Section: ICU

Original Research Article

EVALUATION OF THE PREDICTORS OF SURVIVAL AND MORTALITY IN SUBJECTS ADMITTED TO ICU (INTENSIVE CARE UNIT) WITH TTP (THROMBOCYTOPENIC PURPURA)

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Received *: 11/10/2024*
Received in revised form *: 05/12/2024*
Accepted *: 21/12/2024*

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DOI: 10.70034/ijmedph.2024.4.233

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (4); 1277-1281

ABSTRACT

Background: TTP (thrombocytopenic purpura) presents a multisystem disorder that has characteristics of widespread microthrombosis which usually predisposes affected subjects to multiple organ failure. Existing literature data is scarce concerning the outcomes of critically ill subjects with TTP managed in the ICU. **Aim:** The present study aimed to evaluate the predictors of survival and mortality in subjects admitted to ICU (intensive care unit) with TTP (thrombocytopenic purpura). The study also compared the nosocomial infection incidence in subjects who did/did not receive plasma exchange (PE).
Material and Methods: The study assessed critically ill adult subjects with TTP managed in the ICU. For all the included subjects, the data were gathered from the hospital data and records for further assessment. Data reporting was done with non-parametric statistics. The data gathered were statistically analyzed for results formulation.
Results: Among 267 screened subjects, 34 met the inclusion criteria and were assessed. Mortality of 41.17% (n=14) was seen in subjects with TTP. Female to male ratio was 7:3. Compared to survivors, higher levels of lactate dehydrogenase, thrombocytopenia, and anemia were seen in non-survivors with 2124 (1939-3317) u/L vs 2985 (1902-3612) U/L with p=0.69, 21x101µl vs 17x101 µl with p=0.61, and 7.4g/dl (5.9-8.7) vs 5.2g/dl (4.6-6.9) with p=0.04 respectively. 55.88% (n=19) subjects had AKI (acute kidney injury) whereas 57.89% (n=11) subjects survived. Among these 11 subjects, 5 progressed to end-stage renal disease and 6 completely recovered. PE therapy had no significant influence on rates of nosocomial infections.
Conclusion: The present study concludes that TTP is more common in females with high mortality rates. The predictors for poor survival in TTP subjects are higher platelet transfusions, low hemoglobin, and old age. Irrespective of PE therapy, rates of nosocomial infection were comparable.
Key Words: ICU, outcomes, survival rate, thrombocytopenia, TTP.

INTRODUCTION

TMA or thrombotic microangiopathy is a pathological condition diagnosed pathologically and is usually assessed from thrombocytopenia and MAHA (microangiopathic hemolytic anemia). TTP (thrombotic thrombocytopenic purpura) is one of the vital causes of primary TMA syndromes and hemolytic emergencies having a high mortality rate of up to 90% with no specific treatment. TTP presents with additional clinical presentations such as renal, neurological, and fever. However, with AKI (acute kidney injury) as the main feature in diagnosing hemolytic uremic syndrome (HUS).[1,2] Subjects having TTP may need admission to the ICU (intensive care unit) in cases of organ failure

and need for plasma exchange (PE) therapy. These subjects are at higher risk of acquiring nosocomial infections, particularly CLABSI (central line-associated bloodstream infection) owing to the need for central venous exchange for plasma exchange. They usually are administered with immunosuppressants and steroids in the treatment plan for the disease. All these factors predispose these subjects to nosocomial infections and further progression to multi-organ failure and sepsis.[3,4]

In ICU care, it is challenging to differentiate TTP from other causes of TMA such as sepsis, preeclampsia, HELL (hemolysis, elevated liver enzymes, low platelet count) syndrome, atypical HUS, and HUS owing to significant overlap in clinical features and laboratory parameters. In these cases, ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13) protease activity testing is not a valuable tool. However, high cost and non-availability make other prediction models as the PLASMIC score more vital to predicting deficient activity of ADAMTS13 enzyme.[5]

The existing literature data is scarce concerning critically ill subjects with TTP admitted to the ICU facility. Further, Indian studies are few with fewer reported cases. Also, the existing literature is limited exposing the burden of nosocomial infections using corticosteroids and PE therapy in the subjects admitted to ICU with TPP.[6] The present study aimed to assess the cause of mortality which is non-attributed or attributed to TTP and to assess the predictors of mortality in subjects with TPP admitted to ICU. The study also compared the nosocomial infection in subjects receiving plasma exchange and subjects without plasma exchange therapy.

MATERIALS AND METHODS

The present retrospective clinical study was aimed to assess the cause of mortality which is non-attributed or attributed to TTP and to assess the predictors of mortality in subjects with TPP admitted to ICU. The study also compared the nosocomial infection in subjects receiving plasma exchange and subjects without plasma exchange therapy. The study was done at Intensive Care Unit, ESIC Medical Collage and Hospital, Faridabad, Haryana. Verbal and written informed consent were taken before study participation.

The study assessed subjects from both genders with a provisional diagnosis of TTP during hospitalization or admission. Probable TTP was taken as thrombocytopenia presence with MAHA and along with visceral organ involvement as gastrointestinal, neurological, renal, or cardiac involvement and no other alternative etiology to explain clinical presentation. Probable TTP was diagnosed by treating personnel in consultation with a pathologist.

All the subjects were screened for eligibility using HIS (hospital information system). The inclusion criteria for the study were subjects aged more than 18 years, managed in ICU, and suspected to have TTP. In HIS, a peripheral smear was assessed for microangiopathic hemolytic anemia, fragmented cells, and schistocytes. The exclusion criteria for the study were subjects having acute fatty liver of pregnancy, HELLP syndrome, pre-eclampsia, vasculitis, DIC (disseminated intravascular coagulation), septic shock, malignancies, accelerated hypertension, snakebite, autoimmune causes of hemolysis, atypical HUS, or HUS.

In all the included subjects, data extracted from the previous hospital records were plasma infusion, adjuvant steroid use, PE, daily SOFA (sequential organ failure assessment) scores, admission APACHE (acute physiology and chronic health evaluation) II, presenting symptoms, medical history, and demographic data. Presenting symptoms were divided into thrombotic symptoms as peripheral vascular thrombosis, gastrointestinal as abdominal pain, diarrhea, and vomiting, as visual disturbances, headache, focal deficits, coma, seizures, and stroke, renal as fluid overload, anuria, oliguria, hematuria, and proteinuria, and cardiovascular as arrhythmias, left ventricular dysfunction, NSTEMI (non-ST elevation myocardial infarction) and myocardial infarction.

As ADAMTS 13 activity was not assessed, the PLASMIC score was used to assess the risk of ADAMTS 13 deficiency. A score of 1 was allotted to each variable for a platelet count of <2.5% or undetectable haptoglobin, indirect bilirubin >2mg/dl, creatinine <2mg/dl, INR <1.5, mean corpuscular volume <90 fl, history of stem cell or solid organ transplant, or active cancer (cancer treatment in past 1 year. A combined 6-7 score was taken as a deficiency of ADAMST 13.[7]

Clinical outcomes assessed were nosocomial infection rates, invasive mechanical ventilation days, hospital stay duration, ICU stay duration, and mortality in ICU. Healthcare-associated infections or nosocomial infections were taken as infections assessed and diagnosed during the hospital stay with no previous pathogen evidence in the incubation period at admission. CLABSI was taken as an infection confirmed in the laboratory with central venous access in place for >2 calendar days before positive culture and was there the day before culture. CAUTI (catheter-associated urinary tract infection) was taken as urinary tract infection with indwelling urinary catheter placement for >2 days consecutively in an inpatient location on the event date and IVAC (infection-related ventilator-associated complication) was taken following CDC (Centers for Disease control and prevention) and NHSN (national healthcare safety network) surveillance.[8] AKI was defined following Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines as serum creatinine increase by >0.3 mg/dl in 48 hours or serum creatinine increase

to >1.5 times from baseline which is considered to occur in the past 7 days or urine volume of <0.5 ml/kg/hour for 6 hours.[9]

The data gathered were analyzed statistically using SPSS (Statistical Package for the Social Sciences) software version 16.0 (SPSS Inc., Chicago, USA) for assessment of descriptive measures. The results were expressed as mean and standard deviation and frequency and percentages. The p-value of <0.05 was considered statistically significant. The significance of study parameters on the categorial scale was assessed using the Chi-square test. Inter-group analysis was done using one-way ANOVA (analysis of variance). In cases where ANOVA showed significant results, post-hoc Turkey analysis was done.

RESULTS

The present retrospective clinical study was aimed to assess the cause of mortality which is non-attributed or attributed to TTP and to assess the predictors of mortality in subjects with TPP admitted to ICU. The study also compared the nosocomial infection in subjects receiving plasma exchange and subjects without plasma exchange therapy. Among 267 screened subjects, 34 met the inclusion criteria and were assessed. The mean age range in alive and dead subjects was significantly higher in dead subjects with p=0.01. the gender distribution was comparable in dead and alive subjects with p=0.09. BMI was comparable in alive and dead subjects with p=0.35. Hypertension and diabetes distribution was comparable with p=0.26 and 0.95 respectively, whereas, hypothyroidism was significantly higher in dead subjects with p=0.02. Mean PLASMIC scores, day 1 ICU SOFA scores, and mean APACHE II scores were comparable in dead and alive subjects with p=0.71, 0.4, and 0.3 respectively. Creatinine, reticulocyte, total bilirubin, hemoglobin, LDH (lactate dehydrogenase), and platelet levels at admission were statistically comparable in dead and alive subjects with p=0.24, 0.44, 0.98, 0.05, 0.73, and 0.66 respectively. Days from symptom to admission in the hospital and Days from symptom to admission in ICU were also comparable with p=0.22 and 0.17 respectively. Cardiac, neurological, fever, GI, renal, hemorrhagic, and thrombotic presentations were statistically comparable in dead and alive subjects with p=0.26, 1.0, 0.75, 0.32, 0.6, 0.14, and 0.7 respectively (Table 1).

Plasma exchange therapy was needed in 15 and 7 alive and dead subjects respectively with p=0.25. mean PE days were comparable in dead and alive subjects with 0.36. The need for FFP (fresh frozen plasma) without PE and steroids was comparable in dead and alive subjects with p=0.64 and 0.35 respectively. TTP complications were seen in 11 and 12 subjects from the alive and dead group with p=0.07. Hospital-acquired infections were comparable in the two groups with p=0.07. Renal replacement therapy was needed in 5 and 8 subjects with 0.56. Need of platelet transfusion was needed in significantly higher subjects from the alive group with p=0.02. The number of mean packed cell transfusions was significantly higher in alive subjects with 4.5±0.3 compared to 2.2±0.4 in dead subjects with p=0.01. The total steroid dose needed was comparable in dead and alive subjects with p=0.41 as shown in Table 1.

On assessing the complications in subjects with TTP admitted to ICU, the most prevalent complication was refractory status epilepticus recorded in 14.70% (n=5) study subjects followed by acute severe pancreatitis and hyperkalemia cardiac arrest in 11.76% (n=4) study subjects each, acute cerebrovascular accident and cerebral edema was seen in 8.82% (n=3) study subjects each, mesenteric ischemia was seen in 5.88% (n=2) study subjects, and anaphylactic reaction to FPP was seen in 2.94% (n=1) study subject respectively as summarized in Table 2.

The study results showed that for comparison of infection and mortality in subjects given PE or no PE in the study subjects, ICU mortality was seen in 3.63% (n=8) subjects with plasma exchange therapy and in 58.33% (n=70 subjects without PE depicting statistically non-significant difference with p=0.25. HAP and IVAC were seen in 18.18% (n=4) of subjects who received plasma exchange therapy. CLABSI was seen in 13.62% (n=3) subjects that received PE and in 16.6% (n=2) subjects that did not receive PE. CAUTI was seen in 4.54% (n=1) and 8.33% (n=1) subjects that received PE and did not receive PE respectively. HAI was seen in 45.45% (n=10) subjects that received PE and in 25% (n=3) subjects that did not receive PE as summarized in Table 3.

Table 1: Demographic and disease data in study subjects

Characteristics	Alive		Dead		p-value
	n=20	%	n=14	%	
Mean age (years)	30.56±1.7		42.02±4.4		**0.01**
Female gender	12		12	85.71	0.09
Mean BMI (kg/m2)	25.5±3.9		21.1±0.2		0.35
Comorbidities					
Hypothyroidism	1	5	6	42.85	**0.02**
Hypertension	5	25	4	28.57	0.95
Diabetes mellitus	2	10	2	14.28	0.26
Mean PLASMIC scores	5.3±0.1		5.5±0.1		0.71
Mean day 1 ICU SOFA	7.4±0.4		11.2±3.4		0.4

Mean APACHE II	15.5±1.6		17.5±2.1		0.3
AKI during a hospital stay	12	60	8	57.14	0.64
Creatinine (admission)	2.11		1.54		0.24
Reticulocyte	12.6		8.3		0.44
Total bilirubin	2.2		2.27		0.98
Hemoglobin (admission) mg/dl	7.4		5.2		0.05
LDH (admission)	2124		2985		0.73
Platelet (admission) per cu mm	215000		170000		0.66
Cardiac presentation	1	5	3	21.42	0.26
Neurological presentation	14	70	10	71.42	1.0
Fever at presentation	12	60	7	50	0.75
Days from symptom to admission in hospital	7 (4-10)		7.5 (4-10)		0.22
Days from symptom to admission in ICU	7 (4-10)		7 (4-10)		0.17
GI presentation	13	65	6	42.85	0.32
Renal presentation	17	85	10	71.42	0.6
Hemorrhagic presentation	4	20	6	42.85	0.14
Thrombotic presentation	2	10	2	14.28	0.7
PE	15	75	7	50	0.25
Mean PE day	1.3±0.1		1.1±0.1		0.36
FFP without PE	3	20	3	21.42	0.64
Steroids	12	60	10	71.42	0.35
TTP complications	11	55	12	85.71	0.07
Hospital-acquired infections	5	25	8	57.14	0.07
HAP	0	0	2	14.28	-
IVAC	1	5	3	21.42	-
CLABSI	4	20	1	7.14	-
CAUTI	0	0	2	14.28	-
Renal replacement therapy needs	5	25	8	57.14	0.56
Platelet transfusion number	10	50	7	50	**0.02**
Mean Packed cell transfusion number	4.5±0.3		2.2±0.4		**0.01**
Total steroid dose	455±133		309±120		0.41

Table 2: Complications of TTP in ICU in study subjects

Complications	Number (n)	Percentage (%)
Anaphylactic reaction to FFP	1	2.94
Mesenteric ischemia	2	5.88
Cerebral edema	3	8.82
Acute cerebrovascular accident	3	8.82
Hyperkalemia cardiac arrest	4	11.76
Acute severe pancreatitis	4	11.76
Refractory status epilepticus	5	14.70

Table 3: Comparison of infection and mortality in subjects given PE or no PE in the study

Infections	PE given (n=22)		NO PE (n=12)		p-value
ICU mortality	8	3.63	7	58.33	0.25
HAP	4	18.18	0	0	-
IVAC	4	18.18	0	0	-
CLABSI	3	13.63	2	16.6	-
CAUTI	1	4.54	1	8.33	-
HAI	10	45.45	3	25	0.47

DISCUSSION

For the present study among 267 screened subjects, 34 subjects met inclusion criteria and were assessed. The mean age range in alive and dead subjects was significantly higher in dead subjects with p=0.01. the gender distribution was comparable in dead and alive subjects with p=0.09. BMI was comparable in alive and dead subjects with p=0.35. Hypertension and diabetes distribution was comparable with p=0.26 and 0.95 respectively, whereas, hypothyroidism was significantly higher in dead subjects with p=0.02. Mean PLASMIC scores, day 1 ICU SOFA scores, and mean APACHE II scores were comparable in dead and alive subjects with p=0.71, 0.4, and 0.3 respectively. Creatinine, reticulocyte, total bilirubin, hemoglobin, LDH (lactate dehydrogenase), and platelet levels at admission were statistically comparable in dead and alive subjects with p=0.24, 0.44, 0.98, 0.05, 0.73, and 0.66 respectively. Days from symptom to admission in the hospital and Days from symptom to admission in ICU were also comparable with p=0.22 and 0.17 respectively. Cardiac, neurological, fever, GI, renal, hemorrhagic, and thrombotic presentations were statistically comparable in dead and alive subjects with p=0.26, 1.0, 0.75, 0.32, 0.6, 0.14, and 0.7 respectively. These data were similar to the studies of Datta P et al,[10] in 2014 and Gudivada KK et al,[11] in 2017 where authors assessed subjects with demographic data comparable to the present study.

It was seen that plasma exchange therapy was needed in 15 and 7 alive and dead subjects

respectively with p=0.25. mean PE days were comparable in dead and alive subjects with 0.36. The need for FFP (fresh frozen plasma) without PE and steroids was comparable in dead and alive subjects with p=0.64 and 0.35 respectively. TTP complications were seen in 11 and 12 subjects from the alive and dead group with p=0.07. Hospital-acquired infections were comparable in the two groups with p=0.07. Renal replacement therapy was needed in 5 and 8 subjects with 0.56. Need of platelet transfusion was needed in significantly higher subjects from the alive group with p=0.02. The number of mean packed cell transfusions was significantly higher in alive subjects with 4.5±0.3 compared to 2.2±0.4 in dead subjects with p=0.01. The total steroid dose needed was comparable in dead and alive subjects with p=0.41. These results were consistent with the studies of Goel R et al,[12] in 2015 and Redant S et al,[13] in 2021 where similar presentation and clinical data similar to the present study were reported by the authors in their respective studies.

The study results showed that on assessing the complications in subjects with TTP admitted to ICU, the most prevalent complications was refractory status epilepticus recorded in 14.70% (n=5) study subjects followed by acute severe pancreatitis and hyperkalemia cardiac arrest in 11.76% (n=4) study subjects each, acute cerebrovascular accident and cerebral edema was seen in 8.82% (n=3) study subjects each, mesenteric ischemia was seen in 5.88% (n=2) study subjects, and anaphylactic reaction to FPP was seen in 2.94% (n=1) study subject respectively. These findings were in agreement with the results of Zafrani L et al,[14] in 2015 and Tsai H-M,[15] in 2007 where complications in TTP subjects reported by the authors in their studies were comparable to the present study.

It was seen that for comparison of infection and mortality in subjects given PE or no PE in the study subjects, ICU mortality was seen in 3.63% (n=8) subjects with plasma exchange therapy and in 58.33% (n=70 subjects without PE depicting statistically non-significant difference with p=0.25. HAP and IVAC were seen in 18.18% (n=4) of subjects who received plasma exchange therapy. CLABSI was seen in 13.62% (n=3) subjects that received PE and in 16.6% (n=2) subjects that did not receive PE. CAUTI was seen in 4.54% (n=1) and 8.33% (n=1) subjects that received PE and did not receive PE respectively. HAI was seen in 45.45% (n=10) subjects that received PE and in 25% (n=3) subjects that did not receive PE. These results were in line with the studies of Hassan S et al,[16] in 2015 and Joly BS et al,[17] in 2017 where the comparison of infection and mortality in subjects as seen in the present study was similar to the results reported by the authors in their respective studies.

CONCLUSION

Within its limitations, the present study concludes that TTP is more common in females with high mortality rates. The predictors for poor survival in TTP subjects are higher platelet transfusions, low hemoglobin, and old age. Irrespective of PE therapy, rates of nosocomial infection were comparable. Further future longitudinal studies are needed to reach a definitive conclusion.

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