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FFP Transfusion and Nosocomial Infection in Cardiac Surgery: A Systematic Review

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ABSTRACT

Context: In some studies, Fresh Frozen Plasma (FFP) transfusion in severely ill patients was accompanied with an increase in the risk of nosocomial infection. However, there are no comprehensive data in terms of FFP transfusion and its relationship with nosocomial infection in heart surgery. Hence, the present systematic review and meta-analysis aimed to investigate the relationship between FFP transfusion and nosocomial infection risk in the patients undergoing cardiac surgery.

Evidence Acquisition: ***Study selection:*** The present study included all the studies, which probed into nosocomial infection after FFP transfusion in patients with cardiac surgery. ***Data sources:*** Medline, Web of Science, Embase, Central, and Scopus electronic databases were searched to the end of March 2019.

Results: Finally, five articles and three abstracts that studied nosocomial infection were entered into the present systematic review. FFP increased the rate of nosocomial infection in cardiac surgery in one article, but this was not the case in the remaining four articles. The three abstracts also reported that FFP increased the rate of nosocomial infection in cardiac surgery.

Conclusion: The studies indicated that the benefit of FFP administration outweighed the probable risk of infection. Indeed, none of the studies indicated a strong relationship between FFP transfusion and infection rate after cardiac surgery.

1. Context

Since the mid-1940s, heart surgery had a remarkably fast development. Most of the surgeries, which were once considered to be experimental, have now become prevalent and rudimentary. For instance, thousands of open-heart surgeries are performed in the United States annually. Indeed, approximately one million patients underwent heart surgery all over the world in 2016 (1). Nowadays, Coronary Artery Bypass Graft (CABG) is the most prevalent cardiac surgery in the world (2). As there is a high risk of bleeding in major vascular and open-heart surgeries, Fresh Frozen Plasma (FFP) is occasionally transfused to these patients to reduce the volume of bleeding (3, 4). Not only FFP is used in active bleeding due to the lack of coagulation factors along with abnormal coagulation tests, but it is also applied in some other cases like preplanned elective surgeries or invasive surgeries in the presence of abnormal coagulation tests (5). In addition to treatment of bleeding, FFP is used in a number of cases to prevent bleeding. Yet, it should not be disregarded that its presence has some side effects, as well (3). Plasma has been increasingly used in surgeries over the last two decades. Hence, there is an increasing concern regarding the unjustified use of plasma transfusion (6). Although FFP is widely used, there is no evidence to prove that the prophylactic use of FFP can affect the volume of bleeding during heart surgeries (7). On the other hand, there is no evidence to indicate the beneficial effects of FFP transfusion on mortality rate in heart surgeries (8).

Plasma transfusion is not without risks and the consequent complications of plasma transfusion might be more compared to the transfusion of other blood components (6). One of the inherent risks of FFP transfusion is transmission of infections (6). Nosocomial infection is one of the

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unpleasant and horrible side effects in heart surgery, which leads to increase in mortality rate, hospitalization length, and expenses (9). Some studies have demonstrated that FFP transfusion in severely ill patients was accompanied with an increase in the risk of nosocomial infection (10). However, there are no comprehensive data in terms of FFP transfusion and its relationship with nosocomial infection in heart surgery. Hence, the present systematic review and meta-analysis aims to determine the relationship between FFP transfusion and risk of nosocomial infection in the patients undergoing cardiac surgery.

2. Evidence Acquisition

In the present systematic review, PICO was defined as follows: problem or the population under study (P): the candidates for cardiac surgery, index test (I): fresh plasma transfusion, comparisons (C): comparison to a control group with no fresh plasma transfusion, and outcome (O): nosocomial infection.

2.1. Eligibility Criteria

All the studies, which probed into nosocomial infection after FFP transfusion in patients with cardiac surgery were included. The studies that were carried out up to the end of March 2019 and those in which infection was the primary or secondary effect after FFP transfusion were also included. In three studies, only the abstracts were available (11-13). Thus, first the researchers wrote to the authors of the articles. Out of the three cases, one responded saying that the article was not published completely. However, the second author did not respond to the letter, and no E-mail was available for the last one.

2.2. Search Strategy

An extensive search was carried out in electronic databases and sources of the related articles. The search in electronic databases was performed in a systematic way in accordance with a Liberian's instruction and under the supervision of a specialist and researcher in the field of cardiac anesthesia. In this phase, the related key terms were selected through Mesh and Emtree databases, consultation with the experts of the field, and searching the titles and abstracts of the related articles. Then, search strategy for each of the databases was defined through resorting to the

Database	Search Terms
MEDLINE (PubMed)	1- "Coronary Vessel" [Mesh] OR "Coronary Artery Bypass" [Mesh] OR "Internal Mammary-Coronary Artery Anastomosis" [Mesh] OR "Coronary Artery Bypass, Off-Pump" [Mesh] OR "Cardiac Surgical Procedures" [Mesh] OR "Cardiovascular Surgical Procedures" [Mesh] OR "Vascular Surgical Procedures" [Mesh] OR "Surgical" [Mesh] OR "Cardiac Surgical Procedures" [tiab] OR "Procedure, Cardiac Surgical" [tiab] OR "Procedures, Cardiac Surgical" [tiab] OR "Surgical Procedure, Cardiac" [tiab] OR "Surgical Procedures, Cardiac" [tiab] OR "Surgical Procedures, Heart" [tiab] OR "Cardiac Surgical Procedure" [tiab] OR "Heart Surgical Procedures" [tiab] OR "Procedure, Heart Surgical" [tiab] OR "Procedures, Heart Surgical" [tiab] OR "Surgical Procedure, Heart" [tiab] OR "Heart Surgical Procedure" [tiab] OR "Coronary Artery Surgery" [tiab] OR " Coronary Artery Bypass" [tiab] OR "Coronary Vessel" [tiab] OR "Vessel, Coronary" [tiab] OR "Vessels, Coronary" [tiab] OR "Coronary Arteries" [tiab] OR "Arteries, Coronary" [tiab] OR "Artery, Coronary" [tiab] OR "Coronary Artery" [tiab] OR "Coronary Veins" [tiab] OR "Coronary Vein" [tiab] OR "Vein, Coronary" [tiab] OR "Veins, Coronary" [tiab] OR "Sinus Node Artery" [tiab] OR "Arteries, Sinus Node" [tiab] OR "Artery, Sinus Node" [tiab] OR "Sinus Node Arteries" [tiab] OR "Artery Bypass, Coronary" [tiab] OR "Artery Bypasses, Coronary" [tiab] OR "Bypasses, Coronary Artery" [tiab] OR "Coronary Artery Bypasses" [tiab] OR "Coronary Artery Bypass Surgery" [tiab] OR "Bypass, Coronary Artery" [tiab] OR "Aortocoronary Bypass" [tiab] OR "Aortocoronary Bypasses" [tiab] OR "Bypass, Aortocoronary" [tiab] OR "Bypasses, Aortocoronary" [tiab] OR "Bypass Surgery, Coronary Artery" [tiab] OR "Coronary Artery Bypass Grafting" [tiab] OR "Anastomosis, Internal Mammary-Coronary Artery" [tiab] OR "Anastomosis, Internal Mammary Coronary Artery" [tiab] OR "Coronary-Internal Mammary Artery Anastomosis" [tiab] OR "Coronary Internal Mammary Artery Anastomosis" [tiab] OR "Internal Mammary Coronary Artery Anastomosis" [tiab] OR "Coronary Artery Bypass, Off Pump" [tiab] OR "Coronary Artery Bypass, Beating Heart" [tiab] OR "Off-Pump Coronary Artery Bypass" [tiab] OR "Off Pump Coronary Artery Bypass" [tiab] OR "Beating Heart Coronary Artery Bypass" [tiab] OR "Artery Bypass, Coronary" [tiab] OR "Artery Bypasses, Coronary" [tiab] OR "Bypasses, Coronary Artery" [tiab] OR "Coronary Artery Bypasses" [tiab] OR "Coronary Artery Bypass Surgery" [tiab] OR "Bypass, Coronary Artery" [tiab] OR "Aortocoronary Bypass" [tiab] OR "Aortocoronary Bypasses" [tiab] OR "Bypass, Aortocoronary" [tiab] OR "Bypasses, Aortocoronary" [tiab] OR "Bypass Surgery, Coronary Artery" [tiab] OR "Coronary Artery Bypass Grafting" OR "Coronary artery bypass graft surgery" [tiab] OR "CABG"[tiab] OR "Cardiovascular Surgical" [tiab] OR "Cardiovascular Surgical Procedure" [tiab] OR "Procedures, Cardiovascular Surgical" [tiab] OR "Cardiovascular Surgical Procedures" [tiab] 2- "Plasma" [Mesh] OR "Plasma" [tiab] OR "Blood Plasma" [tiab] OR "Blood Plasmas" [tiab] OR "Fresh Frozen Plasma" [tiab] OR "Fresh Frozen Plasmas" [tiab] OR "Frozen Plasma, Fresh" [tiab] OR "Frozen Plasmas, Fresh" [tiab] OR "Plasma, Fresh Frozen" [tiab] OR "Plasmas, Fresh Frozen" [tiab] OR "FFP" [tiab] 3- #1 AND #2

instructions of that database. It is worth mentioning that Medline, Web of Science, Embase, Central, and Scopus electronic databases were searched to the end of March 2019. Search strategy for Medline database has been presented below as a model.

2.3. Study Selection

Two independent assessors read the titles and abstracts and chose the related articles based on the study objectives.

2.4. Quality Assessment and Data Extraction

Two independent assessors were responsible for screening and summarizing the articles, entering the data into the study checklist, and controlling the quality of the mentioned articles. Any disagreement between the two assessors was resolved through discussion with a third researcher. The articles were summarized based on the checklist, which was designed in accordance with PRISMA statement instructions (14). The extracted data included some information about the study design, sample properties, control group (age), and number of samples. If the required data were not presented in the article, they were asked for by means of calling the corresponding author. The process of quality assessment of the included articles has been depicted in Figure 1.

2.5. Statistical Analysis

The data were analyzed descriptively. All the studies were summarized and categorized based on the study variables.

2.6. Ethical

There was no need for gaining the approval of the Ethics Committee.

3. Results

3.1. Describing the Studies' Properties

The search carried out in the aforementioned databases resulted in access to 2412 non-duplicate records. Then, screening was done and the data extracted from five articles were ultimately entered into the present systematic review (8, 15-18) (Figure 2). The characteristic of the articles that probed into the rate of nosocomial infection after FFP transfusion in cardiac surgery have been presented in Table 1. Three abstracts, which studied nosocomial infection, were also found in the resources (11-13). Nevertheless, as the E-mail of the corresponded author was not available, E-mails were sent to two other authors, only one of whom replied and he had just published the abstract unfortunately. By adding up these three abstracts, a total of eight articles were explored in this review.

3.2. Infection Status after FFP Transfusion

Banbury's article involved 15592 patients with cardiovascular surgeries 13% (n = 1926) of whom received FFP injection. The results indicated that the more Red Blood Cell (RBC) and FFP transfusion was, the higher the rates of bacteremia and septicemia would be (coefficient = 0.97). However, if RBC was transfused by more than six units, FFP led to a protective effect on the incidence of bacteremia and septicemia (coefficient = 0.072) (15). Moreover, there was no significant difference between the infection rate of the superficial sternal wound and deep sternal wound with FFP (Among the patients, 351 experienced bacteremia, 353 had superficial infections, and 212 had deep infections; however, none reported overlap with each other or net number with FFP) (15).

Chenouard et al. studied 233 children aged under one year old who were hospitalized in Pediatric Intensive Care Unit (PICU) after cardiac surgery. The results of univariate analysis indicated a high relationship between nosocomial infection and FFP (OR = 4.1; 95% CI: 2.1 - 7.9; P < 0.0001). Similarly, the results of multivariate analysis with no propensity score revealed a high relationship between nosocomial infection and FFP (OR = 3.7; 95% CI: 1.8 - 7.6; P = 0.0005). However, considering the propensity score, there was no significant relationship between nosocomial infection and FFP (OR = 1.5; 95% CI: 0.5 - 4.0; P = 0.50) (16).

Figure 1. Assessment of the Quality of the Included Articles

First Author, Year, Country	1	2	3	4	5	6	7	8
Banbury, 2006, U.S.A.	☺	☹	☹	?	☹	☺	☹	☹
Chenouard, 2015, France	☺	☺	☹	?	☹	☺	☹	☺
Doussau, 2013, France	☺	☺	☹	☺	☹	☺	☺	☹
Sreeram, 2005, U.K.	☺	☹	☹	☹	☹	☺	☹	☹
TOPAL, 2012, U.S.A.	☺	☹	☹	☹	☹	☺	☹	☹

1. Publication in peer-reviewed journals, 2. Number of patient groups, 3. Sample size calculation, 4. Description of the control group, 5. Exclusion criteria, 6. Description of statistical analyses, 7. Statement of any potential conflict of interests, 8. Use of an appropriate test to prove the hypothesis.

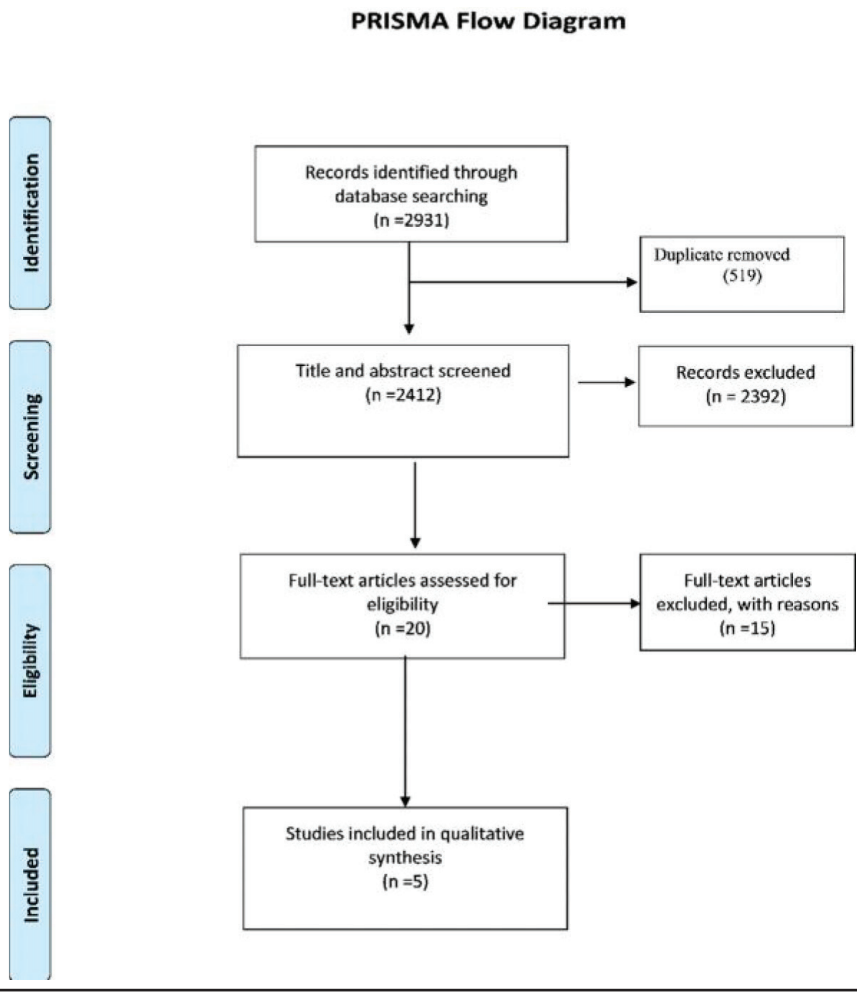

Figure 2. Prisma Flow Diagram of the Present Study

Table 1. The Characteristics of the Included Studies

First Author, Year of Publication, Country	Type of Study	Article Language	Total Sample Size	Male Gender	Age	Effect of FFP on Nosocomial Infection
Banbury, 2006, U.S.A.	observational	En	15592	67%	adult	increase
Chenouard, 2015, France	observational	En	243	67%	under one year	none
Doussau, 2013, France	observational	En	967	68%	adult	none
Sreeram, 2005, U.K.	retrospective	En	6721	64%	adult	none
Topal, 2012, U.S.A.	retrospective	En	162	51%	adult	none

In the research by Doussau et al., 24 out of the 562 patients who had received FFP were inflicted with sepsis. On the other hand, five out the 405 patients who had not received FFP were not inflicted with sepsis. The results demonstrated no significant relationship between FFP volume and sepsis rate. Although the rate of sepsis was higher in the patients receiving FFP, the researchers did not compare them in terms of significance. Nonetheless, the patients who had received FFP had higher comorbidities and more disruptive tests in comparison to those who had not received FFP. The results of univariate analysis showed that the patients who had received FFP had a higher mortality rate in comparison to the other group. In propensity score analysis, however, there was no significant relationship between FFP transfusion and mortality rate (8).

Sreeram et al. reported that 418 out of the 6721 patients were inflicted with nosocomial infection. However, their results showed no significant relationship between FFP transfusion and nosocomial infection. It should be noted that all patients had received other blood components along with FFP (17).

In Topal's study, 21 out of the 162 studied patients were inflicted with pneumonia, which was attributed to three factors, namely RBC transfusion volume, previous Constructive Obstructive Pulmonary Disease (COPD), and post-operative atrial fibrillation (AF). However, this showed no significant relationship with FFP transfusion (18).

In the research by González Pérez A et al., 256 out of the 3563 patients with heart surgery experienced pneumonia after getting hospitalized in ICU. The rate of pneumonia was higher in the FFP group compared to the others. It was also accompanied with some other more hazardous factors, including longer Cardiopulmonary Bypass (CPB) period and aortic clamp time (OR for the FFP group was about

1.149 (1.046 - 12.61)) (11, 19).

Iwade M et al. considered 158 and 76 patients with heart surgery in two studies. According to their results, the infection rate increased with the increase in FFP consumption (12, 13).

4. Discussion and Conclusion

The present study aimed to probe into the relationship between FFP transfusion and nosocomial infection in heart surgery. The included studies indicated no significant relationship between FFP transfusion and infection rate after heart surgery. However, the findings showed that Packed Red Blood Cell (PRBC) transfusion increased nosocomial infections in patients with heart surgery. Regarding the benefits of FFP in decreasing bleeding without increasing the infection rate in cardiac surgeries, no forbiddance should be taken into consideration regarding its use.

This systematic review included five related studies, which probed into the effects of FFP transfusion on the rate of nosocomial infection. Banbury conducted a study on 15592 patients and reported that the higher the RBC and FFP transfusion was, the higher the rates of bacteremia and septicemia would be (15). The findings of another study demonstrated no significant relationship between the infection rates of superficial and sternal deep wounds and FFP transfusion (15). However, the number of patients who had only received FFP and were inflicted with nosocomial infection was not reported in that study (15). It should also be noticed that the patients who had received FFP without receiving RBC or other blood components were not determined in that study. Hence, it is not possible to make a sound judgment in this regard. In another study, the results of univariate analysis indicated a high relationship between nosocomial infection and FFP. Considering the propensity score, however, there was no significant relationship between the two (16). In the research by Doussau et al., although the rate of sepsis was higher in the patients receiving FFP, the researchers did not compare the patients who had received FFP and those who had not in terms of significance. On the other hand, the patients who had received FFP had higher comorbidities and more disruptive tests in comparison to the group receiving no FFP. In the univariate analysis, the patients who had received FFP had a higher mortality rate in comparison to the other group. In the propensity score analysis, however, there was no significant relationship between FFP transfusion and mortality rate (8). The results of the fourth study also revealed no significant relationship between FFP transfusion and nosocomial infection. It should be noted that the patients in that study had received other blood components along with FFP (17). In the fifth study, no significant association was observed between FFP transfusion and three factors, namely RBC transfusion volume, previous COPD, and post-operative AF (18). On the whole, the articles indicated no significant relationship between nosocomial infection and FFP transfusion in heart surgery. Although the three retrieved abstracts revealed an increase in the infection rate with increase in FFP consumption, these studies did not consider some disruptive factors like the presence of comorbidities and/or longer surgery periods.

In conclusion, the included studies indicated that the benefits of FFP administration outweighed the probable infection risk. Indeed, none of the studies indicated a strong relationship between FFP transfusion and infection rate after cardiac surgery.

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Authors' Contribution

All authors had a role in designing the study. BN, FS, and AA read the titles and abstracts and chose the relevant articles. GF performed data extraction and summarization. SA wrote the draft of the manuscript. All authors read and accepted the final version.

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The authors have no financial interests related to the material in the manuscript.

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