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

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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 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

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: ['haemophilia' A or 'B'] 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-hemophilic 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**

| Author, Country, year | Study Design | Sample Size | aPCC Data Source | Average of Dosage | Bleeding Reduction |
|-----------------------|--------------|-------------|------------------|-------------------|-------------------|
| Dimichele De, 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 | 600 μg/kg | 90% bleeding stopped |
| Astermark, 2007 (FENOC) (10) | Randomized trial | 48 bleeds | 48 bleeds | 85 IIU/kg | 2.205 mic/kg | 77.8% efficacy rate |
| Knight, UK, 2003 (11) | Cost minimization | NA | NA | 200 U/kg | 207 mic/kg | 88% efficacy rate |
| Odeyemi et al, UK, 2002 (12) | CMA | NA | NA | Literature and panelists evaluation | 90*2.3 207 mic/kg | 92% efficacy rate |
| Chung et al, USA, 2004 (13) | Decision tree | NA | NA | 75 U/kg | 90 mic/kg | 78% efficacy rate |
| Putnam, USA, 2005 (14) | Decision tree | NA | NA | Literature and panelists evaluation | 166.8 U/kg | 204 mic/kg | 79% of bleeds treated |
| Dundar et al, Turkey, 2005 (15) | Decision tree | 9 joint bleeds | 28 joint bleeds | 168.8 U/kg | 204 mic/kg | 79% of bleeds treated |
| Joshi et al, USA, 2006 (16) | Decision analytic | NA | NA | Literature and panelists evaluation | 180 U/kg | 207 mic/kg | 78% efficacy rate |
| Ozelo et al, Brazil, 2007 (17) | Decision tree | 67 bleeds | 36 bleeds | 260.2 U/kg | 189.9 mic/kg | 56.7% efficacy rate |
| You et al, South Korea, 2009 (18) | Decision tree | 25 bleeds | 31 bleeds | 168 U/kg | 136 mic/kg | 63.6% efficacy rate |
| Kavakli et al, Turkey, 2006 (19) | Randomized trial | - | 40 bleeds | NA | 90 mic/kg | 70% 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 | 70% with 270 mic/kg 65% bleeds resolved |
| Holme et al, Europe, 2009 (21) | Prospective | 214 joint bleeds | NA | 75 IIU/kg | 90 mic/kg 85% efficacy rate | 86% efficacy rate |
| Smejkal et al, Europe, 2009 (22) | Prospective | 45 joint bleeds | - | 60 UU/kg | - | 95% effective |
| Mauler-Bunschoten, Netherlands (23) | Prospective | - | 43 bleeds | NA | 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 IIU/kg | 270 mic/kg 90 mic/kg | 27.3% |

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 literature 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.
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 in 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 et al, 2006 | 0.700 | 0.473 | 0.859 | 1.736 | 0.082 |
| Kavaki et al, 2006 | 0.650 | 0.426 | 0.823 | 1.320 | 0.187 |
| Mauser-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, I\(^2\) = 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 had affected the efficacy of therapies in this study.

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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