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A systematic review and meta-analysis of effect of synthetic erythropoietin on hemoglobin in dialysis patients

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ABSTRACT

Introduction: Anemia is a common complication of chronic kidney disease (CKD) due to the insufficient production of erythropoietin by the kidneys. The administration of erythropoietin is one of the most common methods for the treatment of patients with anemia.
Objectives: This study aimed to investigate the effect of the administration of synthetic erythropoietin on hemoglobin levels in dialysis patients using a systematic review and meta-analysis.
Methods: In order to identify the related studies, the international databases of Web of Science, PubMed, Scopus, and Embase were searched from 2015 to 2020 using standard and valid keywords. The data were analyzed using STATA software (version 14), and a p-value of less than 0.05 was considered statistically significant.
Results: In 12 reviewed articles with a sample size of 4060 individuals, the standard effect size of the effect of synthetic erythropoietin on Hb in dialysis patients was reported as 2.08 (95% CI: 1.53-2.63), which was statistically significant; however, erythropoietin biosimilars did not show similar results.
Conclusion: The administration of erythropoietin to hemodialysis patients increases Hb levels by more than 2 units.

Implication for health policy/practice/research/medical education:
In this systematic review and meta-analysis, SMD of the effect of synthetic erythropoietin (intravenous or subcutaneous) on Hb in dialysis patients was 2.08 (95% CI: 1.53, 2.63), which was statistically significant. In the analysis performed separately by the method of erythropoietin consumption (intravenous and subcutaneous), in a group of patients who administered erythropoietin subcutaneously; no significant effect on increasing Hb level was detected. However, in the analysis by country, patients' Hb levels significantly increased in Germany, Greece and India.

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Introduction

Anemia is a common complication of chronic kidney disease (CKD) resulting from the inadequate production of erythropoietin by the kidneys leading to decreased erythropoiesis (1). The decreased total amounts of red blood cell and hemoglobin (Hb), which impair the ability of blood to carry oxygen, is called anemia (2). Renal anemia in patients with CKD, especially those undergoing hemodialysis, is associated with an increased risk of decreasing the quality of life, hospitalization, cardiac complications, and mortality (3,4). Although the administration of erythropoiesis-stimulating agents

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(ESAs) is a standard treatment for anemia in patients with kidney diseases, controlling anemia in CKD remains a challenge (5,6).

Before the availability of recombinant ESAs, anemia in end-stage renal disease was treated with repeated blood transfusions. Since desensitization through blood transfusions can impair patients' ability to receive a kidney transplant, the minimization of blood transfusions is a significant benefit of ESA (7). Although ESA is effective in the treatment of anemia in many patients with CKD, it also has some limitations. In non-dialysis-dependent CKD or dialysis-dependent CKD patients with secondary anemia, ESA tests have shown an increased risk of cardiovascular events associated with an excessive increase in target Hb levels (8-10).

Three forms of ESA are available for clinical use, namely epoetin alfa, epoetin beta, and methoxy polyethylene glycol-epoetin beta, as persistent erythropoietin receptor activators (11,12). Epoetin alfa was the first recombinant human erythropoietin (epoetin) approved by the US Food and Drug Administration for the treatment of anemia in patients with CKD (13,14). The subcutaneous (SC) or intravenous (IV) administration of epoetin in patients with CKD and anemia leads to a significant increase in Hb levels, reduces the need for blood transfusions, and shows effectiveness in both corrective and preventive actions (15, 16).

Due to the different results of previous studies, diversity of erythropoietin used in these studies, and its different doses and types of administration (i.e., IV or SC), the present meta-analysis aimed to investigate the effect of synthetic erythropoietin on Hb in dialysis patients by reviewing the studies carried out since 2015 up to 2020.

Methods

Study design

The present study is a systematic review and meta-analysis conducted on the effect of synthetic erythropoietin on Hb concentration in dialysis patients.

Strategy search

All of the interventional studies that were performed to investigate the effect of synthetic erythropoietin on Hb concentration in dialysis patients were evaluated. To identify the related articles, several international databases, including Scopus, PubMed, Web of Science, and Embase, were searched using the keywords of "Erythropoietin", "Hemoglobin", "Dialysis", "Subcutaneous", "Intravenous", and their various combinations using AND/OR operators. No language restrictions were applied to the search process; however, a time limit was imposed between 2015 to 2020.

Inclusion criteria

Interventional studies examining the effect of synthetic erythropoietin on Hb in dialysis patients were included in the present review.

Exclusion criteria

The exclusion criteria were the articles with a lack of reporting the data needed for analysis, studies on the effects of synthetic erythropoietin on Hb on individuals other than dialysis patients, and papers on the effect of synthetic erythropoietin on blood factors other than Hb.

Qualitative evaluation of the studies

After the selection of primary studies, two authors independently evaluated them using the evaluation checklist of the Cochrane Library. This checklist has seven different items, each of which assesses one important aspect of bias in clinical trials. Moreover, each item in the checklist is scored as high risk of bias, low-risk of bias, and unknown risk of bias. After the assessment of all the studies, firstly, the inconsistencies between the evaluation results of the two authors were identified and resolved in order to reach a unanimous decision.

Data extraction

A total of 12 studies with desirable quality were selected for the data extraction step. To extract the data from the articles, a checklist was prepared by the researchers to provide the necessary information, such as the name of authors, year of publication, country, sample size, mean age, mean values (±standard deviation [SD]) of the Hb scores before and after using synthetic erythropoietin, type of pharmaceutical manufacturer, duration of treatment, dosage of the drug, and route of drug administration (i.e., SC or IV).

Statistical analysis

The extracted studies were combined according to sample size and mean (±SD). The standardized mean difference (SMD) index, which is a classical effect size index, indicates the strength of the relationship between the intervention and studied outcome. The SMD represents the difference in scores before and after the intervention. The selected studies were combined regarding their sample size, mean, and SD. Furthermore, Cochran's Q test and I^2 index were used to evaluate the heterogeneity of the studies. The fixed and random-effects models were frequently used for low and high heterogeneities, respectively. Therefore, for the purpose of the study, the random-effects model was employed in the present review. Data analysis was performed in STATA software (version 14). Furthermore, a P value of less than 0.05 was considered statistically significant.

Results

Study selection

Firstly, 812 papers were identified by searching the databases; then, 395 duplicate articles and 198 studies unrelated to the current meta-analysis were removed

by reviewing the titles and abstracts, respectively. By reviewing the full-texts of the remaining articles, 207 papers that met the exclusion criteria were removed. The remaining articles were assessed in terms of quality using the Cochrane checklist, and finally 12 articles entered the meta-analysis stage (Figure 1). Table 1 tabulates the specifications of the extracted data from the reviewed articles.

In 12 reviewed articles with 4,060 dialysis patients within the age range of 44.8 to 70 years published during 2016 and 2020, the standard effect size of erythropoietin on Hb in dialysis patients was 2.08 (95% CI: 1.53-2.63). This result indicates that the use of erythropoietin has significantly increased the Hb level of dialysis patients and this relationship is statistically significant (Figure 2). Some of the selected studies used several types of erythropoietin; however, the current review included the results of different types of erythropoietin; therefore, 19 different conditions were created out of which in 8 cases the effect of erythropoietin on Hb in dialysis patients was negative, which is statistically significant. Moreover, in three cases, the administration of erythropoietin increased Hb in dialysis patients, which is statistically significant. In other eight cases, the effect of erythropoietin on Hb in dialysis patients was not statistically significant. One study examined the effect of glycol-epoetin beta on the Hb levels of patients which was removed after the analysis of the subgroups, thereby remaining 18 different states (Figure 2 and Table 2).

As Figure 2 illustrates, in the group receiving erythropoietin, the Hb levels of patients increase by 2 units, but not in other erythropoietin biosimilars, and even cause a slight decrease.

The publication bias diagram shows that the sources positively reporting the effect of erythropoietin on Hb in dialysis patients were more likely to be published (Figure 3). In the analyses performed in the United States, Japan, and Thailand, erythropoietin decreased Hb levels in dialysis patients, which was statistically significant; nonetheless, in Germany, Greece, and India, erythropoietin increased Hb levels in dialysis patients, both of which were statistically significant. However, in Macedonia, the effect of erythropoietin on the Hb levels of dialysis patients was not statistically significant (Table 2).

In this analysis, glycol-epoetin beta was removed because only one study was identified with the administration of this type of drug and it could not be investigated in a separate group. Other studies were categorized based on the type of drug used by patients. Three studies used darbepoetin alfa to increase the Hb

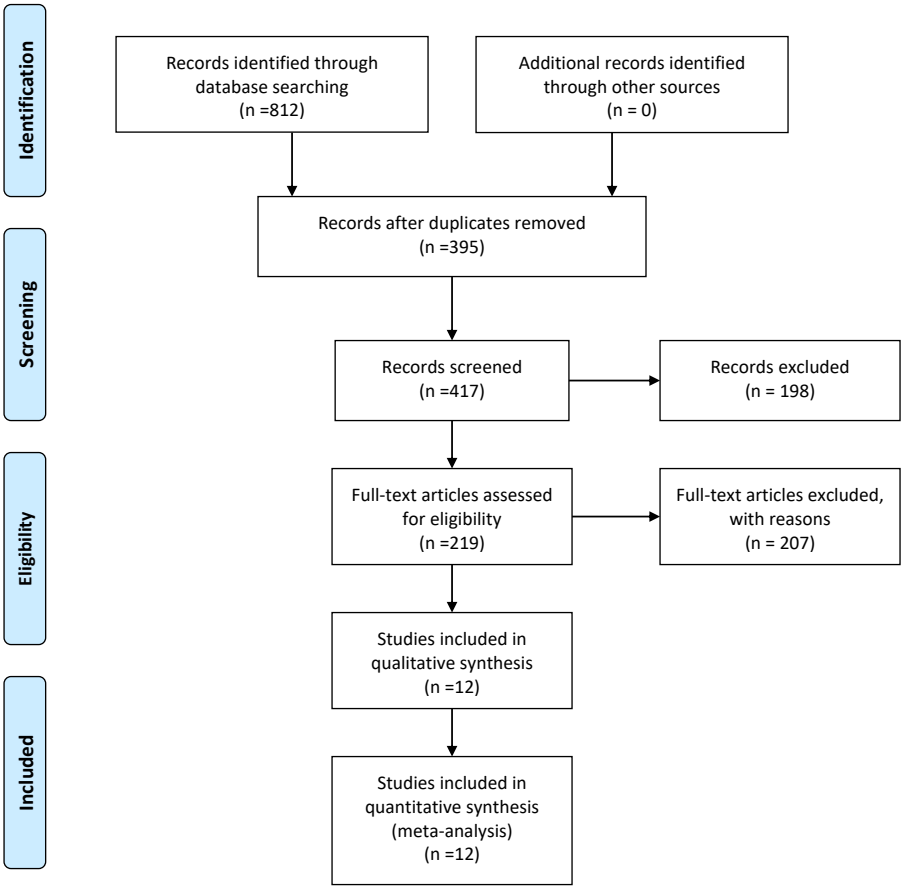

Figure 1. Flowchart representing the process of study selection from selected databases.

Table 1. Extracted data from articles entered into the systematic review and meta-analysis process

Author	Year of publication	Countries	Type of drug	Dose of drug	Duration (wk)	IV/SC	Age (year)	Sample size	Number of female	No. of male	Hemoglobin levels before intervention		Hemoglobin levels after intervention	
											Mean	SD	Mean	SD
Fishbane S (17)	2018	USA	Epoetin Alfa	89.79 U/kg	4	Intravenous	57	304	129	175	10.4	0.7	10.28	0.05
Fishbane S (17)	2018	USA	Epoetin Alfa-epbx	90.16 U/kg	4	Intravenous	55	301	145	156	10.4	0.8	10.17	0.05
Nishi S (18)	2020	Japan	JR-131	18.6 µg	24	Intravenous	67.3	111	33	78	11.03	0.57	10.61	0.79
Nishi S (18)	2020	Japan	Darbepoetin Alfa	18.2 µg	24	Intravenous	67.5	112	34	78	10.99	0.52	10.56	0.86
Malyszko J (19)	2016	Germany	Eprex	3485 IU			65	68	33	35	10.74	1.61	11.14	1.5
London G (20)	2018	10 European countries	HX575	106.5 IU/kg/wk	104	Intravenous	>18	2086			11.9	1.14	11.25	1.19
Provenzano R (21)	2016	USA	Epoetin Alfa	136.3 IU/kg/wk	6	Intravenous	59.5	13	4	9	11.6		11.5	0.6
Provenzano R (21)	2016	USA	Epoetin Alfa	173.4 IU/kg/wk	19	Intravenous	57	23	9	14	11.6		11.2	1
Kacarska II (22)	2020	Macedonia	Glycol-epoetin beta	115.2 µg	8	Intravenous	58	179			11.03	8.7	11.08	
Kacarska II (22)	2020	Macedonia	Glycol-epoetin beta	115.2 µg	16	Intravenous	58	155			11.03	8.7	11.13	
Kacarska II (22)	2020	Macedonia	Glycol-epoetin beta	115.2 µg	24	Intravenous	58	161			11.03	8.7	11.12	
Kacarska II (22)	2020	Macedonia	Glycol-epoetin beta	115.2 µg	48	Intravenous	58	130			11.03	8.7	11.14	13.6
Mitsopoulos E (23)	2020	Greece	Erythropoetin	69.1 U/kg/wk	4	Intravenous	70	15			10	0.9	10.9	1.2
Mitsopoulos E (23)	2020	Greece	Erythropoetin	82.2 U/kg/wk	12	Intravenous	70	15			10	0.9	10.9	1.4
Sinha SD (24)	2019	India	Darbepoetin alfa	26.12 µg	4	Subcutaneous	44.8	63	24	39	8.39	0.9	8.66	1.24
Sinha SD (24)	2019	India	Erythropoetin alfa	3038.3 IU	4	Subcutaneous	48.8	63	17	46	8.8	0.89	9.5	1.81
Satirapoj B (25)	2017	Thailand	Epoetin alfa	116.9 U/kg/wk	4	Subcutaneous	58.47	30	14	16	11.1	0.7	11	0.9
Satirapoj B (25)	2017	Thailand	Epoetin alfa	116.9 U/kg/wk	8	Subcutaneous	58.47	30	14	16	11.1	0.7	11.1	1.4
Satirapoj B (25)	2017	Thailand	Epoetin alfa	116.9 U/kg/wk	12	Subcutaneous	58.47	30	14	16	11.1	0.7	10.9	1.7
Satirapoj B (25)	2017	Thailand	Epoetin alfa	116.9 U/kg/wk	16	Subcutaneous	58.47	30	14	16	11.1	0.7	11.4	1.2
Satirapoj B (25)	2017	Thailand	Epoetin alfa	116.9 U/kg/wk	20	Subcutaneous	58.47	30	14	16	11.1	0.7	10.9	1.1

Table 1. Continued

Author	Year of publication	Countries	Type of drug	Dose of drug	Duration (wk)	IV/SC	Age (year)	Sample size	Number of female	No. of male	Hemoglobin levels before intervention		Hemoglobin levels after intervention	
											Mean	SD	Mean	SD
Satirapoj B (25)	2017	Thailand	Epoetin alfa	116.9 U/kg/wk	24	Subcutaneous	58.47	30	14	16	11.1	0.7	10.5	1.1
Satirapoj B (25)	2017	Thailand	Lyophilized powder EPO	126.4 U/kg/wk	4	Subcutaneous	57.42	33	15	18	11.2	0.9	10.9	1
Satirapoj B (25)	2017	Thailand	Lyophilized powder EPO	126.4 U/kg/wk	8	Subcutaneous	57.42	33	15	18	11.2	0.9	10.9	1.2
Satirapoj B (25)	2017	Thailand	Lyophilized powder EPO	126.4 U/kg/wk	12	Subcutaneous	57.42	33	15	18	11.2	0.9	10.5	1.2
Satirapoj B (25)	2017	Thailand	Lyophilized powder EPO	126.4 U/kg/wk	16	Subcutaneous	57.42	33	15	18	11.2	0.9	10.8	1.4
Satirapoj B (25)	2017	Thailand	Lyophilized powder EPO	126.4 U/kg/wk	20	Subcutaneous	57.42	33	15	18	11.2	0.9	10.7	1.4
Satirapoj B (25)	2017	Thailand	Lyophilized powder EPO	126.4 U/kg/wk	24	Subcutaneous	57.42	33	15	18	11.2	0.9	10.5	1.4
Fishbane S (26)	2019	USA	Epoetin Alfa	85.91 U/kg	4	Subcutaneous	57	122	67	55	10.28	0.78	10.12	0.07
Fishbane S (26)	2019	USA	Epoetin Alfa	85.91 U/kg	8	Subcutaneous	57	122	67	55	10.28	0.78	10.19	0.08
Fishbane S (26)	2019	USA	Epoetin Alfa-epbx	93.53 U/kg	4	Subcutaneous	55	124	61	63	10.36	0.78	10.16	0.07
Fishbane S (26)	2019	USA	Epoetin Alfa-epbx	93.53 U/kg	8	Subcutaneous	55	124	61	63	10.36	0.78	10.19	0.08
Nand N (27)	2017	India	Erythropoetin	12000 IU/wk	12	Subcutaneous	45.55	20	5	15	6.78	0.75	10.01	0.54
Nand N (27)	2017	India	Erythropoetin	12000 IU/wk	12	Subcutaneous	49.8	20	8	12	7.25	0.88	7.41	0.69
Weir MR (28)	2017	USA	HX575	9488 IU/wk	52	Subcutaneous	59.8	217	82	135	10.53	0.635	10.42	0.826
Weir MR (28)	2017	USA	Epoetin Alfa	6447 IU/wk	53	Subcutaneous	57.6	218	103	115	10.5	0.615	10.51	0.873

Table 2. Results of standard size analysis of the effect of erythropoietin on hemoglobin and its subtypes

	Subgroups	SMD	Low	Up	*P* value	I^2 (%)
Country	USA	-0.22	-0.34	-0.10	0.047	52.9
	Japan	-0.61	-0.80	-0.42	0.981	0
	Germany	0.26	0.08	0.59	---	---
	Macedonia	0.01	-0.23	0.25	---	---
	Greece	0.76	0.02	1.51	---	---
	India	1.23	0.19	2.27	<0.001	94
	Thailand	-0.62	-0.98	-0.26	0.878	0
Type of drug	Epoetin alfa	-0.40	-0.45	-0.36	<0.001	88.7
	Darbepoetin alfa	-0.42	-0.59	-0.25	<0.001	88.7
	Erythropoietin	2.08	1.53	2.63	<0.001	97
Duration (week)	3	0.26	-0.08	0.59	---	---
	4	-0.01	-0.36	0.33	<0.001	89
	8	-0.23	-0.41	-0.06	0.425	0
	12	1.89	-0.34	4.12	<0.001	95.4
	19	-0.42	-1.01	0.16	---	---
	24	-0.61	-0.88	-0.44	0.999	0
	48	0.01	-0.23	0.25	---	---
	52	-0.15	-0.34	0.04	---	---
	53	0.01	-0.17	0.20	---	---
	104	-0.56	-0.62	-0.50	---	---
Type of use	Intravenous	-0.35	-0.53	-0.17	<0.001	83.9
	Subcutaneous	0.12	-0.20	0.43	<0.001	91.3
Age (year)	45-49	0.37	0.12	0.62	0.342	0
	50-54	2.54	-2.11	7.18	<0.001	97.7
	55-59	-0.25	-0.38	-0.11	0.009	60.8
	60-64	-0.15	-0.34	0.04	---	---
	65-69	-0.33	-0.85	0.19	<0.001	89.6
	70-74	0.76	0.02	1.51	---	---

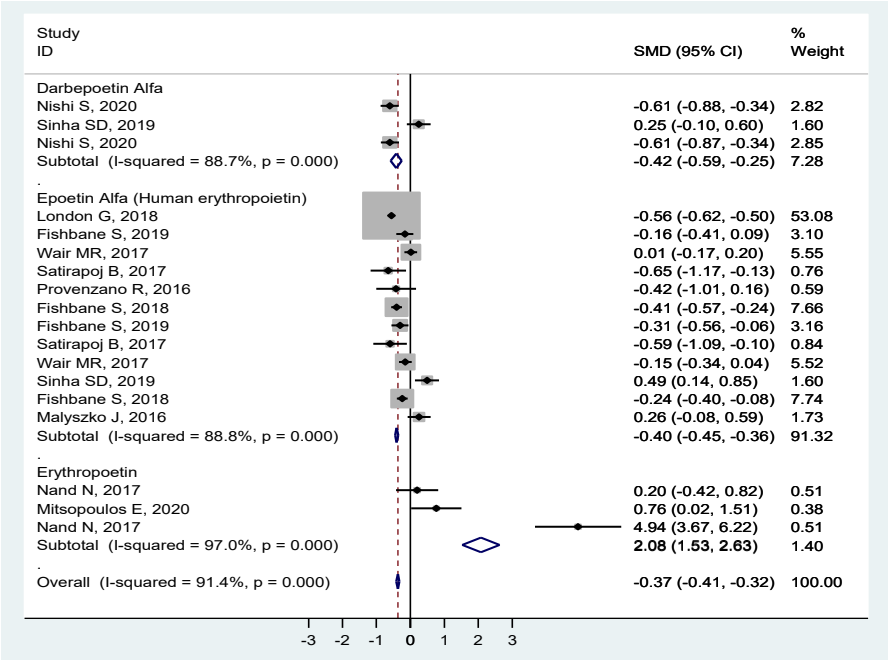

Figure 2. Standard effect size of the effect of erythropoietin on hemoglobin in dialysis patients and its 95% confidence interval.

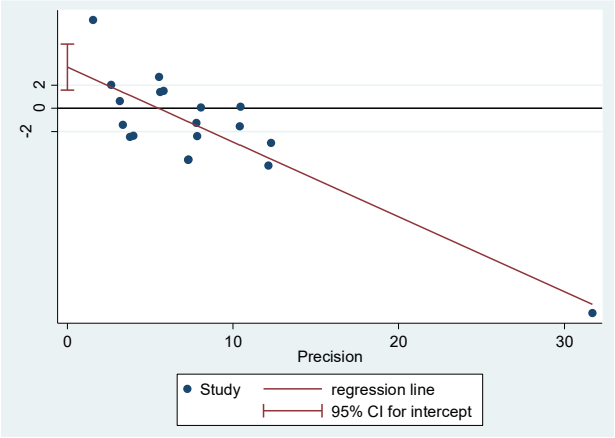

Figure 3. Publication bias of the review studies.

concentrations of patients; nevertheless, it was finally concluded that overall it caused a slight decrease in the Hb levels of the patients (OR = -0.42; 95% CI: -0.59–-0.52). In three studies, erythropoietin was administered for the improvement of patients' Hb, and it was concluded that erythropoietin consumption significantly increased Hb levels (OR = 2.08; 95% CI: 1.53-2.63). In another 12 studies that used epoetin alpha to improve the plasma Hb values of patients, it was observed that the administration of epoetin alpha in patients caused a slight decrease in their Hb levels (OR = -0.40; 95% CI: -0.45–-0.36; Table 2).

The administration of IV erythropoietin in dialysis patients led to a significant decrease in Hb levels. However, the SC method increased Hb, which was not statistically significant. Based on the age group of dialysis patients, the effect of erythropoietin on Hb increase was statistically significant in the age groups of 49-49 and 74-70 years; nonetheless, in the age group of 59-55 years, the administration of erythropoietin decreased Hb levels, which was statistically significant. There was no statistically significant relationship in other age groups (Table 2).

Discussion

According to the results of the current study, dialysis patients around the world use different doses, methods, and types of erythropoietin for the treatment of their anemia. Moreover, the patients' age group, race, gender, and length of treatment affect the impact of erythropoietin on Hb levels in dialysis patients. In a study conducted by Palmer et al in 2014, a comparison of ESAs in CKD was performed using network meta-analysis. In the aforementioned study, 56 articles with a sample size of 15,596 individuals were evaluated. Based on the results, it was shown that the administration of different types of synthetic erythropoietin increased the Hb levels of patients and reduced the risk of anemia. In fact, the preventive role of different types of erythropoietin in the aforementioned study was evident (epoetin alfa [OR = 0.18; 95% CI: 0.05-0.59], darbepoetin alfa [OR = 0.17; 95% CI: 0.05-0.57], methoxy polyethylene glycol-epoetin beta [OR = 0.15; 95% CI: 0.03-0.70], and epoetin beta [OR = 0.09; 95% CI: 0.02-0.38]) (29).

However, in a meta-analysis carried out by Adamu et al in 2012, four eligible pilot studies were identified involving 114 participants, about 83.33% of whom were male with a mean age of over 50 years. At the end of the experiment, the difference between the mean Hb due to the administration of nandrolone and erythropoietin was -0.11 (95% CI: 0.80-0.58), which was not statistically significant. The aforementioned meta-analysis demonstrated no difference between nandrolone and erythropoietin in the treatment of CKD anemia (30).

In a study performed by Weir et al in 2017, after 52 weeks of the SC administration of HX575, the Hb level of dialysis patients decreased from 10.53 to 10.42; however, this decrease was not statistically significant (28), which is exactly in line with the results of the present study. In contrast, the results of a study carried out by Nand et al in 2017 in India showed that the SC administration of erythropoietin significantly increased the Hb levels of patients, which was statistically significant (27) and inconsistent with the results of the current study. A high dose used by patients and association of erythropoietin with iron and vitamin C may be the reasons for this increase in Hb.

In 2018, in a study conducted by Fishbane et al in the United States, dialysis patients intravenously received 89.79 U/kg of epoetin alfa in four weeks, and their plasma Hb levels decreased from 10.4 to 10.28. In the aforementioned study, in the group receiving IV epoetin alfa-epbx, the Hb levels decreased from 10.4 to 10.17, which was also statistically significant (17). The results of the aforementioned study are consistent with the findings of the current study, probably due to the short duration of the treatment. In 2020, a study was carried out by Mitsopoulos et al in Greece in which during 12 weeks of the IV administration of erythropoietin, the Hb levels increased from 10 to 10.9, which was statistically significant (23). However, these patients also received iron during their treatment. The results of the aforementioned study are inconsistent with the findings of the current meta-analysis. One of the reasons may be the administration of iron by patients during the treatment.

The results of another study performed by Kacarska et al showed that in dialysis patients, during 48 weeks of the IV administration of glycol-epoetin beta, the mean Hb level increased from 11.03 to 11.14, which was not statistically significant (22) and consistent with the findings of the present study. Differences and contradictions in the results of studies carried out on the effect of erythropoietin on Hb in dialysis patients led to conducting the present meta-analysis. In addition, due to the limited number of studies, it is suggested to carry out further studies in this regard.

Limitations of the study

The limitations of the current study included the incomplete information of some articles, lack of uniform distribution of studies in different countries and age groups, and limited number of papers examining secondary outcomes (e.g., hematocrit and transferrin saturation); therefore, the result of the aforementioned studies cannot be generalized to the whole dialysis population. Some secondary outcomes, such as serum ferritin, iron, and creatinine, were not statistically reported in the studies and the effect of erythropoietin on them could not be evaluated. Only in two studies, the names of subsidiary drugs used by dialysis patients were mentioned; as a result, it was not possible to assess and compare the effect of the administration of erythropoietin alone and with iron, vitamin C, folic acid, or omega 3. A limited number of studies evaluated the effects of erythropoietin on Hb based on the number of weeks. Therefore, the present study could not compare the effects of erythropoietin on the Hb concentration of dialysis patients in different weeks or evaluate the effect of drug duration on the level of Hb.

Conclusion

The standard effect size of synthetic erythropoietin on Hb in dialysis patients was reported as 2.08 (95% CI: 1.53-2.63), which was statistically significant. This 2-unit increase in the Hb level of dialysis patients improves the problems caused by anemia among the patients. However, erythropoietin biosimilars did not show similar results. Due to the differences in the number of studies and differences in age, gender, race, and treatment period of the patients, the aforementioned results cannot be generalized with certainty to the whole dialysis population. Therefore, it is necessary to carry out further clinical studies on larger sample sizes.

Authors' contributions

MF, DS, ZA, MR, HN, AH, and MA were included in the preparation of the concept and design. DS and MF analyzed the data. AH and HN interpreted the results. HN and MF revised the manuscript and critically evaluated the intellectual contents. All the authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. All the authors have also read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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