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Safety and Efficacy of Secondary Prophylactic in Patients with Severe Hemophilia Type A and B: A Systematic Review and Meta-Analysis Study

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Abstract

Context: Patients with hemophilia receive coagulation factor replacement for a lifetime. In Iran, on-demand treatment method is used as a standard. Clinical studies have shown significant improvements in clinical and economic outcomes as a result of the use of prophylaxis compared with other therapies. The aim of this study was to evaluate the safety and efficacy of prophylaxis in patients with severe hemophilia type A and B.

Evidence Acquisition: This is a systematic review and meta-analysis in order to evaluate the safety and efficacy of prophylaxis treatment in patients with severe hemophilia. To this response, all clinical trials, cohorts, and case-control studies, which have been investigated, were published between 1970 to Sep of 2017. STROBE and CONSORT checklists have been used according to the type of study to assess the quality of the study reports, and the results have been analyzed in STATA by meta-analysis methods.

Results: A total of 1439 studies were found in primary search and 17 of them had an inclusion criteria. The mean annual bleeding rate in prophylays treatment was 2.8 times per person/year. This study also showed that in prophylaxis, the average incidence of adverse effects was 0.13 cases, and the severe adverse effects was 0.06 cases per person/year.

Conclusions: The analysis of the studies entered in this evaluation showed that the adverse effects were significantly lower in patients treated with prophylaxis than in patients treated with on-demand treatment. This difference was observed in severe adverse effect, however, it was not statistically significant; this shows that prophilaxis is safer than the on-demand method. The lower annual bleeding rate in prophylaxis compared with the on-demand treatment method is also a sign of the effectiveness of prophilaxis.

Keywords: Prophilaxis Treatment; Severe Haemophilia; Safety; Efficacy; Systematic Review

1. Context

Hemophilia is a rare X chromosome linked disorder, which is due to a lack of coagulation factors and increase suffering ability to bleeding. It is more common in men (1) and its prevalence is 1 per 10000 male births (2). According to the World Hemophilia Federation, about 450000 people in the world are affected by hemophilia (3). A total of 10984 patients with hemophilia live in Iran (4).

This chronic disease imposes a lot of costs on the patient's family and society. The cost of medication, doctor's visits, hospitalization costs, surgical procedures, and tests are directly forced to the individual and the community, in addition, the absence of school and workplace, disability from treatment, and death are among the most important costs that are indirectly caused by hemophilia (5). In Iran, coagulation disorders are among the 20 main causes of the death in infants and children under the age of five (6).

Hemophilia patients are at risk of bleeding in various parts of the body, especially the joints (7). Repeated bleeding (8) and complications resulting from it, greatly affect the quality of life, physiological well-being, and the social life of the patient and damage his productivity and usefulness (9, 10). Hemophilia patients should receive lifelong replacement of coagulation factor in order to prevent bleeding and its effects on tissues and joints (11). The purpose of prophylaxis is to raise the level of coagulation factors in the patient's blood to prevent spontaneous bleeding and reduce the complications of the disease (12).

Clinical studies have shown that prophylactic treatment will result in significant improvements in clini-

cal and economic outcomes. These include preventing joints and total bleeding, preventing joint damage, reducing disability, reducing school and workplace absenteeism and its efficiency reduction, reducing hospitalization, outpatient and daily visits, and quality of life improvements (13-19).

Like other chronic diseases, hemophilia has a high cost, especially when treated with prophylaxis (20). Although hemophilia treatment is expensive and only achievable for 20% of patients with hemophilia, hemophilic individuals treated with coagulation factors can have an almost normal life and become productive and responsible citizens (21).

The aim of this study was to compare the safety (adverse effects and risks of using prophylaxis and on-demand treatment) and effectiveness (the effect of prophylaxis and treatment methods on improving quality of life and returning to daily life, reducing complications and disability, and so on) that will be done through systematic review and meta-analysis.

2. Evidence Acquisition

In this study, the safety and efficacy of prophylaxis was evaluated for patients with severe hemophilia via systematic review and meta-analysis.

2.1. Search Strategies

EMBASE, PubMed, Cochrane Library, Medline, Scopus, OVID, Magiran, SID and Iranmedex databases were searched by using following strategies: Hemophilia AND ("prophylaxis" OR "episodic treatment" OR "on-demand treatment") OR ("hemophilia" AND "prophylaxis" AND "treatment") OR ("hemophilia prophylaxis" OR "hemophilia on-demand treatment" OR "hemophilia episodic treatment") OR ("hemophilia treatment" OR "hemophilia prophylaxis") AND ("sever hemophilia") AND ("hemophilia A" AND "hemophilia B"). Articles and documentations related to the safety and efficacy of prophylactic treatment in patients with hemophilia from 1970 to September 2017 were investigated. In order to further search, the sources of the articles were also reviewed.

2.2. Study Selection

First, duplicated articles were removed by using the EndNote software, then, the abstract of the studies was investigated and the studies that did not examine the safety and efficacy were deleted. In the next step, all sites searched for full text and the articles whose full text was not available were excluded from the study. Evaluation of articles include, exclude and extraction of data were done by two individuals independently and articles were divided into three groups: related; non-relevant and required to be reviewed by the third person.

2.3. Inclusion and Exclusion Criteria

In this study, efficacy studies, clinical trials, or cohort studies included that were written in English or Farsi examined the hemophilic treatment method; the intervention used in them was prophylaxis. Studies on animal populations, studies that have not addressed the desired outcomes, case study articles, and studies without full text in Farsi or English were excluded from this study.

2.4. Studies Quality Assessment

To assess the quality of the study reports, STROBE and CONSORT checklists have been used according to the type of study. The scoring of the STROBE checklist is made up of 44, which is considered to be 1 to 15 weak, 16 to 30 medium, and 31 to 44 to qualify. Studies whose scores were higher than 16 were entered into meta-analysis. The CONSORT checklist has 25 items, each with a score of 1 and a maximum score of 25. Studies that were completed with this checklist above 13 have been entered into meta-analysis.

2.5. Data Extraction

The bibliographic data of the studies, such as the author of the article, the year of publication, study population, location of the study, type of study, time of the study, and the reported outcome in each study were extracted and collected. ABR (annual bleeding rate), AE (adverse effects), and SAE (severe adverse effects) used to quantitative analysis.

2.6. Statistical Analysis

The data were analyzed using STATA 12SE. The heterogeneity of the studies was studied using Cochran test and I2 statistics and I2 more than 50% was considered as heterogeneity. The random effect model in Meta-analysis was studied on the desired variables. Meta-analysis was performed based on the type and timing of the studies.

3. Results

A total of 395 articles, of the 1439 articles found in the initial searches, have been selected because they were related to the topic. Of these papers, only 11 articles were eligible for entry (Figure 1). All of these 11 articles were in English and have all reported an annual bleeding rate, however, adverse effects are only reported in 5 articles and 5 articles with severe adverse effects. The most number of samples belong to Fisher et al. (22), with 179 patients, and the least of them belonging to the Collins et al. (23), study with 20 patients. A total of eight of these studies were clinical trial trials and seven of these eight trials were randomized clinical trials, two were cohort, and one study was case-control (Table 1).

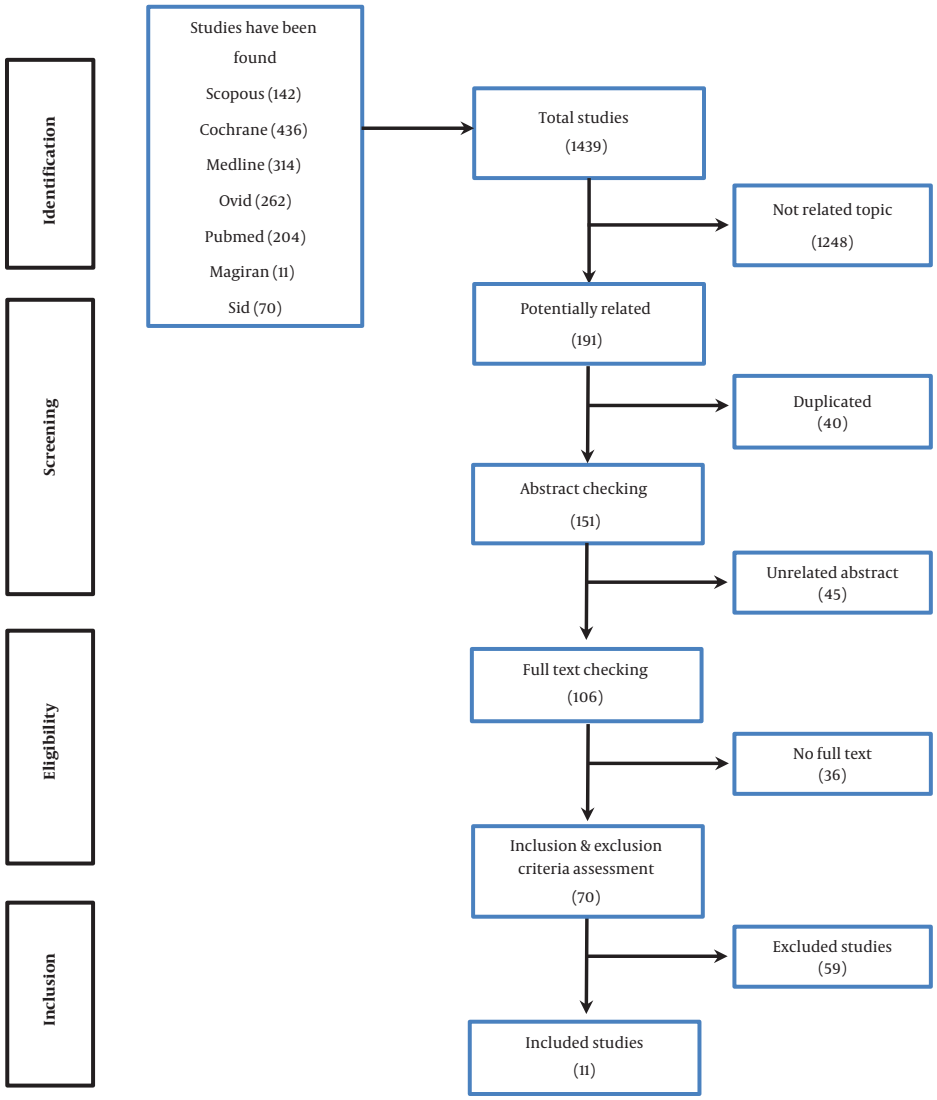

Figure 1. Identification and inclusion of studies

Table 1. Annual Bleeding Rate in Hemophilic Patients Treated by Prophylaxis Method

No.	Author	Place	Year	Type of Study	ABR (Mean ± SD)	Quality Assessment Score
1	Smith et al. (15)	USA	1996	Cohort	2.8 ± 3.7	30 (44)
2	Fischer et al. (22)	France - Netherlands	2002	Case-control	2.8 ± 0.9	32 (44)
3	Fischer et al. (24)	France	2003	Cohort	0.5 ± 0.5	30 (44)
4	Manco-Johnson et al. (14)	USA	2007	RCT	1.2 ± 6.2	16 (25)
5	Collins et al. (23)	USA	2010	CT	0.0 ± 0.8	14 (25)
6	Gringeri et al. (25)	Italy	2011	RCT	25.0 ± 59.4	18 (25)
7	Valentino et al. (26)	USA	2012	RCT	1.1 ± 4.9	16 (25)
8	Manco-Johnson et al. (27)	USA	2013	RCT	17.0 ± 9.2	16 (25)
9	Kavakli et al. (28)	[a]	2015	RCT	2.0 ± 6.8	16 (25)
10	Antunes et al. (29)	[b]	2014	RCT	7.9 ± 8.1	16 (25)
11	Zhao et al. (30)	China	2017	RCT	3.0 ± 5.9	18 (25)

[a]11 countries from Europe, South Africa, America and Asia
[b]Brazil, USA, Ukraine, Russia, New Zealand

In this study, we used ABR to assess prophylaxis effectiveness and AE and SAE to assess safety of prophylaxis treatment in hemophilic patients. In the annual bleeding rate assessment, the heterogeneity test between the studies showed that the studies are homogeneous and there is no difference in the estimated value of the mean annual bleeding rate between fixed and random models. Analysis showed that the mean ABR in prophylaxis was 0.88 (SD = 0.37) times per year (Figure 2).

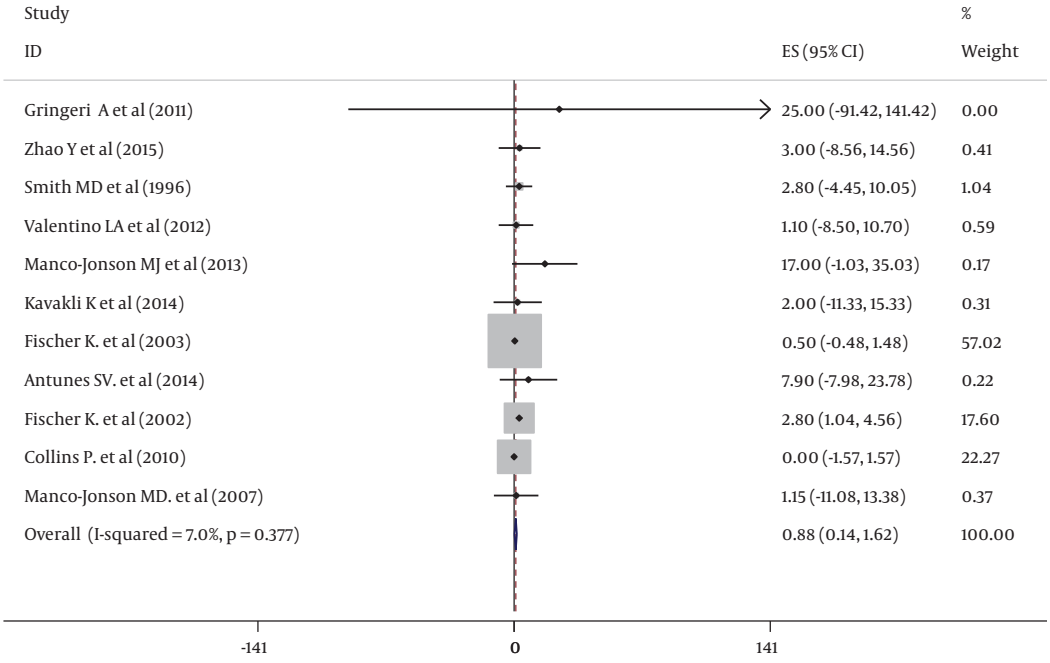

Figure 2. Accumulation chart of mean annual bleeding in hemophilic patients treated by prophylaxis method

As shown in Figures 3 and 4, the results of the analysis of the studies reported in this study have shown that, in compare with on-demand treatment, the risk of adverse effects in the patient treated with prophylaxis is (0.18 ± 0.44) per year and the risk of severe adverse effects is 0.059 (±0.001) per year.

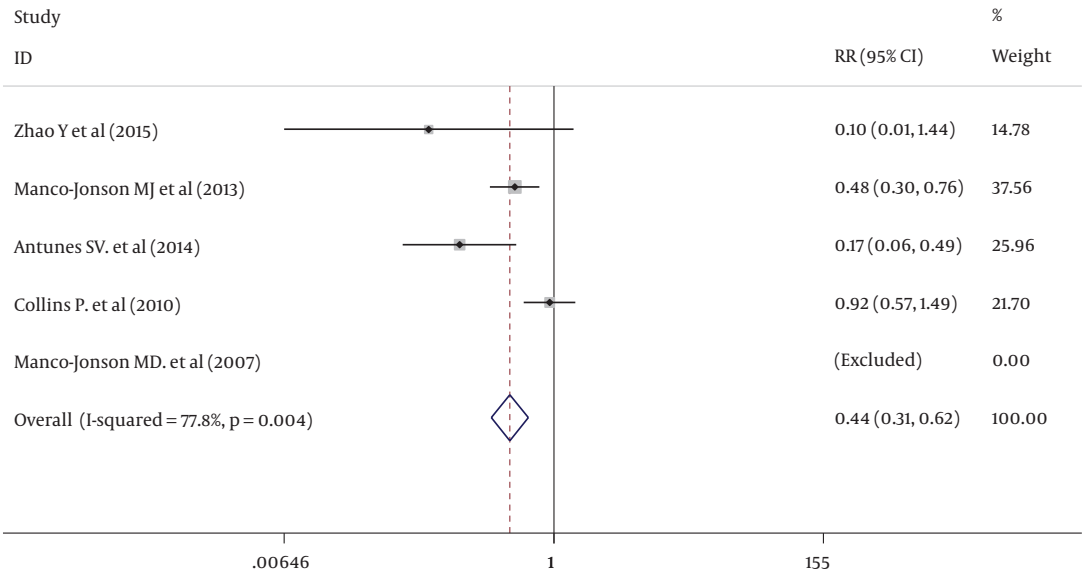

Figure 3. Accumulation chart of adverse effects relative risk in hemophilic patients treated by prophylaxis method

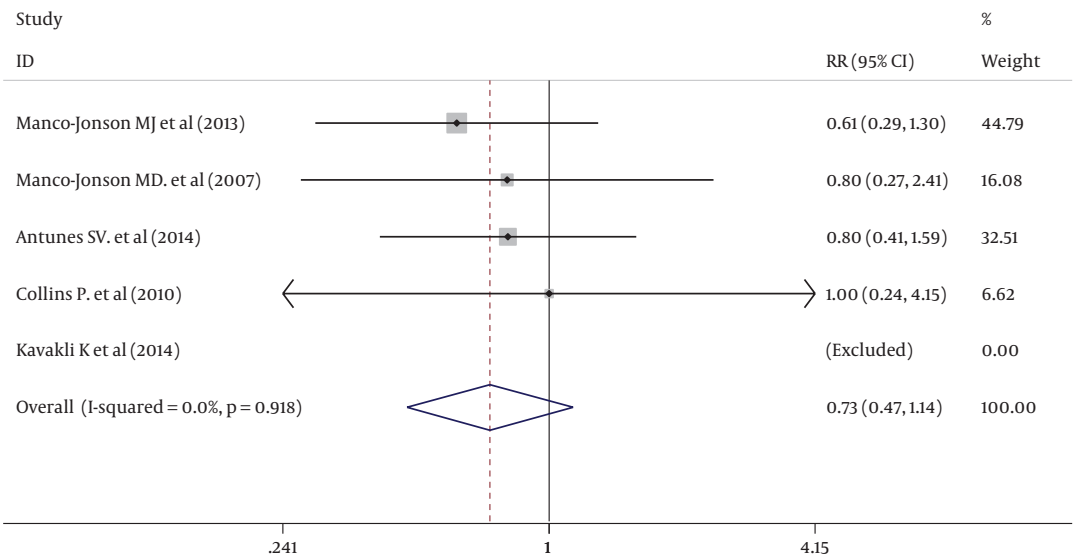

Figure 4. Accumulation chart of severe adverse effects relative risk in hemophilic patients treated by prophylaxis method

4. Discussion

The aim of this study was to assess the safety and efficacy of prophylaxis in patients with severe hemophilia. In this study, to evaluate the safety of the methods, the variables AE and SAE and to evaluate the effectiveness of the method the variable ABR were analyzed by systematic and Meta-analysis, then compared with on-demand method.

The survey of AE and SAE in the studies entered into study showed that the RR related to AE in patients treated with prophylaxis was 0.44 than patients treated with on-demand treatment ($P < 0.0001$). In the randomized clinical trial of Zhao et al. (30), RR obtained 0.09 and Collins et al. (23), in their clinical trial, in 2010, showed that RR is 0.92. Other studies have reported the amounts between these two RR. The reason for this difference can be seen in the type of study and the study population.

In evaluating the SAE value, the calculated RR was 0.73, which was not statistically significant ($P = 0.164$). This observation suggests that the risk of developing SAE in patients with severe hemophilia treated with on-demand treatment is greater than that of prophylaxis-treated patients.

Following frequent joints hemorrhages, the tissues of the joint will change and a chronic swelling develops in the joint, which can damage the constructive surfaces of the joint (31). When people with severe hemophilia experience recurrent hemorrhages and chronic hemophilia arthropathy, they will not only experience more hospital visits and consume coagulation factors, but will also experience long-term disabilities, pain, and increased financial costs. Apart from joint hemorrhages, other bleeding, especially intracranial hemorrhage, can be the main causes of mortality and adverse effects in these individuals (32). The results of these studies indicate that ABR is much more likely in on-demand treatment than the prophylaxis method. The largest difference was found in ABR in a randomized clinical trial conducted by Valentino et al., in 2012. ABR in patients with severe hemophilia, treated by the on-demand method (43.9), was 40 times more than patients treated with prophylaxis (0.99), and the lowest difference observed in this study (3.6 fold) was seen in a randomized clinical trial, which was conducted by Antunes et al. (29), in 2014 on 36 patients with severe hemophilia. In this study, ABR was 28.7% in patients treated with the on-demand method and 7.9% in patients treated with prophylaxis. In general, and regardless of the type of study, in all studies, the amount of ABR after use on-demand treatment is significantly greater than this outcome after use of prophylaxis (14, 15, 22-30).

Limitations of this study include the lack of access to unpublished studies, especially theses. There is also a lack of relevant studies in Iran, making decisions about generalizing the results obtained in this study to Iranian patients with hemophilia will be more difficult. Therefore, it is suggested that with further studies, more documentation be provided to prove that the prophylaxis is safer and more effective than the on-demand treatment in Iranian patients with severe hemophilia.

5. Conclusion

This study showed that the levels of AE and SAE in patients with severe hemophilia treated with prophylaxis are far less than the patient treated with on-demand treatment method; this suggests a greater safety of the prophylactic treatment method than on-demand. Also, the lower incidence of ABR in patients with severe he-

mophilia treated with prophylaxis, has been shown that prophylaxis is more effective than on-demand treatment. Although in Iran, as in many developing countries, the on-demand treatment is used as a standard treatment for severe hemophilia patients, the results of this study can be a basis for health system decision-makers to further explore the issue to determine prophylaxis as a standard method for patients with severe hemophilia.

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