Systematic Review and Meta-Analysis

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Clinical effect of trimetazidine on prevention of contrast-induced nephropathy in patients with renal insufficiency

An updated systematic review and meta-analysis

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Abstract

Background: With the continuous development of cardiac interventional medicine, the incidence of contrast-induced nephropathy (CIN) is increasing every year, which is a serious threat to people's physical and mental health. Trimetazidine (TMZ) is a type of anti-ischemic drug developed in recent years, which can significantly reduce the incidence of CIN. At present, a systematic review and meta-analysis was conducted to evaluate the clinical effect of TMZ on prevention of CIN in patients with renal insufficiency. However, the study did not include patients from other countries and speaking different languages. So we conducted this study to update the previous meta-analysis that investigated the effects of TMZ on prevention of CIN in patients with renal insufficiency, and provided some theoretical reference for clinical.

Methods: By searching PubMed, Embase, the Cochrane Library, Web of Science, CBM, CNKI, VIP database, and Wang Fang database for randomized controlled trial, which is comparing TMZ versus conventional hydration for prevention of CIN. Two researchers independently screened literature, and then evaluated the quality of literature and extracted the relevant data. Stata 11.0 software was used for statistical analysis.

Results: Finally, this updated review showed that 3 studies that were not included in the previous meta-analysis were included in our study (3 articles were published in the Chinese Journal, 1 study for CIN, 1 study for CIN, serum creatinine (Scr), and superoxide dismutase, 1 study for CIN and Scr), and 1 outcome (Scr) reflecting the change of renal function was additionally included in our study. Of the 932 studies, 6 randomized controlled trials met the criteria, including 377 patients in TMZ group and 387 patients in control group. This meta-analysis for all studies showed that TMZ can significantly reduce the incidence of CIN (relative risk 0.27, 95% confidence interval [CI] 0.16, 0.46, $P=0.000$), and can decrease the level of Scr after operation, including Scr of postoperative 24 hours (standardized mean difference [SMD] −0.30, 95% CI −0.51, −0.09, $P=0.005$), Scr of postoperative 48 hours (SMD −0.66, 95% CI −1.23, −0.10, $P=0.022$), and Scr of postoperative 7 days (SMD −0.74, 95% CI −1.36, −0.11, $P=0.021$). However, the Scr of postoperative 72 hours between TMZ group and control group has no statistical significance ($P=0.362$).

Conclusion: Our study showed that when comparing with conventional hydration, TMZ can significantly reduce the incidence of CIN and the level of postoperative Scr. Therefore, we could suggest that TMZ was superior to conventional hydration for the treatment of CIN in patients with renal insufficiency. However, due to the restriction of quality and number of included articles, it still needs to carry out multicenter, randomized, double-blind clinical trials to confirm this conclusion in the future.

Abbreviations: AMI = acute myocardial infarction, CIN = contrast-induced nephropathy, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, Scr = serum creatinine, SOD = superoxide dismutase, TMZ = trimetazidine.

Keywords: contrast-induced nephropathy, meta-analysis, renal insufficiency, systematic review, trimetazidine

1. Introduction

Acute myocardial infarction (AMI)[1,2] is a sharp reduction or interruption of coronary artery blood supply on the basis of coronary artery disease, which makes the corresponding myocardial serious and persistent ischemic necrosis. At present, emergency percutaneous coronary intervention (PCI) is the primary choice in the treatment of AMI.[3–5] It can just open the occluded blood vessel and shorten the total time of ischemia. As we all know, contrast agent[6,7] plays an important role in the operation of PCI. However, with the increasing use of contrast agents, contrast-induced nephropathy (CIN)[8,9] has become the third cause of acute renal failure in a hospital, which has aroused wide attention of clinical cardiovascular physicians.

Research results[10,11] have shown that the total incidence of CIN was about 3% to 14%, and the incidence rate of CIN was higher in high-risk patients with renal failure and diabetes

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mellitus, which was up to 20%. When comparing with elective PCI, the incidence of CIN in emergency PCI was higher. The reason may be linked to the instability of hemodynamics and the inadequate treatment of hydration in patients with AMI, and the contrast agent can lead to the increase of oxygen-free radicals, which can draw up a cytotoxic effect on the renal tubular epithelial cells, thus prolonging the hospital stay, and may lead to the occurrence of long-term adverse events. However, there is no effective treatment for CIN.

Trimetazidine (TMZ)[12–14] is a kind of myocardial metabolism drug, which can promote glucose oxidation in myocytes, and improve myocardial ischemia. At present, some studies have also found that TMZ has the function of antioxidant and ischemia/reperfusion injury. Oxygen-free radical release and ischemic injury are part of the pathogenesis of CIN; through metabolic mechanism, TMZ can enhance mitochondrial activity, reduce the release of oxygen-free radicals, prevent cell lysis and endometrial damage, and decrease the toxicity of contrast agent on renal tubular epithelial cells.

At present, TMZ is widely used in patients undergoing coronary angiography, but the results are not consistent. In 2015, Nadkarni et al[15] performed a meta-analysis in which a randomized controlled trial (RCT) investigated the clinical effect of TMZ on prevention of CIN in patients with renal insufficiency. From this study, we observed that TMZ could significantly reduce the incidence of CIN. However, the previous meta-analysis only included English-language studies, and did not include studies of other languages and from different countries, lacking a certain representation. Furthermore, the previous meta-analysis is 1-year-old, and some prospective cohort studies have been published since 2015. Therefore, we conducted this study to update the previous systematic review and meta-analysis that investigated the clinical effect of TMZ on prevention of CIN in patients with renal insufficiency, and provide some theoretical reference for clinical.

2. Methods

2.1. Literature search

According to the statement of the preferred reporting items for systematic reviews and meta-analyses, 2 researchers independently searched the published article that investigated the clinical effect of TMZ on prevention of CIN in patients with renal insufficiency. The retrieved database including PubMed, Embase, the Cochrane Library, Web of Science, CBM, CNKI, VIP database, and Wang Fang database, the retrieval time limit being from inception to September 10, 2016. Relevant keywords relating to TMZ in combination as MeSH terms and text words ("Centrophène" or "Alpharma Brand of Trimetazidine Dihydrochloride" or "Vastarel" or "Biopharma Brand of Trimetazidine Dihydrochloride" or "Idaptan" or "Danval Brand of Trimetazidine Dihydrochloride" or "Trimétazidine Irex" or "Irex Brand of Trimetazidine Dihydrochloride" or "Vasartel" or "Trimetazidine Dihydrochloride" or "Dihydrochloride, Trimetazidine") were used in combination with words relating to CIN and renal insufficiency ("Renal Insufficiency" or "Renal Insufficiencies" or "Kidney Insufficiency" or "Insufficiency, Kidney" or "Kidney Insufficiencies" or "Kidney Failure" or "Failure, Kidney" or "Failures, Kidney" or "Kidney Failures" or "Renal Failure" or "Failure, Renal" or "Failures, Renal" or "Renal Failures" or "Contrast-induced nephropathy"). The retrieval language was limited to Chinese and English. At the same time, the reference literature of the extracted articles was also retrieved. When multiple studies for a single study were found, we used the latest publication and supplemented it. If it is necessary, with data from the most complete or updated publication. The flow diagram of study selection is shown in Fig. 1. All analyses were based on previously published studies; thus no ethical approval and patient consent is required.

2.2. Study selection

We identified studies that prospectively evaluated the clinical effect of TMZ on prevention of CIN in patients with renal insufficiency. Inclusion criteria included the following: ① the study was limited to RCTs, and the purpose of the study was to evaluate the efficacy of TMZ on the prevention of CIN; ② at least 1 of the observation group was applied TMZ in experiment group; ③ the does and duration time of TMZ were not limited; ④ the article should provide enough data for analyzing; ⑤ the study participants were patients with renal insufficiency, and coronary angiography was performed; ⑥ language type was restricted to Chinese and English only; ⑦ the indexes of all patients before operation were comparable, including age, body mass index (BMI), height, serum creatinine (Scr), and superoxide dismutase (SOD); ⑧ all patients were undergoing coronary angiography or PCI; all of these depended on the results of coronary angiography. Exclusion criteria were as follows: ① retrospective, nonrandomized trial: ② semi-RCT, the grouping method of the participants in the experiment was not strictly random (such as the date of birth, the length of hospitalization, or the date of admission), and it was not included in our meta-analysis; ③ compare the effects of different interventions on the prevention of CIN without the establishment of a placebo-controlled trial; ④ articles of incomplete or erroneous data. The definition of CIN is as follows: it is generally believed that when the level of Scr is higher than that of 50% to 25% or 50% to 100 mg/L before the use of contrast agent, which can be used to diagnose CIN.[16–18]

2.3. Data extraction

The contents of the retrieved articles were reviewed by 2 researchers (ZY and HL), to determine whether the article meets the inclusion criteria, according to the standard data extraction table for data extraction. Data to be extracted included basic data of subjects (average age, male-to-female ratio, creatinine level and diabetes patients, and so on), type of contrast, subject inclusion and exclusion criteria, dosage and type of contrast medium, hydration scheme, TMZ and placebo administration programs, and so on.

2.4. Statistical analyses

We used the Stata 11.0 to pool and analyze results from the individual studies. Pooled results were reported as relative risks (RRs) and standardized mean difference (SMD), and presented with 95% confidence intervals (CIs) with 2-sided P values by using a random-effects model. $P<0.05$ indicates that the difference was statistically significant. Heterogeneity of the inclusion study was assessed by I^2 statistic, which assessed the appropriateness of pooling the individual study results. When $I^2<50\%$, the heterogeneity of the study was considered small. When $I^2>50\%$, the heterogeneity of the study was considered substantial, and subgroup analysis and sensitivity analysis were performed to investigate the sources of heterogeneity. If necessary, meta-regression analysis was carried out to explore

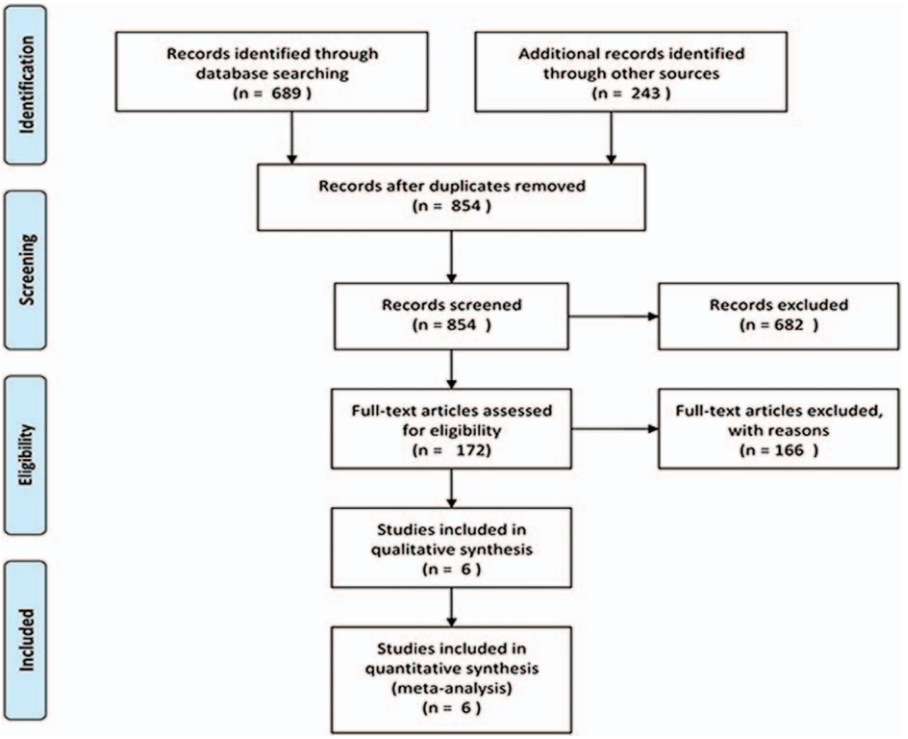

Figure 1. Flow chart for study selection.

and investigate the effects of various characteristics of studies on the study estimates of RRs.

3. Results

Our study has searched the relevant articles in Chinese and English published from inception to September 10, 2016. Finally, based on the original meta-analysis, 3 articles in Chinese were additionally included in this study, and English-language articles were excluded. All the 3 articles were written in Chinese—1 article presented the CIN as the clinical outcome, 1 article presented the CIN, Scr, and SOD as the clinical outcome, and 1 article presented the CIN and Scr as the clinical outcome. Characteristics of these recent studies are shown in Table 1. Taken together, a total of 6 studies were included and entered into the final analysis. As a whole, 764 patients were included in this updated analysis. Among them, 377 patients were included in TMZ group and 387 patients in control group. Included samples ranged in size from 42 to 115, with a follow-up time that ranged from 24 hours to 7 days.

Table 1

Characteristics of studies included in meta-analysis.

First author	Year	Country	Renal insufficiency	Sample number		Average age, y		Hydration method		Type of contrast agent	Observation index	Type of procedure	Definition of CIN
				E	C	E	C	E	C				
Wang[19]	2010	China	Yes	102	115	63	64.3	Hydration+Alprostadil	Hydration	Iohexol	CIN	Coronary angiography	①
Huaizhou[20]	2014	China	Yes	50	50	56.8±6.3	56.8±6.3	Hydration+Alprostadil	Hydration	No clear	CIN, Scr, SOD	Coronary angiography	②
Chen[21]	2014	China	Yes	64	60	64.2±9.6	66.4±7.8	Hydration+Alprostadil	Hydration	Ioversol	CIN, Scr	Coronary angiography or PCI	③
Liu[22]	2015	China	Yes	62	70	59.0±11.2	58.3±10.7	Hydration+Alprostadil	Hydration	Iodixanol	CIN, Scr, CysC,	Coronary angiography or PCI	④
Onbasili[23]	2014	Turkey	Yes	40	42	61±10	60±11	Hydration+Alprostadil	Hydration	Iopramide	CIN, Scr,	Angiography	⑤
Shehata[24]	2014	Egypt	Yes	50	50	58±6	59±5	Hydration+Alprostadil	Hydration	Iopramide	CIN, Scr, GFR	Coronary angiography or PCI	⑥

CIN is defined as the impairment of renal function determined by either a 25% increase in SCr from baseline or 0.5 mg/dL (44 mmol/L) increase in absolute value, within 48 to 72 hours of intravenous contrast administration.

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CIN is defined as the increase of Scr by 25% the use of contrast agent within 48 hours, or Scr absolute value increased by 44 mmol/L (0.5 mg/L), and need to exclude other factors of kidney damage.

CIN is defined as the impairment of renal function determined by either a 25% increase in SCr from baseline or 0.5 mg/dL (44 mmol/L) increase in absolute value, within 48 to 72 hours of intravenous contrast administration.

The endpoint of the study was the development of CIN, which was defined as an absolute increase in serum creatinine of 0.5 mg/dL, or a relative increase of 25% in serum creatinine at 24 or 48 hours after the procedure compared with the baseline.

CIN was defined as an absolute increase of at least 0.5 mg/dL or a relative increase of at least 25% in the serum creatinine level recorded after PCI, compared with the baseline value.

C = control group, CIN = contrast-induced nephropathy, E = TMZ group, GFR = glomerular filtration rate, Scr = serum creatinine, SOD = superoxide dismutase.

Table 2

Assessment of methodological quality of included studies.

First author	Random allocation	Hidden distribution	Blind method	Incomplete outcome data	Selective reporting of results	Other bias	Quality grade
Wang[19]	Not clear	Not clear	Not clear	Low	Low	Low	B
Huaizhou[20]	Randomized	Not clear	Not clear	Low	Low	Low	B
Chen[21]	Randomized	Low	Single-blind	Low	Low	Low	A
Liu[22]	Randomized	Low	Single-blind	Low	Low	Low	A
Onbasili[23]	Randomized	Low	Double-blind	Low	Low	Low	A
Shehata[24]	Randomized	Low	Single-blind	Low	Low	Low	A

3.1. Quality evaluation of literature

Six studies[19–24] included in our study were prospective RCTs; 5 studies[20–24] described the random method, but 1 study[19] was not described in detail. Also, the distribution of the 4 studies[21–24] were of low bias, but the distribution of the remaining2 studies[19,20] was not described in detail. A single-blind implementation method was adopted in 3 studies.[21,22,24] A double-blind implementation scheme was adopted in 1 study[23], and the implementation methods of the 2 studies[19,20] were not described in detail. Incomplete outcome, selective reporting of results, and another bias in 6 studies[19–24] were low bias. Quality evaluation of literature is shown in Table 2. At the same time, the number of CIN occurred as a funnel plot analysis, which is shown in Fig. 2. Funnel plot shows that there is no significant publication bias in the literature, and the quality of the literature is higher, so the conclusion of meta-analysis was more reliable.

3.2. Incidence rate of CIN

Six articles[19–24] reported the incidence rate of CIN, including 377 patients in TMZ group and 387 patients in control group. Results of the meta-analysis showed that: $I^2=0\%$, $P=0.773$, and the heterogeneity of each study was low. The incidence of CIN in the TMZ group was 5.83% (22/377), the incidence of CIN in the control group was 19.38% (75/387), and the difference was statistically significant between the 2 groups (RR 0.27, 95% CI 0.16, 0.46, $P=0.000$; Fig. 3). According to the different populations, all patients were divided into Asian and non-Asian populations. For Asian population, the results of the meta-analysis showed that: $I^2=0\%$, $P=0.613$, and the heterogeneity of each study was low. The incidence of CIN in the TMZ group was 5.39% (15/278), the incidence of CIN in the control group was 18.30% (54/295), and the difference was statistically significant between the 2 groups. For non-Asian population, the results of the meta-analysis showed that: $I^2=0\%$, $P=0.404$, and the heterogeneity of each study was low. The incidence of CIN in the TMZ group was 7.07% (7/99), the incidence of CIN in the control group was 22.83% (21/92), and the difference was statistically significant between the 2 groups (Fig. 4).

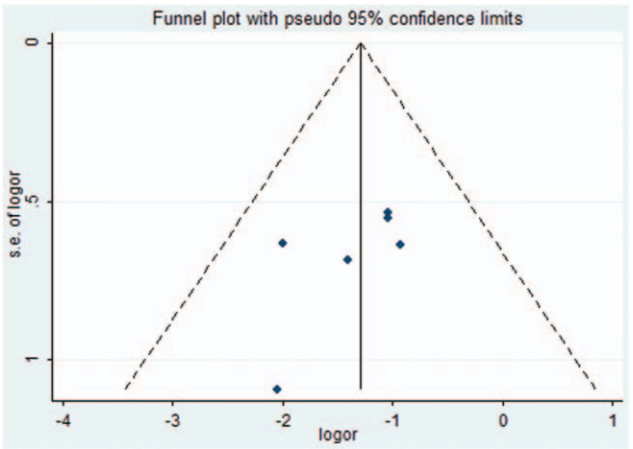

Figure 2. Funnel plots of literature quality assessment.

3.3. Scr of 24 hours after operation

Three articles[20–22] reported Scr of 24 hours after the operation, including 176 patients in TMZ group and 180 patients in control group. Meta-analysis showed that: $I^2=0\%$, $P=0.679$, and the heterogeneity of each study was low. The results showed that the Scr level of TMZ group was significantly lower than that of control group 24 hours after operation; the difference was statistically significant (SMD −0.30, 95% CI −0.51, −0.09, $P=0.005$; Fig. 5).

3.4. Scr of 48 hours after operation

Three articles[21–23] reported Scr of 48 hours after the operation, including 166 patients in TMZ group and 172 patients in control group. Meta-analysis showed that: $I^2=84.5\%$, $P=0.002$. The results showed that the Scr level of TMZ group was significantly lower than that of control group 48 hours after operation, and the difference was statistically significant (SMD −0.66, 95% CI −1.23, −0.10, $P=0.022$; Fig. 6).

3.5. Scr of 72 hours after operation

Two articles[20,22] reported Scr of 72 hours after operation, including 112 patients in TMZ group and 120 patients in control group. Meta-analysis showed that: $I^2=97.2\%$, $P=0.000$. The results showed that compared with the control group, the Scr of 72 hours after operation in TMZ group was not statistically significant (SMD −0.79, 95% CI −2.50, 0.91, $P=0.362$; Fig. 7).

3.6. Scr of 7 days after operation

Three articles[20,21,22] reported Scr of 7 days after operation, including 154 patients in TMZ group and 152 patients in control group. Meta-analysis showed that: $I^2=85.7\%$, $P=0.001$. The results showed that the Scr level of TMZ group was significantly lower than that of control group 7 days after the operation, and the difference was statistically significant (SMD −0.74, 95% CI −1.36, −0.11, $P=0.021$; Fig. 8).

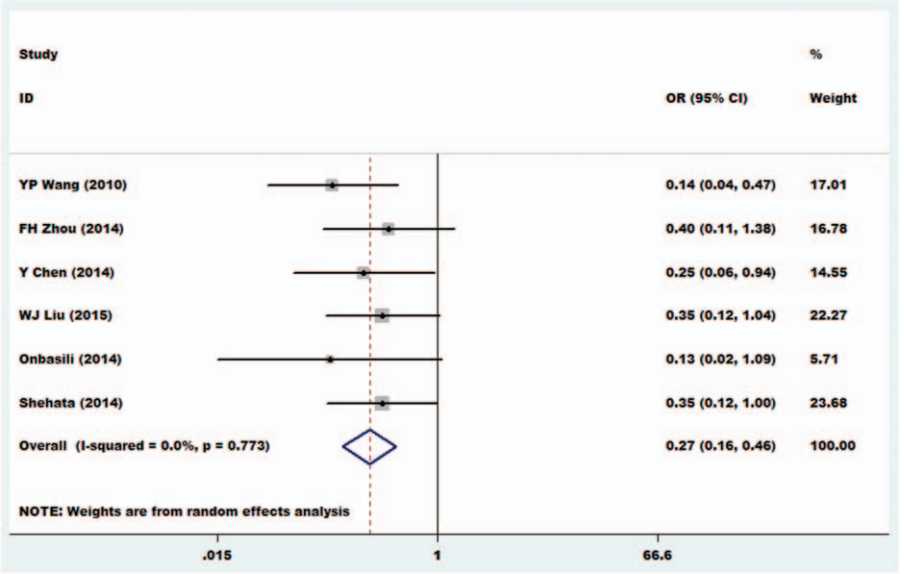

Figure 3. Forest plot showing contrast-induced nephropathy (CIN) risk difference between trimetazidine versus hydration.

3.7. Type of contrast agent

In our meta-analysis, 1 study used iohexol, 1 study used ioversol, 1 study used iodixanol, 2 studies used iopramide, and the type of contrast agent was not clearly pointed out in 1 article. Because the type of contrast agent used was largely different, the sensitivity and subgroup analyses were not performed in our study.

4. Discussion

In our updated meta-analysis, we found that TMZ can significantly reduce the incidence of CIN, which is consistent with the findings from the study by Nadkarni et al.[15] In addition, our results showed that TMZ can also reduce postoperative serum creatinine levels, including the Scr levels after 24 hours, 48 hours, and 7 days. As we all know, the level of Scr is 1 of the important indicators reflecting the changes of renal function; the decrease of Scr level suggests the function of kidney is better. Therefore, we could suggest that TMZ can prevent the occurrence of CIN and protect the renal function in patients. Meanwhile, we need to be aware that for the effect of TMZ on serum creatinine, the heterogeneity for long-term analyses is very high (above 75% in all cases). Some reasons may explain this phenomenon: ① articles included in our meta-analysis is less, the number of population does not have a good representation; ② in

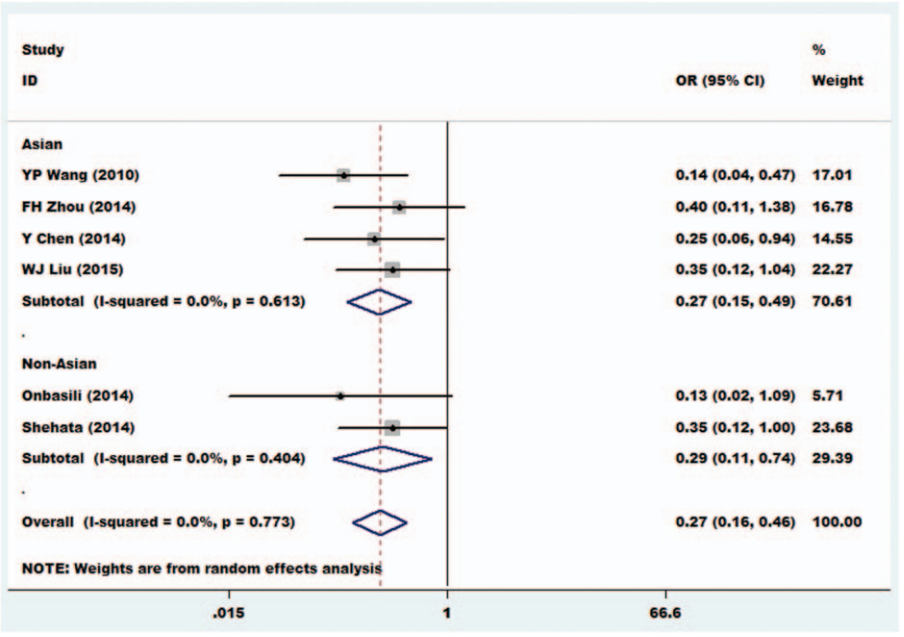

Figure 4. Forest plot showing contrast-induced nephropathy (CIN) risk difference between trimetazidine versus hydration (Asian population and non-Asian population).

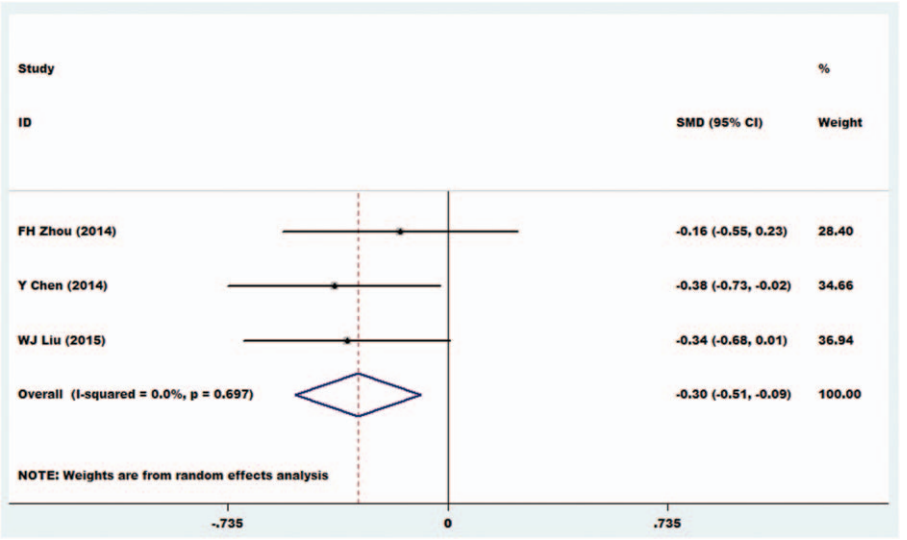

Figure 5. Forest plot showing the serum creatinine level of the experimental group was significantly lower than that of the control group 24 hours after operation.

addition, because of the population difference, the effect of TMZ on human body is different; ③ there were some differences in the age of patients in each study (average age ranged from 56.8 ± 6.3 to 66.4 ± 7.8 years); ④ the inconsistencies of the testing instruments also may led to this phenomenon.

Contrast-induced nephropathy is a disease of acute renal function damage, which was due to the contrast agent after 2–3 days later. It is generally believed that when the level of Scr is higher than that of 50% to 25%, or 50% to 100 mg/L before the use of contrast agent, which can be used to diagnose CIN.[16–18] At present, many studies have shown that CIN is 1 of the main reasons for the increase in hospitalization time and the incidence of cardiovascular events in emergency patients undergoing PCI. The main mechanism may be as follows[25–28]: ① the increase of oxygen-free radicals after ischemia and reperfusion resulted in renal tubular injury; ② contrast agent can directly cause the contraction of the renal vessel spasm, renal medullary ischemia, and hypoxia; ③ the high permeability of contrast agent can cause the increase of uric acid salt, which leads to renal tubular obstruction and poor drainage; ④ effective circulating blood volume decreased, and renal hypoperfusion was induced by factors of CIN.

At present, there is no effective way for the treatment of CIN. Some scholars believe that oxygen-free radical injury plays a major role in the pathogenesis of CIN. TMZ is a piperazine derivative, which is a inhibitor of mitochondrial long-chain 3-acyl coenzyme A. Basic research[29,30] confirmed that TMZ can inhibit the production of oxygen-free radical, reduce apoptosis, prevent mitochondrial swelling, enhance mitochondrial activity, and prevent cell lysis, thereby protecting the cell function. In addition, TMZ can improve the concentration of intracellular SOD, which is a part of the main substances in removing oxygen-free radicals. Studies have found that TMZ protects myocardial cells and also plays a role in reducing the generation of free radicals and inhibition of inflammatory responses in vivo. Moreover, TMZ can also reduce the H^+, Ca^{2+}, and Na^+ overload

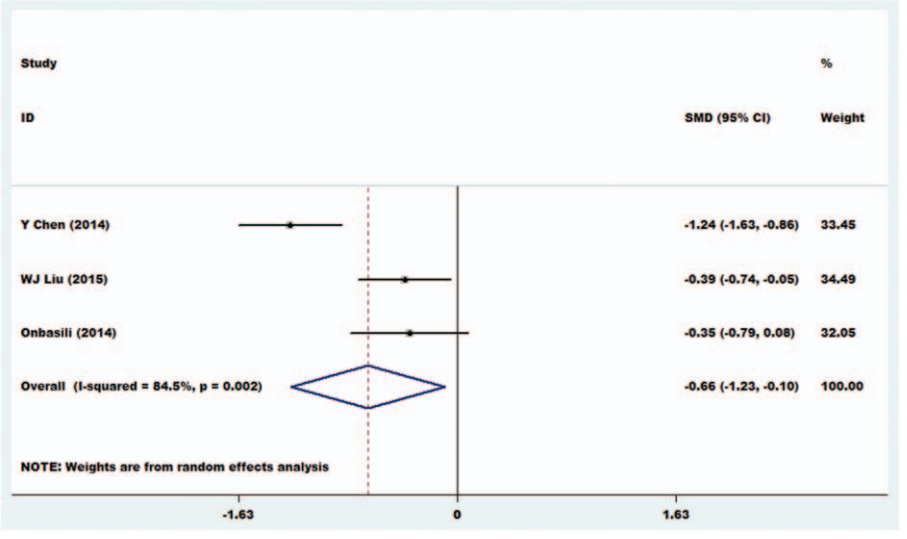

Figure 6. Forest plot showing the serum creatinine level of the experimental group was significantly lower than that of the control group 48 hours after operation.

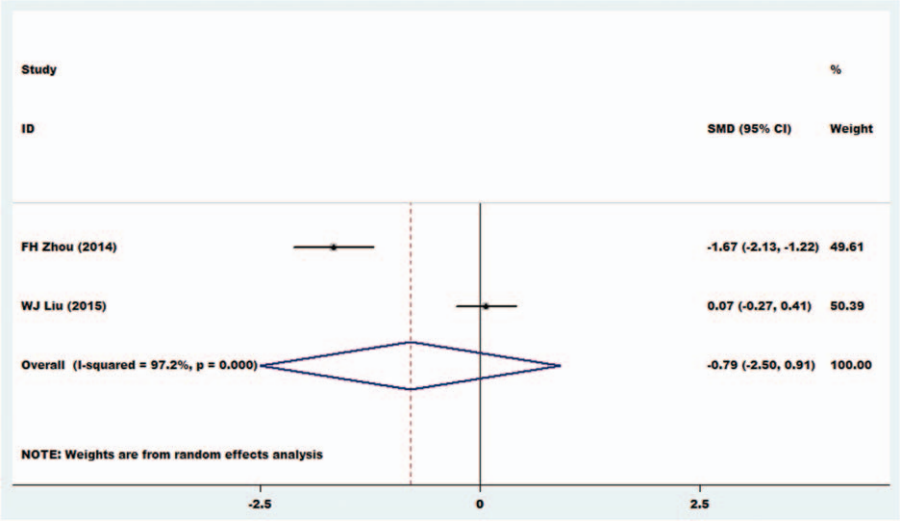

Figure 7. Forest plot showing compared with the control group, the serum creatinine of 72 hours after operation in the experimental group was not statistically significant.

in intracellular. At the same time, TMZ can improve the utilization rate of lactic acid, decrease cell ketogenesis, improve lipid metabolism, and inhibit the effective circulating blood volume decreased and acidosis due to renal insufficiency. It can also decrease the acute kidney injury caused by renal toxic drugs, which can reduce the incidence of CIN.[31,32]

Our updated meta-analysis has some advantages, which are as follows: ① Chinese and English articles were systematically searched, the number of articles included was increased, reducing the bias due to different regions, countries, and populations, thus increasing the reliability of the results. ② Scr level is 1 of the important indexes of renal function. In a previous meta-analysis, Scr was not used as an indicator of renal function due to some reason; the previous meta-analysis only evaluated the TMZ effect by assessing the incidence of CIN. In our updated meta-analysis, the level of Scr at 24 hours, 48 hours, 72 hours, and 7 days after surgery was included to evaluate the changes in renal function after operation. ③ According to different groups, the patients were divided into the Asian group and the non-Asian group. Our results showed that for Asian and non-Asian populations, TMZ could both reduce the incidence of CIN and the postoperative Scr level.

The limitations of our study include the following: ① the included studies are mainly from the Asian and African regions, lacking the randomized clinical trials from Europe and North America; ② there is no consistency for dosage, use method, and utility time for TMZ in the preoperative and postoperative; ③ although studies included were RCTs, the distribution of studies was hidden, the specific random method was not a complete description, and the possibility of the existence of patient selection bias could not be ruled out; ④ short-term changes in CIN and Scr were included in the articles, but short-term changes in CIN and Scr are not the long-term outcome, so extended follow-up is still needed to determine the final outcome of patients.

Our study suggests that several aspects should be paid attention to in the follow-up study in the future, which are as follows:

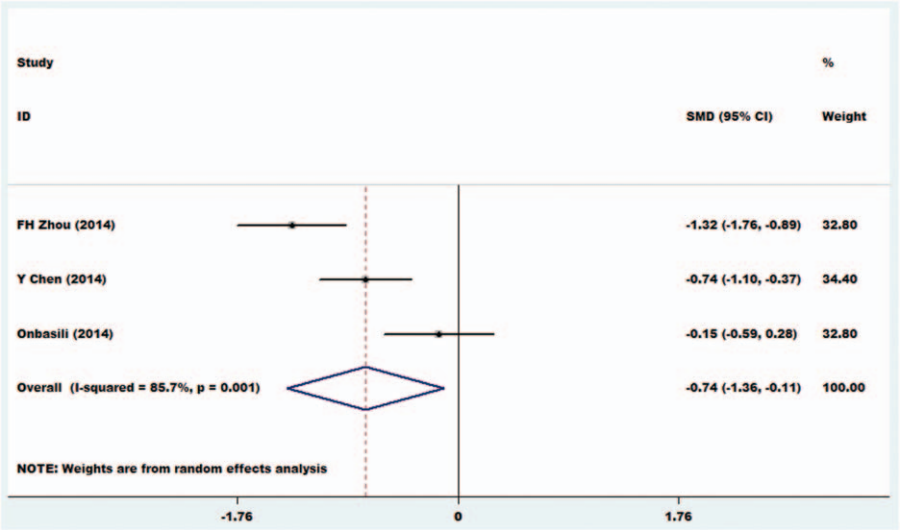

Figure 8. Forest plot showing the serum creatinine level of the experimental group was significantly lower than that of the control group 7 days after operation.

① because of different ethnic, regional, and national differences, to verify the clinical efficacy of a drug, multiregional, multicenterRCTs need to be conducted; ② the use of a drug, the time when a drug should be used, and methods of use should be regulated; ③ detailed description of the specific method of random grouping, single-blind or double-blind, and the implementation of the method reduces confounding bias; ④ follow-up time should be extended; moreover, a number of observation indicators should be included, such as glomerular filtration rate, blood urea nitrogen, survival time and quality of life, and so on, a multifaceted evaluation of the effectiveness of drugs should be achieved.

5. Conclusions

In conclusion, this meta-analysis showed that TMZ has preventive effects on CIN, which can effectively reduce the incidence of CIN in patients undergoing coronary angiography. However, we still need to find a suitable program for TMZ in the future, including the dose, usage, and use time. It also requires more and more large-scale design rigorous RCT and long-term follow-up, to obtain a wealth of clinical data, draw a more credible conclusion, so as to guide clinical drug use.

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