Fresh Frozen Plasma Transfusion before Invasive Procedure in Patients with Cirrhosis and Severe Coagulopathy

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Key words:
Cirrhosis, Fresh frozen plasma, Coagulation, Transfusion.

Introduction and aim of the work: Fresh frozen plasma (FFP) is frequently transfused prior to the invasive procedure in patients with significant coagulopathy to reduce presumed high bleeding risk. The work aimed to assess the efficacy of prophylactic FFP transfusion before the invasive procedures in cirrhotic patients with severe coagulopathy.

Patients and Methods: A prospective study enrolled 42 adult patients with cirrhosis and severe coagulopathy as defined by deranged coagulation test INR ≥ 2, who was planned to have an invasive procedure. The patients were recruited from the hospitalized or endoscopy list of the Nizwa General Hospital from January 2021 to January 2022. patients were randomized to receive FPP transfusion 6 hours before a procedure at a dose of 10 cc per kg (group A) or no transfusion (group B). The following outcomes were traced; transfusion side effects, INR levels before and after FFP transfusion, post-procedure bleeding incidence, INR and hemoglobin level changes from the baseline levels for two days.

Results: The change of INR after FFP transfusion was significantly higher in group A than in group B (- 0.38 ± 0.22 vs. - 0.02 ± 0.08 respectively) and continued over the consecutive two days post-procedure two patients had procedure-related bleeding in Group B with a significant hemoglobulin drop of ≥ 2 gm compared to one patient in group A ($p > 0.05$).

Conclusion: FPP transfusion decreases INR significantly but with no apparent significant impact on bleeding incidence, suggesting transfusion to be conducted on an individual basis in high-risk cirrhotic patients before invasive procedures.

INTRODUCTION

Bleeding is a featured complication in cirrhotic patients with significant coagulopathy **[1,2]**. Coagulopathy, as defined by deranged conventional coagulation tests, international normalized ratio (INR), and activated partial thromboplastin time (aPTT), is directly related to the severity of cirrhosis. Guidelines have recommended the correction of coagulation test (INR, aPTT) through the use of fresh frozen plasma (FFP) before invasive procedures to prevent bleeding **[3,4]**. Consequently, FFP is frequently transfused before the invasive procedure in patients with advanced decompensated cirrhosis and a deranged coagulation test to reduce presumed high bleeding risk **[5,6]**. This practice was traced by a British study that reported that 30% of the patients with cirrhosis were transfused with FFP; furthermore, 24 to 48 % of the transfused plasma in the United States was prophylactically requested for patients undergoing an invasive procedure **[7,8]**. However, clinical evidence is still scarce for this practice **[8,9]**. This work aimed to assess the efficacy of prophylactic FFP transfusion before the invasive procedures in patients with cirrhosis and severe coagulopathy.

PATIENTS AND METHODS

This randomized pilot study enrolled 42 adult patients with cirrhosis and deranged coagulation test (INR ≥ 2) who was planned to have an invasive procedure. The patients were recruited from the hospitalized or endoscopy list of the Nizwa General Hospital, Ministry of Health, Sultanate of Oman from July 2021 to January 2022. Cirrhosis was

diagnosed on clinical, laboratory, imaging, and/or histology.

***Exclusion criteria*:** Platelet count ≤ 50000/ul, anticoagulant or antiplatelet medications, ongoing bleeding, congenital or acquired coagulation disorder unresponsive to FFP transfusion, previous or current thromboembolic event sepsis and hemodialysis n last seven days, preexisting heart failure or acute lung injury. After informed consent, patients were randomly distributed to 1:1 rato to receive FPP transfusion (group A) or no transfusion (group B). FFP was entirely transfused within 6 hours before a procedure at a dose of 10 cc per kg (maximum five units) with concomitant diuretic administration as needed per the attending physician. Demographic and clinical characters were recorded, and routine blood chemistry was performed. Post-procedure; the patients were clinically re-examined daily after the procedures, recording any bleeding if it occurred. INR and hemoglobin levels were done daily for two days *post-procedure*. The following outcomes **were traced;**

Pre-procedure:

- Mean INR levels before and after FFP transfusion.
- Transfusion side effects within 6 hours, e.g., new heart failure or acute lung injury.

Post-procedure:

- Occurrence of bleeding either overt, hemoglobin drop requiring transfusion for target hemoglobin goal of 7-8 g/dl, or significant hemoglobin drop more than 2 gm from the pre-procedure level within the next two days after the procedure.
- Mean change INR levels for the following two days after the procedure.
- Mean difference of hemoglobin and INR levels from the pre-procedure level to the least in the next two days after the procedure.

Data analysis

The data were analyzed using SPSS (IBM SPSS Statistics 28.0, United States). Mean and standard deviation (SD) was used for summarizing quantitative data, and a t-test was conducted for their significance assessment. Number and percentages were used to summarize qualitative data, while Chi-square and Fisher's exact test was conducted for their significance assessment. A P value of < 0.05 was statistically significant.

RESULTS:

The enrolled 42 patients in the study had a mean age of 58 ± 18, 71% were men, and 29% were female. There was no significant difference between the two groups in the pre-procedure characters (body weight, etiology of cirrhosis, MELD score, CTP score, and class). Patients with a CTP class C represented 54.7 % of the study population. Two patients had transfusion-related adverse effects in the form of volume overload and could be managed by diuretics. On the other side, three patients had procedure-related bleeding (2 group B with a significant hemoglobulin drop of ≥ 2 gm and one in group A without a significant hemoglobulin drop) (table 1). Paracentesis was the most common procedure (38.1%), esophageal varices band ligation (19.05%), as shown in table 2. Table 3 showed no significant difference in the pre-procedure INR level between the two groups before randomization (2.26 ± 0.2 and 2.31 ± 0.22 respectively). However, the pre-procedure change of INR in group A after FFP transfusion was significantly higher than in group B (- 0.38 ± 0.22 and - 0.02 ± 0.08 respectively) and continued over the consecutive two days post-procedure. There was no significant difference in the pre-procedure hemoglobulin level between the two groups and no significant difference in post-procedure hemoglobulin level change to the lowest within the two consecutive days.

Table (1): Clinical characteristics of the patients included in the study.

Characteristics	Total (n = 42)	Group A (n = 21)	Group B (n = 21)
Age (y), Mean ± SD	58 ± 18	52 ± 19	60 ± 15
Sex n (%)			
Female	12 (29%)	7 (34%)	5 (24%)
Males	30 (71%)	14 (66%)	16 (76%)
Body weight, Mean ± SD	62.5 ± 9.5	60.2 ± 10	63.6 ± 9
Cirrhoss aetiology n (%)			
CHCV	16 (38.1%)	9 (42.8%)	7 (33.3%)
CHBV	13 (30.9%)	5 (23.8%)	8 (38.1%)
Alcohol related	7 (16.6%)	3 (14.3%)	4 (19%)
Other	5 (11.9%)	3 (14.3%)	2 (9.5%)
MELD score, Mean ± SD	22.2 ± 9.9	22.4 ± 8.6	21.6 ± 9.8
CTP score, Mean ± SD	10.5 ± 2.7	10.3 ± 2.8	10.6 ± 2.4
CTP class n (%)			
A	3 (7.2%)	1 (4.75%)	2 (9.5%)
B	16 (38.1%)	9 (42.8%)	7 (33.3%)
C	23 (54.7%)	11(52.45%)	12 (57.2%)
Transfusion-related adverse effects	1 (2.35%)	1 (4.75%)	0
Procedure-related bleeding	3 (7.2%)	1 (4.75%)	2 (9.5%)

CHCV; chronic hepatitis C virus. CHBV; chronic hepatitis B virus. MELD; model of end-stage liver disease.. CTP; Child-Turcotte-Pugh.

Table (2): Procedure type and distribution between the two groups.

Procedure type	Total (n = 42) N (%)	Group A (n = 21) N (%)	Group B (n = 21) N (%)	P value*
Colonoscopy with polypectomy	3 (7.2%)	2 (9.5%)	1 (4.75%)	0.92
Esophageal varices band ligation	8 (19.05%)	5 (24%)	3 (14.3%)	
Paracentesis	16 (38.1%)	9 (42.8%)	7 (33.3%)	
Thoracocentesis	5 (11.9%)	3 (14.3%)	2 (9.5%)	
Lymph node biopsy	1 (2.35%)	0	1 (4.75%)	
Catheter placement	5 (11.9%)	2 (9.5%)	3 (14.3%)	
Percautaneous gastrostomy tube	2 (4.7%)	1 (4.75%)	1 (4.75%)	
Central vein cannulation	1 (2.35%)	1 (4.75%)	0	
Others	1 (2.35%)	1 (4.75%)	0	

**Fisher´s exact test. P < 0.05 is significant.*

Table (3): Pre-procedure and Post-Procedure INR and HGB levels

	Group A (n = 21)		Group B (n = 21)		P value*
	Mean	SD	Mean	SD	
Pre-procedure INR					
- Before randomization	2.26	0.2	2.31	0.22	0.43
- Pre-procedure Change	- 0.38	- 0.22	- 0.02	0.08	< 0.01
Post-procedure INR					
- Change after one day	- 0.28	- 0.34	0.00	0.011	< 0.01
- Change after two days	- 0.24	- 0.22	- 0.03	0.14	< 0.01
Pre-procedure HGB level	9.1	1.5	9.6	2.1	0.34
Post-procedure HGB change to the lowest witin two days	- 0.5	1.0	- 0.8	1.1	0.19

** t-test p value (significant < 0.05).* HGB*; hemoglobulin. INR: international normalized ratio.*SD; standard deviation

DISCUSSION

FFP is widely transfused prior to either diagnostic or therapeutic interventional procedures in patients with moderately prolonged INR, expecting bleeding to be prevented or reduced **[9]**. Most guidelines adopt arbitrary cutoffs based on INR > 1.5 times the normal value to initiate FFP transfusion prior to invasive procedures **[10]**. However, no suffient clinical evidence demonstrate that FFP transfusion is safe and efficacious in preventing or decreasing the bleeding risk **[11]**. Furthermore, it might produce substantial costs and increased risk for volume expansion, especially in liver cirrhosis. Thus can theoretically produce a paradoxical increase of bleeding risk due to increased portal pressure **[12]**. This work aimed to assess the efficacy of prophylactic FFP transfusion prior the invasive procedures in patients with cirrhosis and severe coagulopathy.

In patients with INR between 1.5 and 1.9, many physicians have a concept that plasma transfusion has no role. However, in patients with INR 2.0-2.5, other physicians always decide to transfuse plasma **[13]**. The range of INR eligible for this trial was ≥ 2, but this has substantially reduced the number of eligible patients for enrolment. Though the change in the INR levels after FPP transfusion was small, It demonstrated a statistically significant difference between the FFP transfusion and no transfusion groups on the day of the procedure and the next two days after the procedure, and 40 % of the patients achieved a target INR of < 2. This matches with what was reported before by Cason et al. (45%) and others who achieved comparable results **[13,14,15]**. On the other side, several studies have shown that FFP transfusion results in the normalization of conventional coagulation tests in a small number of patients with chronic liver disease **[11,16]**.

In this study, FFP was transfused within the range (10 cc/kg) recommended by current guidelines **[17,18]**. Higher rates were avoided because most of the patients were CTP class C cirrhosis (54 %) and were expected to be fluid overloaded. This could explain the modest change in the INR after plasma transfusion. In addition, there is considerable variability in both INR and factor levels in patients with cirrhosis, inadequately reflecting hemostatic changes and poorly correlating with bleeding risk **[19]**. The INR of plasma can be as high as 1.3 **[15]**, and large volumes of FPP are needed to decrease INR to < 1.6 **[20]**; furthermore, transfusion has a slight effect on a minimally elevated INR **[21,22]**. It was anticipated that the hemoglobin level would drop more in patients with no FFP transfusion than those who received FFP transfusions. However, there were no significant differences in the HGB change between the two groups (0.5 g/dl and 0.8 g/dl, respectively). This could be explained by the dilutional effect of FFP transfusion, which will compensate for the HGB drop related to the procedure. The only published trial assessed the transfusion of FFP prior to an invasive procedure reported against a significant difference in bleeding in 72 patients with prolonged prothrombin time **[23]**, which is in concordance with procedure-related bleeding incidence n this study (2 in group A vs. 1 in group B). Ths study did not identify any significant differences in clinical outcomes (transfusion-related adverse effects, procedure-related bleeding, and post-procedure significant HGB change), which could be attributed to the small sample size of 42 patients and to the exclusion of cirrhotic patients who are most likely to suffer from coagulation alterations , i.e., sepsis. Furthermore, the bleeding risk of invasive procedures depends on many factors, including underlying coagulopathy itself, high or low-risk procedures, experts of the intervening physicians, and local complications of the procedure **[8,23]**. Further studies evaluating the bleeding incidence according to specific invasive procedures and subgroups of cirrhosis (sepsis vs. no sepsis) will better clarify the impact of correcting significant coagulopathy with FPP transfusion. Physicians should choose wisely, and The decision of FFP transfusion should be taken on an individual basis and not on arbitrary cutoff levels of conventional coagulation tests.

CONCLUSION

FPP transfusion decreases INR significantly but with no apparent significant impact on bleeding incidence, suggesting transfusion to be conducted on an individual basis in high-risk cirrhotic patients before invasive procedures.

Ethical considerations: All the patients signed written formed consent. The study protocol was approved by the review board of Health Studies

& Research Approval Committee (HSRAC), Centre of Studies & Research – Ministry Of Health, Sultanate of Oman and conducted according to the code of ethics (declaration of Helsinki).

Funding: None.
Conflicts of interest: No conflict of interest.

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