

Comparison of Bypassing Agents in Bleeding Reduction in Treatment of Bleeding Episodes in Patients With Haemophilia and Inhibitors

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Context: Mild-to-moderate bleeding disorders in haemophilia are primarily treated via recombinant activated factor VII a (rFVIIa) or activated prothrombin complex concentrate (aPCC). However, the efficacy of each bypassing agents may vary and none of them is universally effective.

Evidence Acquisition: After reviewing the databases of PubMed, Scopus, MD Consult, Ovid, Trip database, Google Scholar, ProQuest and the Cochrane Library, finally, 17 papers published from 2000 to 2013 were extracted. We used as a random effect model in meta-analysis. Comprehensive meta-analysis (CMA) software was used for calculating and estimating the mean of bleeding reduction and performing meta-analysis.

Results: The mean of bleeding reduction in aPCC and rFVIIa were 71.2% with CI 95% (lower limit 86.8% and upper limit 82%) and 72.3% with CI 95% (lower limit 57.6% and upper limit 83.4%), respectively.

Conclusions: Although differences between the two products were very close to each other, they reported similar effects on joint bleeds. Further clinical studies should be performed by incorporating a standardized measurement in comparative efficacy of aPCC and rFVIIa.

Keywords: Haemophilia; Meta-Analysis; Bleeding

1. Context

Management of treatment for patients with haemophilia A or B with factor VIII/IX inhibitors is primarily conducted by administration of either recombinant activated factor VII (rFVIIa) or plasma-derived activated prothrombin complex concentrate (aPCC) (1). Patients with haemophilia and inhibitors have an increased risk of developing joint damage, leading to reducing the quality of life, compared to patients without inhibitors (2). Haemophilia is not only treated with a wide variety of products, but its dose is also managed from the lowest to the maximum in similar cases (3). Prevention from joint bleed or interrupting target joint bleeding in patients without inhibitors is primarily conducted by the use of regular prophylactic doses of factor concentrates (4). Haemophilia treatment is mainly aimed at decreasing the joint bleed and arresting the progression of joint destruction, to increase the quality of life (5). The efficacy of any bypassing agent varies, as seen in many studies; factor eight inhibitor bypassing activity (FEIBA) is effective in 80-100% of cases (6). On the other hand, other studies have reported more than 90% success, which was close to 60% when rFVIIa was used in treating acute bleeds (7). However, these studies demonstrate that bypassing agents are effective

in most cases, although none of them is universally effective (6). To sum up the studies by now and by adding the knowledge of the bleeding reduction via bypassing agents in the treatment of joint bleed in patients with haemophilia and inhibitors, a systematic review of data was carried out by using a meta-analytic approach.

2. Evidence Acquisition

A systematic search was conducted among the published literature on studies that have compared the bleeding reduction of bypassing agents in treatment of haemophilia in patients with inhibitors. For including all the relevant studies, an initial search was conducted in PubMed, Scopus, MD Consult, Ovid, Trip database, Google Scholar, ProQuest and the Cochrane Library to identify papers published from 2000 to 2013. The search terms included a combination of the following: ['hemophilia' A or 'haemophilia'] and ['inhibitor' or 'antibody'] or ['recombinant factor' or 'rFVIIa'] or ['prothrombin complex concentrate' or 'aPCC'], bleed, bleeds, bleeding, haemorrhage, bypassing agent, bleeding reduction, bleeding stopped, bleeding controlled, cessation of bleeding,

bleeding resolved, bleeding treated and haemostasis. Each database had its own characteristics which led to varying search strategies and a specific algorithm. All the searches were in English. Although in two relevant studies authors have received grants, in many other studies authors had no conflict of interests. For the initial screening, papers were excluded if they were irrelevant to comparing bleeding reduction with bypassing agents based on the titles and abstracts and full texts were obtained and reviewed if the relevancy was not sufficiently determined by title and abstract. If aPCC and rFVIIa were used for prophylaxis or immune tolerance induction, treating bleeds in surgical patients or non-hemophiliac patients,

those studies were excluded. The standardized extraction table contains information such as study design, year of publication, geographical region, drug type, dosage, number of joint bleeds evaluated, and the amount of bleeding reduction. If the information was not found in abstract or full text, the corresponding author was contacted to obtain the required information; if they were not available, they were excluded. After searching the databases, manual search through some valid journals in this field was performed. To increase the confidence of identification and analysis of the articles, the reference lists of the selected articles were also searched. We used two reviewers for evaluating all the papers. Kappa

Table 1. Detailed Characteristics of 17 Articles Included in the Systematic Review on the Efficacy of Bypassing Agents in Bleeding Reduction^a

Author, Country, year	Study Design	Sample Size		aPCC Data Source	Average of Dosage		Bleeding Reduction	
		aPCC	rFVIIa		aPCC	rFVIIa	aPCC	rFVIIa
Dimichele D, USA, 2006 (8)	Retrospective post-licensure survey	163 joint bleeds	-	Retrospective post-licensure survey	72 U/kg	-	67% Cessation of bleeding	-
G. Young, USA, 2012 (9)	Retrospectively review	-	129 inhibitor	literature	-	630 µg/kg	-	90% bleeding stopped
Astermark, 2007 (FENOC) (10)	Randomized trial	48 bleeds	48 bleeds	NA	85 IU/kg	2.205 mic/kg	77.8% efficacy rate	75.6% efficacy rate
Knight, UK, 2003 (11)	Cost minimization	NA	NA	literature	180 U/kg	207 mic/kg	88% efficacy rate	92% efficacy rate
Odeyemi et al. UK, 2002 (12)	CMA	NA	NA	Literature and panelists evaluation	75*3 225 U/kg	90*2.3 207 mic/kg	79% of bleeds treated	92% of bleeds treated
Chung et al. USA, 2004 (13)	Decision tree	NA	NA	literature	75 U/kg	90 mic/kg	78% efficacy rate	87.5% efficacy rate
Putnam, USA, 2005 (14)	Decision tree	NA	NA	Literature and panelists evaluation	75 U/kg	270 mic/kg	75% efficacy rate	90% efficacy rate
Dundar et al. Turkey, 2005 (15)	Decision tree	9 joint bleeds	28 joint bleeds	Literature and panelists evaluation	166.8 U/kg	204 mic/kg	79% of bleeds treated	89.3% of bleeds treated
Joshi et al. USA, 2006 (16)	Decision analytic	NA	NA	literature	180 U/kg	207 mic/kg	78% efficacy rate	92% efficacy rate
Ozelo et al. Brazil, 2007 (17)	Decision tree	67 bleeds	36 bleeds	Observational and retrospective study	260.2 U/kg	189.9 mic/kg	56.7% efficacy rate	100% efficacy rate
You et al. South Korea, 2009 (18)	Decision tree	25 bleeds	31 bleeds	Observational and retrospective study	168 U/kg	136 mic/kg	63.6% efficacy rate	87.1% efficacy rate
Kavakli et al. Turkey, 2006 (19)	Randomized trial	-	40 bleeds 90 mic/kg and 270 mic/kg	NA	-	90 mic/kg 270 mic/kg	-	With 90 mic/kg 70% bleeds with 270 mic/kg 65% bleeds resolved
Santagostino, Italy, 2006 (20)	Randomized trial	-	32 joint bleed	NA	-	90 mic/kg	-	31% efficacy rate
Holme et al. Europe, 2009 (21)	Prospective	214 joint bleeds	NA	Prospective study	75 IU/kg	90 mic/kg	85% efficacy rate	86% efficacy rate
Smejkal et al. Europe, 2009 (22)	Retrospective	45 joint bleeds	-	NA	60 IU/kg	-	95% effective	-
Mauser-Bunschoten, 2002, Netherlands (23)	Prospective	-	43 bleeds	Prospective study	-	90 mic/kg	-	80% effective
G. Young, USA, 2008 (24)	Randomize clinical trial	22 bleed events	24 bleed events 22 bleed events	Trial study	75 IU/kg	270 mic/kg 90 mic/kg	27.3%	37.5% with 270 mic/kg 54.5% with 90 mic/kg

^a Abbreviations: aPCC, activated prothrombin complex concentrate; NA, not available; rFVIIa, recombinant activated factor VII; FENOC, FEIBA NovoSeven comparative.

coefficient between the reviewers was calculated via SPSS as 16 (K = 0.82). To assess the quality of the selected articles, reviewers evaluated the articles according to the checklist of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Consolidated Standards of Reporting Trials (CONSORT).

2.1. Statistical Analysis

For excluding some studies regarding the weaknesses of methodological and administration point of view, from 17 entered articles, 11 were entered into meta-analysis. Due to lack of information on sample size, six studies were excluded. In this study, considering the Cochran's Q test result indicating heterogeneity among different study results, a model with random effect in meta-analysis was used. Comprehensive meta-analysis (CMA) software was used for calculating and estimating the mean of bleeding reduction and performing meta-analysis. Forest plots were used for reporting the results, as the size of each square represents the sample size and the lines drawn on each side of the square represent 95% confidence interval (CI) for the mean of bleeding reduction in each study.

3. Results

The search identified 553 studies in PubMed, 24 in Trip, 11 in MD consult, 170 in ProQuest, and 29 studies were identified manually and in gray literatures of some valid journals. Finally, 17 studies were chosen out of 787 potentially relevant ones. The flowchart of the study selection process is shown in Figure 1. The details of the studies included in the review are shown in Table 1. The results of

this study showed that the mean of bleeding reduction in aPCC and rFVIIa were respectively 71.2% with CI 95% (lower limit 86.8% and upper limit 82%) and 72.3% with CI 95% (lower limit 57.6% and upper limit 83.4%). Figure 2 indicates the mean of efficacy of aPCC in bleeding reduction with 95% CI of total studies. In Figure 3, the funnel plot indicates the mean of aPCC efficacy in bleeding reduction. Figure 4 indicates the mean of rFVIIa efficacy in bleeding reduction based on the randomized model, which was estimated at 72.3% with CI 95% (lower limit 57.6% and upper limit 83.4%) (Q value = 68.1, df = 9, P value < 0.001, I² = 80.5). In Figure 5, the funnel plot indicates the mean of rFVIIa efficacy in bleeding reduction.

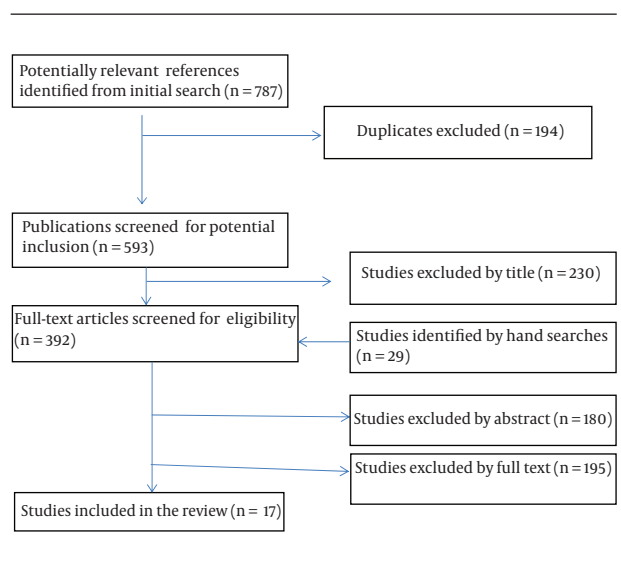


Figure 1. Flow Chart of Systematic Search

Figure 2. Mean of aPCC Efficacy in Bleeding Reduction Based on Randomized Model

Model	Study name	Statistics for each study					Event rate and 95% CI				
		Event rate	Lower limit	Upper limit	Z-Value	p-Value	-1.00	-0.50	0.00	0.50	1.00
	Dimichele: USA, 2006	0.670	0.594	0.738	4.251	0.000					
	Astermark, 2007 (FENOC)	0.778	0.640	0.874	3.611	0.000					
	Dundar et al: Turkey, 2005	0.790	0.431	0.949	1.619	0.105					
	Ozelo et al : Brazil, 2007	0.567	0.447	0.680	1.094	0.274					
	You et al: South Korea, 2009	0.635	0.435	0.797	1.333	0.183					
	Holme et al: Europe, 2009	0.850	0.796	0.892	9.061	0.000					
	Smejkal et al: Europe, 2009	0.950	0.833	0.986	4.305	0.000					
	Young: USA, 2008	0.273	0.128	0.490	-2.047	0.041					
Random		0.712	0.574	0.820	2.925	1.003					

It was estimated 71.2% with CI 95% (lower limit 86.8% and upper limit 82%); Q value = 53.4; df = 7; P value < 0.001, I² = 86.6

Treatment of patients with haemophilia is challenging and highly costing for effective management (25). Because of the important role of bypassing agents in the treatment of patients with haemophilia, an important point is understanding their relative effectiveness in reducing the rate of bleeding (26). The mean of bleeding reduction in aPCC and rFVIIa were respectively 71.2% and 72.3%. The FEIBA NovoSeven comparative (FENOC) study compared 75 IU kg⁻¹ of aPCC with 2 × 90 µg kg⁻¹ of rFVIIa. The results showed that there was no significant difference between the two treatments at no time. The bypassing agents showed similar efficacy on joint bleeds (10). This study indicated that with 95% CI, these products exhibited similar effects on joint bleeds. Given that the effectiveness of bypass agents differs in several studies, the results of this study showed that these differences are very close to each other. Zhou et al. (26) compared the pooled efficacy of bypassing agents via classic meta-analysis approach. About 2400 joint bleeds from 19 studies were analyzed, which suggested that there was no statistically significant difference between aPCC and rFVIIa in efficacy when it is used for treating joint bleeds. The efficacy of bypassing agents to control bleeding episodes has been documented in the literature with success rates ranged 80-90% (27-30). There is variability in response (31). Excluding the FENOC trial data (10), the bypassing agents data from cohort studies suggest that bleeds would be more quickly resolved if treated with rFVIIa rather than with aPCC; it is more than 90% for rFVIIa at nine hours and between 36% and 52% for aPCC (32). This is also similar to the finding of Treur et al. (33) meta-analysis, which

calculated that 75% of bleeds treated with rFVIIa would be resolved by 12 hours compared with only 36% of bleeds treated with aPCC.

3.1. Study Limitations

This study, like many other ones, is influenced by publication bias. Studies without significant differences between comparisons have not been published much (34). Sometimes, heterogeneity could not be evaluated from the available data. Early treatment of bleeding episodes is

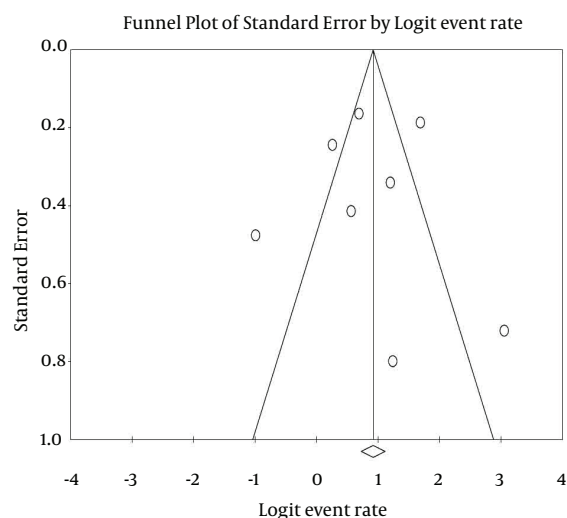


Figure 3. Funnel Plot Indicating the mean of aPCC in Bleeding Reduction

Figure 4. Mean of Efficacy of rFVIIa in Bleeding Reduction Based on Randomized Model

Model	Study name	Statistics for each study					Event rate and 95% CI				
		Event rate	Lower limit	Upper	Z-Value	p-Value	-1.00	-0.50	0.00	0.50	1.00
	Astermark, 2007 [FENOC)	0.756	0.616	0.857	3.365	0.001					
	Dundar et al: Turkey, 2005	0.893	0.749	0.959	4.043	0.000					
	Ozelo et al : Brazil, 2007	0.990	0.912	0.999	3.966	0.000					
	You et al: South Korea, 2009	0.871	0.703	0.951	3.564	0.000					
	Kavaki at al, 2006 (1)	0.700	0.473	0.859	1.736	0.082					
	Kavaki et al, 2006 (2)	0.650	0.426	0.823	1.320	0.187					
	Mausser-bunschoten, 2002	0.800	0.671	0.887	4.037	0.000					
	Young: USA, 2008 [1]	0.375	0.169	0.689	-0.925	0.355					
	Young: USA, 2008 [2]	0.545	0.374	0.706	0.508	0.611					
	Santagostino, Italy < 2006	0.310	0.154	0.526	-1.736	0.083					
Random		0.723	0.576	0.834	2.877	0.004					

It was estimated 72.3% with CI 95% (lower limit 57.6% and upper limit 83.4%); Q value = 68.1, df = 9, P value < 0.001, I² = 80.5

possible via at-home therapy, while, if it is associated with less severe bleeds, the specific sites of bleeds may affect the efficacy rates (35). In some cases, it is recommended to combine two agents or employ them sequentially for improving the effectiveness of treatment (35). However, the efficacy may be influenced by the specific bleeds sites (eg, elbow, knee, ankle, etc.). Sjamsoedin et al. (36) found that aPCC in treatment of elbow bleeds was more effective than in treatment of knee bleeds. This may therefore have affected the efficacy of therapies in this study.

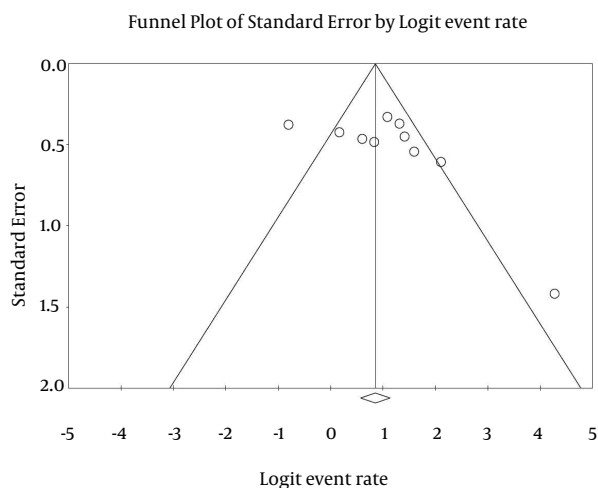


Figure 5. Funnel Plot Indicating the Mean of rFVIIa Efficacy in Bleeding Reduction

4. Conclusions

The results of this study indicated that although differences between the two products were very close, they had similar effects on joint bleeds. Further clinical studies should be performed on incorporating a standardized measurement for comparative efficacy of aPCC and rFVIIa.

4.1. Strong Points of Our Study

A strong point of our study was that although a few studies have been conducted in this field in Iran, meta-analysis is used to analyze the results of this study. In addition, most of the previous studies have investigated the efficacy of these products, but we tried to consider the type of effectiveness in reducing bleeding such as bleeding cessation, bleeding controlled and also reduction of the amount of bleedings.

4.2. Weak Points of Our Study

First, the authors searched the articles in Farsi database; but, due to lack of appropriate literature consistent with the search strategies, the search was restricted to English articles. Restrictions on access to full texts or lack of them were among the limitations of this study.

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Authors' Contributions

All the authors contributed equally in editing this paper. They all read and approved the final manuscript.

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Dr Peyman Eshghi has acted as an invited speaker and consultant to NovoNordisk, Baxter, CSL, Aryogen and some other Pharmaceuticals Inc and he has not received any funding for research carried out in this work. The other authors had no interests in which might be perceived as posing a conflict or bias.

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