding from IV sites	15	20.3

- According to the above table (Table III), maximum number of patients had subconjunctival haemorrhage (32.4%) as a presenting sign.

4)Table-IV: Relation of Type of infection with mortality

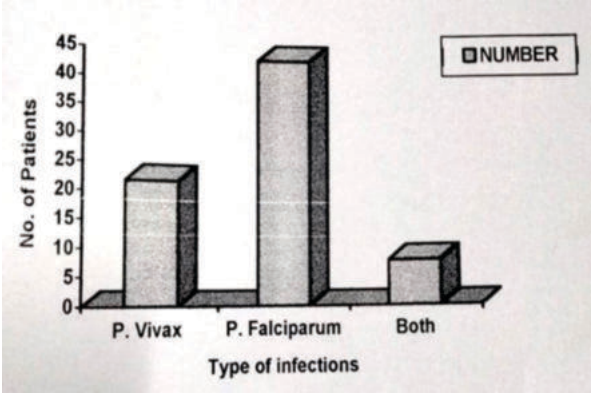
	Outcome		Total
	Survived	Expired	
P.Vivax	16(72.7%)	6 (273%)	22 (100%)
P.Falciparum	31 (70.5%)	13(29.5%)	44 (100%)
Both	8 (87.5%)	1(12.5%)	8 (100%)

Chi square test

	Value	Df	Asymp sig.
Pearson chi square tests	0.998	2	0.607

This shows that 29.5% of patients with P. falciparum expired however the relation of type of infection with mortality is not statistically significant (p>0.05)

Maximum number of patients with coagulation abnormality i.e. 44/ 74 (59.46%) had P. Falciparum type of infection. (As shown in graph I)



Graph- I: Type of infection

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5)Table –V: Relation of infestation rate with mortality

Infestation rate	Outcome		Total
	Survived	Expired	
<2	20 (95.2%)	1 (4.8%)	21 (100%)
21-5	3(100%)	0	3(100%)
5.1-10	15 (100%)	0	15(100%)
10.1-20	12 (100%)	0	12(100%)
20.1-40	2 (40%)	3 (60%)	5(100%)
>40	2 (11.1%)	16 (88.9%)	18(100%)
Total	54 (73%)	20 (27%)	74 (100%)

Chi square test

	Value	Df	Asymp sig.
Pearson chi square tests	654.073	5	0.000

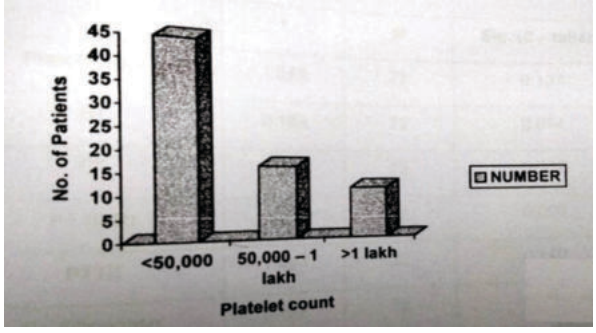
The above table V shows that as the infestation rate increased i.e. >40% the mortality also increased (p<0.05)

6)Table – VI : Coagulation abnormalities in relation to mortality

a. Platelet count

This showed that maximum patients (60.8%) had platelet count <50,000.

As shown in graph II



Graph – II: Platelet Count

b. Table VI: Mean values of coagulation abnormality

Parameters	Outcome	Number	Mean	Std. Deviation
Platelet count	Survived	54	62.0185/ mm3	52.1263
	Expired	20	42.75000/mm3	32.4112
T	Survived	54	3.2315mins	7.0.66
	Expired	20	2.9775 mins	1.6526
CT	Survived	54	10.3148 mins	4.4247
	Expired	20	13.3000 mins	3.0796
PT (INR)	Survived	54	1.5019 mins	0.7022
	Expired	20	2.6160 mins	1.0974
PTTK	Survived	54	36.8519 secs	11.7737
	Expired	20	42.0400secs	16.7417
Sr.Fibrinogen	Survived	54	237.444 mins	82.6214
	Expired	20	173.200 mins	65.0389
Sr.FDP	Survived	54	1.39	0.49
	Expired	20	1.85	0.37

Independent Sample Test

T – test equality of mean

	t	Df	Sig. (2 - tailed)
Platelet count	1.543	72	0.127

BT	0.159	72	0.874
CT	-2.773	72	0.117
PT (INR)	-5.159	72	0.000
PTTK	1.494	72	0.140
Sr. Fibrinogen	3.132	72	0.003
Sr.FDP	-3.811	72	0.000

Above tables shows that-

Mean clotting time of patients who expired was 13.300 minutes which was higher as Compared compared to mean clotting time of patients who survived (10.3148 minutes) and this was statistically significant (p<0. 005).

Patients who expired had a mean PT (INR) of 2.616 which was higher as compared to patients who survived with a mean PT of 1.5019 and this was statistically significant (p<0 05).

Mean serum fibrinogen level of patients who expired was 173.200 which was less than mean serum fibrinogen level of patients who survived(237.44) which was statistically significant (p<0 05)

Patients who expired had a mean Sr FDP levels raised (1.85) than the patients who survived (1.39) which was statistically significant (P<0.05)

7)Table – VII: Mortality in relation to coagulation failure

	Outcome		Total
	Survived	Expired	
Only thrombocytopenia	29 (93.5%)	2(6.5%)	31 31 (100%)
Patients with DIC (includes increase PT, increase PTTK, decease platelet, decrease Sr. Fibrinogen, decease Sr. FDP	25 (58.1%)	18 (41.9%)	43 (100%)
Total	54(73.8%)	20(27%)	74 (100%)

Chi square

	Value	Df	Asymp Sig
Pearson chi square tests	11.451	1	0.001

This shows that 18/43 patients with DIC expired while only 2/ 31 patients with only thrombocytopenia expired. Above test shows that patients with DIC had a grave prognosis and increased mortality in in relation to patients with only thrombocytopenia which was statistically significant (p<0.05) This was similar to study done by Ivo M. B. Francischetti,1,* Karl B. Seydel,2 and Robson Q.Monteiro (reference1)andJuliaRiedl 1, Benjamin Mordmüller 2, SilviaKoder 3, IngridPabinger 4, PeterGKremsner 5, StephenLHoffman 6, Michael Ramharter 7, Cihan Ay 8(reference 2).

8)Table – VII – Blood and blood products (as treatment) relation with mortality

	Outcome		Total
	Survived	Expired	
FFP	4 (66.7%)	2 (33.3%)	6 (100%)
Platelet concentrate	4 (100%)	0	4 (100%)
Blood	17 (94.4%)	1 (5.6%)	18 (100%)
FFP and Platelet concentrate	1(100%)	0	1 (100%)
Blood and FFP	13 (72.2%)	5(27.8%)	18 (100%)
Blood, FFP, platelet concentrate	6(100%)	0	6 (100%)
No Product	5 (29.4%)	12(70.6%)	17 (100%)

This shows that –

- All patients who received blood with FFP with Platelet or FFP with platelet or platelet only survived
- While most of the patients who did not received any blood products i.e.12 /17 died.
- 17/ 18 patients who received only blood also survived
- 4/ 6 patients who received FFP only survived.

Hence this shows that blood products helped in the treatment and deceased mortality.

9)Table – VIII: Drug treatment relation with mortality

Drugs	Outcome		Total
	Survived	Expired	
Artesunate	41(70.68%)	17(29.32%)	58 (100%)
Artesunate+Doxycycline	13(81.25%)	3(18.75%)	16 (100%)

From above table best drug treatment would be Artesunate with Doxycyline

DISCUSSION

This was a hospital based time bound study of to evaluate coagulation abnormalities in patients with malaria. Duration of this study was 1 year .from May 2021 to May 2022. We had a total of 74 patients presenting with malaria in the MICU of the hospital. All the patients had peripheral smear for malaria positive and had one form of coagulation abnormality..

1. Maximum number of patients ie 56 8% (42/74 patients) were aged between 12 to 30 years.
2. 26/ 74 patients (35.1%) had malena as the commonest presenting symptom similar .
3. 24/ 74 patients (32 4%) had subconjunctival haemorrhage as the commonest presenting signs.
4. P. Falciparum type of infection ie. 44/74 patients (59 46%) was the commonest associated with the coagulation abnormality similar to study by Pantep A.ngchaisuksiri 2014(reference 3).Also by Kanjaksha Ghosh 1, Shrimati Shetty(reference 4) and by S K Sharma 1, R K Das, B K Das, P K Das(reference 5)..
5. 29.5% (13/44 patients) expired with P. falciparum infection showing that P. falciparum was related to mortality in patients with coagulation abnormality.
6. As the infestation rate increased ie >40%, 16/18 patients ie 88.9% expired
7. Maximum number of patients had platelet count less than 50.000 i e. 45/74 patients (60.8%).A similar study by Anabire, N.G., Aryee, P.A. & Helegbe, G.K. 2018 show the7same(Reference 6).Also by Kelton JG, Keystone J, Moore J et al(reference 7), Essien E(reference 8) and Looareesuwan S. Davis JG, Allen DL et al(reference 9).
8. All patients who expired had severe coagulation abnormalities (Mean values) in form of
   - Low platelet count (42.75 cell/mm) as shown by Puknttayakamee S, White N.J., Clemens R. et al 1989(Reference 10).
   - Increased clotting time (133 min).This was similar to study done by Udeinya IJ and Miller LH(reference 11).
   - Increased PT (NR) (2.1616) similar to study done by Karolina S Akinosoglou 1, Elena E Solomou, Charalambos A Gogos(Reference 12), coagulation abnormalities
   - Increased PTTK (42.04 sec)
   - Increased Sr. FDP
   - Decreased Sr. fibrinogen (173.00mg/dl)
9. 18/43 patients ie. 41.9% having DIC in form of decreased platelet Count, increase PT. increase PTTK decreased Sr. fibrinogen, increased Sr. FDP) expired as against only 2 out of 31 patients having only thrombocytopenia showing that the mortality increased with the severity of coagulation abnormality .This is similar to study done by Laltanpuii Sailo, Debasis Pradhan, Rakesh Nongthombam, and Prithwis Bhattacharyya(Reference 13).Also similar studies by Mohapatra, S., Samantaray, J.C., Arulselvi, S. et al (reference 14) and Mohanty D, Marwaha N, Ghosh K, Chauhan A.P, Shah S. Sharma, Das KC(reference 15) showed the same.
10. Artesunate with doxycycline was a good Combination in treatment of patients with coagulation abnormalities as 81.25% survived similar to study done by Lee B. Barradell and Andrew Filton(Reference 16).
11. Artesunate with doxycycline was a good Combination in treatment of patients with coagulation abnormalities as 81.25% survived.
12. Blood and blood products helped in the improvement of the outcome as all patients (100%) who received either blood with FFP with platelet or FFP with platelet or only platelets sSurvived whereas most of the patients who did not received any blood or blood products i.e. 12 /17 patients (70.6%) expired.Similar study was done by Nicholas J. White(Reference 17).

CONCLUSION

From this exploratory study, We we could conclude that maximum number of Malaria malaria patients having Coagulation coagulation Abnormalities abnormalities were infested with falciparum species.

Mortality increased with the infestation rate and with the severity of coagulation abnormality (In in form of DIC against only thrombocytopenia). Artesunate with doxycycline decreased mortality whereas. , blood and blood products helped in the improvement of the outcome of the disease.

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