BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043436
Article Type:	Original research
Date Submitted by the Author:	04-Aug-2020
Complete List of Authors:	Wei, Ling; Second Xiangya Hospital, Department of Nephrology Zhang, Weizhi; Second Xiangya Hospital, Department of Cardiothoracic Surgery Yang, Yifeng; Second Xiangya Hospital, Department of Cardiothoracic Surgery Li, Dongping; Second Xiangya Hospital, Department of Cardiothoracic Surgery
Keywords:	Radiation biology < RADIOTHERAPY, Interventional radiology < RADIOLOGY & IMAGING, Acute renal failure < NEPHROLOGY, Coronary intervention < CARDIOLOGY

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Pentoxifylline for the prevention of contrast-induced nephropathy: systematic review and meta-analysis of randomized controlled trials

Ling Wei[1], Weizhi Zhang[2], Yifeng Yang[2], Dongping Li[2]

[1] Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China;

[2] Department of Cardiothoracic Surgery, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

Correspondence: Dongping Li

Department of Cardiothoracic Surgery

The Second Xiangya Hospital of Central South University

139 Middle Renmin Road, Changsha, Hunan, 410011, China

Tel: (+86) 731-8529-6106

Fax: (+86) 731-8529-6606

Email: dongpingli@csu.edu.cn

Abstract:

Objectives: To summarize current evidence of pentoxifylline for the prevention of contrast-induced nephropathy

Methods: PubMed, Embase and CENTRAL database were searched for randomized controlled trials on patients with and without pentoxifylline undergoing contrast media exposure. We analyze the incidence of contrast-induced nephropathy and serum creatinine change before and after contrast media exposure. All statistical analyses were conducted with Review Manager v.5.3.

Results: We finally enrolled in seven randomized controlled trials with a total of 1484 patients in this analysis. There is no significant reduction in contrast-induced nephropathy rate observed in the patients treated with pentoxifylline compared to the control groups (OR 0.81, 95%CI 0.57, 1.13, I2=0, p=0.21). However, it is interesting to note that perioperative therapy of pentoxifylline did reduce serum creatinine change compared to the control groups (MD -0.02; 95%CI -0.03,-0.02, I2=0, p<0.00001).

Conclusion: Perioperative administration of pentoxifylline to patients undergoing angioplasty significantly lower serum creatinine increase but did not significantly reduce the development of contrast-induced nephropathy. Pentoxifylline might be a potential agent for renoprotection to contrast-induced nephropathy.

Keywords: pentoxifylline, contrast-induced nephropathy, angioplasty, serum creatinine change

Strengths and limitations of this study

1. This is the first meta-analysis to summarize current evidence of pentoxifylline for the prevention of contrast-induced nephropathy
2. The results was reported according to PRISMA checklist and Cochrane handbook.
3. Given the small number of trials included in each analysis, we fail to assess the publication bias and small study effects with funnel plots.

Introduction

Contrast-induced acute kidney injury, which is also known as Contrast-induced nephropathy (CIN), is defined as the development of acute kidney injury (AKI) following contrast medium exposure, without an alternative etiology [1]. With the wide application of cardiac catheterizations and nearly 30 million doses of contrast media injection annually [2], CIN constitutes the third leading cause of hospital-acquired AKI [3]. CIN is associated with the in-hospital need for dialysis, long-term kidney failure and overall mortality, and consequently prolong hospital stay and increase the cost of hospitalization [4]. Even if serum creatinine (Scr) would recover to the baseline quickly in most CIN patients, they still suffer worse long-term outcomes than these without CIN [5]. In light of the vast threaten to people's health and public costs, it has become imperative to carry out work on the prevention of CIN.

Pentoxifylline (PTX) is a methyl-xanthine derivative with powerful properties of antioxidation, anti-inflammation and anti-immunity. It is generally used to treat peripheral vascular diseases. PTX improves the flexibility and oxygen delivery capacity of the red blood cell, resulting in the improvement of hemodynamics. Besides, studies in animal models showed that PTX could effectively attenuate kidney injury induced by contrast media or Escherichia coli [6, 7]. In fact, several clinical trials suggested that PTX may be a potential candidate for renal protection [8-10].

PTX has been investigated in randomized controlled trials (RCTs) as a potential agent to prevent CIN [11-17]. However, neither systematic reviews nor meta-analyses have been conducted to date to the best of our knowledge. Therefore, we perform this systematic review and meta-analysis of currently available RCTs to summarize and evaluate the renal protective capacity of PTX under contrast media stress.

Material and methods

Search strategy

We searched electronic databases (PubMed, Embase and Cochrane Central Register of Controlled Trials (Central)) for potential clinical trials up to 29 June 2020 with no language

restriction, using combinations of the main terms “contrast-induced nephropathy” and “pentoxifylline”. The details of the search strategy were shown in Appendix.1. Two authors (LW and DL) performed the literature search independently. We also checked relevant reviews and the reference lists of the original articles for further suitable publications.

Study selection

LW and DL independently screened the titles, abstracts or full texts and assessed their eligibility. We included studies that met the following criteria: RCTs enrolled population underwent contrast media exposure; trials used PTX for prevention of CIN; and trials reported CIN rate and/or Scr change after exposure. The exclusion criteria were: animal studies; non RCTs; lack of necessary data. Any disagreements were resolved by discussion with a third author (ZW).

Data extraction

Two independent reviewers (LW and DL) extracted data from each eligible study. Data extracted from studies included study characteristics, patient characteristics, details regarding PTX groups and control groups, and outcome assessments. Outcomes of interest for this study were the incidence of CIN and Scr change after exposure.

Risk of bias

The risk of bias was assessed through the Cochrane Collaboration Tool. Six domains were evaluated: sequence generation for randomization, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Suppose one or more items rated as having a high risk of bias, or multiple items rated as “unclear risk”, studies were classified as “high risk”. Studies were classified as “low risk” when all components were rated as “low risk”.

Outcomes

The primary outcome was the incidence of CIN, defined as a minimum 0.5mg/dl or 25% increase in Scr 48h after contrast media exposure. The secondary outcomes were Scr change

after exposure, defined as the difference between Scr after and before the procedure; hospital mortality and the new requirement for dialysis.

Statistical analysis

Meta-analysis was performed using Review Manager 5.3. We used Chi^2 and I^2 were used to verify the heterogeneity among the studies. Values of the index of under 25%, between 25% and 50%, and over 50% indicated low, moderate, and high heterogeneity, respectively. Statistical significance of heterogeneity was set at a p-value of 0.05. If no substantial heterogeneity was observed ($p \geqslant 0.05$ or $I2 < 50\%$), the fixed-effect model was used.Conversely, we presented the results with the random effect model. Mean difference (MD) and Odds ratio (OR) with the 95% confidence interval (CI) were used to evaluate the continuous and binary variables, respectively. Sensitivity analysis was performed to detect the robustness and reliability of our results, by sequentially omitting every single study. We used the funnel plot to evaluate the potential publication bias.

Results

Study selection and characteristics of included studies

Figure. 1 shown the literature searching process. We found 109 records from the database. After exclusion of duplicates and irrelevant studies, we finally enrolled seven randomized controlled trials [11-17] with a total of 1484 patients in this meta-analysis. Characteristics of the included trials were presented in Table. 1. All of 7 included studies were performed in patients undergoing angioplasty or stenting. Five of seven trials enrolled ordinary patients [11-15]; one study enrolled diabetic patients [16,] and the remaining one enrolled high-risk patients [17]. There were 740 patients in the PTX groups and 744 in the control groups.

Primary outcome

Data on the incidence of CIN were available in all studies included in this meta-analysis. The overall rate of CIN were 8.8% and 10.4% in the PTX groups and control groups, respectively. However, there is no significant reduction in CIN rate was observed in the patients treated with

PTX compared to the control groups (OR 0.81, 95%CI 0.57, 1.13, I2=0, p=0.21) (Figure. 2). Similarly, incidences of CIN were also comparable between groups in the ordinary patients subgroups (OR 0.79, 95%CI 0.56, 1.12, I2=8%, p=0.19) (Figure. 3).

Secondary outcome

Data on Scr change after exposure were available in four of seven trials [13, 15-17] included in this meta-analysis. Figure. 4 presented that the PTX groups had lower Scr increase after contrast media exposure compared to the control groups (MD -0.02; 95%CI -0.03,-0.02, I2=0, p<0.00001). All studies reported that no hospital mortality and the new requirement for dialysis during the trials.

Risk of bias assessment and sensitivity analysis

The risk of bias is presented in Figure.2. The randomization procedure was not described in three studies [11, 14, 15]. Six studies did not use the placebo as control and were thus not blinded [11-16]. However, as the development of CIN and Scr change are objectively defined, and hence less likely to bias. Outcome assessors in all trials were blinded to the trial protocol. All trials were free of selective outcome reporting.

Given the limited number of studies included in this meta-analysis, the funnel plot is not applicable for evaluating the publication bias and small-study effects.

Sensitivity analysis was performed by sequentially omitting every single study. CIN rate remained comparable between groups after excluded each trial, indicating that our result was reliable and not skewed by a single dominant study.

Discussion

This is the first systematic review and meta-analysis to summarized current evidence of PTX for the prevention of CIN. The results suggested that perioperative administration of PTX to patients undergoing angioplasty or PCI significantly lower Scr increase but did not significantly reduce the development of AKI.

Our primary outcome was the incidence of CIN. There was no significant impact of PTX on this predefined primary outcome. A reasonable explanation was that although we pooled 7 studies with a total of 1484 patients in this meta-analysis, the number of CIN rates was limited. Therefore, the CIs for CIN prevention effect of PTX treatment are wide and so its renoprotective effects may be underestimated in the included trials. Consequently, more trials with larger sample sizes are needed to evaluate the role of PTX in CIN prevention.

However, it is interesting to note that perioperative therapy of PTX did reduce Scr change. In a database analysis, Weisbord and colleagues reported that even a small increase of the post-operation Scr had been associated with adverse outcomes in the coronary arteriography population [18]. Losito and colleagues also showed that the increase of Scr below the AKI threshold is still closely correlated with increased long-term mortality [19]. Therefore, PTX's impact on Scr may raise growing interest in future studies as a potential agent for renoprotection to CIN. Besides, compared with de novo drug development for CIN prevention, repurposing PTX obviously saves money and time, and it can be speedily applied in clinical practice.

CIN is a kind of AKI with complex and poorly understood mechanisms. Several studies have found that contrast media would lead to renal vascular contraction and subsequently decrease of peripheral medullary blood flow, resulting in renal tubular anoxia and oxidative stress injury [20-22]. Besides, a higher concentration of contrast agent in the renal tubular leads to viscosity increase and result in tubule blocked [23]. PTX is a methyl-xanthine derivative with multiple biochemical properties and is commonly used to treat peripheral vascular disease caused by peripheral vascular disease [24]. PTX is a non-selective inhibition of phosphodiesterases, which can increase the intracellular levels of cAMP, leading to an improvement of oxygen delivery and a decrease of oxygen free radicals production [25]. This property, together with its capability of reducing blood viscosity and therefore increasing intraglomerular pressure [26], supporting the speculation on underlying renoprotective effects of PTX.

The present study had several limitations. First, most studies use Scr to evaluate the renal function, and only 3 trials reported Scr changes before and after contrast media exposure. Future studies should use more sensitive markers to assess the renal function, allowing a

comprehensive evaluation of the renal condition. Second, given the small number of trials included in each analysis, we fail to assess the publication bias and small study effects with funnel plots. Third, it would have been interesting to know if PTX treatment in subgroups such as the elderly and women would also be favorable compared to control. However, we failed to make a subgroup analysis because of lacking data.

Conclusion

Perioperative administration of PTX to patients undergoing PCI or angioplasty significantly lower Scr increase but did not significantly reduce the development of CIN. PTX might be a potential agent for renoprotection to CIN.

Acknowledgments

None

Disclosure

The author reports no conflicts of interest in this work.

Funding

This study was supported by the National Natural Science Foundation of China （2017YFC1308102）

Patient and public involvement

Since this is a meta-analysis, no patient and public involved in the design and the implementation of this study.

Author's Contributions

(I)Conception and design: D.L (II) Administrative support: Y.Y and W.Z (III) Provision of study materials or patients: L.W and D.L (IV) Collection and assembly of data: L.W and D.L (V) Data analysis and interpretation: L.W and D.L (VI) Manuscript writing: All authors (VII) Final approval of manuscript: All authors

Word count: 3155

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Table 1 Baseline characteristics of included studies.

Study ID	PTX dosage regimen	Contrast media	CIN definition	Number		Outcomes	CIN number	
				PTX	Control		PTX	Control
Firouzi 2012	400mg/Tid from 24h before to 24h after procedure	Ultravist/ Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	140	146	CIN rate	12	20
Shakeryan 2013	400mg/Tid from 24h before to 24h after procedure	Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	164	164	CIN rate	14	23
Yavari 2014	400mg/Tid from 24h before to 24h after procedure	Visipaque	Minimum 25% increase in Scr 48h after procedure	97	102	CIN rate/ ∆ Scr	6	6
Firouzi 2015	400mg/Tid from the initiation of the study to 24h after procedure	Ultravist/ Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	148	148	CIN rate	18	22
Eshraghi 2016	400mg/Tid from the initiation of the study to 24h after procedure	Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	91	84	CIN rate/ ∆ Scr	6	8
Aslanabadi 2019	1200mg /once 2-4h before ptocedure	Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 24h after procedure	45	45	CIN rate/ ∆ Scr	4	3
Barzi 2019	400mg/Tid from 24h before to 48h after procedure	Visipaque 320	Minimum 0.5mg/dl increase in Scr 24h after procedure	55	55	CIN rate/ ∆ Scr	2	2

Notes: Tid, Three Times a Day; ∆ Scr, serum creatinine change before and after contrast media exposure

Abbreviations: CIN, contrast-induced nephropathy; Scr, serum creatinine

Figure legends

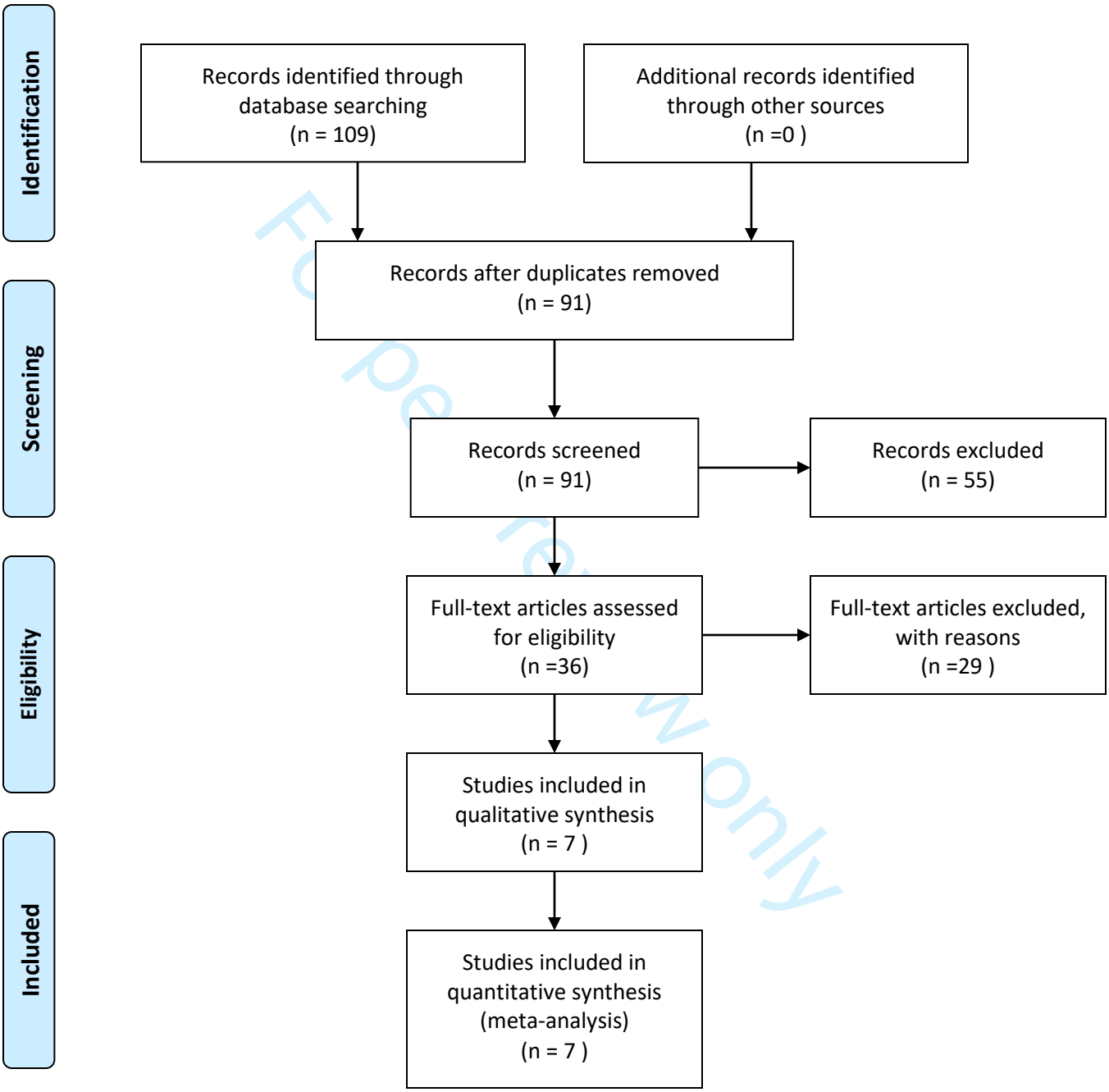
Figure 1 Flow chart of the literature searching process.

Figure. 2 Evaluation of the incidence of contrast-induced nephropathy between the pentoxifylline group and the control.

Figure. 3 Evaluation of the incidence of contrast-induced nephropathy in the ordinary patient subgroups between the pentoxifylline group and the control.

Figure. 4 Evaluation of the serum creatinine change before and after contrast media exposure between the pentoxifylline group and the control.

PRISMA 2009 Flow Diagram



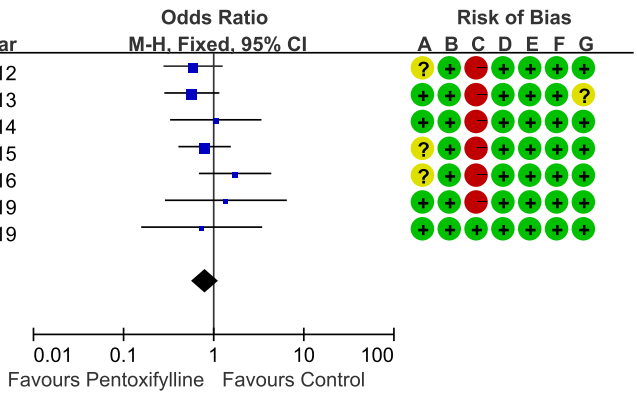
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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

Study or Subgroup	Pentoxifylline Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Firouzi 2012	12	140	20	146	23.2%	0.59 [0.28, 1.26]	2012
Shakeryan 2013	14	164	23	164	27.2%	0.57 [0.28, 1.16]	2013
Yavari 2014	6	97	6	102	7.1%	1.05 [0.33, 3.39]	2014
Firouzi 2015	18	148	22	148	25.0%	0.79 [0.41, 1.55]	2015
Eshraghi 2016	14	91	8	84	9.1%	1.73 [0.69, 4.35]	2016
Aslanabadi 2019	4	45	3	45	3.5%	1.37 [0.29, 6.48]	2019
Barzi 2019	3	55	4	55	4.9%	0.74 [0.16, 3.45]	2019
Total (95% CI)		**740**		**744**	**100.0%**	**0.81 [0.58, 1.13]**	
Total events	71		86				

Heterogeneity: Chi² = 4.83, df = 6 (P = 0.57); I² = 0%

Test for overall effect: Z = 1.26 (P = 0.21)



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

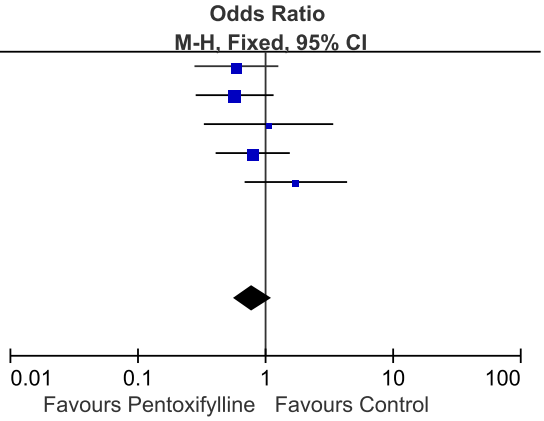
(**F**) Selective reporting (reporting bias)

(**G**) Other bias

Study or Subgroup	Pentoxifylline Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Firouzi 2012	12	140	20	146	25.3%	0.59 [0.28, 1.26]	2012
Shakeryan 2013	14	164	23	164	29.7%	0.57 [0.28, 1.16]	2013
Yavari 2014	6	97	6	102	7.8%	1.05 [0.33, 3.39]	2014
Firouzi 2015	18	148	22	148	27.3%	0.79 [0.41, 1.55]	2015
Eshraghi 2016	14	91	8	84	9.9%	1.73 [0.69, 4.35]	2016
Aslanabadi 2019	4	45	3	45	0.0%	1.37 [0.29, 6.48]	2019
Barzi 2019	3	55	4	55	0.0%	0.74 [0.16, 3.45]	2019
Total (95% CI)		**640**		**644**	**100.0%**	**0.79 [0.56, 1.12]**	
Total events	64		79				

Heterogeneity: Chi² = 4.36, df = 4 (P = 0.36); I² = 8%

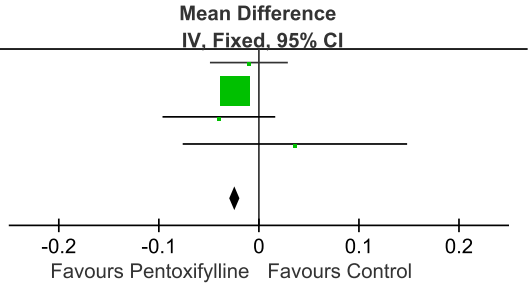
Test for overall effect: Z = 1.32 (P = 0.19)



Study or Subgroup	Pentoxifylline Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Yavari 2014	0.23	0.14	97	0.24	0.14	102	1.5%	-0.01 [-0.05, 0.03]	2014
Eshraghi 2016	0.066	0.011	91	0.09	0.02	84	97.6%	-0.02 [-0.03, -0.02]	2016
Aslanabadi 2019	0.11	0.14	40	0.15	0.11	36	0.7%	-0.04 [-0.10, 0.02]	2019
Barzi 2019	0.03	0.35	55	-0.006	0.24	55	0.2%	0.04 [-0.08, 0.15]	2019
Total (95% CI)			**283**			**277**	**100.0%**	**-0.02 [-0.03, -0.02]**	

Heterogeneity: Chi² = 1.90, df = 3 (P = 0.59); I² = 0%

Test for overall effect: Z = 9.76 (P < 0.00001)



Pubmed

((contrast induced nephropathy[MeSH Terms]) OR (((((("contrast media"[MeSH Terms]) OR ("contrast media"[Title/Abstract])) OR ("contrast meidum"[Title/Abstract])) OR (“contrast material”[Title/Abstract])) AND ((((((((((acute kidney failure[MeSH Terms]) OR (kidney diseases[MeSH Terms])) OR ("kidney diseases")) OR ("nephropathy")) OR ("acute kidney injure")) OR ("kidney disease")) OR ("acute kidney injury")) OR ("acute renal injury")) OR ("renal disease")) OR ("renal diseases")))) AND ((((((("pentoxifylline"[MeSH Terms]) OR ("pentoxifylline"[Title/Abstract])) OR ("oxpentifylline"[Title/Abstract])) OR ("trental"[Title/Abstract])) OR ("Torental"[Title/Abstract])) OR ("BL‐191"[Title/Abstract]))

Embase

Session Results

.....

No.	Query	Results	Date
#12.	#3 AND #11	82	29 Jun 2020
#11.	#4 OR #10	20,804	29 Jun 2020
#10.	#8 AND #9	18,782	29 Jun 2020
#9.	#5 OR #6 OR #7	1,032,150	29 Jun 2020
#8.	'contrast medium'/exp OR 'contrast agent':ti,ab,kw OR 'contrast media':ti,ab,kw OR 'contrast material':ti,ab,kw OR 'contrast medium':ti,ab,kw	195,954	29 Jun 2020
#7.	'kidney disease':ti,ab,kw OR 'nephropathy':ti,ab,kw OR 'acute kidney injury':ti,ab,kw OR 'renal disease':ti,ab,kw OR 'acute renal injury':ti,ab,kw	269,746	29 Jun 2020
#6.	'acute kidney failure'/exp	88,480	29 Jun 2020
#5.	'kidney disease'/exp	1,004,086	29 Jun 2020
#4.	'contrast induced nephropathy'/exp	4,953	29 Jun 2020
#3.	#1 OR #2	14,012	29 Jun 2020
#2.	'pentoxifylline':ti,ab,kw OR 'oxpentifylline':ti,ab,kw OR 'trental':ti,ab,kw OR 'torental':ti,ab,kw OR 'bl‐191':ti,ab,kw	5,902	29 Jun 2020
#1.	'pentoxifylline'/exp	13,629	29 Jun 2020

Central

#1 MeSH descriptor: [Kidney Diseases] explode all trees 15824

#2 ("kidney disease"):ti,ab,kw OR ("nephropathy"):ti,ab,kw OR ("acute kidney injury"):ti,ab,kw OR ("renal disease"):ti,ab,kw OR ("acute renal injury"):ti,ab,kw (Word variations have been searched)24798

#3 MeSH descriptor: [Contrast Media] explode all trees 2673

#4 ("contrast agent"):ti,ab,kw OR ("contrast media"):ti,ab,kw OR ("contrast material"):ti,ab,kw OR ("contrast-medium"):ti,ab,kw (Word variations have been searched) 5166

#5 #1 OR #2 31673

#6 #3 or #4 5166

#7 #5 AND #6 992

#8 MeSH descriptor: [Pentoxifylline] explode all trees 574

#9 ("pentoxifylline"):ti,ab,kw OR ("oxpentifylline"):ti,ab,kw OR ("trental"):ti,ab,kw OR ("Torental"):ti,ab,kw OR ("PTF"):ti,ab,kw (Word variations have been searched) 1380

#10 ("PTXF"):ti,ab,kw OR ("agapurin"):ti,ab,kw OR ("BL - 191"):ti,ab,kw (Word variations have been searched) 10

#11 #8 OR #9 OR #10 1381

#12 #7 AND #11 14

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
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.	N
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.	3-4
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.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3-4
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).	4
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.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
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.	5

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).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
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.	5
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.	5
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).	6
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.	6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6
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).	6-7
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).	7-8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
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.	8

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(7): e1000097. doi:10.1371/journal.pmed1000097

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Pentoxifylline for the prevention of contrast-induced nephropathy: systematic review and meta-analysis of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043436.R1
Article Type:	Original research
Date Submitted by the Author:	17-Nov-2020
Complete List of Authors:	Wei, Ling; Second Xiangya Hospital, Department of Nephrology Zhang, Weizhi; Second Xiangya Hospital, Department of Cardiothoracic Surgery Yang, Yifeng; Second Xiangya Hospital, Department of Cardiothoracic Surgery Li, Dongping; Second Xiangya Hospital, Department of Cardiothoracic Surgery
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Renal medicine
Keywords:	Radiation biology < RADIOTHERAPY, Interventional radiology < RADIOLOGY & IMAGING, Acute renal failure < NEPHROLOGY, Coronary intervention < CARDIOLOGY

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Pentoxifylline for the prevention of contrast-induced nephropathy: systematic review and meta-analysis of randomized controlled trials

Ling Wei[1], Weizhi Zhang[2], Yifeng Yang[2], Dongping Li[2]

[1] Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China;

[2] Department of Cardiothoracic Surgery, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

Correspondence: Dongping Li

Department of Cardiothoracic Surgery

The Second Xiangya Hospital of Central South University

139 Middle Renmin Road, Changsha, Hunan, 410011, China

Tel: (+86) 731-8529-6106

Fax: (+86) 731-8529-6606

Email: dongpingli@csu.edu.cn

Abstract:

Objectives: To summarize current evidence of pentoxifylline for the prevention of contrast-induced nephropathy

Methods: PubMed, Embase and CENTRAL database were searched for randomized controlled trials on patients with and without pentoxifylline undergoing contrast media exposure. We analyze the incidence of contrast-induced nephropathy and serum creatinine change before and after contrast media exposure. All statistical analyses were conducted with Review Manager v.5.3.

Results: We finally enrolled in seven randomized controlled trials with a total of 1484 patients in this analysis. All of 7 included studies were performed in patients undergoing angioplasty or stenting. The overall rate of CIN were 8.8% and 10.4% in the PTX groups and control groups, respectively. However, there is no significant reduction in CIN rate was observed in the patients treated with PTX compared to the control groups (OR 0.81, 95%CI 0.57, 1.13, I^2=0, p=0.21). All studies reported that no hospital mortality and the new requirement for dialysis during the trials.

Conclusion: Perioperative administration of pentoxifylline to patients undergoing angioplasty did not significantly reduce the development of contrast-induced nephropathy, but showed some weak tendency of lower serum creatinine increase. Based on the available trials, the evidence does not support the administration of pentoxifylline for the prevention of contrast-induced nephropathy. More trials with larger sample sizes are needed to evaluate the role of pentoxifylline in contrast-induced nephropathy prevention.

Keywords: pentoxifylline, contrast-induced nephropathy, angioplasty, serum creatinine change

Strengths and limitations of this study

1. This is the first meta-analysis to summarize current evidence of pentoxifylline for the prevention of contrast-induced nephropathy
2. The results was reported according to PRISMA checklist and Cochrane handbook.

3. Given the small number of trials included in each analysis, we fail to assess the publication bias and small study effects with funnel plots.

Introduction

Contrast-induced acute kidney injury, which is also known as Contrast-induced nephropathy (CIN), is defined as the development of acute kidney injury (AKI) following contrast medium exposure, without an alternative etiology [1]. With the wide application of cardiac catheterizations and nearly 30 million doses of contrast media injection annually [2], CIN constitutes the third leading cause of hospital-acquired AKI [3]. CIN is associated with the in-hospital need for dialysis, long-term kidney failure and overall mortality, and consequently prolong hospital stay and increase the cost of hospitalization [4]. Even if serum creatinine (Scr) would recover to the baseline quickly in most CIN patients, they still suffer worse long-term outcomes than these without CIN [5]. In light of the vast threaten to people's health and public costs, it has become imperative to carry out work on the prevention of CIN.

Pentoxifylline (PTX) is a methyl-xanthine derivative with powerful properties of antioxidation, anti-inflammation and anti-immunity. It is generally used to treat peripheral vascular diseases. PTX improves the flexibility and oxygen delivery capacity of the red blood cell, resulting in the improvement of hemodynamics. Besides, studies in animal models showed that PTX could effectively attenuate kidney injury induced by contrast media or Escherichia coli [6, 7]. In fact, several clinical trials suggested that PTX may be a potential candidate for renal protection [8-10].

PTX has been investigated in randomized controlled trials (RCTs) as a potential agent to prevent CIN [11-17]. However, neither systematic reviews nor meta-analyses have been conducted to date to the best of our knowledge. Therefore, we perform this systematic review and meta-analysis of currently available RCTs to summarize and evaluate the renal protective capacity of PTX under contrast media stress.

Material and methods

Search strategy

We searched electronic databases (PubMed, Embase and Cochrane Central Register of Controlled Trials (Central)) for potential clinical trials up to 29 June 2020 with no language restriction, using combinations of the main terms “contrast-induced nephropathy” and “pentoxifylline”. The details of the search strategy were shown in Appendix.1. Two authors (LW and DL) performed the literature search independently. We also checked relevant reviews and the reference lists of the original articles for further suitable publications.

Study selection

LW and DL independently screened the titles, abstracts or full texts and assessed their eligibility. We included studies that met the following criteria: RCTs enrolled population underwent contrast media exposure; trials used PTX for prevention of CIN; and trials reported CIN rate and/or Scr change after exposure. The exclusion criteria were: animal studies; non RCTs; lack of necessary data. Any disagreements were resolved by discussion with a third author (ZW).

Data extraction

Two independent reviewers (LW and DL) extracted data from each eligible study. Data extracted from studies included study characteristics, patient characteristics, details regarding PTX groups and control groups, and outcome assessments. Outcomes of interest for this study were the incidence of CIN and Scr change after exposure.

Risk of bias

The risk of bias was assessed through the Cochrane Collaboration Tool. Six domains were evaluated: sequence generation for randomization, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Suppose one or more items rated as having a high risk of bias, or multiple items rated as “unclear risk”, studies were classified as “high risk”. Studies were classified as “low risk” when all components were rated as “low risk”.

Outcomes

The primary outcome was the incidence of CIN, defined as a minimum 0.5mg/dl or 25% increase in Scr 48h after contrast media exposure. The secondary outcomes were Scr change after exposure, defined as the difference between Scr after and before the procedure; hospital mortality and the new requirement for dialysis. The general population was defined as Mehran score < 11, and the high-risk patients were defined as the population with Mehran score ⩾ 11. Subgroup analysis of low- and high-risk patients was done when possible.

Statistical analysis

Meta-analysis was performed using Review Manager 5.3. We used Chi^2 and I^2 were used to verify the heterogeneity among the studies. Values of the index of under 25%, between 25% and 50%, and over 50% indicated low, moderate, and high heterogeneity, respectively. Statistical significance of heterogeneity was set at a p-value of 0.05. If no substantial heterogeneity was observed (p⩾ 0.05 or I2 < 50%), the fixed-effect model was used.Conversely, we presented the results with the random effect model. Mean difference (MD) and Odds ratio (OR) with the 95% confidence interval (CI) were used to evaluate the continuous and binary variables, respectively. Sensitivity analysis was performed to detect the robustness and reliability of our results, by sequentially omitting every single study. We used the funnel plot to evaluate the potential publication bias.

Results

Study selection and characteristics of included studies

Figure. 1 shown the literature searching process. We found 109 records from the database. After exclusion of duplicates and irrelevant studies （There are 21 reviews, 3 case report, 10 animal study, 5 comments, and 45 no relevant studies）, we finally enrolled seven randomized controlled trials [11-17] with a total of 1484 patients in this meta-analysis. Characteristics of the included trials were presented in Table. 1. All of 7 included studies were performed in

patients undergoing angioplasty or stenting. Five of seven trials enrolled the general population [11-15]; one study enrolled diabetic patients [16,] and the remaining one enrolled high-risk patients [17]. All the enrolled patients were pre-hydrated with normal saline. In addition, Aslanabadi's and Barzi's studies[16-7] used oral 600 mg N-acetyl cysteine twice daily before and after the procedure. There were 740 patients in the PTX groups and 744 in the control groups.

Primary outcome

Data on the incidence of CIN were available in all studies included in this meta-analysis. The overall rate of CIN were 8.8% and 10.4% in the PTX groups and control groups, respectively. However, there is no significant reduction in CIN rate was observed in the patients treated with PTX compared to the control groups (OR 0.81, 95%CI 0.57, 1.13, I2=0, p=0.21) (Figure. 2). Similarly, incidences of CIN were also comparable between groups in the the general population subgroups (OR 0.79, 95%CI 0.56, 1.12, I2=8%, p=0.19) (Figure. 3).

Secondary outcome

Data on Scr change after exposure were available in four of seven trials [13, 15-17] . However, the study report by Eshraghi contributes most data. So the meta -analysis of Scr was waived. All studies reported that no hospital mortality and the new requirement for dialysis during the trials.

Risk of bias assessment and sensitivity analysis

The risk of bias is presented inFigure.4. Six studies did not use the placebo as control and were thus not blinded [11-16]. However, as the development of CIN and Scr change are objectively defined, and hence less likely to bias. Outcome assessors in all trials were blinded to the trial protocol. All trials were free of selective outcome reporting.

Given the limited number of studies included in this meta-analysis, the funnel plot is not applicable for evaluating the publication bias and small-study effects.

Sensitivity analysis was performed by sequentially omitting every single study. CIN rate remained comparable between groups after excluded each trial, indicating that our result was reliable and not skewed by a single dominant study.

Discussion

This is the first systematic review and meta-analysis to summarized current evidence of PTX for the prevention of CIN. The results suggested that perioperative administration of PTX to patients undergoing angioplasty or PCI significantly lower Scr increase but did not significantly reduce the development of AKI.

Our primary outcome was the incidence of CIN. There was no significant impact of PTX on this predefined primary outcome. A reasonable explanation was that although we pooled 7 studies with a total of 1484 patients in this meta-analysis, the number of CIN rates was limited. Therefore, the CIs for CIN prevention effect of PTX treatment are wide and low statistical power results in poor precision. . Consequently, the results of these trails should be cautiously interpreted, and more trials with larger sample sizes are needed to evaluate the role of PTX in CIN prevention.

However, it is interesting to note that perioperative therapy of PTX did reduce Scr change in some studies[13, 15-17], though the reduction was small(just 0.01-0.04 mg/dl) In a database analysis, Weisbord and colleagues reported that even a small increase (0.25 to 0.50 mg/dl) of the post-operation Scr had been associated with adverse outcomes in the coronary arteriography population [18]. Losito and colleagues also showed that the increase of Scr below the AKI threshold (a 20% increase) is still closely correlated with increased long-term mortality [19]. It would be interesting to study that if the reduction of Scr change and adverse outcomes would show a dose-response effect. Therefore, PTX's impact on Scr may raise growing interest in future studies as a potential agent for renoprotection to CIN. Besides, compared with de novo drug development for CIN prevention, repurposing PTX obviously saves money and time, and it can be speedily applied in clinical practice.

Effective prevention strategies and strengthen management are the key to reduce the CIN incidence. Choosing the optimal contrast medium, reducing contrast volume, and personalized hydration are direct and effective strategies to reduce CIN. In addition, remote ischemic preconditioning and statins have potential benefits for patients at risk for CIN, but their efficacy needs further study[20-26].

CIN is a kind of AKI with complex and poorly understood mechanisms. Several studies have found that contrast media would lead to renal vascular contraction and subsequently decrease of peripheral medullary blood flow, resulting in renal tubular anoxia and oxidative stress injury [27-28-]. Besides, a higher concentration of contrast agent in the renal tubular leads to viscosity increase and result in tubule blocked[29]. PTX is a methyl-xanthine derivative with multiple biochemical properties and is commonly used to treat peripheral vascular disease caused by peripheral vascular disease [30]. PTX is a non-selective inhibition of phosphodiesterases, which can increase the intracellular levels of cAMP, leading to an improvement of oxygen delivery and a decrease of oxygen free radicals production[31]. This property, together with its capability of reducing blood viscosity and therefore increasing intraglomerular pressure[32-33], supporting the speculation on underlying renoprotective effects of PTX.

The present study had several limitations. First, most studies use Scr to evaluate the renal function, and only 3 trials reported Scr changes before and after contrast media exposure. Future studies should use more sensitive markers to assess the renal function, allowing a comprehensive evaluation of the renal condition. Second, given the small number of trials included in each analysis, we fail to assess the publication bias and small study effects with funnel plots. Third, it would have been interesting to know if PTX treatment in subgroups such as the elderly and women would also be favorable compared to control. However, we failed to make a subgroup analysis because of lacking data.

Conclusion

Perioperative administration of PTX to patients undergoing PCI or angioplasty significantly lower Scr increase but did not significantly reduce the development of CIN. PTX might be a potential agent for renoprotection to CIN.

Acknowledgments

None

Disclosure

The author reports no conflicts of interest in this work.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information

Funding

This study was supported by the National Natural Science Foundation of China （2017YFC1308102）

Patient and public involvement

Since this is a meta-analysis, no patient and public involved in the design and the implementation of this study.

Author's Contributions

(I)Conception and design: D.L (II) Administrative support: Y.Y and W.Z (III) Provision of study materials or patients: L.W and D.L (IV) Collection and assembly of data: L.W and D.L (V) Data

analysis and interpretation: L.W and D.L (VI) Manuscript writing: All authors (VII) Final approval of manuscript: All authors

Word count: 3622

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33. Dettelbach HR, Aviado DM. Clinical pharmacology of pentoxifylline with special reference to its hemorrheologic effect for the treatment of intermittent claudication. *J Clin Pharmacol.* 1985;25(1):8-26.

Table 1 Baseline characteristics of included studies.

Study ID	PTX dosage regimen	Contrast media	CIN definition	Number		Outcomes	CIN number	
				PTX	Control		PTX	Control
Firouzi 2012	400mg/Tid from 24h before to 24h after procedure	Ultravist/ Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	140	146	CIN rate	12	20
Shakeryan 2013	400mg/Tid from 24h before to 24h after procedure	Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	164	164	CIN rate	14	23
Yavari 2014	400mg/Tid from 24h before to 24h after procedure	Visipaque	Minimum 25% increase in Scr 48h after procedure	97	102	CIN rate/ ∆ Scr	6	6
Firouzi 2015	400mg/Tid from the initiation of the study to 24h after procedure	Ultravist/ Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	148	148	CIN rate	18	22
Eshraghi 2016	400mg/Tid from the initiation of the study to 24h after procedure	Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	91	84	CIN rate/ ∆ Scr	6	8
Aslanabadi 2019	1200mg /once 2-4h before ptocedure	Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 24h after procedure	45	45	CIN rate/ ∆ Scr	4	3
Barzi 2019	400mg/Tid from 24h before to 48h after procedure	Visipaque 320	Minimum 0.5mg/dl increase in Scr 24h after procedure	55	55	CIN rate/ ∆ Scr	2	2

Notes: Tid, Three Times a Day; ∆ Scr, serum creatinine change before and after contrast media exposure

Abbreviations: CIN, contrast-induced nephropathy; Scr, serum creatinine

Figure legends

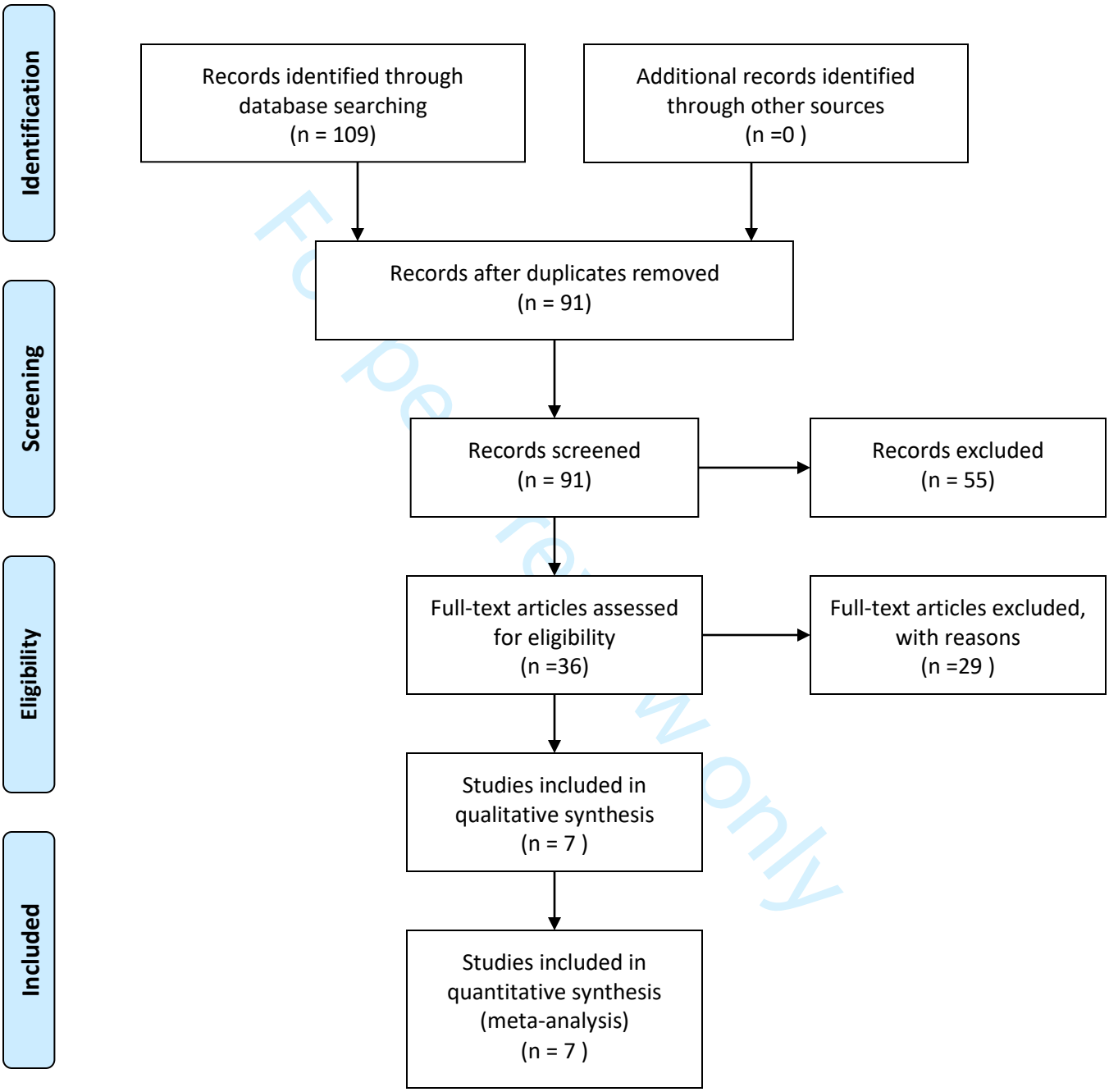
Figure 1 Flow chart of the literature searching process.

Figure. 2 Evaluation of the incidence of contrast-induced nephropathy between the pentoxifylline group and the control.

Figure. 3 Evaluation of the incidence of contrast-induced nephropathy in the the general population **subgroups between the pentoxifylline group and the control.**

Figure. 4 Risk of bias assessment of included studies..

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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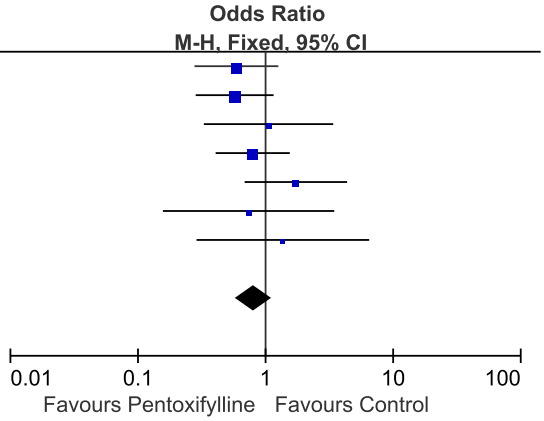
Study or Subgroup	Pentoxifylline Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Firouzi 2012	12	140	20	146	23.2%	0.59 [0.28, 1.26]	2012
Shakeryan 2013	14	164	23	164	27.2%	0.57 [0.28, 1.16]	2013
Yavari 2014	6	97	6	102	7.1%	1.05 [0.33, 3.39]	2014
Firouzi 2015	18	148	22	148	25.0%	0.79 [0.41, 1.55]	2015
Eshraghi 2016	14	91	8	84	9.1%	1.73 [0.69, 4.35]	2016
Barzi 2019	3	55	4	55	4.9%	0.74 [0.16, 3.45]	2019
Aslanabadi 2019	4	45	3	45	3.5%	1.37 [0.29, 6.48]	2019
Total (95% CI)		**740**		**744**	**100.0%**	**0.81 [0.58, 1.13]**	
Total events	71		86				

Heterogeneity: Chi² = 4.83, df = 6 (P = 0.57); I² = 0%

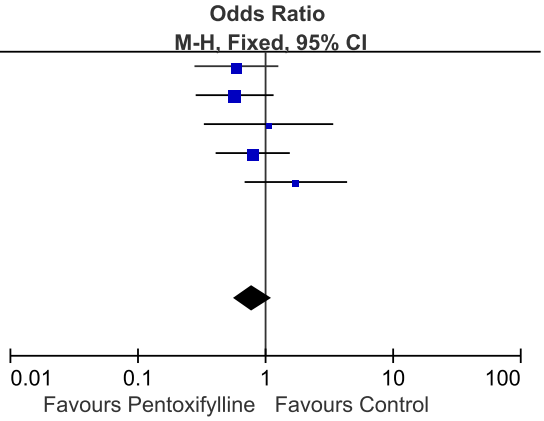
Test for overall effect: Z = 1.26 (P = 0.21)

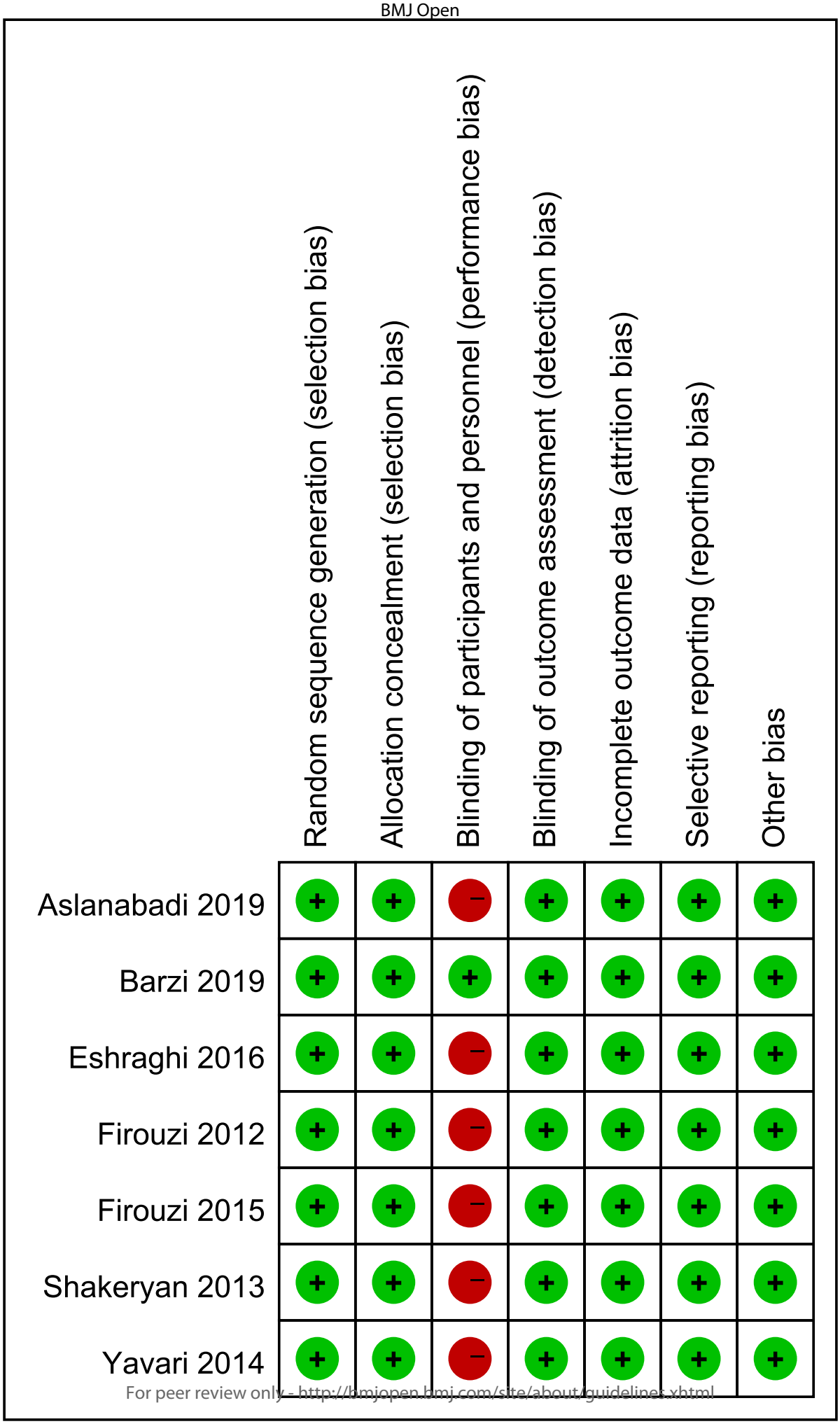


Study or Subgroup	Pentoxifylline Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Firouzi 2012	12	140	20	146	25.3%	0.59 [0.28, 1.26]	2012
Shakeryan 2013	14	164	23	164	29.7%	0.57 [0.28, 1.16]	2013
Yavari 2014	6	97	6	102	7.8%	1.05 [0.33, 3.39]	2014
Firouzi 2015	18	148	22	148	27.3%	0.79 [0.41, 1.55]	2015
Eshraghi 2016	14	91	8	84	9.9%	1.73 [0.69, 4.35]	2016
Aslanabadi 2019	4	45	3	45	0.0%	1.37 [0.29, 6.48]	2019
Barzi 2019	3	55	4	55	0.0%	0.74 [0.16, 3.45]	2019
Total (95% CI)		**640**		**644**	**100.0%**	**0.79 [0.56, 1.12]**	
Total events	64		79				

Heterogeneity: Chi² = 4.36, df = 4 (P = 0.36); I² = 8%

Test for overall effect: Z = 1.32 (P = 0.19)




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Aslanabadi 2019
Barzi 2019
Eshraghi 2016
Firouzi 2012
Firouzi 2015
Shakeryan 2013
Yavari 2014

Pubmed

((contrast induced nephropathy[MeSH Terms]) OR (((((("contrast media"[MeSH Terms]) OR ("contrast media"[Title/Abstract])) OR ("contrast meidum"[Title/Abstract])) OR (“contrast material”[Title/Abstract])) AND ((((((((((acute kidney failure[MeSH Terms]) OR (kidney diseases[MeSH Terms])) OR ("kidney diseases")) OR ("nephropathy")) OR ("acute kidney injure")) OR ("kidney disease")) OR ("acute kidney injury")) OR ("acute renal injury")) OR ("renal disease")) OR ("renal diseases")))) AND ((((((("pentoxifylline"[MeSH Terms]) OR ("pentoxifylline"[Title/Abstract])) OR ("oxpentifylline"[Title/Abstract])) OR ("trental"[Title/Abstract])) OR ("Torental"[Title/Abstract])) OR ("BL‐191"[Title/Abstract]))

Embase

Session Results

.....

No.	Query	Results	Date
#12.	#3 AND #11	82	29 Jun 2020
#11.	#4 OR #10	20,804	29 Jun 2020
#10.	#8 AND #9	18,782	29 Jun 2020
#9.	#5 OR #6 OR #7	1,032,150	29 Jun 2020
#8.	'contrast medium'/exp OR 'contrast agent':ti,ab,kw OR 'contrast media':ti,ab,kw OR 'contrast material':ti,ab,kw OR 'contrast medium':ti,ab,kw	195,954	29 Jun 2020
#7.	'kidney disease':ti,ab,kw OR 'nephropathy':ti,ab,kw OR 'acute kidney injury':ti,ab,kw OR 'renal disease':ti,ab,kw OR 'acute renal injury':ti,ab,kw	269,746	29 Jun 2020
#6.	'acute kidney failure'/exp	88,480	29 Jun 2020
#5.	'kidney disease'/exp	1,004,086	29 Jun 2020
#4.	'contrast induced nephropathy'/exp	4,953	29 Jun 2020
#3.	#1 OR #2	14,012	29 Jun 2020
#2.	'pentoxifylline':ti,ab,kw OR 'oxpentifylline':ti,ab,kw OR 'trental':ti,ab,kw OR 'torental':ti,ab,kw OR 'bl‐191':ti,ab,kw	5,902	29 Jun 2020
#1.	'pentoxifylline'/exp	13,629	29 Jun 2020

Central

#1 MeSH descriptor: [Kidney Diseases] explode all trees 15824

#2 ("kidney disease"):ti,ab,kw OR ("nephropathy"):ti,ab,kw OR ("acute kidney injury"):ti,ab,kw OR ("renal disease"):ti,ab,kw OR ("acute renal injury"):ti,ab,kw (Word variations have been searched)24798

#3 MeSH descriptor: [Contrast Media] explode all trees 2673

#4 ("contrast agent"):ti,ab,kw OR ("contrast media"):ti,ab,kw OR ("contrast material"):ti,ab,kw OR ("contrast-medium"):ti,ab,kw (Word variations have been searched) 5166

#5 #1 OR #2 31673

#6 #3 or #4 5166

#7 #5 AND #6 992

#8 MeSH descriptor: [Pentoxifylline] explode all trees 574

#9 ("pentoxifylline"):ti,ab,kw OR ("oxpentifylline"):ti,ab,kw OR ("trental"):ti,ab,kw OR ("Torental"):ti,ab,kw OR ("PTF"):ti,ab,kw (Word variations have been searched) 1380

#10 ("PTXF"):ti,ab,kw OR ("agapurin"):ti,ab,kw OR ("BL - 191"):ti,ab,kw (Word variations have been searched) 10

#11 #8 OR #9 OR #10 1381

#12 #7 AND #11 14

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
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.	N
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.	3-4
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.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3-4
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).	4
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.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
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.	5

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).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
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.	5
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.	5
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).	6
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.	6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6
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).	6-7
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).	7-8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
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.	8

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(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Pentoxifylline for the prevention of contrast-induced nephropathy: systematic review and meta-analysis of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043436.R2
Article Type:	Original research
Date Submitted by the Author:	20-Jan-2021
Complete List of Authors:	Wei, Ling; Second Xiangya Hospital, Department of Nephrology Zhang, Weizhi; Second Xiangya Hospital, Department of Cardiothoracic Surgery Yang, Yifeng; Second Xiangya Hospital, Department of Cardiothoracic Surgery Li, Dongping; Second Xiangya Hospital, Department of Cardiothoracic Surgery
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Renal medicine
Keywords:	Radiation biology < RADIOTHERAPY, Interventional radiology < RADIOLOGY & IMAGING, Acute renal failure < NEPHROLOGY, Coronary intervention < CARDIOLOGY

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Pentoxifylline for the prevention of contrast-induced nephropathy: systematic review and meta-analysis of randomized controlled trials

Ling Wei[1], Weizhi Zhang[2], Yifeng Yang[2], Dongping Li[2]

[1] Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China;

[2] Department of Cardiothoracic Surgery, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

Correspondence: Dongping Li

Department of Cardiothoracic Surgery

The Second Xiangya Hospital of Central South University

139 Middle Renmin Road, Changsha, Hunan, 410011, China

Tel: (+86) 731-8529-6106

Fax: (+86) 731-8529-6606

Email: dongpingli@csu.edu.cn

Abstract:

Objectives: To summarize current evidence on the use of pentoxifylline to prevent contrast-induced nephropathy (CIN).

Methods: The PubMed, Embase and CENTRAL databases were searched for randomized controlled trials including patients with and without pentoxifylline undergoing contrast media exposure. We analyzed the incidence of contrast-induced nephropathy and serum creatinine changes before and after contrast media exposure. All statistical analyses were conducted with Review Manager v.5.3.

Results: We finally enrolled in seven randomized controlled trials with a total of 1484 patients in this analysis. All of 7 included studies were performed in patients undergoing angioplasty or stenting. The overall rates of CIN were 8.8% and 10.4% in the PTX groups and control groups, respectively. However, no significant reduction in the CIN rate was observed in the patients treated with PTX compared to the control groups (OR 0.81, 95%CI 0.57, 1.13, I^2=0, p=0.21). All studies reported no hospital mortality and the new requirement for dialysis during the trials.

Conclusion: Perioperative administration of pentoxifylline to patients undergoing angioplasty did not significantly reduce the development of contrast-induced nephropathy, but showed some weak tendency of lower serum creatinine increase. Based on the available trials, the evidence does not support the administration of pentoxifylline for the prevention of contrast-induced nephropathy. More trials with larger sample sizes are needed to evaluate the role of pentoxifylline in contrast-induced nephropathy prevention.

Keywords: pentoxifylline, contrast-induced nephropathy, angioplasty, serum creatinine change

Strengths and limitations of this study

1. This is the first meta-analysis to summarize current evidence of pentoxifylline for the prevention of contrast-induced nephropathy

2. The results were reported in accordance with the PRISMA checklist and Cochrane handbook.
3. Given the small number of trials included in each analysis, we failed to assess publication bias and small study effects with funnel plots.

Introduction

Contrast-induced acute kidney injury, which is also known as contrast-induced nephropathy (CIN), is defined as the development of acute kidney injury (AKI) following contrast medium exposure, without an alternative etiology [1]. With the wide application of cardiac catheterizations and nearly 30 million doses of contrast media injection annually [2], CIN constitutes the third leading cause of hospital-acquired AKI [3]. CIN is associated with the in-hospital need for dialysis, long-term kidney failure and overall mortality, and consequently prolongs hospital stay and increases the cost of hospitalization [4]. Even if serum creatinine (Scr) would recover to the baseline quickly in most CIN patients, these patients still suffer worse long-term outcomes than those without CIN [5]. In light of the vast threaten to people's health and public costs, it has become imperative to research the prevention of CIN.

Pentoxifylline (PTX) is a methyl-xanthine derivative with powerful antioxidative, anti-inflammatory and anti-immunity properties . It is generally used to treat peripheral vascular diseases. PTX improves the flexibility and oxygen delivery capacity of red blood cells, resulting in improved hemodynamics. In addition, studies in animal models showed that PTX could effectively attenuate kidney injury induced by contrast media or Escherichia coli [6, 7]. In fact, several clinical trials have suggested that PTX may be a potential candidate for renal protection [8-10].

PTX has been investigated in randomized controlled trials (RCTs) as a potential agent to prevent CIN [11-17]. However, neither systematic reviews nor meta-analyses have been conducted to date to the best of our knowledge. Therefore, we performed this systematic review and meta-analysis of currently available RCTs to summarize and evaluate the renal protective capacity of PTX under contrast media stress.

Material and methods

Search strategy

We searched electronic databases (PubMed, Embase and Cochrane Central Register of Controlled Trials (Central)) for potential clinical trials up to 29 June 2020 with no language restriction, using combinations of the main terms “contrast-induced nephropathy” and “pentoxifylline”. The details of the search strategy are shown in Appendix.1. Two authors (LW and DL) performed the literature search independently. We also checked relevant reviews and the reference lists of the original articles for further suitable publications.

Study selection

LW and DL independently screened the titles, abstracts or full texts and assessed their eligibility. We included studies that met the following criteria: RCTs enrolled population underwent contrast media exposure; trials used PTX for prevention of CIN; and trials reported CIN rate and/or Scr change after exposure. The exclusion criteria were: animal studies; non-RCTs; lack of necessary data. Any disagreements were resolved by discussion with a third author (ZW).

Data extraction

Two independent reviewers (LW and DL) extracted data from each eligible study. Data extracted from studies included study characteristics, patient characteristics, details regarding PTX groups and control groups, and outcome assessments. Outcomes of interest for this study were the incidence of CIN and Scr changes after exposure.

Risk of bias

The risk of bias was assessed through the Cochrane Collaboration Tool. Six domains were evaluated: sequence generation for randomization, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. According to Cochrane Handbook[18], The risk of biases are classified into three categories, low risk, unclear risk, and high risk. Low risk meant all categories were classified as low risk. Unclear risk means one category

was classified as unclear risk. High risk means high risk of bias in one or more categories or an unclear risk in two or more categories.

Outcomes

The primary outcome was the incidence of CIN, defined as a minimum 0.5 mg/dl or 25% increase in Scr 48 h after contrast media exposure. The secondary outcomes were Scr change after exposure, defined as the difference between Scr after and before the procedure; hospital mortality and the new requirement for dialysis. The general population was defined as having a Mehran score < 11, and the high-risk patients were defined as the population with Mehran score ⩾ 11. Subgroup analysis of low- and high-risk patients was performed when possible.

Statistical analysis

Meta-analysis was performed using Review Manager 5.3. We used Chi^2 and I^2 to verify the heterogeneity among the studies. Values of the index of under 25%, between 25% and 50%, and over 50% indicated low, moderate, and high heterogeneity, respectively. Statistical significance of heterogeneity was set at a p-value of 0.05. If no substantial heterogeneity was observed (p⩾ 0.05 or I2 < 50%), the fixed-effect model was used.Conversely, we presented the results with the random effect model. Mean difference (MD) and odds ratio (OR) with the 95% confidence interval (CI) were used to evaluate the continuous and binary variables, respectively. Sensitivity analysis was performed to detect the robustness and reliability of our results, by sequentially omitting every single study. We used the funnel plot to evaluate the potential publication bias.

Results

Study selection and characteristics of included studies

Figure. 1 shown the literature searching process. We found 109 records from the database. After exclusion of duplicates and irrelevant studies (21 reviews, 3 case reports, 10 animal studieds, 5 comments, and 45 no relevant studies), we finally enrolled seven randomized controlled trials [11-17] with a total of 1484 patients in this meta-analysis. The characteristics of the

included trials were presented in Table. 1. All of 7 included studies were performed in patients undergoing angioplasty or stenting. Five of seven trials enrolled patients from the general population [11-15]; one study enrolled diabetic patients [16,] and the remaining s6tudy enrolled high-risk patients [17]. All the enrolled patients were pre-hydrated with normal saline. In addition, Aslanabadi's and Barzi's studies[16-7] used 600 mg N-acetyl cysteine orally twice daily before and after the procedure. There were 740 patients in the PTX group and 744 in the control group.

Primary outcome

Data on the incidence of CIN were available in all studies included in this meta-analysis. The overall rates of CIN were 8.8% and 10.4% in the PTX groups and control groups, respectively. However, no significant reduction in the CIN rate was observed in the patients treated with PTX compared to the control groups (OR 0.81, 95%CI 0.57, 1.13, I2=0, p=0.21) (Figure. 2). Similarly, the incidences of CIN were also comparable between groups in the the general population subgroups (OR 0.79, 95%CI 0.56, 1.12, I2=8%, p=0.19) (Figure. 3).

Secondary outcome

Data on Scr change after exposure were available in four of seven trials [13, 15-17] . However, the study report by Eshraghi contributes most of the data. Thus the meta-analysis of Scr was waived. All studies reported no hospital mortality or the new requirement for dialysis during the trials.

Risk of bias assessment and sensitivity analysis

The risk of bias is presented inFigure.4. Six studies did not use the placebo as control and were thus not blinded [11-16]. However, the development of CIN and Scr changes are objectively defined, and hence less likely to bias. Outcome assessors in all trials were blinded to the trial protocol. All trials were free of selective outcome reporting.

Given the limited number of studies included in this meta-analysis, the funnel plot is not applicable for evaluating the publication bias and small-study effects.

Sensitivity analysis was performed by sequentially omitting every single study. CIN rate remained comparable between groups after excluding each trial, indicating that our results were reliable and not skewed by a single dominant study.

Discussion

This is the first systematic review and meta-analysis to summarize current evidence of PTX for the prevention of CIN. The results suggested that perioperative administration of PTX to patients undergoing angioplasty or PCI significantly lower Scr increase but did not significantly reduce the development of AKI.

Our primary outcome was the incidence of CIN. There was no significant impact of PTX on this predefined primary outcome. A reasonable explanation was that although we pooled 7 studies with a total of 1484 patients in this meta-analysis, the number of CIN rates was limited. Therefore, the CIs for the CIN prevention effect of PTX treatment are wide and low statistical power results in poor precision. Consequently, the results of these trials should be cautiously interpreted, and more trials with larger sample sizes are needed to evaluate the role of PTX in CIN prevention.

However, it is interesting to note that perioperative therapy with PTX did reduce Scr changes in some studies[13, 15-17], althoughthe reduction was small (just 0.01-0.04 mg/dl) In a database analysis, Weisbord and colleagues reported that even a small increase (0.25 to 0.50 mg/dl) in postoperative Scr was associated with adverse outcomes in the coronary arteriography population [19]. Losito and colleagues also showed that the increase in Scr below the AKI threshold (a 20% increase) is still closely correlated with increased long-term mortality [20]. It would be interesting to study whether the reduction of Scr change and adverse outcomes would show a dose-response effect. Therefore, PTX's impact on Scr may raise growing interest in future studies as a potential agent for renoprotection to CIN. Besides, compared with de novo drug development for CIN prevention, repurposing PTX obviously saves money and time, and it can be speedily applied in clinical practice.

Effective prevention strategies and strengthened management are the keys to reduce the CIN incidence. Choosing the optimal contrast medium, reducing contrast volume, and personalized hydration are direct and effective strategies to reduce CIN. In addition, remote ischemic preconditioning and statins have potential benefits for patients at risk for CIN, but their efficacy needs further study[21-27].

CIN is a kind of AKI with complex and poorly understood mechanisms. Several studies have found that contrast media would lead to renal vascular contraction and a subsequent decrease of peripheral medullary blood flow, resulting in renal tubular anoxia and oxidative stress injury [28-29-]. Besides, a higher concentration of contrast agent in the renal tubular leads to viscosity increase and results in tubule blocked[30]. PTX is a methyl-xanthine derivative with multiple biochemical properties and is commonly used to treat peripheral vascular disease caused by peripheral vascular disease [31]. PTX is a nonselective inhibitior of phosphodiesterases, which can increase the intracellular levels of cAMP, leading to an improvement of oxygen delivery and a decrease of oxygen free radicals production[32]. This property, together with its capability of reducing blood viscosity and therefore increasing intraglomerular pressure[33-34], supporting the speculation on underlying renoprotective effects of PTX. Pre- and post-hydration with IV saline or even drinking a few cups of broth can also reduce the blood viscosity. And periprocedural hydration maybe the most effective preventive measure for patients at risk of CIN. However, hydration may increase the risk of heart failure, arrhythmia, and short-term mortality in high-risk patients. Therefore, the reduction in blood viscosity of PTX should not be ignored.

The present study had several limitations. First, most studies used Scr to evaluate the renal function, and only 3 trials reported Scr changes before and after contrast media exposure. Future studies should use more sensitive markers to assess the renal function, allowing a comprehensive evaluation of the renal condition. Second, given the small number of trials included in each analysis, we failed to assess the publication bias and small study effects with funnel plots. Third, it would have been interesting to know if PTX treatment in subgroups such as the elderly and women would also be favorable compared to control. However, we failed to make a subgroup analysis because of lacking data. Fourth, some included studies were single-blinded,

single-center designs, so the possibility of bias cannot be ruled out. However, all studies used objective indicators (e.g. Scr) to evaluate CIN. Nevertheless, a prospective multi-centre, double-blind, placebo-controlled study would make the conclusions more convincing.

Current evidence barely strong enough to support the renoprotection of pentoxifylline to contrast-induced nephropathy. If we assume that the CIN incidence in PTX treated group is 8%, and 11% in control group, with a noninferiority limit of 1.5% with power of at least 80% and 1-side type 1 error rate of 2.5%. More than 1000 participants are needed. More trials with larger sample sizes are needed to evaluate the role of pentoxifylline in contrast-induced nephropathy prevention.

Conclusion

Perioperative administration of pentoxifylline to patients undergoing angioplasty did not significantly reduce the development of contrast-induced nephropathy, but showed some weak tendency of a lower serum creatinine increase. Based on the available trials, the evidence does not support the administration of pentoxifylline for the prevention of contrast-induced nephropathy. More trials with larger sample sizes are needed to evaluate the role of pentoxifylline in contrast-induced nephropathy prevention.

Acknowledgments

None

Disclosure

The author reports no conflicts of interest in this work.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information

Funding

This study was supported by the National Natural Science Foundation of China

（2017YFC1308102）

Patient and public involvement

Since this is a meta-analysis, no patient and public involved in the design and the implementation of this study.

Author's Contributions

(I)Conception and design: D.L (II) Administrative support: Y.Y and W.Z (III) Provision of study materials or patients: L.W and D.L (IV) Collection and assembly of data: L.W and D.L (V) Data analysis and interpretation: L.W and D.L (VI) Manuscript writing: All authors (VII) Final approval of manuscript: All authors

Word count: 3905

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Table 1 Baseline characteristics of included studies.

Study ID	PTX dosage regimen	Contrast media	CIN definition	Number		Outcomes	CIN number	
				PTX	Control		PTX	Control
Firouzi 2012	400mg/Tid from 24h before to 24h after procedure	Ultravist/ Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	140	146	CIN rate	12	20
Shakeryan 2013	400mg/Tid from 24h before to 24h after procedure	Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	164	164	CIN rate	14	23
Yavari 2014	400mg/Tid from 24h before to 24h after procedure	Visipaque	Minimum 25% increase in Scr 48h after procedure	97	102	CIN rate/ ∆ Scr	6	6
Firouzi 2015	400mg/Tid from the initiation of the study to 24h after procedure	Ultravist/ Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	148	148	CIN rate	18	22
Eshraghi 2016	400mg/Tid from the initiation of the study to 24h after procedure	Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 48h after procedure	91	84	CIN rate/ ∆ Scr	6	8
Aslanabadi 2019	1200mg /once 2-4h before ptocedure	Visipaque	Minimum 0.5mg/dl or 25% increase in Scr 24h after procedure	45	45	CIN rate/ ∆ Scr	4	3
Barzi 2019	400mg/Tid from 24h before to 48h after procedure	Visipaque 320	Minimum 0.5mg/dl increase in Scr 24h after procedure	55	55	CIN rate/ ∆ Scr	2	2

Notes: Tid, Three Times a Day; ∆ Scr, serum creatinine change before and after contrast media exposure

Abbreviations: CIN, contrast-induced nephropathy; Scr, serum creatinine

Figure legends

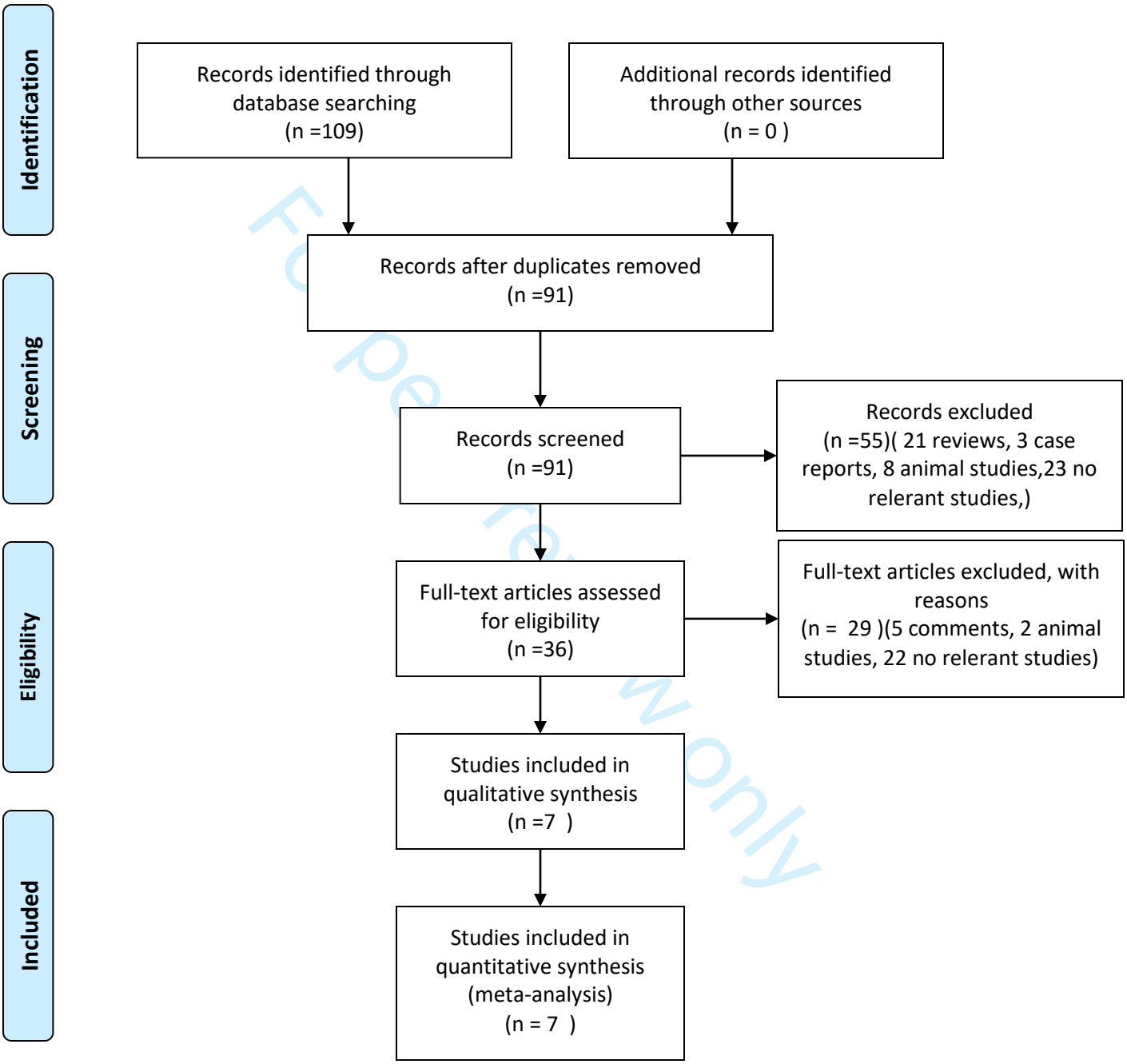
Figure 1 Flow chart of the literature searching process.

Figure. 2 Evaluation of the incidence of contrast-induced nephropathy between the pentoxifylline group and the control.

Figure. 3 Evaluation of the incidence of contrast-induced nephropathy in the the general population **subgroups between the pentoxifylline group and the control.**

Figure. 4 Risk of bias assessment of included studies..

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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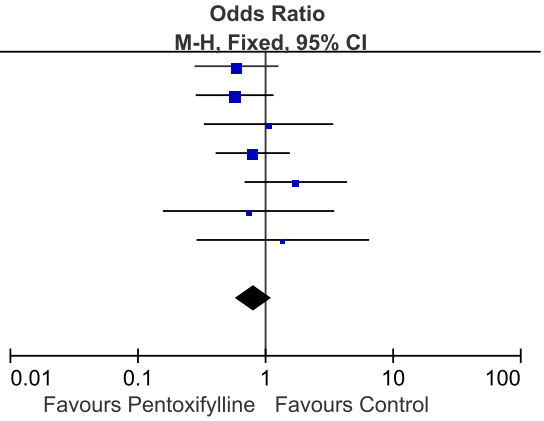
Study or Subgroup	Pentoxifylline Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Firouzi 2012	12	140	20	146	23.2%	0.59 [0.28, 1.26]	2012
Shakeryan 2013	14	164	23	164	27.2%	0.57 [0.28, 1.16]	2013
Yavari 2014	6	97	6	102	7.1%	1.05 [0.33, 3.39]	2014
Firouzi 2015	18	148	22	148	25.0%	0.79 [0.41, 1.55]	2015
Eshraghi 2016	14	91	8	84	9.1%	1.73 [0.69, 4.35]	2016
Barzi 2019	3	55	4	55	4.9%	0.74 [0.16, 3.45]	2019
Aslanabadi 2019	4	45	3	45	3.5%	1.37 [0.29, 6.48]	2019
Total (95% CI)		**740**		**744**	**100.0%**	**0.81 [0.58, 1.13]**	
Total events	71		86				

Heterogeneity: Chi² = 4.83, df = 6 (P = 0.57); I² = 0%

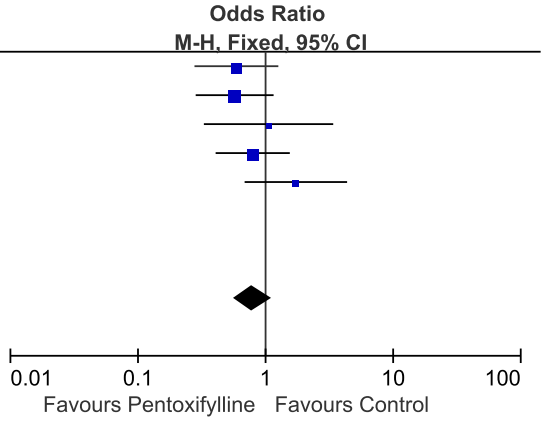
Test for overall effect: Z = 1.26 (P = 0.21)

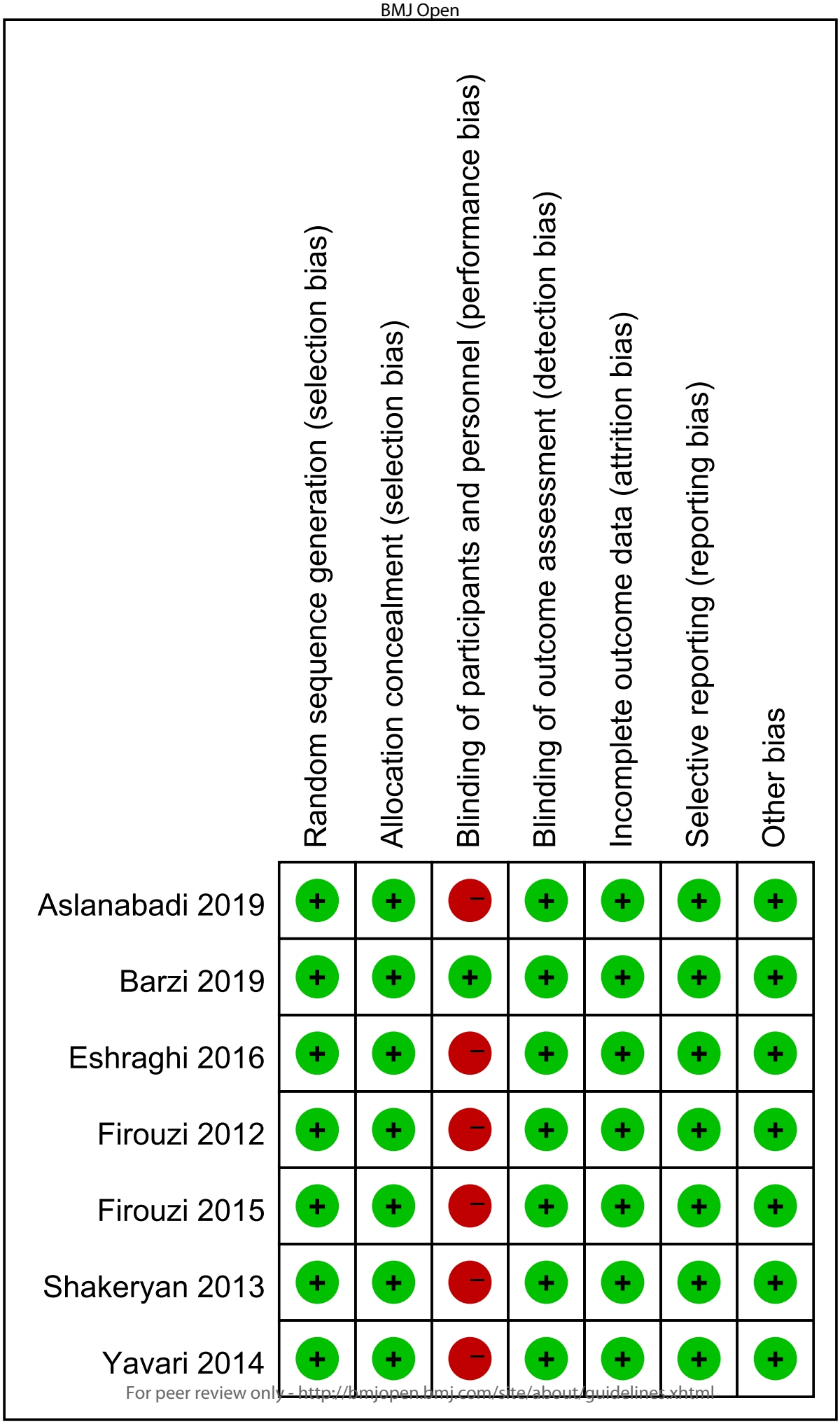


Study or Subgroup	Pentoxifylline Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Firouzi 2012	12	140	20	146	25.3%	0.59 [0.28, 1.26]	2012
Shakeryan 2013	14	164	23	164	29.7%	0.57 [0.28, 1.16]	2013
Yavari 2014	6	97	6	102	7.8%	1.05 [0.33, 3.39]	2014
Firouzi 2015	18	148	22	148	27.3%	0.79 [0.41, 1.55]	2015
Eshraghi 2016	14	91	8	84	9.9%	1.73 [0.69, 4.35]	2016
Aslanabadi 2019	4	45	3	45	0.0%	1.37 [0.29, 6.48]	2019
Barzi 2019	3	55	4	55	0.0%	0.74 [0.16, 3.45]	2019
Total (95% CI)		**640**		**644**	**100.0%**	**0.79 [0.56, 1.12]**	
Total events	64		79				

Heterogeneity: Chi² = 4.36, df = 4 (P = 0.36); I² = 8%

Test for overall effect: Z = 1.32 (P = 0.19)





Pubmed

((contrast induced nephropathy[MeSH Terms]) OR (((((("contrast media"[MeSH Terms]) OR ("contrast media"[Title/Abstract])) OR ("contrast meidum"[Title/Abstract])) OR (“contrast material”[Title/Abstract])) AND ((((((((((acute kidney failure[MeSH Terms]) OR (kidney diseases[MeSH Terms])) OR ("kidney diseases")) OR ("nephropathy")) OR ("acute kidney injure")) OR ("kidney disease")) OR ("acute kidney injury")) OR ("acute renal injury")) OR ("renal disease")) OR ("renal diseases")))) AND ((((((("pentoxifylline"[MeSH Terms]) OR ("pentoxifylline"[Title/Abstract])) OR ("oxpentifylline"[Title/Abstract])) OR ("trental"[Title/Abstract])) OR ("Torental"[Title/Abstract])) OR ("BL‐191"[Title/Abstract]))

Embase

Session Results

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No.	Query	Results	Date
#12.	#3 AND #11	82	29 Jun 2020
#11.	#4 OR #10	20,804	29 Jun 2020
#10.	#8 AND #9	18,782	29 Jun 2020
#9.	#5 OR #6 OR #7	1,032,150	29 Jun 2020
#8.	'contrast medium'/exp OR 'contrast agent':ti,ab,kw OR 'contrast media':ti,ab,kw OR 'contrast material':ti,ab,kw OR 'contrast medium':ti,ab,kw	195,954	29 Jun 2020
#7.	'kidney disease':ti,ab,kw OR 'nephropathy':ti,ab,kw OR 'acute kidney injury':ti,ab,kw OR 'renal disease':ti,ab,kw OR 'acute renal injury':ti,ab,kw	269,746	29 Jun 2020
#6.	'acute kidney failure'/exp	88,480	29 Jun 2020
#5.	'kidney disease'/exp	1,004,086	29 Jun 2020
#4.	'contrast induced nephropathy'/exp	4,953	29 Jun 2020
#3.	#1 OR #2	14,012	29 Jun 2020
#2.	'pentoxifylline':ti,ab,kw OR 'oxpentifylline':ti,ab,kw OR 'trental':ti,ab,kw OR 'torental':ti,ab,kw OR 'bl‐191':ti,ab,kw	5,902	29 Jun 2020
#1.	'pentoxifylline'/exp	13,629	29 Jun 2020

Central

#1 MeSH descriptor: [Kidney Diseases] explode all trees 15824

#2 ("kidney disease"):ti,ab,kw OR ("nephropathy"):ti,ab,kw OR ("acute kidney injury"):ti,ab,kw OR ("renal disease"):ti,ab,kw OR ("acute renal injury"):ti,ab,kw (Word variations have been searched)24798

#3 MeSH descriptor: [Contrast Media] explode all trees 2673

#4 ("contrast agent"):ti,ab,kw OR ("contrast media"):ti,ab,kw OR ("contrast material"):ti,ab,kw OR ("contrast-medium"):ti,ab,kw (Word variations have been searched) 5166

#5 #1 OR #2 31673

#6 #3 or #4 5166

#7 #5 AND #6 992

#8 MeSH descriptor: [Pentoxifylline] explode all trees 574

#9 ("pentoxifylline"):ti,ab,kw OR ("oxpentifylline"):ti,ab,kw OR ("trental"):ti,ab,kw OR ("Torental"):ti,ab,kw OR ("PTF"):ti,ab,kw (Word variations have been searched) 1380

#10 ("PTXF"):ti,ab,kw OR ("agapurin"):ti,ab,kw OR ("BL - 191"):ti,ab,kw (Word variations have been searched) 10

#11 #8 OR #9 OR #10 1381

#12 #7 AND #11 14

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
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.	N
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	4
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.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
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.	5

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).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
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.	5
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.	5
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).	6
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.	5-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6
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).	7
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).	8-9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
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.	10

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(7): e1000097. doi:10.1371/journal.pmed1000097

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