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Review Article

Effectiveness and safety of recombinant factor VII in pediatric cardiac surgery aged 13 years or less: A meta-analysis

Hanan Abu Hassan[1], Faisal Rustom[2], Hend Ali Bafaqih[3], Reem Mohamed Beheri[4], Shawana Farooq Shaikh[1], Sultan Al Dalbhi[5]

[1]Department of Pediatric Intensive Care, Prince Sultan Cardiac Center, Riyadh 11159, Saudi Arabia, [2]College of Medicine, Alfaisal University, Riyadh 11421, Saudi Arabia, [3]Department of Pediatric Intensive Care, Prince Sultan Military Medical City, Riyadh 11159, Saudi Arabia, [4]Pediatric Cardiac Intensive Care, Heart center, King Faisal Specialist Hospital and Research Center, Riyadh 12713, Saudi Arabia, [5]Department of Adult Nephrology, Prince Sultan Military Medical City, Riyadh 11159, Saudi Arabia

Address for correspondence:
Sultan Al Dalbhi, Department of Adult Nephrology, Prince Sultan Military Medical City, Riyadh 11159, Saudi Arabia.
E-mail: saldalbhi_2014@hotmail.com

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ABSTRACT

Objectives: Bleeding is the most serious complication of cardiac surgery among pediatric patients. Recombinant factor VII (rFVII) is a widely used coagulant, despite a lack of evidence on its effectiveness. The current study aimed to summarize the effectiveness and safety of using rFVII in pediatric cardiac surgery using data from existing double-arm studies.

Methods: After a systematic search of existing databases and careful scrutiny by two independent researchers, seven double-arm studies were shortlisted. Of these seven studies, there was one randomized control trial, one cohort study, and five case–control studies, which together had 1117 pediatric patients of cardiac surgery. rFVII was administered in the intervention arm group, whereas either a placebo or blood products were given to the control group for bleeding. Pooled risk ratio was the summary measure of association for thrombotic complications, reexploration, and mortality among the two groups. The standard mean difference was calculated for comparing mean chest tube output before and after the administration of rFVII between the two groups using the random-effects model. The heterogeneity coefficient was calculated for each outcome measure.

Results: No statistically significant difference was observed for mean chest tube output (before – [mean difference = 3.36, 95% confidence interval (CI) = −0.60, 7.31, $P = 0.10$] and after – [mean difference = −0.34, 95% CI = −0.26, 2.01, $P = 0.78$] administering rFVII), thrombotic complications (RR = 1.39, [95%] CI = 0.69–2.81) and mortality (relative risk [RR] = 1.19 [95%] CI = 0.82–1.74). However, the rate of reexploration was 1.86 times more in the intervention arm as compared to the control arm (RR = 1.86 (95%] CI = 1.16–2.98). There were insufficient data for length of stay in intensive care unit and hospital, and volumes of transfused blood for deriving summary measure.

Conclusions: The administration of rFVII does not provide any added advantage for bleeding control among pediatric patients of cardiac surgery. However, it increased the rate of reexploration among the intervention arm. However, due to the small sample sizes of the included studies, the results need to be taken cautiously.

Keywords: Cardiac surgery, control group, pediatric patients, placebo, recombinant factor VII

Introduction

Bleeding is the most common and serious complication after cardiac surgery, especially cardiopulmonary bypass (CPB), which has substantial morbidity and mortality related to it. The complications are more pronounced among infants and children as their coagulation system is weak and immature, due to the deficiency of various coagulant proteins. The long duration of surgery in a hypothermic environment and extensive suture lines are established risk factors for bleeding post- CPB surgery among neonates and children. The condition is worsened if the child presents with the underlying cyanotic condition as well. Hence, there was a pressing need for an effective pharmacological agent which could prevent post-surgery coagulopathy.[1-4]

Until 2007, aprotinin (Trasylol®; Bayer Pharmaceuticals Corporation, West Haven, CT) was being used for this purpose. After its discontinuation, the pediatricians were left with only a few choices like recombinant factor VII (rFVII).

rFVII (rFVIIa; NovoSeven® RT, Novo Nordisk, Bagsvaerd, Denmark) is a synthetic coagulation factor, cloned in hamster kidney cells, and is genetically similar to human coagulation factor VII (FVII). In 1999, the Food and Drug Administration approved its usage among hemophilia A and B patients for treating bleeding episodes. Later in 2005, FVII was also applied among non-hemophiliac patients for the treatment of bleeding episodes and for preventing excessive bleeding during surgeries or invasive procedures among patients having a congenital deficiency.[1-3]

Recently, Witmer *et al*. (2011) analyzed the data of Pediatric Health Information System from 2000 to 2007 in a retrospective multicentric cohort study to investigate the various conditions in which FVII was used among children <18 years. They found that of 3764 children, about 89% of children received rFVII for an off-label indication. Of the entire off label indications, the major portion was attributed to cardiology and cardiothoracic surgeries, accounting for around 20%.[5] Keeping in view the requirement for administering rFVII in such surgeries, it becomes important to assess the effectiveness, efficacy, and safety profile of rFVII administration among pediatric patients.

During our literature search, we found many studies, including randomized controlled trials (RCTs), as well as a conclusive good-quality meta-analysis which have assessed the effectiveness of rFVII among adults.[2,6,7] However, there is a scarcity of such studies, especially RCTs among pediatric patients. To date, we could find only one RCT which attempted to explore the various domains of this therapy.[8] However, there is an abundance of double arm observational studies having different designs which are also a good source of evidence in the absence of level 1 studies.[9-12]

Due to the scarcity of literature, we could find only one meta-analysis conducted by Warren *et al*. (2007) to answer the questions related to the efficacy of rFVII. Albeit, in their meta-analysis, they considered only two studies of the pediatric age group and the rest of the studies were among adults.[2] Hence, his meta-analysis was not powered enough to draw conclusions on the pediatric population. Similarly, Okonta *et al*. and Guzetta *et al*. conducted systematic reviews in 2012 among the pediatric population reporting the usage of rFVII among cardiac surgery cases. However, it was a narrative review which did not analyze the data as is done in a meta-analysis.[13] Hence, they could not recommend whether RFVII should be used or not for cardiac surgery among pediatric patients.

With the above background, in the absence of any concrete evidence provided by earlier researchers and in the light of new upcoming studies after 2012, we decided to carry out this meta-analysis considering the limitations of previous systematic reviews and meta-analysis. The current study has been planned to summarize the effectiveness and safety of using rFVII in pediatric cardiac surgery from the existing double-arm studies.

Objectives

The objectives of the study were to assess the effectiveness of rFVII among children undergoing cardiac surgery in terms of reducing time to chest closure, reexploration, intensive care unit (ICU) stay, length of hospital stay (LOHS) stay, volumes of transfused blood, platelet concentrates, fresh-frozen plasma, thrombotic complications, and mortality as compared to children who were administered either no treatment, a placebo, or standardized treatment other than rFVII administration.

Methodology

Search strategy and selection criteria

We performed this study as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. As a first step, we developed a pre-specified well-elaborated search strategy with the assistance of an experienced research librarian. To capture a broad universe, we included all published studies regardless of intervention setting, and study design (with the exception of case reports) from PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Google Scholar, and manual searching by screening the references of the relevant studies. All studies available in English and published between 2000 and August 2018 were included in the study. We used three major themes that are pediatric cardiac surgery, role of rFVII, and double arm trial search the studies.

The criteria followed for narrowing down the search was:

Intervention arm: Administration of Recombinant Activated FVII among pediatric cardiac surgery patients.

Control arm: Placebo or no treatment or any other standardized treatment such as blood or plasma transfusion

Outcome variables: Thrombotic complications, time to chest closure, reexploration, ICU stay, LOHS, volumes of transfused blood, platelet concentrates, and fresh-frozen plasma and mortality

Search strategies were independently designed and performed by two separate investigators. We used the following medical subject headings (MeSH) terms or keywords in different combinations and permutations for searching studies in advanced PubMed search:

"Cardiac surgery among Pediatric population," "heart surgery," "rFVII," "control arm," and "placebo."

The search strategies described above provided a list of studies. The titles and abstracts of all the retrieved studies were screened independently by two authors. The irrelevant studies were discarded in the first attempt. Later on, the full-text version of the shortlisted studies was analyzed for the presence of measurable outcome variables, as described above.

We did not pose any restrictions on the language of the articles as most of the articles could be translated by the google translate tool, which most of the journals supported for language conversion. Ultimately, we chose only full-text articles where detailed data were available for extraction and analysis.

Data extraction

We extracted the following study features: First author, publication year, study setting, sample size in intervention, and control group, respondent characteristics such as age and weight, mean chest closure output and time, mean length of hospital and ICU stay, volumes of transfused blood, platelet concentrates, and fresh-frozen plasma; rate of thrombotic complications and mortality among two groups. Outcomes reported in two or more articles were analyzed for meta-analysis.

Quality assessment of studies

Two authors analyzed each included study using the GRACE checklist to assess the quality of each study. The GRACE checklist consists of 11 questions that address the key components of double arm observational studies. This process was performed iteratively. Two authors reviewed all the studies and then the group met for a consensus conference. Disagreements were resolved by group consensus. Finally, it was decided to include those studies which met at least six of the 11 criteria suggested by the GRACE checklist.[14]

Data analysis

Extracted data were entered and analyzed using RevMan 5.3. For dichotomous variables such as thrombotic complications, need for reexploration and mortality, and summary measure were expressed as risk ratios and 95% confidence interval (CIs). For continuous variables such as chest tube output, blood, and plasma concentrate, summary mean difference and 95% CI were calculated. Heterogeneity in the studies was evaluated using the Cochrane Q test and I^2 statistics were used to assess the degree of inter-study variation. I^2 values of 0% to 24.9%, 25% to 49.9%, 50% to 74.9%, and 75% to 100% were considered as having no, mild, moderate, and significant thresholds for statistical heterogeneity.

As we had broad criteria of study selection, it was anticipated to use a random-effects model for generating summary measures. Funnel plots were made to explore the possibility of publication bias for the thrombotic complications outcome.

Ethical approval

The permission for conducting this meta-analysis was granted by the Institute's Ethical Committee. There was no need for the patient's consent as the original studies had already taken care of this, and our meta-analysis involved the secondary data analysis.

Results

Study selection and quality assessment

The combined literature search identified around 97 studies that contained the MeSH terms either in the title or abstract. After reviewing the title, we included 25 studies for abstract review. Finally, only seven studies matched the inclusion criteria.[8-12,15,16] The excluded studies were rejected on various grounds described in Figure 1.

The eligible studies were conducted between 2004 until 2017. Of total seven eligible studies, one was an RCT[8] and one was a cohort study[12] and the remaining five were retrospective case–control studies carried out in different parts of the World[9-11,15,16] as described in Table 1. Four of the seven studies were conducted in the USA.[9-11,15] The total population covered was 1117. The age of pediatric patients varied from 4 months to 10 years. It was observed that the administered dose of rFVII was different in all the studies, thereby indicating a lack of standard dosage guidelines. Except for a study by Ekert *et al*. (2006) where the authors administered a placebo in similar dosage to the intervention drug; in all other studies, standard hemostatic agents, and blood products other than rFVII were used to control bleeding in the non-intervention arm.

The quality of the included studies was found to be satisfactory as per GRACE checklist. It was found that except for a study by Niebler *et al*., all the studies had described the dosage of rFVII administration. Only the studies conducted by Karsies *et al*., Downy *et al*., and Yinan *et al*. had addressed confounding factors at the design stage by doing the

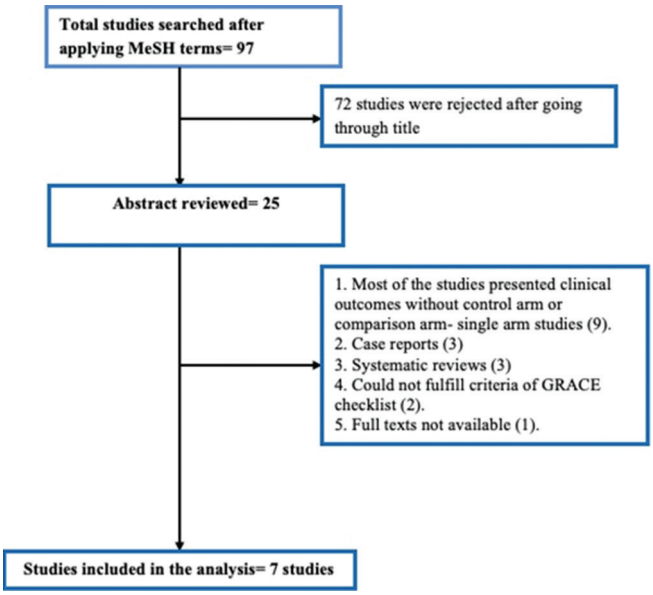

Figure 1: Flowchart showing the selection of studies

Table 1: Matrix showing characteristics of selected studies

First author, year	Design	Country	Study period	Patient disease profile	Age rFVII treated/ Controls	Total sample size	Intervention arm drug dosage	Control arm (placebo/blood products infusion
Tobias *et al*., 2004[12]	Cohort with control group matched	Dominican Republic	2003	Tetralogy of Fallot, ventricular septal defect, mitral valve repair, sinus venosus atrial septal defect, primum atrial septal defect	Mean=9±4/10±3 years	17	90 mcg/kg	Managed with blood products only
Ekert *et al*., 2006[8]	Randomized double blind parallel group and placebo controlled	Australia	NA*	Transposition of great vessels, tetralogy of Fallot, complete atrioventricular septal defect	Median=4 Months	76	40 mcg/kg	Placebo-40 mcg/kg
Aggarwal *et al*., 2007[9]	Retrospective unmatched case–control	USA	2000–2004	Hypoplastic left heart syndrome, transposition of great arteries, aortic stenosis, bi-directional Glenn Shunt, ECMO	9.5/7 years (median)	45	43±22.9 mcg/dose	Managed with blood products only
Karsis *et al*., 2010[10]	Retrospective matched case control	USA	1999–2005	AS/A1, d-TGA, TAPVR, HLHS	50±15/56±11 months	75	70±28 mcg/kg	Managed with blood products only
Niebler *et al*., 2010[11]	Retrospective case series	USA	2003–2006	Cardiac surgery patients during extracorporeal membrane oxygenation support	0.1 (0–14)/0.1 (0–17) years – median	40	Dose not specified	Different hemostatic agents were administered
Downy *et al*., 2017[15]	Retrospective propensity matched case control	USA	2011–2013	Unspecified	median=3.3/4.5 years	426	median dosage=89.5 (48.9–103.4) mcg/kg	Managed with blood products only
Li *et al*., 2017[16]	Retrospective propensity matched case control	China	2013–2016	Unspecified	1 (0.4–4)/0.8 (0.34–3) years Median	438	median dosage=62.5 (50–90) mcg/kg	Managed with blood products only

*Information on period of data collection is not available

propensity score matching for cases and controls. Age, sex, body weight, neonate, prematurity, previous sternotomy, CPB, deep hypothermic circulatory arrest time, aortic cross-clamp time, and operative surgeon were the variables which were matched in these studies. Rest all the quality criteria were fulfilled by all studies such as the objectivity of the primary outcome (rate of thrombotic complication) and the same outcome measure was used to compare the intervention as well as the control arm, etc.

Summary measures of primary and secondary outcomes

During the review, we found that all the studies have used varied primary and secondary outcomes to assess the effectiveness of rFVII. We have included all these outcomes in this meta-analysis [Figures 2-7]. The primary outcomes such as time of chest closure, length of ICU, and hospital stay have been considered by only one or two studies, so we could not do the summary analysis. Hence, we have described the findings of these variables qualitatively (Table 2).

Length of ICU stay (LOIS)

Downy *et al*. reported the median LOIS among intervention arm to be 8 days (4–24 days), whereas Yinan *et al*. found it to be 5.65 (3–12.28) days. Among the control arm, it was found to be 5 (2–10) days and 3.91 (1.83–6.77) days, respectively, by Downy *et al*. and Yinan *et al*.

LOHS

The median LOHS was found to be 20 (9–44) days in the intervention arm and 11 (7–23) days in the placebo arm in the study by Downy *et al*.

Time to chest closure

Ekert *et al*. found that time to chest closure was significantly higher ($P = 0.0263$) among intervention arm as compared to the control arm (98.82 min vs. 55.31 min).

Mean chest tube output (mL/kg/h) at 0–4 h post-surgery but before administering rFVII or placebo

The summary mean difference of three studies indicated that there was no significant difference in the mean chest tube output among two groups before administering intervention or

placebo, that is, at the baseline after surgery (mean difference = 3.36, 95% CI = −0.60, 7.31, $P = 0.10$). There was significant heterogeneity among the selected studies for this outcome measure ($\tau^2 = 11.91$, $\chi^2 = 89.52$, df = 2, $P = 0.00001$, $I^2 = 98\%$).

Mean chest tube output after administering rFVII (mL/kg/h) or placebo

The summary mean difference of three studies indicated that there was no significant difference in the mean chest tube output among two groups after administering interventions or placebos (mean difference = −0.34, 95% CI = −0.26, 2.01, $P = 0.78$). There was significant heterogeneity among the selected studies for this outcome measure ($\tau^2 = 4.18$, $\chi2 = 78.62$, df = 3, $P = 0.00001$, $I^2 = 96\%$).

Volumes of transfused blood

The range of transfused blood (ml/kg) among the intervention group varied from 2.2 to 116 ml/kg in the studies conducted by Niebler *et al*. and Ekert *et al*. Similarly, the range varied from 20.1 to 100 ml/kg in the control arm across these two studies. Keeping in view such a broad range of transfused volumes blood, we did not attempt to find the summary mean difference in the two groups.

Comparing Incidence of thrombotic complications in two groups

It was found that that there was no significant difference in the rate of thrombotic complications between two groups (relative risk [RR] = 1.39 [0.69–2.81], $P = 0.36$). The heterogeneity was found to be moderate among the selected studies ($I^2 = 56\%$, $\tau^2 = 0.31$, $\chi^2 = 8.99$, df = 4).

Rate of reexploration

It was found that the rate of reexploration was 1.86 times more in the intervention arm as compared to the control arm. Moreover, this difference in the rate of reexploration was found to be statistically significant (RR = 1.86 (1.16–2.98), $P = 0.01$]. The heterogeneity was found to be very low and statistically insignificant among the selected studies ($I^2 = 3\%$, $\tau^2 = 0.00$, $\chi^2 = 1.03$, df = 1, $P = 0.31$).

Mortality rate among two groups

It was found that that there was no significant difference in the rate of mortality between the two groups (RR = 1.19 [0.82–1.74], $P = 0.35$). The heterogeneity was found to be zero among the selected studies ($I^2 = 0\%$, $\tau^2 = 0.00$, $\chi^2 = 1.72$, df = 2, $P = 0.42$).

Discussion

The hemostatic consists of an integrated system of coagulation factors, platelets, endothelium, and regulatory proteins that work in harmony at the site of vascular injury to prevent blood loss without occluding the entire vessel. Under certain instances like cardiac surgery with CPB, the whole system gets activated, thereby initiating the chain of both bleeding and thrombotic complications. Complications being more pronounced among the pediatric age group has led to the development and usage of specific interventions like the administration of rFVII to control refractory bleeding.[3,5,17]

During a literature search, we came across three major areas where clinicians have used rFVII for extra hemostasis among this age group after cardiac surgery.[1] The first being the prophylactic use of rFVII after CPB but before administering any other blood products. Ekert *et al*. (2007) have reported such usage in their double-blinded RCT. They have compared the efficacy of rFVII in terms of time to chest closure, volume of transfused products 48–72 h post-surgery, and blood loss in the first 12 h post-surgery among the intervention and placebo arm. There were no significant differences in any of the measures of efficacy in their study.

The second indication for its usage is "routine" administration along with other blood products to contain the bleeding. However, we could not find any study which has documented this indication for cardiac surgery. Although, rFVII has been routinely used for achieving hemostasis among children suffering from dengue hemorrhagic fever.

The third indication for using rFVII is rescue therapy for controlling refractory blood loss during cardiac surgery. Most of the studies pertain to this section of indication. Many case series, case reports, and case–control studies (included in this metanalysis) have reported this usage. The case reports and case series have documented bleeding control after the administration of this factor. However, as these studies lacked a control arm, the findings may not be as valid. However, none of the case–control studies have found any significant positive effect or adverse effect of administering rFVII. Although Downy *et al*. (2017) reported a statistically higher rate of thrombotic complications among the intervention group as compared to the control group.[15]

Hence, the findings of individual studies are in sync with this metanalysis. In our study, we found that there was no difference in the effectiveness of using rFVII over placebo or simply using other blood products in terms of chest tube closure output or volumes of transfused blood and blood products.[9,11,12] Similarly, there was no difference in the rate of complications such as thrombosis or mortality among the two groups.[9,10,16] However, the rate of reexploration was significantly higher among the intervention group as compared to the control group, as reported by Yinan *et al*. also.[16] However, the systematic review by Guzetta *et al*. recommends the usage of rFVII for rescue therapy to control refractory bleeding in the light of findings from case series and case reports.[1] However, their finding needs to be cautiously interpreted in the light of existing knowledge about the mechanism of action of rFVII as a hemostatic agent.

The general fact about the hemostatic action of rFVII is that it acts through a combination of tissue factor (TF)

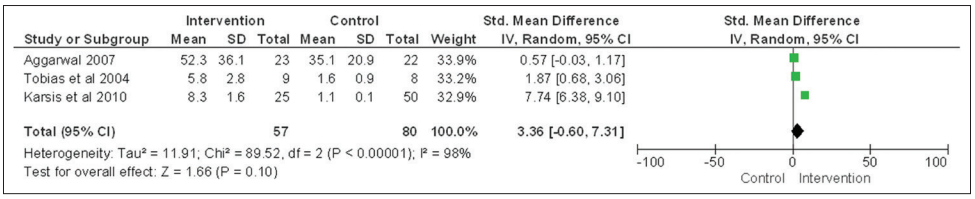

Figure 2: Mean chest tube output (mL/kg/h) at 0–4 h post-surgery but before administering recombinant factor VII or placebo

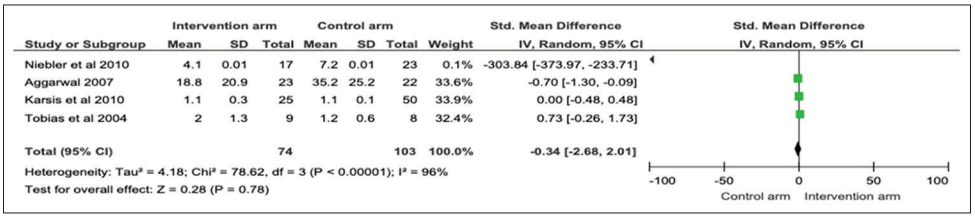

Figure 3: Mean chest tube output after administering recombinant factor VII (mL/kg/h) or placebo

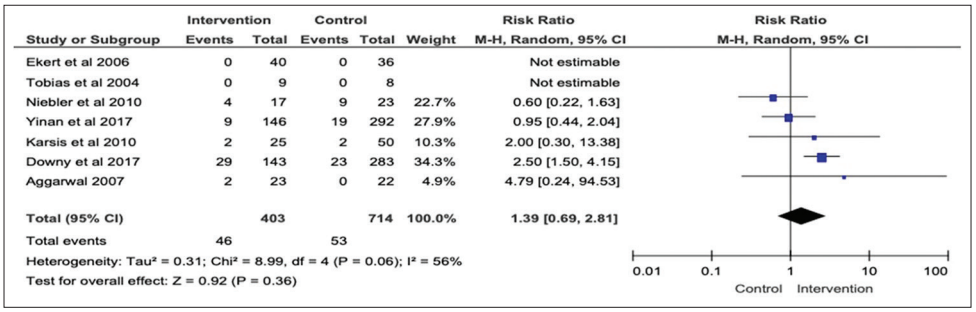

Figure 4: Comparing the incidence of thrombotic complications in two groups

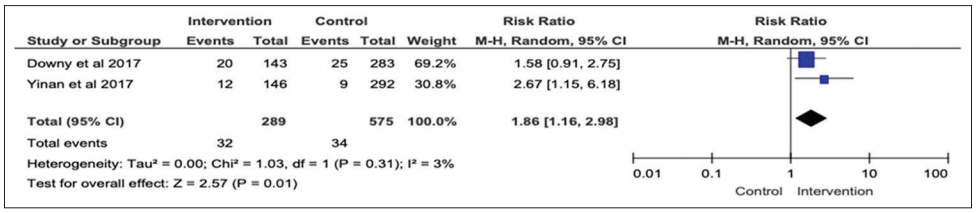

Figure 5: Rate of reexploration

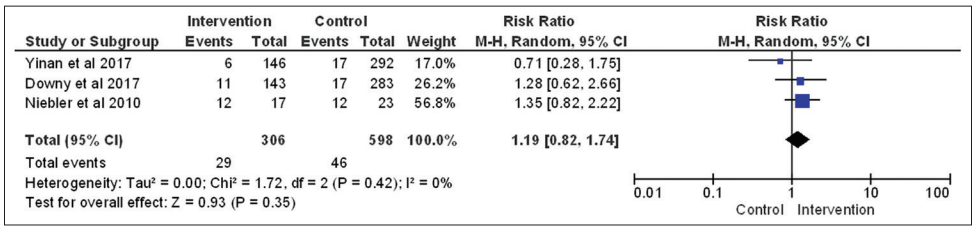

Figure 6: Mortality rate among two groups

dependent and TF independent pathways. In the case of TF dependent pathway, thrombin formation is mostly mediated by TF as it has a larger affinity for rFVIIa as compared to its affinity for the activated platelet surface. In the case of TF independent mechanism, increased concentrations of rFVIIa can induce large-scale thrombin generation on the surface of activated platelets, anywhere they are present, and form a more stable clot. Hence, it is clear from the physiologic mechanism that activated platelets are the key for rFVII to function well.[17-19]

Now, if we reexamine the facts of the study, we can find a valid reason why the intervention group of rFVII administration had a statistically higher time of chest tube closure as compared to placebo.[7] This was because they had administered rFVII prophylactically before giving other blood products,

Table 2: Quality assessment of studies

GRACE checklist	Tobias *et al*., 2004	Ekert *et al*., 2006	Aggarwal 2007	Karsis *et al*., 2010	Niebler *et al*., 2010	Downy *et al*., 2017	Yinan Li *et al*., 2017
D1. Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data sources?	Yes	Yes	Yes	Yes	No	Yes	Yes
D2. Were the primary outcomes adequately recorded for the study purpose?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D3. Was the primary clinical outcome measured objectively rather than subject to clinical judgment?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D4. Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D5. Was the primary outcome measured or identified in an equivalent manner between the intervention group and the comparison groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D6. Were important covariates that may be known confounders or effect modifiers available and recorded?	No	No	No	Yes	No	Yes	Yes
M1. Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
M2. If 1 or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparison groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
M3. Were important confounding and effect modifying variables taken into account in the design and/or analysis?	No	No	No	Yes	No	Yes	Yes
M4. Is the classification of exposed and unexposed person-time free of "immortal time bias"?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
M5. Were any meaningful analyses conducted to test key assumptions on which primary results are based?	NA	NA	NA	NA	NA	NA	NA

specifically platelets. Due to delayed administration of platelets and heavy blood loss after CPB, rFVII could not initiate clot formation due to a lack of activated platelets. However, once the blood products were transfused, it formed a better clot as compared to the placebo group. Furthermore, in the study by Ekert *et al*., the prophylactic doses of rFVII used were way below the recommended dosage of >90 mcg/kg. This study also could not find out any added benefit which could be incurred after the administration of rFVII.[8]

Now coming to the second scenario of case–control studies where rFVII was administered to the intervention arm and blood products were given in the control arm to control profuse bleeding after CPB. These studies concluded that there was no difference in the efficacy of rFVII usage over standardized treatment with blood products.[9-11,15,16]

We hypothesize that if rFVII is administered along with blood products in one arm and only blood products on the other arm, there is a substantial possibility that the time of chest tube closure will be less in the intervention arm as compared to control arm. However, the effectiveness of the treatment may remain the same in both groups. For this, a large sample size clinical trial needs to be carried out to test this hypothesis.

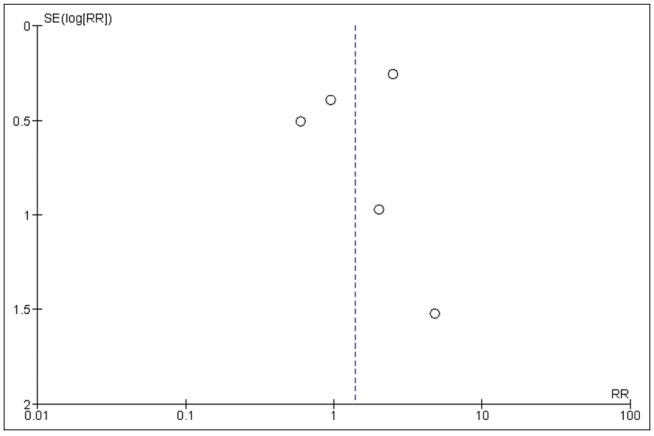

Figure 7: Funnel plot based on effect size for thrombotic complication

To the best of our knowledge, this is the first meta-analysis which has been carried out to assess the efficacy and

effectiveness of rFVII among cardiac surgery pediatric patients. In this metanalysis, we have considered only double-arm studies for inclusion and based on this, we have put forward a specific hypothesis or research question which needs to be answered in future research. Another issue which we have tried to highlight through this review is the standardized dose of rFVII administration. All the trials and studies have used varying dosages which also needs to be uninformed.

The small sample size of the individual studies, varying types of cardiac surgeries, different age groups of children, different doses of rFVII administration, and different study designs have added heterogeneity to the summary measures as reflected by the funnel plot diagram as well. Data were available from all the studies for thrombotic complications only. The hollow dots as per convention indicate small sample sized studies, but these are equally distributed about the null value. Thereby, indirectly indicating that the included studies were of good quality though with small sample size and hence, affect size.

This may be considered a limitation of this meta-analysis. However, if we review the findings of this meta-analysis in light of the physiological mechanism of rFVII action, we can better understand that the usability of rFVII is governed by its mode of action, not merely the protocol. Hence, it is imperative for clinicians to consider the clinical need to administer rFVII after considering its physiologic pathway.

The future research must focus on conducting well planned, sufficiently powered RCTs with an adequate sample size. Furthermore, there is a need to standardize the clinical dose of Rfvii administration so that standardized protocols are followed throughout to obtain desired results.

Conclusions

To conclude, administration rFVII alone (without transfusing blood products) does not provide added benefit in terms of reducing mean chest tube output, or reducing time for chest tube closure or reducing LOHS as compared to control arm managed with only blood products. However, it has been associated with increased risk of reexploration though the factors or covariates need to be explored.

Authors' Declaration Statements

Ethics approval and consent to participate

Not applicable.

Availability of data and material

The data used in this study are available and will be provided by the corresponding author on a reasonable request.

Competing Interests

There are no conflicts of interest.

This manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Funding Statement

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Authors' Contributions

Hanan AbuHassan conceived the study aims and design, made decisions on inclusion and exclusion of the articles contributed to the data extraction; Faisal Rustom, Hend Bafaqih, and Reem Beheri have contributed to study design, planned the analysis, interpreted the results, and drafted the final version of the paper manuscript development and critical review, final approval of the version to be published; Shawana Shaikh and Sultan Al Dalbhi have reviewed the manuscript critically, contributed to the article critically for important intellectual content and epidemiological aspects.

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ORCID link of the submitting author: https://orcid.org/0000-0002-0721-0057

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