SYSTEMATIC REVIEW

Effect of Erythropoiesis Stimulating Agents on Clinical Outcomes in Breast Cancer Patients: A Systematic Review of Randomised Controlled Trials

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ABSTRACT

The impact of erythropoiesis stimulating agents (ESAs) on clinical outcomes among breast cancer patients is debatable. Current review is aimed to ascertain the efficacy of ESAs among breast cancer patients. Randomised controlled trials (RCTs) were electronically searched. Primary outcomes were mortality, blood transfusion requirements and thromboembolic events (TEEs); whereas, secondary outcomes were safety, tumor progression, anemia treatment, hemoglobin levels and quality of life (QOL). Out of 11 RCTs including 6,849 participants, 9 RCTs reported 2,312 deaths with overall mortality of 33.7%. Mortality reported for epoetin alfa (EA), epoetin beta (EB) and darbepoetin alfa (DA) was 41.24%, 73.1% and 8.99% respectively. TEEs reported for EA, EB and DA were 5.88%, 9.28% and 2.85%, respectively. Serious adverse events were 39.04%, 36.29%, 1.53% for EA, EB and DA, respectively. Tumor progression for EA and EB was 37.53% and 95.46%, respectively. No tumor progression was reported with DA. Erythropoietin reported no mortality, TEEs, serious ADRs and tumor progression. About 9% patients required transfusions during ESA therapy. Current evidence suggests that use of ESA reduces transfusion need but increases mortality and risks of TEEs.

Key Words: *Chemotherapy, Randomised controlled trials, Anemia, Breast cancer, Erythropoiesis stimulating agents, Mortality, Tumor progression, Survival, Quality of life, Transfusion requirements, Safety.*

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INTRODUCTION

Anemia is one of the major problems in patients receiving cancer chemotherapy for which blood transfusions or erythropoietin stimulating agents (ESAs) are considered. ESAs have demonstrated promising roles in decreasing transfusion requirement, improving hemoglobin levels and quality of life (QOL) in chemotherapy-induced anemia (CIA) among various types of cancer.[1-7] CIA in breast cancers (BC) has been corrected with the use of ESAs. However, contradictory results have surfaced about numerous clinical outcomes of ESAs such as increased mortality, tumor progression and increased number of thromboembolic events.[8-18] The use of ESAs is still debatable and researchers are trying to evaluate their benefits which can outweigh the risks.

Though various trials have evaluated the efficacy of ESAs in BC patients,[8-18] but composite evidence regarding the use of ESAs in BC is limited. A recent review investigated the impact of ESAs in managing cognitive alterations among BC patients.[19] Another review concentrated on assessing the benefits of epoetin therapy among BC patients undergoing chemotherapy.[20] Aapro *et al.*, conducted a pooled analysis of 9 RCTs to investigate the efficacy and safety of ESAs in BC patients.[21] However, there are few trials which were not incorporated in their study due to predetermined criteria of quantitative analysis. In this context, current systematic review was performed to accentuate the effects of ESAs for BC patients by including all available trials.

METHODOLOGY

This systematic review complies with the PRISMA statement.[22] Cochrane Library, Google Scholar, Elsevier and PubMed were systematically searched for RCTs from 1989 to 2018. Search terms were chemotherapy, randomised controlled trials, anemia, breast cancer, erythropoiesis stimulating agents, erythropoietin, epoetin, darbepoetin, methoxy polyethylene glycolepoetin beta, mortality, tumor progression, survival, quality of life, transfusion requirements and safety.

Titles and abstracts were independently assessed by two authors (SS and RN). The inclusion of study in the

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review was based on full-text assessment. Dissent among researchers concerning the worth of studies was resolved through discussion and mutual consent. All RCTs conveying the effect of ESAs in BC were included. Studies conducted on other types of cancers, published in language other than English and having ambiguous inclusion were excluded. Primary outcome measures were mortality, blood transfusion requirements and thromboembolic events (TEEs). Secondary outcome measures were safety, tumor progression, anemia treatment, hemoglobin levels and quality of life (QOL).

Employing a pre-structured data collection form (DCF), data were independently extracted by two authors (MK & FN). All the studies were evaluated to determine the effect of ESAs on predefined clinical outcomes (Figure 1).

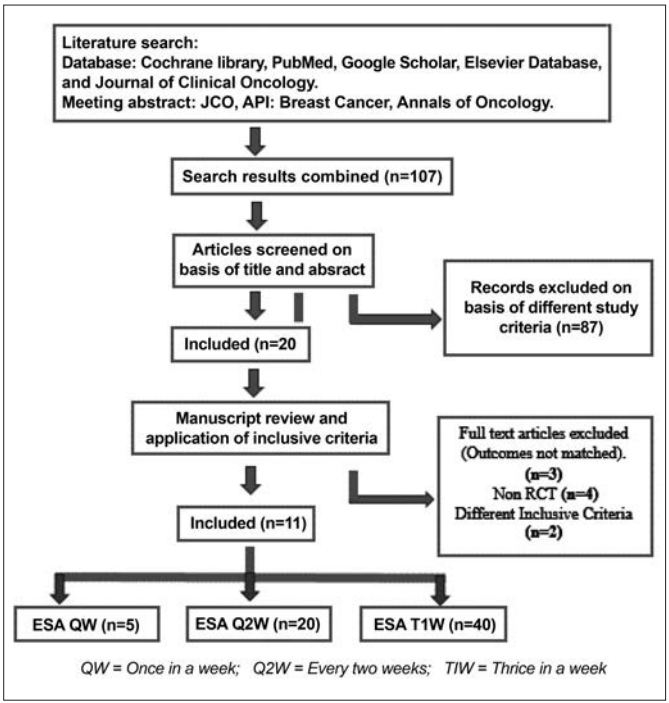

Figure 1: Schematic diagram representing the assortments of studies.

RESULTS

Characteristics of selected studies:

Eleven RCTs reporting the predetermined outcomes with the use of ESAs were included in current review.

The risk of bias within studies was assessed on the PRISMA criteria (Figure 2). All RCTs were adequately randomised, and appropriately concealed; most trials gave follow-up status up to last extent. Blinding of patients was done in only three trials.[9,11,17] One trial stopped early for benefits and all the studies followed the intent to treat principle.[11]

RCTs were conducted on 6,849 BC patients with CIA of age ≥18 years (Table I). Four trials were conducted in Germany,[14-17] four were located in multiple countries[11-13,18] and the remaining three were from Italy, USA and Canada each.[8-10]

The interventions were ESAs in varying doses and frequencies with chemotherapy. Five RCTs had once weekly dosing,[9-12,18] two had twice weekly dosing[14,15] and four RCTs had thrice weekly dosing.[8,13,16,17]

All trials had at least one predefined outcome measure. Timings of outcome measures varied with different follow-up duration in these trials.

Impact of ESAs on clinical outcomes:

Nine trials reported mortality ranging from 1.9% to 73.1% in interventional group (IG) and 6% to 72.8% in control group (CG), suggesting the higher mortality in IG. However, only one study (Aapro *et al.*[12]) reported

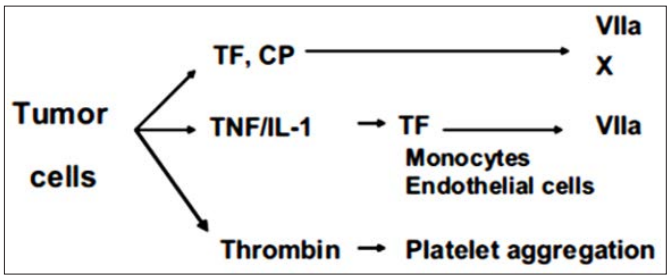

Figure 3: Pathways of activation of coagulation system in cancer patients.[32] *CP=Cancer procoagulant; IL-1=Interleukin-1; TF=Tissue factor; TNF=Tumor necrosis factor.*

Trials	Concealment of randomization	RCT stopped early	Patients blinded	HCP blinded	DC blinded	OA blinded	Proportion of patients lost to follow-up
Del Mastro *et al.* (1997)	✓	×	NA	NA	NA	NA	22
O'Shaughnessy *et al.* (2005)	✓	×	✓	✓	NA	NA	22
Chang *et al.* (2005)	✓	×	×	×	NA	NA	4
Jones *et al.* (2008)	✓	✓	✓	✓	✓	✓	221
Aapro *et al.* (2008)	✓	×	×	×	×	×	123
Pronzato *et al.* (2010)	✓	×	×	×	✓	✓	NA
Untch *et al.* (2011)	✓	×	×	×	✓	✓	NA
Untch *et al.* (2011)	✓	×	×	×	✓	✓	
Moebus *et al.* (2013)	✓	×	NA	NA	NA	NA	70
Nitz *et al.* (2014)	✓	×	✓	✓	✓	✓	NA
Jones *et al.* (2016)	✓	×	×	×	×	×	

HCP = Health care provider; DC = Data collectors, OA = Outcome assessors.

Figure 2: Quality assessment of trials included in the review.

Table I: Summary of included studies evaluating effects of ESA on various outcomes in breast cancer patients.

Authors	N	IG	CG	Age	BC stage	Total duration	Dose	Frequency	Dose	Frequency	Co-intervention	F
Del Mastro *et al*., 1997[8]	62	31	31	29-68	II	28 months	EPO - 150U/kg +3 MC same as CG	3 times weekly E - 60mg/m^2,	C - 600mg/m^2, E- 60MG/m^2 F - 600mg/m^2 (CEF) IV on day1 G - CSF, 5ug/kg subcutaneously from day 4 to day 11	Every 2 weeks	Ferrous sulfate 325 mg/d in specific cases	6 months
O'Shaughnessy *et al*., 2005[9]	100	51	49	>18	I-III	10 months	EA - 40,000 U, increased to 60,000 U if Hb level did not improve + MC same as CG	Once weekly	Placebo + MC	Once weekly	.	Monthly
Chang *et al*., 2005[10]	354	177	177	>18	I-IV	7 months	EA - 40,000 U + MC	Once weekly	SC + MC		200 mg/day oral iron	Weekly
Jones *et al*., 2005[11]	939	469	470	≥18	I-IV	12 months	EA - 40,000 U +	Once weekly	Placebo for 12 months +	Once weekly		3 months
Aapro *et al*., 2008[12]	463	231	232	≥18		43 months	EB - 30,000 U + MC same as CG	Once weekly	BSC + A/T BC	Iron supplementation		Monthly for 6 months then 3 months
Pronzato *et al*., 2010[13]	223	110	113	>18	I-IV	19 months	EA- initiated at 10,000 IU(5000 IU if patient weight <45kg) + MC same as CG	3 times weekly	BSC + MC			6 months then annually
Untch *et al*., 2011[14]	733	356	377	18-65	I-IV	32 months	DA- 4.5 µg/kgbody weight + Chemotherapy same as CG		E- 90 mg/m^2 + C- 600 mg/m^2 by T-175 mg/ m^2 (EC-T), OR E-150 mg/ m^2 followed by T- 225 mg/m^2 with PF (5 µg/kg/d, d3-d10) followed by CMF (C- 500 mg/ m^2 M-40 mg/ m^2, F- 600 mg/ m^2) on days 1 and 8 (E_{dd}-T_{dd}-CMF).	same as CG q14d x 3		Annually
Untch *et al*., 2011b[15]	733	356	377	18-65	I-IV	32 months	DA- 4.5 µg/kg body weight + Chemotherapy same as CG	Q2W	E -90 mg/m^2 + C- 600 mg/m^2 followed by T- 175 mg/ m^2 (EC-T), OR E- 150 mg/ m^2 followed by T- 225 mg/m^2 with PF (5 µg/kg/d, d3-d10) followed by CMF (C- 500 mg/ m^{2}M-40 mg/ m^2, F- 600 mg/m^2) on days 1 and 8 (E_{dd}-T_{dd}-CMF).	q21d × 4 q14d × 3		Annually
Moebus *et al*., 2013[16]	643	324	319	18-65	I-III	53 months	EA- 150 IU/kg + Chemotherapy Same as CG	3 times weekly- Started on Day 1 upto Day 14 after	IDD chemotherapy- Sequential adminis-tration of each of three cycles of E-(150 mg/m^2 intravenously as a bolus infusion), T- (225 mg/ m^2 intravenously as a 3-hour infusion), and C-(2500 mg/ m^2 intravenously as a 2-hour infusion), respectively. All patients received filgrastim SC (5 µg/kg body weight per day) from days 3 to 10 of each cycle.	every 2 weeks	200 mg/day oral iron .	Annually
Nitz *et al*., 2014[17]	1,234	615	619	>18		53 months	DA- 300µg-500µg + MC same as CG	3 times weekly	SC + MC			Annually
Jones *et al*., 2016[18]	2,098	1,050	1,048	>18	I-IV	100 months	EA-40,000IU + MC same as CG	Once Weekly	BSC + MC		Oral & IV iron therapy	

IDD= Intense Dose Dense, E=Epirubicin, T=Paclitaxel, C= Cyclophosphamide, M=Methotrexate, F= Fluorouracil, PF= Pegfilgrastim, EA=Epoetin Alfa, EB=Epoetin Beta, A/T BC=Anthracycline and/or Taxane Based Chemotherapy, DA= Darbepoetin Alfa, IG = Intervention Group, CG = Control Group, BSC= Best Standard Care, SC= Standard Care, MC= Myelotoxic Chemotherapy, FLC= First-Line Chemotherapy, G-CSF = Granulocyte Colony-Stimulating Factor.

statistically insignificant difference in mortality rate between both groups. Highest mortality rate was observed with EB.[12]

Eight trials reported transfusion requirements for anemia ranging from 0% to 14.2% in IG and 0% to 28.1% in CG. Moebus *et al.*[16] reported considerably higher transfusion rate in CG (28.1%) than IG (12.8%). Need of transfusions was statistically higher in IG as compared to CG in six trials (Table II). Studies using DA reported lowest transfusion rate.[15]

TEEs were reported in eight trials ranging from 2.8% to 16% in IG and 0.8% to 14% in CG, suggesting the higher events in IG. A statistically higher proportion of TEEs in IG were reported in five trials (Table II).

Nine studies reported adverse events (AEs) ranging from 0.28% to 57.6% in IG and 0.28% to 60% in CG. Serious AEs included extra-cardiac, erythrocyte, platelet, bleeding/clotting, gastric/duodenal, small/large bowel and mucous membrane disorders. Two studies indicated statistically higher AEs in IG as compared to CG, (Table III).[11,17] DA is associated with minimum number of ADEs in patients.[15]

Five trials reported tumor progression ranging from 41% to 95.2% in IG and 43% to 96% in CG, indicating the

Table II: RCTs evaluating effects of ESAs on mortality, transfusion requirements and thromboembolic events.

Outcomes	Mortality				Transfusion Requirements				Thromboembolic Events			
Author, Year	Total	IG	CG	p-value	Total No. of patients receiving transfusion	IG	CG	p-value	Total No. of thrombo-embolic events	IG	CG	p-value
Del Mastro et al., 1997[8]					2	0%	6.4%					
O'Shaughnessy *et al.*, 2005[9]	1	1.9%										
Chang *et al.*, 2005[10]	51	13.5%	15.2%		55	8.6%	22.9%	<0.0001	33	10.8%	7.8%	
Jones *et al.*, 2005[11]	249	28%	23%	0.02	113	10%	14%	0.06	141	16%	14%	
Aapro *et al.*, 2008[12]	338	73.1%	72.8%	0.522	96	14.2%	27%	?0.001	43	12.5%	6%	0.012
Pronzato *et al.*, 2010[13]	43	20.9%	17.7%	0.86	26	7.5%	16.5%	0.059	5	3.6%	0.8%	
Untch *et al.*, 2011[14]	107	17%	13%	0.450								
Untch *et al.*, 2011[15]					1	0.28%	0%	-	32	6%	3%	0.055
Moebus *et al.*, 2013[16]	116	19%	17%		131	12.8%	28.1%	<0.0001	33	7%	3%	0.030
Nitz *et al.*, 2014[17]	70	5.4%	6%	0.77					24	3%	1%	0.013
Jones *et al.*, 2016[18]	1,337	64.8%	63%		180	5.8%	11.4%	<0.001	44	2.8%	1.4%	0.038

IG=Intervention Group, CG=Control Group

Table III: RCTs evaluating effects of ESAs on safety, tumor progression and hemoglobin levels.

Outcomes	Safety				Tumor progression				Hemoglobin levels			
Author, Year	Total No. of serious AEs	IG	CG	p-value	Total No. of cases of tumor progression	IG	CG	p-value	Total No. of patients with Hb change	IG	CG	p-value
Del Mastro *et al*., 1997[8]										No decline	Decline	<0.001
O'Shaughnessy *et al*., 2005[9]									93	92.1% maintained	6.1% maintained	
Chang *et al*., 2005[10]	Incidence similar between both groups								100	51.4% maintained	5.1% maintained	<0.0001
Jones *et al*., 2005[11]	357	42%	34%	0.02	394	41%	43%	0.98		59% maintained	45% maintained	<0.001
Aapro *et al*., 2008[12]	168	42%	31%		442	95.2%	96%	0.448		68% maintained	14% maintained	<0.001
Pronzato *et al*., 2010[13]	34	16.5%	14.4%		No differences found					62% maintained	28% maintained	<0.001
Untch *et al*., 2011[14]												
Untch *et al*., 2011[15]	2	0.28%	0.28%							No significant change	Significant Decline	
Moebus *et al*., 2013[16]	73	10%	13%		No deleterious effects					No decline	Declined	<0.001
Nitz *et al*., 2014[17]	28	3.3%	1.3%	0.013						10.9% Declined	23.8% Declined	0.025
Jones *et al*., 2016[18]	1,237	57.6%	60%		1,241	58.1%	60.1%					

IG=Intervention Group, CG=Control Group.

Table IV: RCTs evaluating effects of ESAs on anemia treatment and quality of life.

Outcomes	Anemia treatment				Quality of life**			
Author, Year	Total No. of patients treated	IG p-value	CG	p-value	Total No. of patients with increased QOL	IG	CG	p-value
Del Mastro *et al.*, 1997[8]								
O'Shaughnessy *et al.*, 2005[9]					75	78.4%	71.4%	
Chang *et al.*, 2005[10]	333	97.2%	90.9%	-	166	93.8% change from beseline	-95.4% change from baseline	<0.0001
Jones *et al.*, 2005[11]	-	-	-	-	No differences found			0.01
Aapro *et al.*, 2008[12]	359	82.6%	72%	≤0.01	No significant difference			>0.6
Pronzato *et al.*, 2010[13]	-	14.2%* change from baseline	-0.5%* change from baseline	0.002		18.6% change from baseline	-2.7% change from baseline	0.003
Untch *et al.*, 2011[14]								
Untch *et al.*, 2011[15]								
Moebus *et al.*, 2013[16]					Not presented due to missing baseline data			
Nitz *et al.*, 2014[17]	Not presented due to missing baseline data				Not presented due to missing baseline data			
Jones *et al.*, 2016[18]	1,992	96%	93.9%					

*IG=Intervention Group, CG=Control Group; *Assessed by FACT-An Scale; **Assessed by FACT-An, CLAS Scale and LASA Scores.*

higher tumor progression in CG (Table III). EB is associated with maximum tumor progression rates[12] as compared to EA.[11]

Nine trials reported hemoglobin (Hb) change during ESA treatment. Of these, five trials reported that maintaining Hb was significant in IG ranging from 51.4% to 92.1%,[9-13] Hb was maintained 5.1% to 45% patients in CG. Three trials reported significant Hb decline in CG.[8,15,16] (Table IV). Maximum Hb maintenance is reported with EA.[9]

Five out of 11 trials reported data on anemia treatment. Two trials used FACT-An Scale for scoring where Pronzato *et al.*[13] reported 14.2% change of score in IG and -0.5% in CG. Nitz *et al.*[17] reported no significant difference of scores between IG and CG. Other three trials described percentage of patients with anemia free survival ranging from 82.6% to 97.2% in IG and 72% to 93.9% in CG (Table IV). Maximum rate of anemia treatment was associated EA.[10,18]

QOL was assessed in 7 RCTs. Of these, three trials demonstrated no impact on QOL with the use of ESAs.[11,12,17] O'Shaughnessy *et al*.[9] reported improvements in QOL in 78.4% in IG and 71.4% in CG using LASA scoring. Pronzato *et al.*[13] reported results by CLAS Scale. Moebus *et al.*[16] was unable to report QOL due to missing baseline data. All three scales provided statistically significant improvement in QOL in IG (Table IV). EA therapy showed maximum improvements in QOL score.[10]

DISCUSSION

Anemia frequently occurs among cancer patients receiving chemotherapy.[16] ESAs provide survival benefits from CIA in patients with BC.[17] Anthracycline therapy as FEC combination including 5-fluorouracil with epirubicin, and cyclophosphamide induces anemia in almost 42% patients.[16] Current review has analysed the impact of several ESAs on various outcomes among patients with BC.

The high mortality rate after using ESAs is attributed to repopulating capability of tumor from a single stem cell in BC. Reinbothe *et al.* suggested that erythropoietin receptor (EpoR) protein is expressed in breast tumor cells, where it seems to stimulate proliferation by erythropoietin-independent mechanism in estrogen receptor positive (ERα+), expressing in metastatic breast cancerous cells.[23] Phillips *et al.* revealed that over expression of an erythropoietin receptor (EpoR) amplified the clonogenicity of cancer cells resulting in increased mortality after using ESAs.[24] Abundant expression of c-Myc in many cancers is another reason of tumor progression with the use of ESAs.[25] EPO also increases MYC expression in erythroid progenitor cells. MYC is a family of regulator genes as well as proto oncogenes that code for transcription factors.[26]

Previous studies revealed that treatment with epoetin alfa sustained and/or enhanced Hb concentration and patient reported outcomes (PROs).[10] Several quantitative analysis provides evidence of Hb elevation with the use of ESAs, thereby reducing the need of RBCs transfusion.[7,10] Further clarification might include elevated oxygenation of tissue having tumor at greater Hb points.[27] Cancer cells become unaffected by tumor hypoxic conditions, raised oxygenation inhibits hypoxia preserving tumor cells to be sensitive to radiation, and cytostatic therapy. Hypoxia is more prevalent in anemic patients.[27] Epoetin was initially used as optional treatment therapy was for adjustment of anemia to avoid transfusions.[28] European guidelines suggest the dose of erythropoietin as once weekly for patients having Hb between 9 to 11 g/dL with target Hb of 12-13 g/dL.[12]

American guidelines recommends that erythropoietin should be reserved for patients having Hb <10 g/dL to achieve targeted Hb 12 g/dL.[12]

Pronzato *et al*. estimated better tolerability of epoetin alfa with few AEs including thromboembolic events.[13] Though occurrence of venous thrombosis was similar in both groups but serious thrombovascular events were more prevalent in IG receiving epoetin alfa.[13] The drugs for BC have been connected with higher risk of venous TEEs due to thrombus formation in venous circulation.[29] TEEs may reside due to both superficial venous thrombosis and deep venous thrombosis.[30] TEEs can be determined primarily by the differences in underlying cancer population due to disease stage and activation of the coagulation system after using ESAs.[31] Coagulation pathways in BC are precised in Figure 2. ESAs can activate tumor cells to produce TF and cancer procoagulant (CP), which can start the extrinsic pathway by activating certain coagulation factors (VIIa and Xa). Thrombin causes platelet accumulation which intensifies the thrombophilic state. Hereafter, TF can initiate a hypercoagulability state with thrombosis.[32]

Since thrombotic events are second leading cause of death in cancer patients, thromboprophylaxis improves prognosis and QOL in BC patients by inhibiting the thrombotic events.[33] However, Several regulatory authorities have limited the use of ESAs for CIA.[16] Existing data underscored the association of epoetin and darbepoetin with TTEs and amplified mortality.[16] Similar findings have been reported in composite analysis of previous studies.[21] However, epoetin alfa therapy caused substantial decrease in transfusion requirements as well as improvement in QOL.[16]

Del Mastro *et al.* reported that EPO prevents anemia and maintained Hb values along with prevention of anemia among receiving chemotherapy consisting of six cycles (cyclophosphamide, epirubicin, and fluorouracil (CEF) on day 1, every two weeks using granulocyte colony stimulating factor, subcutaneously from day 4 -11).[8] The improved erythropoiesis with EPO therapy led to quick reduction of iron supply as evidenced by decline in iron/transferrin levels in plasma and overall iron stores assessed by total iron binding capacity. The boosted EPO-induced erythropoiesis is predictable to produce low level of ferritin. Representation of RBC is performed by estimation of mean corpuscular Hb (MCH), mean corpuscular volume (MCV), and mean corpuscular Hb concentration (MCHC). Clinically, anemia does not occur in EPO group due to maintenance of Hb levels.[8]

CONCLUSION

Current review suggests that ESAs are generally well endured and can shield against anemia. With the exception of risks of thrombotic complications, ESAs appear to be harmless for the treatment or fundamental anticipation of anemia in CIA. Current evidence also ascertains that ESAs reduce the need for blood transfusions. However, risks of increased mortality and TEEs should not be disregarded during the treatment.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

YHK: Conceptualised the plan for the current study; assisted in interpreting the results; assessed the data quality and approved the final version of the manuscript for submission.

SS, THM, MK: Did the literature search, screening and data extraction.

RN, NJ: Performed critical appraisal of all included studies.

THM: Drafted the manuscript; assessed the data quality and approved the final version of the manuscript for submission.

All authors have critically reviewed the manuscript.

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