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Review Article

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Use of Renal Protective Agents to Prevent Contrast Induced Nephropathy in Renal Failure Patients: A Systematic Review

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Abstract

The aim of this review is to put forward extensively researched available evidence on the prevention of contrast induced nephropathy in renal failure patients using renal protective agents.

Keywords

Nephropathy, Renal

Introduction

Contrast induced nephropathy

Definition

"Nephropathy" is the term used in a medical setting to describe a disease related to the internal organ, kidney. Contrast induced nephropathy is the type of kidney disease that is caused by the use of contrast media. It can be more easily termed as acute renal failure that is detected within a 48-hour frame of being administered intravascular radiographic contrast material or media and cannot be associated with any other source or cause [1]. Although there is no universally accepted definition of this term, three major elements may constitute the basic definition of Contrast induced nephropathy; firstly, there is either a definite or relative rise in serum creatinine levels when compared with the baseline values, there exists a temporal relationship between the increase in serum creatinine levels and the exposure to contrast media, and lastly, there is no other plausible source or cause for the renal failure or dysfunction [2]. In Contrast induced nephropathy, the serum creatinine levels either show an absolute increment of 0.5 mg/dl (44 µmol/L) or more or show a relative increment of 25% from the baseline values, the values being detected within a 48-72 hour framework of being exposed to the contrast media [3].

Major Risk Factors Associated with Contrast Induced Nephropathy

Pre-existing renal dysfunctions

Patients with pre-existing renal dysfunctions or insufficiencies irrespective of their causation are at a greater risk of being affected by Contrast Induced Nephropathy. It is considered the most prevalent risk factor due to the elevated serum creatinine levels [2]. Impaired antioxidant system is a common symptom in patients suffering from Chronic renal failure, which causes an increment in oxidative stress, and is linked to inflammation and endothelial dysfunction [4].

Diabetes mellitus

Diabetes mellitus is considered a risk factor due to its high prevalence in the general population and due to its potential to induce multiple and various cardiovascular diseases, which consequently require the use of contrast media during radiological procedures [2]. Around 56% of patients who suffer from renal dysfunctions attributed to diabetes mellitus and consequently suffer from Contrast induced nephropathy lamencly progress to irreversible renal failure [1].

Nephrotoxic drugs

Nephrotoxic drugs such as aminoglycosides, amphotericin, cisplatin etc, along with the ones that hold the ability to incapacitate the vasodilatory effects of the healing lipids prostaglandins such as non-steroidal anti-inflammatory drugs (NSAIDs) cause vulnerability of kidneys towards contrast media. They may be able to incur damages to the kidney and kidney functions, however their role as an independent risk factor for Contrast induced nephropathy is yet to be tested through clinical trials [1].

Contrast media administration

The amount and type of contrast media administered to patients has also been studied as a risk factor, although it is a debated topic whether or not the type of contrast media has any actual risk associated with Contrast induced nephropathy. Contradictions have been found in studies, where some mention the better effects of one type of contrast media over another, whereas others show no observable differences between any type of contrast media [2]. Although the type of contrast media used is debated upon, the administered volume is a definite risk factor. The greater the doses of contrast media administered to a patient within a 72 hrs frame, the higher are the chances for them to develop Contrast induced nephropathy [1]. It has been reported that low osmolality contrast media (LOCM) such as iohexol and iopamidol, if administered at volumes greater than 30 mL corresponded with a high prevalence of contrast induced nephropathy, along with an increased risk of 65% for every 5 mL added on top of it [1].

Additional risk factors

The age of a patient, conditions such as anaemia, severe congestive heart failure, sepsis, or the occurrence of a renal transplant are all additional risk factors that contribute to the development of Contrast induced nephropathy [1].

The main intention and objective behind this systematic review is to review and evaluate the existing knowledge and understanding of the use of appropriate renal protective agents in the prevention of contrast induced nephropathy in renal failure patients.

Methods

Data sources and searches

The searches in this systematic review were made through the online databases PubMed, Science Direct and Google Scholar. Time period limit for the research articles was not applied. Limitations were applied due to language barrier and only English research articles were screened. The keyword searches made in the online databases focused on three major parts of the review. 1) 'Contrast induced nephropathy', 'CIN', 'nephropathy', 'contrast media', 'contrast materials' 2) 're-no-protective agents', 'renal protective drugs', 'renal protective agents' 3) 'renal failure patients', 'renal insufficiencies', 'renal dysfunctions', 'chronic kidney disease'. Short sentences were also searched in the databases, such as 'CIN in renal failure patients' and 'renal protective agents for CIN'.

Study Selection

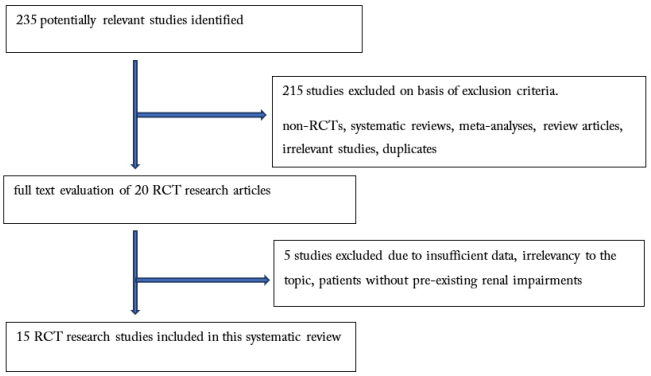
Studies that were selected for this systematic review were the ones that mentioned use of renal protective agents as a source of prevention of Contrast induced nephropathy in patients with renal failure or renal dysfunction. No limitations were applied to the definition of contrast induced nephropathy.

The inclusion criteria were as follows:

1. All studies selected were randomized clinical trials, the basis of the trial being to test the efficacy of a certain renal protective agent against Contrast induced nephropathy.
2. Studies with participants who suffered from renal failure, renal dysfunctions, renal insufficiencies or chronic kidney disease were selected.
3. Language was restricted to English only.
4. The primary outcome of this review was to analyse the incidence (prevalence or prevention) of Contrast induced nephropathy and thus studies that showed relevance to it were selected.

Exclusion criteria for this systematic review were as follows:

1. Non-randomized studies.
2. Studies with insufficient data to analyse.
3. Studies which related to Contrast induced nephropathy but there was no incidence of renal failure, renal dysfunction, renal insufficiencies or chronic kidney disease in patients.
4. Systematic reviews, meta-analysis and duplicates were removed.



Flow diagram of the systematic review

Data Extraction

The literature and data from the selected articles were reviewed by 2 independent reviewers in order to make sure that the chosen research met inclusion criteria, and the data was extracted based on the standard data extraction form.

Results

Upon extensive search of the literature from the online databases, 15 randomized control trial research articles in total met the inclusion criteria for this systematic review. Articles were excluded based upon their titles and abstract, along with any duplicates or systematic reviews and meta-analyses, after which 20 full-text articles were assessed, from which 15 were chosen and 5 were excluded based on exclusion criteria. The included research studies based on randomized control trials used different sources of renal protective agents to prevent the development of Contrast induced nephropathy. All patients present in this research suffered from some form of renal dysfunction, which can be a risk factor for increased incidence of Contrast induced nephropathy.

Nicorandil

4 out of the 15 studies focused on the use of drug Nicorandil as a renal protective agent for prevention against Contrast induced nephropathy. The definition in of Contrast induced nephropathy in two of the studies was the relative increase of 25% from baseline serum creatinine levels or an absolute increase of 0.5mg/dL, the serum creatinine values used as the endpoint to indicate development of Contrast induced nephropathy [5, 6]. One of the four studies used C cystatin levels as an end point to determine Contrast induced nephropathy and claimed it to be superior to serum creatinine as a marker for glomerular filtration rate.[8] The fourth study used both serum creatinine levels as well as C cystatin levels to detect the presence or absence of Contrast induced nephropathy [7]. In one of the randomized control trials, the nicorandil group was administered 10 mg nicorandil orally thrice daily from 2 days before and 3 days after contrast exposure, along with all patients receiving intravenous infusion of 0.9% saline at a rate of 1 ml/kg/hr [0.5 ml/kg/hr for patients with low left ventricular ejection fraction (LVEF) <40%], 6 hours before and 12 hours after the elective coronary procedure [5]. Another study also administered nicorandil orally, where the nicorandil group of patients received 10 mg of nicorandil thrice daily from two days before and two days after elective coronary procedure, along with all patients receiving intravenous infusion of 0.9% saline at a rate of 1 mL/kg/hr 6 hours before and 12 hours after the procedure [6]. The other two studies administered nicorandil intravenously along with the saline, one administering 12 mg of nicorandil diluted in 100 mL of 0.9% saline for 30 minutes before coronary angiography. All patients in the trial including the control group were administered 0.45% saline at a rate of 1 mL/kg/hr [0.5 ml/kg/hr for patients with low left ventricular ejection fraction (LVEF) <40%] 8 hours before and after procedure [7]. The other study administered two vials equal to 48 mg/V of nicorandil dissolved in 100 mL 0.9% saline at a speed of 1 mL/kg/hr to the assigned patients in nicorandil group, starting 4 hours before and ending 24 hours after PCI procedure.[8] Three of the four studies related a positive effect of nicorandil on the incidence of Contrast induced nephropathy [5, 6, 8]. Lower incidence of Contrast induced nephropathy was found in nicorandil group as opposed to the control group (6.67% vs. 17.5%) [5], (6.30% vs. 15.20%) [6], (2.0% vs. 10.7%) [8]. However, one of the studies showed no preventive effects of nicorandil, with the incidence of Contrast induced nephropathy being similar in both nicorandil group and control group (6.8% vs. 6.6%) [7]. Analyses of the studies showed that the presence of nicorandil as a renal protective agent may sow positive results when used for patients with already existing renal dysfunctions [5, 6, 8], but in the contradicting study, it was hypothesized that nicorandil may have some sort of therapeutic effects on the kidney, but it cannot prevent the onset of Contrast induced nephropathy [7].

Trimetazidine

3 of the 15 studies focused on the use of Trimetazidine as a preventive agent for lowering the incidence of Contrast induced nephropathy in patients with renal dysfunctions or impairments. Contrast induced nephropathy in both the studies was defined as a relative increase of 25% serum creatinine from baseline values or an absolute increase of 0.5 mg/dL or more. The first study focused on the sole oral administration of 35 mg Trimetazidine twice daily to patients randomly assigned to the experimental group, starting 48 hours before angiography and lasting a total of 72 hours, along with intravenous isotonic saline administration at the rate of 1 mL/kg/hr for 12 hours before and 12 hours after the procedure [9]. The second study was aimed at elderly patients with renal insufficiencies, the experimental group in this randomized trial being administered with 20 mg of Trimetazidine orally, three times a day, starting 24 hours before the patients' procedures and lasting 72 hours after. All patients in both experimental group and control group received 0.9% sodium chloride isotonic saline intravenously 12 hours before and after the operation, at a rate of 1 mL/kg/hr [0.5 ml/kg/hr for patients with low left ventricular ejection fraction (LVEF) <45%] [10]. The third study aimed to evaluate the efficacy of Coenzyme Q10 along with Trimetazidine for the prevention of Contrast induced nephropathy in renal dysfunctions. In the randomized trial, the Coenzyme Q10 group was administered 20 mg of both Coenzyme Q10 and Trimetazidine thrice daily from 2 days prior to and 3 days after cardiac catheterization. All the patients in both experimental group and control group were administered intravenous infusion of 0.9% saline at a rate of 1 mL/kg/hr [0.5 ml/kg/hr for patients with low left ventricular ejection fraction (LVEF) <40%] 4 hours prior to and 20 hours after the coronary procedure [11]. The results from the first study showed positive results, observing that there was a noticeable decrease in the incidence of Contrast induced nephropathy in patients administered with Trimetazidine as compared to the control group. (10% vs. 26%) [9] The results from the second study showed a significant decrease in incidence of Contrast induced nephropathy when comparison was made between experimental group and control group (3.2% vs 9.7%) [10]. Results from the third study showed positive results as well, with the incidence of Contrast induced nephropathy being

markedly lower in the experimental group administered the Coenzyme Q10 and Trimetazidine as compared to the control group. (6.67% vs. 21.3%) [11].

Statin medication

Three different research studies were found on the effects of statin medication on prevention of Contrast induced nephropathy on patients with renal dysfunctions or chronic kidney disease. Statin medication has been studied due to its anti-inflammatory and antioxidative properties. Three various statin medications were used, namely, Atorvastatin [12], Simvastatin [13] and Pravastatin [14]. In the first study, high doses of Atorvastatin equal to 80 mg/day were administered to the atorvastatin group in the randomized trial 48 hours before and 48 hours after exposure to contrast media, along with administration of intravenous isotonic saline of 0.9% sodium chloride at 1 mL/kg/hr, and 1200 mg of oral NAC twice daily from one day before to one day after the procedure [12]. In another study, high doses of Simvastatin were administered in a short time period, 40 mg after every 12 hours for 2 days, before and after coronary angiography. Thus, in total four 40 mg doses were administered to the simvastatin group of the randomized trial, along with all patients receiving intravenous half-isotonic saline at a rate of 1 mg/kg/hr for 12 hours before and after coronary catheterization [13]. The third study administered Pravastatin in doses of 10 mg/day to the pravastatin group of the randomized trial, with only 2 patients receiving a dose of 20 mg/day, and administration was started 28 days before contrast media exposure [14]. The results from the study using Atorvastatin showed no significant difference in the incidence of Contrast induced nephropathy between the Atorvastatin group and the control group (10% vs. 11%) [12] Similar results were found in the study using Simvastatin, where the incidence of Contrast induced nephropathy did not show any significant differences between the Simvastatin and control group (2.5% vs. 3.4%) [13] However, the study using Pravastatin as a renal protective agent to minimize incidence of Contrast induced nephropathy showed positive results, with a significant lowering in incidence of Contrast induced nephropathy in patients administered Pravastatin as opposed to the ones who were not administered it. (22.2% vs. 47.1%) [14].

N-Acetylcysteine

2 of the 15 studies researched the efficacy of N-acetylcysteine as a protective agent against Contrast induced nephropathy in patients with pre-existing renal impairments. In one of the studies, the experimental group in the randomized trial were administered N-Acetylcysteine intravenously as a mixture of 500 mg N-Acetylcysteine C (2.5 mL of a pyrogenic free 2 g/10 mL NAC solution) and 50 mL of 5% dextrose saline. The infusion was administered for 15 minutes before the exposure to contrast media [15]. In the second study, N-Acetylcysteine was administered orally, dosed at 600 mg twice before the procedure and twice after. Hydration was provided to the patients intravenously, consisting of 1 L of 0.9 normal saline, along with oral hydration through water intake [16]. The definition of Contrast induced nephropathy was taken as the reduction in creatinine clearance of 5 mL/min or more from the baseline [15]. Based on this definition, the results from the first study revealed that N-Acetylcysteine administration did not have any significant effect on the prevention of Contrast induced nephropathy, with little difference between the experimental group and the control group (23.3% vs. 20.7%) [15]. The end point in the second study was the incidence of Contrast induced nephropathy which was defined as a relative increase of 25% serum creatinine from baseline value or an absolute increase of 0.5 mg/dL or more. Again, this study also proved the inability of N-Acetylcysteine to prevent the onset of Contrast induced nephropathy. No significant differences were seen in the experimental group and control group readings (11.1% vs. 14.3%) [16].

Isosorbide dinitrate

One study aimed to evaluate the use of Isosorbide Dinitrate in addition to hydration as a protective agent for patients with chronic kidney disease against Contrast induced nephropathy. In this study as well, the primary end point as the incidence of Contrast induced nephropathy defined as a relative increase of 25% serum creatinine from baseline value or an absolute increase of 0.5 mg/dL or more. The experimental group in this study was administered with 2 mg/hr Isosorbide dinitrate in combination with intravenous infusion of isotonic saline for the purpose of hydration, at the rate of 0.5 mL/kg/hr, 6 hours before and 12 hours after their operations. After determination of end point, the results were observed, which showed that there was a marked lowering in incidence of Contrast induced nephropathy in patients present in the experimental group as opposed to the control group (12.8.% vs. 21. 2%) [17].

Iloprost

Ilporost was a drug studied in this research as a protective agent against Contrast induced nephropathy in patients with pre-existing renal dysfunction. Ilporost was administered to the experimental group intravenously in a dosage of 1 ng/kg/min, the administration starting 30 to 90 minutes before exposure to contrast media and ending 4 hours later. Normal saline was also delivered at a rate of 1.5 mL/kg/hr starting 4 hours before the patients' procedure and lasted 12 hours after. Ilporost was seen to have positive effects on the decrease in incidence of Contrast induced nephropathy when comparison was made between the experimental group and control group (8% vs. 22%) [18].

Central venous pressure–guided fluid administration

One of the studies focused on the efficacy of central venous pressure guided fluid administration as a prevention method for patients suffering from chronic heart failure, chronic kidney disease and patients undergoing coronary angiography. Patients placed under the Central venous pressure (CVP) group were divided into 3 subgroups: group 1 (CVP <6 cm H_2O), group 2 (CVP 6 to 12 cm H_2O), and group 3 (CVP >12 cm H_2O). The rate of fluid administration was also set for all three subgroups as follows: 3 mL/kg/hr for group 1, 1.5 mL/kg/hr for group 2, and 1 mL/kg/hr for group 3. The rate of the intravenous infusion was adjusted in the CVP group patients in accordance with the central venous pressure per hour

during the infusion. As an example, the rate of fluid administration for a patient would be changed from 1.5 mL/kg/hr to 1 mL/kg/hr if their CVP was shown to change from the range of subgroup 2 (CVP 6 to 12 cm of H_2O) to subgroup 3 (CVP> 12 cm H_2O). For the control group, hydration was provided at a constant rate of 1 mL/kg/hr. Intravenous hydration continued for 6 hours pre-procedure to 12 hours post-procedure, the only difference between both groups being the rates at which the hydration is being administered. Results from this study showed that there was a difference between the incidence of Contrast induced nephropathy when the experimental group and the control group were compared (15.9% vs. 29.5%) The study found a total significant reduction of 46% in the primary end point which was the incidence of Contrast induced nephropathy when compared with the control or standard hydration treatment [19, Table 1].

N, number of patients; E.G, experimental group; C.G, control group; CIN, contrast induced nephropathy; CM, contrast media; NaCl, sodium chloride; i.v., intravenous; inf., infusion; ECP, elective coronary procedure; PCI, percutaneous coronary intervention; TMZ, trimetazidine; CC, cardiac catheterization; op., operation; CVP, central venous pressure.

Discussion

This systematic review took into consideration 15 randomized controlled trials which revolved around the idea of use of renal protective agents against Contrast induced nephropathy in patients with pre-existing renal dysfunctions or impairments. The incidence of Contrast induced nephropathy increases significantly with the presence of poor renal functions. Patients with already compromised kidneys undergoing various procedures requiring the use of contrast media are at a higher risk of suffering from Contrast induced nephropathy. There was seen to be an overall incidence of Contrast induced nephropathy in patients with pre-existing renal insufficiencies [20]. Patients need to be kept under check before undergoing any form of procedure using contrast media by keeping a check on the serum creatinine levels and eGFR value, along with ceasing the use of possible nephrotoxic drugs, and giving patients lowest dosage of contrast media possible [21]. Thus, it is imperative that interventions be made to lower the incidence of CIN.

Nicorandil is a drug that can perform as a balanced coronary and peripheral vasodilator, helping in the reduction of both preload and afterload [22]. These Veno dilating properties of nicorandil which are attributable to its structural nitrate group, along with the potassium channel activation which show cytoprotective properties and protect the heart against ischaemic events [23]. A study showed its positive effects in lowering the incidence of Contrast induced nephropathy in patients with coronary heart disease, marking a significant difference between the experimental group and the control group (3.3% vs.10.7%) [24]. The effects of nicorandil as a possible renal protective agent has not been yet researched extensively. Three of the four studies in this systematic review aimed at evaluating the renal protective properties of nicorandil and found positive results [5, 6, 8]. while one showed contradicting results [7]. Upon observation of results from the contradicting study, it has been hypothesized that nicorandil may in fact have protective properties in that it may be able to prevent ischaemic injury to the kidney caused by contrast media, but prevention against development of Contrast induced nephropathy was not seen. [7] However, the role of anti-ischaemic agents showing protective renal properties is yet to be extensively researched. The amount and frequency of dosage may also play an important role in defining the role of any drug as a suitable agent, and so, further research and clinical trials need to be conducted.

Trimetazidine is a medicinal drug, most commonly used as an anti-anginal agent due to its cytoprotective properties. Studies have shown that use of 20 mg trimetazidine thrice daily reduces the risk of myocardial attacks [25]. Trimetazidine has been tested for its renal protective properties as well. All three studies in this review have shown positive results for trimetazidine being used as a renal protective drug against Contrast induced nephropathy [9-11]. The positive results of trimetazidine may be linked to its ability to attenuate oxidative stress, weaken inflammatory cytokine release and thus help in the maintenance of oxygen and energy balance [26].

The renal protective ability of statins has also been tested. One study tested the role of statins in reducing incidence of Contrast induced nephropathy, and showed positive results, with patients administered statin showing significantly better results as compared to the control group [27]. The anti-inflammatory, anti-oxidative and anti-thrombotic properties of statins may be linked to their ability to prevent renal injury, along with its ability to improve endothelial function and NO availability by reducing oxidative stress [28]. Atorvastatin is a statin medication, more specifically a synthetic hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, and plays a role in reducing total cholesterol levels, LDL, VLDL, tri-glycerides and increases levels of HDL when taken in doses of 10-80 mg/day [29]. In this way, it plays a protective role over the heart and helps prevent diseases related to it. One of the studies used in this review administered short term high dose of atorvastatin, and negative results were obtained [12]. Simvastatin is also a statin medication, an HMG-CoA reductase inhibitor, and has the same cytoprotective effects by lowering cholesterol levels [30], and the reviewed study which used simvastatin to evaluate its ability to lower the incidence of Contrast induced nephropathy also showed negative results [13]. However, the reviewed study that administered the use of pravastatin, which is also an HMG-CoA reductase inhibitor and helps reduce plasma cholesterol levels [31], showed positive results with a significant lowering in incidence of Contrast induced nephropathy [14].

N-Acetylcysteine is the acetylated variant of L-cysteine, and have detoxifying capabilities in the body and directly acts as a scavenger for free radicals, and has been known to have protective abilities over the liver and kidneys [32]. Both the reviewed studies in this review showed a lack of effect of N-Acetylcysteine as a renal protective agent to prevent or lower the incidence of Contrast induced nephropathy[15,16]. Although the use and potential benefit of NAC in reducing CIN has been of great interest, the study reviewed here is by

Table 1: RCT of various protective agents against CIN in renal insufficient patients.

Study	N		Intervention in experimental group	Control group	Hydration	Incidence of CIN	
						E.G (%)	C.G (%)
[5]	240		10 mg Oral nicorandil; 3 times daily; 2 days before & 3 days after CM exposure	Placebo as the same method	0.9% i.v. NaCl inf.; 1 mL/kg/hr (0.5 mL/kg/hr for LVEF<40%); 6h before & 12h after ECP.	6.67	17.5
	E.G	120					
	C.G	120					
[7]	252		10 mg oral nicorandil; 3 times daily; 2 days before & 2 days after ECP	0.9% i.v. NaCl inf.	0.9% i.v. NaCl inf.; 1 mL/kg/hr; 6h before & 12h after ECP.	6.30	15.20
	E.G	127					
	C.G	125					
[6]	166		12 mg nicorandil inf., dil. In 100 mL 0.9% NaCl sol.; 30 min. Prior to angiography	100 mL 0.9% i.v. NaCl inf.	0.45% i.v. NaCl inf.; 1 mL/kg/hr (0.5 mL/kg/hr for LVEF<40%); 8h before & after ECP	6.8	6.6
	E.G	81					
	C.G	85					
[8]	213		48mg nicorandil inf. In 100mL 0.9% NaCl sol.; 0.1 mL/kg/hr; 4 h prior & 24 h post PCI	0.9% i.v. NaCl inf.; 1.1 mL/kg/hr	0.9% i.v. NaCl inf.; 1 mL/kg/hr	2.0	10.7
	E.G	106					
	C.G	107					
[9]	100		35 mg oral trimetazidine; twice daily; 48h before & 24h after angiography	Parenteral hydration of isotonic saline; 1 mL/kg/hr; 12h before & 12h after angiography	Parenteral hydration of isotonic saline; 1 mL/kg/hr; 12h before & 12h after angiography	10	26
	E.G	50					
	C.G	50					
[10]	310		20 mg oral trimetazidine; thrice daily; 24 h before & 72 h after PCI	0.9% i.v. NaCl inf.; 1 mL/kg/hr	0.9% i.v. NaCl inf.; 1 mL/kg/hr; 12h before & after PCI; standard hydration sol (1000mL); 1 mL/kg/hr (0.5 mL/kg/hr if h LVEF ⩽45%)	3.2	9.7
	E.G	155					
	C.G	155					
[11]	150		20 mg CoQ10 & TMZ; thrice daily; 2 days before & 3 days after ECC	Placebo as the same method	0.9% i.v. NaCl inf.; 1 mL/kg/hr (0.5 mL/kg/hr for LVEF<40%); 4h before & 20 h after ECC.	6.67	21.3
	E.G	75					
	C.G	75					
[12]	304		High dose 80 mg/day atorvastatin; 48 h before & after CM exposure	Placebo for same method	0.9% i.v. NaCl inf.; 1 mL/kg/hr; 12h before & after procedure	11	10
	E.G	152					
	C.G	152					
[13]	247		40 mg simvastatin; 2 times before & 2 times after CC.	Placebo with same method	i.v. half-isotonic saline inf.; 1 mL/kg/hr; 12 h before & after CC	2.5	3.4
	E.G	124					
	C.G	123					
[14]	431		10 mg pravastatin/day (*n*=192) 20 mg pravastatin/day (*n*=2); 28 days before CM exposure	i.v. half-isotonic saline inf.; 1 mL/kg/hr	i.v. half-isotonic saline inf.; 1 mL/kg/hr; 12h before & after CM exposure	22.2	47.1
	E.G	194					
	C.G	237					
[15]	487		i.v. NAC (500 mg NAC + 50 mL 5% dextrose saline; 15 min., completed before CC.	50 mL 5% dextrose saline	200 mL i.v. NaCl inf. Before CC; i.v. NaCl inf. 1.5 mL/kg/hr 6 h after CC or until discharge	23.3	20.7
	E.G	242					
	C.G	245					
[16]	90		600 mg oral NAC; twice a day for 2 days; 2 doses 24 h before and 24 h after CC	Placebo as same method	Oral hydration approx. 8 glasses (200 mL) 12 h before CC; i.v. 0.9% NaCl inf. Of 1 L	11.1	14.3
	E.G	45					
	C.G	45					

[17]	394		i.v. isosorbide dinitrate inf.; 2 mg/hr + i.v. isotonic saline inf.; 1 mL/kg/hr; 6 h before & 12 h after op.	i.v. isotonic saline inf.; 0.5 mL/kg/hr; 6h before & 12 h after op.	i.v. isotonic saline inf.	12.8	21.2
	E.G	196					
	C.G	198					
[18]	208		1 ng/kg/min Iloprost dil. In saline; 30-90 min before & 4 h after CM exposure	Placebo of same method	i.v. NaCl inf.; 1.5 mL/kg/hr; 4h before & 12h after angiography	8	22
	E.G	103					
	C.G	105					
[19]	264		group 1 (CVP <6 cm H_2O) = 3 mL/kg/hr; group 2 (CVP 6 to 12 cm H_2O) = 1.5 mL/kg/hr; group 3 (CVP >12 cm H2O) = 1 mL/kg/hr; 6 h before & 12 h after op.	Hydration at the rate of 1 mL/g/hr	0.9% i.v. NaCl inf.	15.9	29.5
	E.G	132					
	C.G	132					

far the largest randomized control trial comparing the use of NAC with placebo in renal dysfunction patients [15]. There may be studies showing the potential benefits of NAC against Contrast induced nephropathy, but for these studies including patients with renal impairments or chronic renal disease, NAC has shown no positive effects in lowering the incidence of Contrast induced nephropathy.

Iloprost, a medicinal drug with the ability to inhibit platelet aggregation, vasodilation and although not extensively searched, the potential of cytoprotecting [33]. tested for its renal protective abilities, showed positive results. There may be a bit of a safety concern regarding the onset of hypotension during its administration, but upon initiation of such conditions, inhibition of dosage along with intravenous saline supply brought the situation back to normal [18] Iloprost at the minimal dosage amounts of 1 ng/kg/min showed significantly positive results and has the potential to be further tested as a protective agent against Contrast induced nephropathy.

Hydration is a universally accepted intervention in the inhibition of incidence of Contrast induced nephropathy [17]. The incidence of Contrast induced nephropathy is reduced by the volume expansion with saline by the dilution of contrast media [19]. but it may be possible that cardiac preload is increased due to hydration, which may lead to pulmonary Edema [17]. It is known that nitrates help decrease cardiac preload and reduce chances of pulmonary Edema, and thus the use of Isosorbide dinitrate, a medicinal drug along with hydration has shown to have positive effects on the lowering of incidence of Contrast induced nephropathy[17]. The study using CVP-guided fluid administration incorporated an extra step in the hydration process, whereby the rate of flow of administration of intravenous saline was controlled, and although no proper evidence is present to determine the ideal flow rates, the rates used in this study demonstrated positive results by provision of sufficient hydration and a constant maintenance of intravascular volume, along with help in renal perfusion for the prevention of Contrast induced nephropathy[19].

Conclusion

Contrast induced nephropathy is a serious disease of the kidney, which is caused after exposure to contrast media, used for the medical purposes in the radiology department. Exposure to contrast media in patients with pre-existing renal impairments and dysfunctions is a high-risk factor and can increase the incidence of CIN significantly. Nicorandil has shown positive results as a protective agent against CIN, along with trimetazidine. The use of statin medication has been known to show positive results, although further research needs to be done on patients with pre-existing renal insufficiencies being treated with statin medication. N-acetylcysteine has been of great interest but in studies related to patients with renal insufficiencies, showed a lack of effect. Only one study was found on the use of Iloprost as a protective agent in patients with renal dysfunctions, yet the medication showed promising results and provides basis for further research. Hydration being a universally accepted prevention technique for CIN, but its use being restricted due to cardiac preload and onset of pulmonary Edema, was used along with Isosorbide dinitrate, and showed positive results due to the ability of nitrates to reduce risk of pulmonary Edema and lower cardiac preload. The use of different flow rates guided by central venous pressure has also shown promising results, with the prevention of CIN by maintenance of a constant intravascular volume. The use of renal protective agents has been studied, albeit not extensively, and sparse knowledge is present on the effects of any single renal protective agent.

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