بسمه تعالی

حوزهٔ معاونت پژوهشی دانشگاه علوم پزشکی اصفهان

چکیده‌ای از طرح تحقیقاتی

عنوان طرح:

Effects of Pentoxifylline on anemia in patients with chronic kidney disease:

A systematic review and meta-analysis

کلید واژه‌ها:

Systematic review, Pentoxifylline, Anemia, Chronic kidney disease

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مقدمه و ضرورت اجرای طرح (به صورت خلاصه)

Chronic Kidney Disease (CKD) is a prevalent, worldwide condition, and the number of patients affected continues to increase. Anemia occurs early in development of kidney disease and worsens as kidney function deteriorates. Anemia has been associated with substantial morbidity and mortality. However, with appropriate therapy, anemia can be effectively treated, thereby improving the quality of life in patients with CKD and anemia. Erythropoiesis-stimulating agents (ESAs) and periodic iron supplements are the mainstays of treatment for anemia associated with CKD. However, since ESA started to be used, it has been observed that there is a group of patients with resistance. Besides non-responsiveness as a major concern, the modest benefits on transfusion rates and some quality of life domains are offset by the risk of major side effects.

Pentoxifylline (PTF), derived from methylxanthine, is a nonspecific inhibitor of phosphodiesterase that, besides having rheological properties and being used as a treatment in peripheral vascular disease, has anti-inflammatory activity. The hemorheological properties and the potential to improve circulation and some indices of kidney function led to an interest in the use of PTF as a therapeutic agent in patients with kidney disease. As for the possible benefit of its anti-inflammatory action on anemia in renal patients, some studies show that it increases hemoglobin (Hgb) or hematocrit (Hct) in patients with CKD or patients on a regular hemodialysis program.

Pentoxiphylline is a valuable medication in many conditions namely kidney diseases due to its promising clinical characteristics and considerable profile of safety. However, the decision to prescribe pentoxiphylline for anemia in CKD should be based on evidence accrued from randomized controlled trials (RCTs). Yet, substantial heterogeneity exists in RCTs performed to evaluate pentoxiphylline therapy, particularly in relation to classification of patients, the different quality and research design, sample size, baseline Hgb or Hct, target Hgb or Hct, clinical outcome measures, and definitions of endpoints and clinically meaningful improvements. As a result, assessment of pentoxiphylline in treating anemia of CKD by conducting a systematic review and meta-analysis of the published relevant clinical studies seems rational and promising.

اهداف و فرضیات

الف. هدف کلی:

To document from randomized controlled trials the effect of Pentoxiphylline on anemia in patients with chronic kidney disease, by systematically reviewing the literature and performing meta-analysis

ب. اهداف جزئی (اختصاصی):

1. To determine the effect of Pentoxiphylline therapy on Hemoglobin level in patients with chronic kidney disease
2. To determine the effect of Pentoxiphylline therapy on Hematocrit in patients with chronic kidney disease
3. To determine the effect of Pentoxiphylline on reducing the needed dose of Erythropoietin in patients with chronic kidney disease
4. To assess the possible adverse reactions of Pentoxiphylline therapy in patients with chronic kidney disease

ج. اهداف فرعی:

1. To determine the effect of administered dose of Pentoxiphylline on Hemoglobin level, Hematocrit, reducing the needed dose of Erythropoietin, and emerging the possible adverse reactions of Pentoxiphylline therapy in patients with chronic kidney disease
2. To determine the effect of duration of treatment with Pentoxiphylline on Hemoglobin level, Hematocrit, reducing the needed dose of Erythropoietin, and emerging the possible adverse reactions of Pentoxiphylline therapy in patients with chronic kidney disease
3. To determine the relationship between stage of CKD and the effect of Pentoxiphylline therapy on Hemoglobin level, Hematocrit, reducing the needed dose of Erythropoietin, and emerging the possible adverse reactions of Pentoxiphylline in patients with chronic kidney disease

د. هدف کاربردی:

To provide the highest levels of evidence in order to make the decision to prescribe pentoxiphylline for anemia in patients with kidney diseases

روش اجرا و شیوه‌های تجزیه و تحلیل یافته‌ها (به صورت خلاصه)

The present systematic review will be done in accordance with the PRISMA guideline for systematic reviews and meta-analysis. Peer-reviewed prospective **randomized controlled clinical trials** (parallel group or cross-over trials) with at least four weeks of follow-up will be including in the meta-analysis. Participants of any age with chronic kidney disease condition in whom Pentoxiphylline is prescribed for treating anemia, will be including in final analysis.

Online databases (PubMed/Medline, ISI Web of Science, EmBase, and Scopus) will be searched from January 1970 to December 2014 using selected MeSH terms and free text terms related to the studied topic, including "Pentoxiphylline", [using the set operator] AND "Anemia", "Hemoglobin", and "Hematocrit", limited to studies in humans. We will also review reference lists of the identified publications for additional pertinent studies. No language restrictions will be imposing.

Data will be extracted independently by two reviewers using a standard form and then cross-checked. All numeric calculations and extractions from tables, graphs or figures will be confirmed by a second reviewer. In the case of missing information in the included studies, investigators will be contacted (by email, letter and/or fax) to obtain the missing information.

Overall weighted mean difference (WMD) and 95% CI (confidence interval) will be calculated for the continuous outcomes. If the same continuous outcome is measured differently across studies, an overall standardized mean difference (SMD) and 95% CI will be calculated.

Data will be meta-analyzed if possible according to administered dosage of Pentoxiphylline, and duration of therapy. Within and between study heterogeneities will be assessed using Cochran's Q-statistics and the heterogeneity test will be used to assess the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity is quantified using I square which provides a measure of the degree of inconsistency between studies. As we find no evidence of heterogeneity, a fixed effects model will be used; otherwise, random effects approach, Meta-regression or sub-group analysis will be used in the case of statistical heterogeneity.

Sensitivity analysis will be conducted to explore the extent to which inferences might depend on a particular study or number of publications.

Statistical analyses will be carrying out with Comprehensive Meta-analysis Software, version 2.0 (Englewood, NJ BioStat). *P* values less than 0.05 will be considered statistically significant. All statistical tests will be two-sided.

تعریف واژه‌ها

Systematic Review:

Literature summaries that aim to answer a specific question on the effectiveness of interventions by performing a systematic search in available literature. The term 'systematic' indicates that specific attention is given to formulating the methods of data collection and handling, in order to provide a transparent methodology to the reader who can then make a judgment about the quality of the literature search. This profound method minimizes the risk of bias and results in the "best available scientific evidence" (14).

Pentoxiphylline:

Pentoxifylline (PTF) is a methylxanthine phosphodiesterase inhibitor which has been in clinical use since the late 1970s and was used primarily to treat patients with peripheral vascular disease. In addition to its hemorheologic activity, it has been experimentally shown to have potent antiproliferative, anti-inflammatory, anti-diabetic, anti cellular damage, and antifibrotic effects. The hemorheological properties and the potential to improve circulation and some indices of kidney function led to an early interest in the use of PTF as a therapeutic agent in patients with kidney disease (15).

Anemia:

Internationally anemia is defined as a state in which the quality and/or quantity of circulating red blood cells are below normal. Blood hemoglobin (Hgb) concentration serves as the key indicator for anemia because it can be measured directly, has an international standard, and is not influenced by differences in technology (16). The World Health Organization (WHO) defines anemia as a hemoglobin concentration lower than 13.0 g/dL in men and postmenopausal women and lower than 12.0 g/dL in other women (2).

Chronic kidney disease:

CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health (17). The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) defines CKD based on glomerular filtration rate (GFR) and divides the disease into five distinct stages. In Stage 1 CKD, the GFR is ≥ 90 ml/min/1.73 m^2. Stages 2, 3, and 4 CKD are defined by a GFR of 60–89 ml/min/1.73 m^2, 30–59 ml/min/1.73 m^2, and 15–29 ml/min/1.73 m^2, respectively. The final stage, Stage 5, occurs when the GFR is < 15 ml/min/1.73 m^2 or when patients require dialysis (1).

قسمت دوم- اطلاعات مربوط به طرح پژوهشی

عنوان طرح:

Effects of Pentoxifylline on anemia in patients with chronic kidney disease: A systematic review and meta-analysis

نوع طرح:

بنیادی　　بنیادی- کاربردی　　کاربردی

مقدمه (بیان مسأله، مرور متون)

Chronic kidney disease (CKD) is a prevalent, worldwide condition, and the number of patients affected continues to increase. In the United States, it is estimated that by 2014, more than 2 million people will be afflicted with CKD (1). In chronic kidney disease, as nephrons are progressively lost, the body attempts to maintain homeostasis via multiple adaptive and maladaptive processes, including a complex range of biochemical and physiologic abnormalities. Almost every organ and system seems to be affected, but the main complications are cardiovascular, neurologic, hematologic, musculoskeletal, and immunologic- and all worsen as kidney function declines (2).

Anemia occurs early in the development of kidney disease and worsens with declining kidney function. This complication is very common in patients with chronic kidney disease with an incidence of over 70% in advanced stages of the disease (2). The impact of anemia on patients with CKD is profound. In addition to the well-known symptoms of fatigue, dizziness, and shortness of breath, anemia has been associated with more severe adverse outcomes, such as cardiovascular complications including left ventricular hypertrophy and congestive heart failure (1). Therefore, patients with chronic kidney disease, even those with moderate disease not yet requiring dialysis, need to be periodically monitored for anemia. Although most patients are anemic when they start dialysis, only about a third is receiving treatment for it. Factors likely contributing to anemia in chronic kidney disease include blood loss, shortened red cell life span, vitamin deficiencies, the “uremic milieu”, erythropoietin (EPO) deficiency, iron deficiency, and inflammation (2).

As a result of the potentially severe consequences of anemia in CKD, early recognition and management of anemia are imperative. Correction of anemia has been shown to improve cardiac function possibly by reducing exercise-induced myocardial ischemia. Treatment of anemia associated with CKD has also been shown to result in improvements in exercise capacity, physical performance features such as endurance, energy, and physical mobility (1). Although no randomized trial has fully assessed the consequences of not treating anemia in chronic kidney disease, the consensus is that untreated anemia contributes to the large cardiovascular disease burden in this population (2).

Erythropoiesis-stimulating agents (ESAs) and periodic iron supplements are the mainstays of treatment for anemia associated with CKD. Treatment with ESAs has greatly improved the management of anemia in patients with chronic kidney disease, permitting better outcomes and a higher quality of life for most (3). The high rate of response to this treatment has meant that it has been possible not only to avoid red blood cell transfusion in patients on hemodialysis, but also improve their quality of life substantially. However, since EPO started to be used, it has been observed that there is a group of patients with resistance to ESA. In some cases it is attributable to easily treatable factors, such as iron deficiency, severe hyperparathyroidism, ineffective dialysis, blood loss, vitamin deficiencies, etc.; and in others, inflammation has been suggested as a mechanism involved. In fact, all dialysis patients have a certain degree of inflammation that has been related to a greater or lesser extent, to anemia, according to the cases. Inflammation may result in, not only a lower production of EPO, but also a lower response of the erythropoiesis progenitor cell to the aforementioned treatment (4).

Recent randomized controlled trials (RCTs) have reported risks and benefits in the correction of anemia using ESAs in patients with pre-dialysis CKD or end-stage renal disease (ESRD). Besides non-responsiveness as a major concern, the safety of ESAs in treating severe anemia has not been evaluated in large placebo-controlled trials. The modest benefits on transfusion rates and some quality of life domains are offset by the risk of major side effects. Meta-analysis demonstrated that correction of anemia with ESA was associated with a significantly increased risk of hypertension and vascular access clotting and an increased risk of death that approached statistical significance (3).

Pentoxifylline (PTF), derived from methylxanthine, is a nonspecific inhibitor of phosphodiesterase that, besides having rheological properties (5) and being used as a treatment in peripheral vascular disease, has anti-inflammatory activity. In fact, it has been described that it reduces levels of interleukin-6 (IL-6) and other inflammatory parameters in patients on hemodialysis (6). The hemorheological properties and the potential to improve circulation and some indices of kidney function led to an early interest in the use of PTF as a therapeutic agent in patients with kidney disease. As for the possible

benefit of its anti-inflammatory action on anemia in renal patients, some studies show that it increases hemoglobin (Hgb) in patients with CKD or patients on a regular hemodialysis program (4, 7-12).

Systematic Review

The average physician is faced with increasingly large amounts of new information about medical conditions. This ranges from the latest findings of complex molecular studies to results from randomized controlled trials (RCTs) to case reports of possible therapies for very rare conditions. With this vast amount of information being produced in published journals, presentations at conferences, and now increasingly online, it is virtually impossible for physicians to keep up to date without many hours being spent searching and reading articles.

Review articles traditionally provide an overview of a topic and summarize the latest evidence, thus reducing the time clinicians would need to spend performing literature searches and interpreting the primary data. These review articles, known as narrative reviews, typically address a broad number of issues related to a topic. Narrative reviews do not describe the process of searching the literature, article selection, or study quality assessment. The data are usually summarized but not statistically combined (qualitative summary), and key studies are highlighted. The inferences made from narrative reviews may be, but are not necessarily, evidence based. Narrative reviews are useful for obtaining a broad overview of a topic, usually from acknowledged experts. However, narrative reviews are susceptible to bias if a comprehensive literature search is not performed, or if only selected data are presented which conveys the author's views on a particular topic.

Systemic reviews aim to reduce bias with the use of explicit methods to perform a comprehensive literature search and critical appraisal of the individual studies. Thus, in contrast to narrative reviews, systematic reviews pose a defined clinical question. The process of performing the literature search and the specific inclusion and exclusion criteria used for study selection are described. The quality of the included studies is formally appraised. The data are summarized, and, if the data are statistically combined (quantitative summary), the systematic review is referred to as a meta-analysis. The inferences made from systematic reviews are usually evidence based.

Furthermore, systematic reviews also attempt to identify if certain subtypes of evidence (eg, small negative studies) are absent from the literature; this so-called "publication bias" is an

important cause of incorrect conclusions in narrative reviews. Systematic reviews frequently, but not necessarily, use statistical methods and meta-analysis to combine the data from the literature search to produce a single estimate of effect (13).

ضرورت اجرای طرح:

Pentoxiphylline is a valuable medication in many conditions namely kidney diseases due to its promising clinical characteristics and considerable profile of safety. Furthermore, thanks to its anti-inflammatory properties, it includes substantial beneficial therapeutic effects in different aspects of kidney disease complications such as proteinuria, makes it a notable choice in this vulnerable population. However, the decision to prescribe pentoxiphylline for anemia in CKD should be based on evidence accrued from randomized controlled trials (RCTs). Yet, substantial heterogeneity exists in RCTs performed to evaluate pentoxiphylline therapy, particularly in relation to classification of patients, the different quality and research design, sample size, baseline Hgb or Hct, target Hgb or Hct, clinical outcome measures, and definitions of endpoints and clinically meaningful improvements. As a result, assessment of pentoxiphylline in treating anemia of CKD by conducting a systematic review and meta-analysis of the published relevant clinical studies seems rational and promising.

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فهرست منابع مورد استفاده در این طرح

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The present systematic review will be done in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline (18, 19; PRISMA checklist is attached to the proposal draft). This systematic review is designed methodologically according to the "Standards for systematic reviews" (13, 20-22).

Eligibility criteria for considering studies for this review

Types of studies

Peer-reviewed prospective **randomized controlled clinical trials** (parallel group or cross-over trials) with at least four weeks of follow-up will be including in the meta-analysis. This will be performed by completing the "Defining a question and eligibility criteria" checklist (23; also attached to the proposal draft), describing in detail all the elements which would be explored within the review. Studies will be excluding if they do not provide data that allow us to calculate standard deviation (SD) / standard errors (SE) for effect estimates.

Types of participants

Participants (male/female) of any age with chronic kidney disease condition (stages 3, 4 or 5, according to KDIGO guideline [17]) in whom Pentoxiphylline is prescribed for treating anemia, will be including in final analysis.

Types of interventions

Pentoxiphylline administration at any dose for more than four weeks

Types of outcome measures

Primary outcomes:

Changes in hemoglobin, hematocrit or the needed dose of erythropoietin, as compared to control group

Secondary outcome:

Adverse reactions of Pentoxiphylline therapy

Search methods for identification of studies

Electronic searches

The Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews will be searched for related reviews.

Online databases (PubMed/Medline, ISI Web of Science, EmBase, and Scopus) will be searched from January 1970 to December 2014 using selected MeSH terms and free text terms related to the studied topic, including “Pentoxiphylline”, [using the set operator] AND “Anemia”, “Hemoglobin”, and “Hematocrit”, limited to studies in humans. We will also review reference lists of the identified publications for additional pertinent studies. Clinical trial registries (http://www.clinicaltrialsregister.eu, http://www.clinicaltrials.gov, http://www.irct.ir, and http://www.who.int/ictrp/search/en) will be searched with the same protocol to identify suitable trials and investigators contacted if a trial appeared relevant. No language restrictions will be imposing. Only manuscripts with Full-Text accessibility will be including in final analysis. Search results will be examined with regard to title and abstract and suitable trials identified. Duplicate published researches will be excluding at the final analysis.

Data collection

Data collection

Data will be extracted independently by two reviewers using a standard form (24; details are provided below; also attached to the proposal draft) and then cross-checked. Inconsistencies between authors will be agreed by consensus. All numeric calculations and extractions from tables, graphs or figures will be confirmed by a second reviewer. In the case of missing information in the included studies, investigators will be contacted (by email, letter and/or fax) to obtain the missing information.

Data Extraction

- Name of the author
- Year of publication
- Location/Country
- Clinical setting (primary/secondary care; inpatient/outpatient/residential care)

- Ethics approval
- Inclusion criteria
- Exclusion criteria

Methods:

• Randomization technique

• Allocation concealment

• Blinding of patients/parents/caregivers/clinicians/therapists/assessors

• Nature of control/placebo

• Number of drop-outs

Participants at baseline:

• Number (in each group)

• Gender proportions

• Age range

• Diagnosis and criteria used (CKD staging method, definition of Anemia)

• Sources of recruitment

• Baseline Hemoglobin

• Baseline Hematocrit

• Needed dose of Erythropoietin at baseline

Type of study:

• Single/multi-center; cross-over

Interventions:

• Medication

• Dose

• Type of control

• Assessment of compliance

• Additional treatment components

• Duration

• Length of follow-up

• Number/frequency of follow-up appointments and assessments

Outcomes:

• Mean change in Hemoglobin from baseline and SD of change or SD at the end of treatment

• Mean change in Hematocrit from baseline and SD of change or SD at the end of treatment

• Mean change in the needed dose of Erythropoietin from baseline and SD of change or SD at the end of treatment

• Number of patients reported to be affected by Pentoxiphylline adverse effects

• Intention to treat analysis (Post-baseline data in patients who withdrew will be used as "last observation carried forward" (LOCF) analysis provided less than or equal to 20% of total randomized patients were lost to follow up).

• Patients in whom Hemoglobin and Hematocrit was actually measured at the end of treatment will also be analyzed.

Information on study design, participant characteristics, measurement of anemia improvement, adjustment for potential confounders, and estimates of associations will be extracted independently by two reviewers. Discrepancies will be resolved by discussion.

Data analysis

Summary of data

Overall weighted mean difference (WMD) and 95% CI (confidence interval) will be calculated for the continuous outcomes. If the same continuous outcome is measured differently across studies, an overall standardized mean difference (SMD) and 95% CI will be calculated (25).

Meta-analysis

Data will be meta-analyzed if possible according to administered dosage of Pentoxiphylline, and duration of therapy. As we find no evidence of heterogeneity, a fixed effects model will be used; otherwise, random effects approach, Meta-regression or sub-group analysis will be used in the case of statistical heterogeneity.

Assessment of publication bias

Funnel plots (estimated differences in treatment effects against their standard error) will be drawn if sufficient studies are found.

Assessment of risk of bias in included studies

Methodological quality will be assessed independently by at least two review authors according to the Cochrane Collaboration Handbook (25) and Cochrane Review guidelines (26). Reviewing authors will independently assess the risk of bias within each included study based on the following domains with ratings of 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias):

- Sequence generation
- Allocation concealment
- Blinding
- Incomplete outcome data
- Selective outcome reporting

Dealing with missing data

In the first instance, authors will be contacted to provide missing data or clarification of data from included studies. Missing data and drop-outs/attrition will be assessed for each included study, and the extent to which the results/conclusions of the review could be altered by the missing data will be assessed and discussed.

Assessing the quality of included trials

Quality of included trials will be assessed using CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting of randomized controlled trials and reporting of randomized trials as conference abstracts (27-29; CONSORT checklist is attached to the proposal draft).

Assessment of heterogeneity

Clinical heterogeneity will be assessed by comparing the distribution of important participant factors between trials (e.g. administered dose of Pentoxiphylline, duration of Pentoxiphylline administration, and …), and trial factors (randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type, co-interventions). Within and between study heterogeneities will be assessed using Cochran's Q-statistics and the heterogeneity test will be used to assess the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity is quantified using I square (30) which provides a measure of the degree of inconsistency between studies. As we find no evidence of heterogeneity, a fixed effects model will be used; otherwise, random effects approach, Meta-regression or sub-group analysis will be used in the case of statistical heterogeneity. In addition, a chi-square test of homogeneity will be employed to determine the strength of evidence that heterogeneity is genuine.

Sensitivity analysis

Sensitivity analyses will be conducted to assess the impact of the study quality. A sensitivity analysis compares studies fulfilling and not fulfilling the "Quality" criteria and asks the question, "Are the findings robust to the decisions made in the process of obtaining them?" This involves the removal of studies that meet certain criteria (e.g., poor quality, commercial sponsorship, conference abstract) to determine their effect on the overall result (13). These will be undertaken by including:

1. Only those with low risk of selection bias (associated with sequence generation or allocation concealment);

2. Only those with low risk of performance bias (associated with issues of blinding);

3. Only those with low risk of attrition bias (associated with completeness of data).

Statistical analyses will be carrying out with Comprehensive Meta-analysis Software, version 2.0 (Englewood, NJ BioStat). *P* values less than 0.05 will be considered statistically significant. All statistical tests will be two-sided.

جدول زمانی مراحل اجرا و پیشرفت کار

ردیف	نوع فعالیت	فرد مسئول	طول مدت به ماه	زمان اجرا (ماه)														
				۱	۲	۳	۴	۵	۶	۷	۸	۹	۱۰	۱۱	۱۲	۱۳	۱۴	۱۵
۱	مطالعهٔ متون و جمع‌آوری اطلاعات مورد نیاز جهت نگارش پروپوزال	دانشجو تحت نظارت اساتید راهنما (دکتر بدری، دکتر فیضی)	۲	*	*													
۲	جست‌وجوی منابع و پایگاه‌های اطلاعاتی جهت یافتن مقالات مرتبط با موضوع	دانشجو تحت نظارت استاد راهنما و مشاور (دکتر بدری، دکتر مرتضوی)	۶			*	*	*	*	*	*							
۳	آنالیز مقالات و استخراج داده‌ها در جهت دستیابی به اهداف طرح	دانشجو تحت نظارت استاد راهنما و مشاور (دکتر بدری، دکتر مرتضوی)	۲									*	*					
۴	تحلیل آماری	دانشجو تحت نظارت اساتید راهنما (دکتر بدری، دکتر فیضی)	۲											*	*			
۵	جمع‌بندی، تهیه مقاله و ارائه گزارش نهائی طرح	دانشجو تحت نظارت اساتید راهنما و مشاور (دکتر بدری، دکتر فیضی، دکتر مرتضوی)	۳													*	*	*

جمع کل: ۱۵ ماه

جدول متغیرها

نام متغیر	نقش متغیر	نوع متغیر			
		کیفی		کمّی	
		رتبه‌ای	اسمی	گسسته	پیوسته
Pentoxiphylline administration	Independent		*		
Administered dose of Pentoxiphylline	Confounder				*
Duration of treatment with Pentoxiphylline	Confounder				*
Stage (3, 4, or 5) of CKD	Confounder			*	
Hemoglobin level	Dependent				*
Hematocrit	Dependent				*
Needed dose of Erythropoietin	Dependent				*
Adverse reactions of Pentoxiphylline therapy (number of affected patients for each adverse effect)	Dependent			*	

مشکلات اجرایی در انجام طرح و روش حل مشکلات

در مطالعات "مرور نظام‌مند" یکی از مشکلات پیش‌رو عدم دستیابی به متن کامل (Full text) مقالات مورد مطالعه می‌باشد که در این تحقیق سعی می‌گردد از طریق پایگاه‌های اطلاعاتی تحت پوشش دانشگاه علوم پزشکی اصفهان، و نیز کتابخانه‌های طرف قرارداد با این دانشگاه، امکان دسترسی به مقالات فراهم گردد. در غیر این صورت، مقاله از طریق پایگاه اطلاعاتی ارائه دهنده آن خریداری خواهد شد تا بدین ترتیب همه شواهد موجود در خصوص موضوع مورد مطالعه، در دسترس قرار گیرد.

همچنین، در صورتی که در یک مقاله اطلاعات مورد نیاز به منظور انجام مطالعات آماری مرتبط با "مرور نظام‌مند" ارائه نشده باشد، سعی خواهد شد که از طریق تماس با نویسنده مسئول مقاله و ارائه توضیح در خصوص انجام این تحقیق، اطلاعات لازم از ایشان کسب گردد.

پیشنهادات و کاربرد یافته‌های طرح

از آنجا که هدف از انجام مطالعات ثانویه از قبیل مطالعات "مرور نظام‌مند" در واقع جمع‌آوری و تحلیل کلیه شواهد موجود (به دست آمده از مطالعات بالینی کنترل شده) پیرامون موضوع مورد مطالعه است، لذا انجام چنین مطالعاتی می‌تواند شواهد مستدلی برای مثال در خصوص کارایی یک روش درمانی فراهم آورد و بدین ترتیب در آینده منشأ تصمیم‌گیری‌های بالینی قرار گیرد.

Pages 25 , 26	PRISMA 2009 checklist	Reference No. 19
Pages 27 , 28	CONSORT 2010 checklist	Reference No. 29
Pages 29 , 30	Defining a question and eligibility criteria (Cochrane training)	Reference No. 23
Pages 31-36	Data extraction form	Reference No. 24

ضمائم

۱. در صورت نیاز به اخذ رضایت‌نامه کتبی از واحدهای مورد پژوهش، نمونه‌ای از فرم مذکور ضمیمه گردد.

۲. در صورتی که روش و یا ابزار گردآوری داده‌ها پرسش‌نامه و یا چک لیست می‌باشد، لطفاً نمونه‌ای از آن ضمیمه شود.

۳. در صورت نیاز موافقت کتبی محیط پژوهش اخذ و ضمیمه گردد.

۴. در مورد مجریان خارج دانشگاهی، لطفاً CV علمی مجری ضمیمه گردد.

PRISMA 2009 Checklist

Section / Topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

CONSORT 2010 checklist of information to include when reporting a randomized trial *

Section / Topic	Item No	Checklist item	Reported on page No
Title and abstract	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	

CONSORT 2010 checklist of information to include when reporting a randomized trial *

Section / Topic	Item No	Checklist item	Reported on page No
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

* We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Defining a question and eligibility criteria

Complete the following table, describing in detail all the elements you would like to explore within your review. Consider the prompt questions on the following page to help you. When you have finished, consider which of the elements you have listed will form your eligibility criteria to include/exclude studies from your review.

Population	
Intervention(s)	
Comparison(s)	
Outcome(s)	
Study design(s)	

Prompt questions to develop your eligibility criteria

Population	How is the disease/condition defined? What are the most important characteristics that describe the participants relevant to your review? Are there any relevant demographic factors? (e.g. age, sex, ethnicity) What is the setting? (e.g. hospital, community) Who should make the diagnosis? Are there any comorbidities to be excluded? Are there any other types of people who should be excluded or considered in the review (because they are likely to react to the intervention in a different way)? How will studies involving only a subset of relevant participants be handled?
Intervention(s)	Does the intervention have variations (e.g. dosage, components, mode of delivery, personnel, frequency, duration, timing)? Are all variations to be included (e.g. is there a minimum dose or components without which the intervention may not be expected to work in the same way)? How will trials including the intervention of interest combined with another intervention (co-intervention) be handled? Is the intervention provided or accessed differently in different contexts?
Comparison(s)	What are you interested in comparing the intervention to (e.g. an active intervention, no intervention or placebo, any available comparison)? This depends on the primary question of the review. What is the usual alternative to your intervention of interest in practice? If comparing to a specific intervention, describe in detail as above.
Outcome(s)	What are the important outcomes that you plan to measure in your review? Will the outcomes form part of the selection criteria? Which will be your primary outcomes (maximum of 3)? Which will be your secondary outcomes? Which primary and secondary outcomes will be your main outcomes (maximum of 7) to be included in summaries of the completed review such as your Abstract, Plain Language Summary and Summary of Findings Table? These outcomes should be essential for decision-making, and have an emphasis on patient-important outcomes. Have you included possible adverse effects? How should the outcomes be measured (e.g. validated tools)? Are there important time points at which outcomes should be measured (e.g. long enough to expect an observable effect)? Have you included outcomes relevant to all potential decision-makers?
Study design(s)	Most Cochrane reviews include randomized controlled trials as the most appropriate design to answer questions about the effects of interventions. Do you plan to include other study designs (e.g. quasi-randomized studies, non-randomized studies)? If so, which designs will you include, and what is your rationale?

Based on O'Connor D, Green S, Higgins JPT (editors). Chapter 5: Defining the review question and developing criteria for including studies. In: Higgins JPT, Green S (editors), Cochrane Handbook of Systematic Reviews of Intervention. Version 5.0.1 (updated September 2008). The Cochrane Collaboration, 2008. Available from: www.cochrane-handbook.org.

Data Extraction

Title:

Authors:

Year of publication :

Location / Country :

Clinical setting or Sources of recruitment (primary/secondary care; inpatient/outpatient/residential care) :

Randomization technique :

Allocation concealment :

Blinding of patients/parents/caregivers/clinicians/therapists/assessors :

Nature of control/placebo :

Assessment of how researchers dealt with confounding		
Method for identifying relevant confounders described If yes, describe the method used:	Yes No	☐ ☐
Relevant confounders described: List confounders described under Data extraction, characteristics of participants:	Yes No	☐ ☐
Method used for controlling for confounding At design stage: matching ☐ variables on which subjects matched: …… …… …… …… At analysis stage: stratification ☐ multivariable regression propensity scores (matching) propensity scores (multivariable regression) List confounders controlled for under Data extraction, characteristics of participants:		 ☐ ☐ ☐

Data extraction	Entire study	Intervention	Control
Number of participants identified			
Number of participants: excluded lost to follow-up			
Number of participants included			
All participants accounted for?	Yes ☐ No ☐		
Ethics approval	Yes ☐ No ☐		
Assessment of compliance	Yes ☐ No ☐		
Eligibility / inclusion / exclusion criteria (enter in appropriate column if criteria differ by group)			
Diagnosis and criteria used (CKD staging method, definition of Anemia)			

Characteristics of participants

(Enter characteristics, tick if considered to be a confounder, then enter mean and SD, or frequency and percentage for each characteristic, for entire study population and by group. Finally, for each characteristic, tick last column to indicate whether groups were considered different by the researchers.)

Characteristic	Confounder?	Entire study	Exposed	Unexposed	Different?
Age	☐				☐
Sex	☐				☐
CKD stage	☐				☐
Baseline Hgb	☐				☐
Baseline Hct	☐				☐
The needed dose of EPO (at baseline)	☐				☐
Others:	☐				☐

SD: standard deviation.
CKD: chronic kidney disease; Hgb: haemoglobin; Hct: haematocrit; EPO: erythropoietin.

Intervention

Medication :

Dose :

Additional treatment components :

Duration :

Length of follow-up :

Number/frequency of follow-up appointments and assessments :

Effects of intervention

Outcomes	Number analysed	Unadjusted effect estimate and SE / CI	Number analysed	Adjusted effect estimate and SE / CI	Confounders included in adjusted analysis
Hgb levels		HR ☐ OR ☐ RR ☐		HR ☐ OR ☐ RR ☐	
Intervention vs. control		SE ☐ CI ☐		SE ☐ CI ☐	
Haematocrit		HR ☐ OR ☐ RR ☐		HR ☐ OR ☐ RR ☐	
Intervention vs. control		SE ☐ CI ☐		SE ☐ CI ☐	
Needed dose of EPO		HR ☐ OR ☐ RR ☐		HR ☐ OR ☐ RR ☐	
Intervention vs. control		SE ☐ CI ☐		SE ☐ CI ☐	
Adverse effects *		HR ☐ OR ☐ RR ☐		HR ☐ OR ☐ RR ☐	
Intervention vs. control		SE ☐ CI ☐		SE ☐ CI ☐	

CI: confidence interval; SE: standard error; HR: hazard's ratio; OR: odd's ratio; RR: risk ratio.
Hgb: haemoglobin; EPO: Erythropoietin.
* Number of patients reported to be affected by Pentoxiphylline adverse effects.