Anti-inflammatory Therapy Before Reperfusion Therapy in Patients with Ischemic Vascular Disease on the Incidence of Ischemic Reperfusion Injury: An Evidence-Based Case Report

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ABSTRACT

Background: *Reperfusion serves as a mainstay therapy in almost all ischemic vascular diseases (IVD), but reperfusion may enhance cell damage after an ischemic period time. Increased ROS and inflammatory markers, decreasing organ function parameters, along with systemic inflammatory response and multi-organ damage may occur in ischemic reperfusion injury (IRI). Unfortunately, this series of events is unpredictable and sudden, causing high mortality in patients with IRI. Due to the significant role of inflammation in IRI, how is the effectiveness of anti-inflammatory agents administered before reperfusion therapy to prevent IRI? To know the efficacy of anti-inflammatory agents administered before reperfusion therapy to prevent IRI.* ***Methods:*** *A systematic search was conducted in databases (Pubmed, EMBASE, Scopus) and was later selected according to predetermined inclusion and exclusion criteria. Studies included later critically appraised using the CEBM Oxford questionnaire for randomized control trials and systematic review.* ***Results:*** *Seven studies were included among 1072 studies found in early searching. Six of the studies are randomized control trials, and one is a meta-analysis of randomized control trials. Methylprednisolone, pexelizumab, tirilazad mesylate, and N-acetylcysteine are known anti-inflammatory agents applicable in humans. The highest effectiveness of anti-inflammatory agents is methylprednisolone, with a relative risk reduction (RRR) of 75-85%. Besides that, pexelizumab also had an RRR of 27%, and tirilazad-mesylate had an RRR of 18%. N-acetylcysteine is not effective in preventing IRI. IL-6 levels postoperatively also decreased significantly in patients given anti-inflammatory agents before reperfusion therapy. There are no side effects of the intervention reported.* ***Conclusion:*** *Anti-inflammatory agent administration before reperfusion therapy effectively prevents IRI. The choices of anti-inflammatory agents recommended are methylprednisolone, pexelizumab, and tirilazad-mesylate. Anti-inflammatory agent administration before reperfusion therapy is recommended.*

Keywords: *ischemic reperfusion injury, reperfusion, anti-inflammatory agents.*

INTRODUCTION

Ischemic Vascular Disease (IVD) is a term that includes a group of diseases caused by problems in blood circulation. IVD is a spectrum of diseases that includes ischemic heart disease, ischemic stroke, peripheral artery disease (PAD), ischemic nephropathy etc. IVD has a high mortality and morbidity level, so its

treatment requires speed and accuracy of action. The primary treatment for IVD is reperfusion/ revascularization therapy. It is known that each organ undergoing an ischemic phase has a specific time limit for revascularization or reperfusion therapy so as not to cause loss of organ function. In patients with PAD in the lower limb, it is known that within 12 months, the mortality and amputation rates increase by 22%.[1–3]

However, in some circumstances, the reperfusion can increase cellular dysfunction and death after restoring blood flow. This condition is called ischemic reperfusion injury (IRI), resulting in further cell damage from the previous ischemic period. IRI is extensive cell damage resulting from tissue reperfusion after a previous ischemic period. The organs commonly involved in IRI include the heart, lungs, kidneys, intestines, striated muscles, and brain. IRI can manifest as a systemic disease and lead to multi-organ failure. When reperfusion occurs, there can be increased reactive oxygen species (ROS), microvascular obstruction, and increased inflammation. The course of the disease, when there is an IRI, is also rapid, with the patient deteriorating quickly, leading to death or long-term sequelae.[4,5]

At present, there have been several efforts made to prevent IRI. Currently, a scoring system can detect post-reperfusion microvascular obstruction before reperfusion therapy, namely the ATI score or SAK score. However, this score is still in the development stage and needs to be determined how effective it is. Apart from that, there have also been efforts to carry out preventive therapy, which is currently being carried out in many experimental studies on animals to see its effectiveness, for example, the administration of microRNA, melatonin, and other biological agents that fight specific inflammatory biomarkers. Scientific developments in inflammation and its mediators have also led to many treatment options to prevent excessive inflammation, one of the main pathophysiologies of IRI.[4–6]

As the basic pathogenesis of IRI is generally influenced by inflammation, this literature search aims to see the effectiveness of giving anti-inflammatories before giving action to patients who will undergo reperfusion therapy.

CLINICAL QUESTION

A 67-year-old male patient complained of swollen feet 3 years before entering the hospital. The patient feels that his feet are sometimes cold and often painful. The pain is intermittent and has been felt since three years ago. The pain is like being stabbed, and it is not known what relieves or aggravates the pain. History of DM was denied, but the patient has had hypertension since five years ago. On physical examination, there was swelling in both legs, especially on the left leg, pale conjunctiva, and minimal pulmonary crackles. The stomach feels weak; no muscular defense and decreased bowel sounds are found. The patient finally underwent arteriography and found a total occlusion in the left iliac osteal to the left CFA. There was also a thrombus in the external iliac artery and the right posterior tibial artery. Based on the complaints and the results of the patient's examination, a diagnosis of PAD/peripheral arterial disease was made. After that, the patient was indicated to perform percutaneous transluminal angioplasty to open the blood flow back down where the blood vessel occlusion occurred.

After the procedure, the patient experienced abdominal pain, tightness, decreased blood pressure, and decreased consciousness. The patient then did not respond and was found to be experiencing respiratory and cardiac arrest. The patient was then carried out cardiopulmonary resuscitation and intubation. The initial blood pressure before the procedure was 151/76 mmHg, but after code blue, the patient's blood pressure was never more than 91/40 mmHg. Finally, the patient was transferred to the ICU and monitored and supported through inotropes, vasopressors, and ventilators. The patient was said to be in a coma without sedation during treatment. The patient was also known to have anemia (Hb 9.8), hyperleukocytosis (120300), and increased platelets (443000). In addition, the patient also experienced metabolic acidosis (pH 6.9, pCO2 37.5, pO2 58.3, HCO3 8.3), hyperlactatemia (14.2), and recurrent hypoglycemia (blood glucose level 36). Therapy using bicarbonate of

acid and D40% is given to correct the situation. The patient's acral is also always cold during treatment, and the patient has anuria. The patient's drug support has been given to the maximum, but the patient's condition is getting worse. The patient also experienced repeated cardiac arrest, and finally, the patient died.

The clinical question for this EBCR is: "How is the effectiveness of anti-inflammatory therapy before reperfusion therapy in patients with ischemic vascular disease on the incidence of ischemic reperfusion injury?"

METHODS

The search was carried out on three databases: PubMed, EMBASE, and Scopus. The search was carried out on September 10th, 2023. The keywords used were "ischemic disease", "anti-inflammatory agents", "reperfusion therapy", and "ischemic reperfusion injury". Details regarding the literature search strategy can be seen in **Table 1**—literature search strategy. When the duplication test was carried out, it was found that 74 studies were the same, so they were excluded. Inclusion criteria were studies in ischemic disease patient populations who would undergo reperfusion therapy, studies giving anti-inflammatory agents to patients before reperfusion therapy, and studies looking at the incidence of ischemic reperfusion injury as a result of their studies. Meanwhile, the exclusion criteria were studies that did not have the full text; and studies in a language other than Indonesian or English.

Table 1. Searching Query

Database	Searching Query	Hits
Pubmed	((((((((((("ischemic disease"[All Fields]) OR ("ischemic"[Title/Abstract])) OR (ischemia[MeSH Terms])) OR ("stroke"[Title/Abstract])) OR (stroke[MeSH Terms])) OR (disease, ischemic heart[MeSH Terms])) OR ("ischemic heart disease"[Title/Abstract])) OR ("ischemic limb"[Title/Abstract])) OR (ischemic limb[MeSH Terms])) AND ((((("reperfusion therapy"[All Fields]) OR (reperfusion)) OR ("revascularization"[Title/Abstract]))))) AND ((((((((("anti inflammatory drug"[All Fields]) OR ("anti inflammation"[Title/Abstract])) OR (agents, anti inflammatory[MeSH Terms])) OR ("anti inflammatory agents"[Title/Abstract])) OR (agents, anti inflammatory[MeSH Terms])) OR (agents, non steroidal anti inflammatory[MeSH Terms])) OR (agents, nonsteroidal anti inflammatory[MeSH Terms])) OR (anti inflammatories[MeSH Terms])) OR ("anti inflammatory agents non steroidal"[Title/Abstract])) OR ("anti inflammatory agents steroidal"[Title/Abstract]))) AND ((((reperfusion injury[Title/Abstract]) OR ("reperfusion injury"[MeSH Terms])) OR ("ischemic reperfusion injury"[Title/Abstract])) OR (ischemic reperfusion injury[MeSH Terms]))	792
EMBASE	('ischemic disease':ti,ab,kw OR 'ischemia':ti,ab,kw OR 'ischemic':ti,ab,kw OR 'stroke':ti,ab,kw OR 'ischemic heart':ti,ab,kw OR 'ischemic limb':ti,ab,kw OR 'ischemic cerebral':ti,ab,kw) AND ('reperfusion therapy':ti,ab,kw OR 'reperfusion':ti,ab,kw OR 'revascularization':ti,ab,kw) AND ('anti inflammatory drug?':ti,ab,kw OR 'anti inflammatory agent?':ti,ab,kw OR 'steroid':ti,ab,kw OR 'nsaid':ti,ab,kw OR 'non steroidal anti inflammatory drug':ti,ab,kw) AND ('reperfusion injury':ti,ab,kw OR 'ischemi? reperfusion injury':ti,ab,kw)	215
Scopus	(TITLE-ABS-KEY (ischemic AND disease) AND TITLE-ABS-KEY (reperfusion AND therapy) AND TITLE-ABS-KEY (anti AND inflammatory AND agents) AND TITLE-ABS-KEY (reperfusion AND injury) OR TITLE-ABS-KEY (anti AND inflammatory AND drugs) OR TITLE-ABS-KEY (ischemic AND heart AND disease) OR TITLE-ABS-KEY (ischemic AND limb AND disease) OR TITLE-ABS-KEY (stroke) OR TITLE-ABS-KEY (ischemic AND cerebral AND disease) OR TITLE-ABS-KEY (revascularization) OR TITLE-ABS-KEY (ischemic AND reperfusion AND injury))	138

RESULTS

There are 1145 identified articles. Furthermore, 74 articles were after the duplication test. Subsequently, 1072 articles were screened according to PICO, clinical question type, and study design. Two hundred fifty-eight articles were preclinical reviews, 385 were experimental studies in animals, 42 were in pediatric/neonatal populations, 165 were with interventions other than anti-inflammatory agents, 49 did not compare with standard therapy, and 158 had different outcomes, not an IRI event. Thus, 13 studies were obtained after screening titles and abstracts. After that, four other studies were excluded because they needed the complete text, one other study because they used a language other than Indonesian/English, and one other study only in the form of a research protocol. So there are seven selected articles. The article selection scheme can be seen in **Figure 1**.

a. Study Summary

The studies used in this report are randomized controlled trials and meta-analyses of randomized controlled studies. The study population included patients who underwent reperfusion therapy. Reperfusion therapy was varied in each study, but all procedures still have a hypoxic or ischemic period and a reperfusion period. Several procedures are included in this report, namely primary coronary artery bypass graft (CABG), laparoscopic liver resection (LLR), hepatic resection, and kidney transplant. Of the seven literatures included in this study, none of them describe the role of anti-inflammatory agents specifically in patients with PAD receiving reperfusion therapy. The anti-inflammatory agents used are various, namely N-acetylcysteine (NAC), methylprednisolone (MP), Titilazad-Mesylate (TM), and pexelizumab. Most of

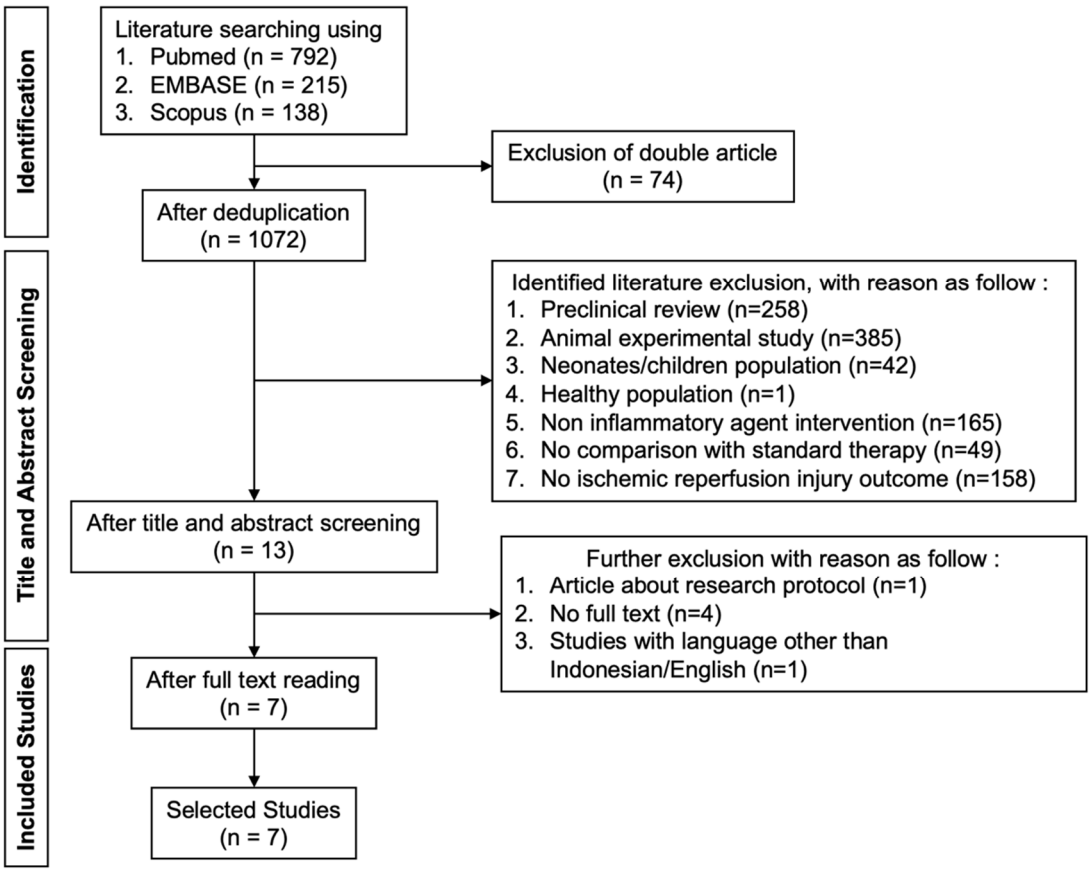


Figure 1. Searching strategy flowchart.

the selected articles use anti-inflammatory agents in the form of MP. The controls in each study were patients who received a placebo with preparations that resembled those in the intervention group.

Meanwhile, the outcomes of the included studies varied. Several studies focused on outcomes such as interleukin 6 (IL-6) levels, glutathione disulfide (GSSG) levels, and specific biomarker levels such as CK-MB, SGOT, SGPT, and bilirubin. In addition, several studies have also looked at the outcome of organ function after reperfusion therapy and death after reperfusion. Details of each study used in this report can be seen in **Table 2**.

b. Critical Appraisal

The authors conducted the critical appraisal using the CEBM University of Oxford English questionnaire set for the randomized controlled study and the CEBM University of Oxford Q-Faith set for the meta-analysis study. Each study was assessed for validity, importance, and applicability. The validity of each study was assessed by answering a set of questions and categorizing the answers to each question into yes, no, and unclear categories. In addition, in the interest section, each available study output data will calculate how relative risk (RR), absolute risk reduction (ARR), relative risk reduction (RRR), and number needed to treat (NNT). Then for applicability, it is displayed as a collection of answers to questions related to applying study results in daily clinics, especially in Indonesia. [7]

c. Validity

All randomized controlled studies included in this report are valid based on the assessment results using a questionnaire tool. Several studies do not all have a "Yes" answer to every tool question, but their validity can still be maintained. First, in the study of El-Hamamsy I et al. (2007)[8], it is known that randomization and how to analyze the research results need to be clearly stated in the text. However, the prospective type of study with a year-long sample collection period made randomization of patients to specific groups, not a problem. In addition, in the biomarker study, not all research subjects had their blood drawn, but only 12 people, through calculations, could be representative of the study population.

In the study of Volk T et al. (2003)[9], it was found that there was also group randomization and an unclear method of analysis. In this study, it has yet to be discovered who is the party that randomized the groups. In addition, this study also compared two drugs at once in 1 study in the same control group. However, with the characteristics of research subjects between groups that did not differ at the outset, the outcomes of each intervention group could be compared to the control group. Then there are also studies by Hasegawa Y et al. (2019)[10] and Aldrighetti et al. (2006)[11], which only included some of the patient population in the study. This is because both use per-protocol analysis, in which patients excluded in the middle of the study will not enter their data for analysis. According to the authors, per protocol analysis is essential in this report because it reduces the influence of procedural errors on the research results.

In addition, a validity study was also carried out on meta-analysis studies from randomized controlled studies, namely from studies by Tohidinezhad F et al. (2020)[12]. The results of the internal validity review can be seen in **Table 4**. This study analyses each agent that can prevent IRI in renal transplant patients. Overall, the study is valid, and what will be analyzed next is the analysis of anti-inflammatory agents in preventing post-reperfusion renal function decline. The quality of this meta-analysis needs special attention because almost all the studies included are of low to moderate quality. In addition, not all study results show the same results. Several studies state that anti-inflammation prevents it effectively, and several studies state that anti-inflammation is ineffective in preventing post-reperfusion function decline.

Table 2. Study Characteristics

No.	Author (year)	Title	Study Design	Population	Intervention	Control	Outcome	Additional Notes
1	El-Hamamsy, et al (2007)	Effect of intravenous N-acetylcysteine on outcomes after coronary artery bypass surgery: A randomized, double-blind, placebo-controlled clinical trial	Randomized Controlled Trial	100 patients who will undergo primary CABG with CPB	50 patients Administration of oral NAC was given 600 mg the day before and the morning before surgery. NAC bolus of 150 mg/kg within 15 minutes before the first incision, followed by an infusion rate of 12.5 mg/kg/hour for 24 hours.	50 patients Oral and IV placebo preparations in the same dosage form and administered according to the same protocol	1. IL-6 levels between the intervention and control groups did not differ significantly, although IL-6 levels in the intervention group were relatively lower. 2. There were three events of postoperative myocardial infarction in the intervention group and one event in the control group	Perioperative administration of NAC to patients undergoing primary CABG with CPB did not improve postoperative clinical and biochemical outcomes.
2	Volk T, et al (2003)	Effects of different steroid treatment on reperfusion-associated production of reactive oxygen species and arrhythmias during coronary surgery	Randomized Controlled Trial	36 patients with three-vessel disease and stable angina pectoris	12 patients were given MP 15 mg/kg 12 patients were given TM 10 mg/kg	12 patients were given an equal volume of placebo 1.5 hours before circulation	1. There was no significant difference in GSSG concentrations between patients on MP, TM, and placebo 2. Malondialdehyde in the MP and TM groups was significantly lower than in the placebo group. 3. 6 placebo patients had arrhythmic disorders, 6 MP patients and 5 TM patients had arrhythmic disorders post revascularization	Giving MP and TM can reduce the damage to the membrane layer. There is no significant effect on post-reperfusion cardiac function
3	Hasegawa Y, et al (2019)	Glucocorticoid use and ischemia-reperfusion injury in laparoscopic liver resection: Randomized controlled trial	Randomized control trial	124 patients who will undergo laparoscopic liver resection (LLR)	50 patients were given MP 500 mg dissolved in saline solution during anaesthesia induction	50 patients were given saline solution alone during anaesthesia induction	1. The two groups did not differ in post-hepatectomy liver failure. 2. IL-6 was significantly lower in the intervention group when compared to the control group	There were 12 patients from the intervention group and 12 patients from the control group excluded because Pringle's maneuver was not performed. Preoperative glucocorticoids can improve patient safety against ischemic reperfusion injury.

4	Aldrighetti EI, et al (2006)	Impact of Preoperative Steroids Administration on Ischemia-Reperfusion Injury and Systemic Responses in Liver Surgery: A Prospective Randomized Study	Randomized control trial	76 patients for elective hepatic resection sequentially	36 patients were given 500 mg of methylprednisolone dissolved in 100 mL of saline before induction of anesthesia	37 patients were administered 100 mL saline solution before induction of anesthesia	1. Outcomes of bleeding (1-0), bile leak (1-0), cardiovascular disorders (3-0), pleural effusion (1-1), and hepatic decompensation (4-2) were more common in control group patients. 2. Body IL-6 levels were significantly lower in the intervention group when compared to the control group	There were two patients from the intervention group and one patient from the control group were excluded. Preoperative steroid administration may reduce the incidence of ischemic reperfusion injury by modulating the inflammatory response.
5	Tohidinezhad F, et al (2020)	Prevention of Ischemia-Reperfusion Injury in Human Kidney Transplantation: A Meta-analysis of Randomized Controlled Trials	Meta-analysis of randomized controlled trials	31,334 kidney transplant patients from 33 RCTs	15,809 Patients were grouped into the innate inhibitor, antioxidant, anti-inflammatory, or CCB interventions	1,525 patients were given the placebo	Administration of anti-inflammatories is not significant to the incidence of delayed graft function. In anti-inflammatory administration, the RR was 0.85 [0.61; 1.17].	Delayed graft function as a manifestation of ischemic reperfusion injury. Giving natural inhibitors can have significant side effects, such as infection.
6	Pulitano C, et al (2007)	Prospective randomized study of the benefits of preoperative corticosteroid administration on hepatic ischemia-reperfusion injury and cytokine response in patients undergoing hepatic resection	Randomized control trial	43 consecutive elective hepatic resection patients	21 patients were given 500 mg methylprednisolone before surgery	22 patients were given the placebo before surgery	1. Postoperative complications in the control group were 14 out of 22 people, while those in the steroid group were 2 out of 21. 2. Serum IL-6 in both was significantly lower in the intervention group when compared to the control group.	Preoperative steroid administration may be a protective strategy against ischemic reperfusion injury.
7	Verrier ED, et al (2004)	Terminal Complement Blockade With Pexelizumab During Coronary Artery Bypass Graft Surgery Requiring Cardiopulmonary Bypass	Randomized control trial	3,099 patients who underwent CABG surgery without valve surgery	1,553 patients receiving pexelizumab (2 mg/kg bolus and 0.05 mg/kg/hour for 24 hours	1,546 patients received a placebo and continuous infusion	Death from any cause within four days after CABG in patients in the intervention group was reduced by 24%.	The study uses intervention analysis both by intention to treat and per protocol. Giving pexelizumab can be a new approach to prevent perioperative myocardial infarction and has a good safety profile.

Table 3. Validity Appraisal of Randomized Controlled Studies

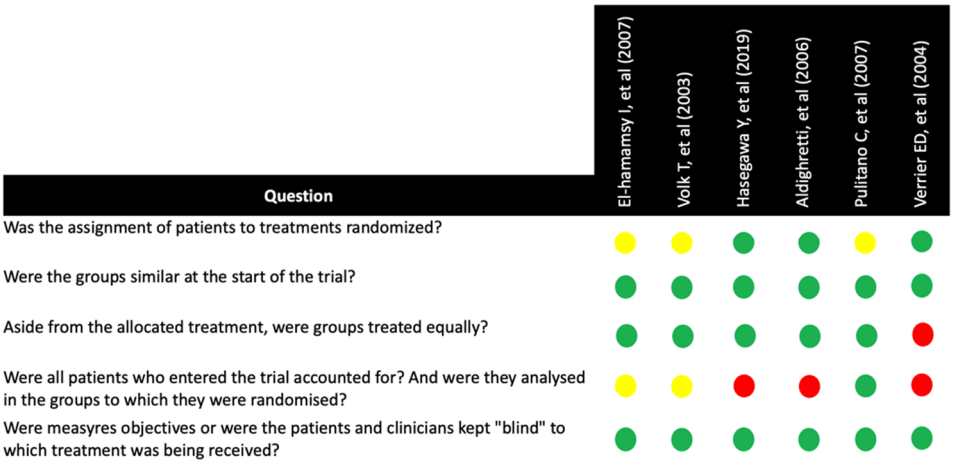
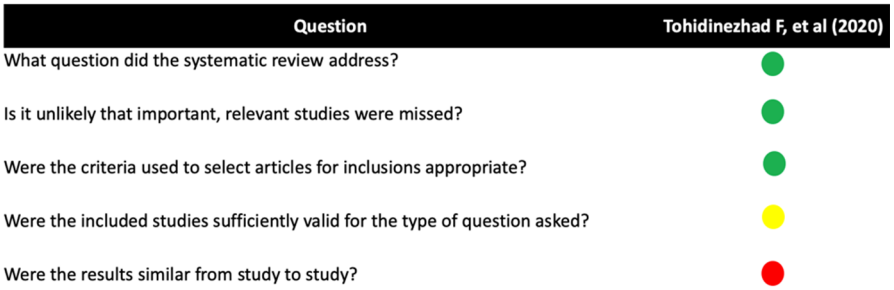


Table 4. Validity Appraisal of Systematic Review



d. Importance

The author calculates the importance of each study by calculating the control event rate (CER), event event rate (EER), RR, ARR, RRR, and NNT. Calculations were performed manually by considering output data such as organ function, mortality, or morbidity from the intervention patient group and post-intervention controls. The importance of each intervention in each study was calculated, and the combined importance of each study is shown in **Table 5**.

Table 5. The Effect of Anti-inflammatory Therapy on Ischemic Reperfusion Injury (IRI).

Type of intervention		NAC	MP	TM	MP	MP	Anti-Inflammation	MP	Pexelizumab
No	Parameter	El-Hamamsy (2007)	Volk T, et al (2003)		Hasegawa, et al (2019)	Aldrighetti, et al (2006)	Tohidinezad, et al	Pulitano C, et al (2007)	Verrier ED, et al (2004)
1	CER	0.46	0.5	0.5	0.04	0.54	0.28	0.636	0.093
2	EER	0.54	0.5	0.41	0.04	0.138	0.24	0.095	0.067
3	RR	1.17	1	0.82	1	0.256	0.85	0.149	0.73
4	ARR	0.09*	0	0.09	0	0.402	0.04	0.541	0.025
5	RRR	17*	0	18%	0	74.44%	14.44%	85%	27%
6	NNT	11*	0	11	0	3	25	2	40

Abbreviation: CER = control event rate; EER = event rate; RR = relative risk; ARR = absolute risk reduction; RRR=relative risk reduction; NNT= number needed to treat; NAC= N-acetylcysteine; MP = methylprednisolone; TM = tirilazad-mesylate. *=ARR converted to absolute risk induction (ARI), relative risk induction (RRI), and number needed to harm (NNH).

The results of the importance of each study also varied, where there were studies that had ineffective and ineffective intervention results. In the intervention with N-acetylcysteine (NAC), it is known that NAC therapy before reperfusion is not effective in preventing IRI and even tends to be more dangerous because there are more bad outcomes in patients with NAC intervention than the control group. In addition, the methylprednisolone (MP) intervention in the study of Volk T et al. (2003)[9] and the MP intervention in Hasegawa study, et al. (2019)[10] found that MP was not effective in preventing IRI due to the same outcome between the control group and the intervention group. Then, in several interventions such as Tirilazad-Mesylate (TM) in the study of Volk T et al. (2003)[9], MP in the study of Aldrighetti L et al. (2006)[11] and Pulitano C et al. (2007)[13], anti-inflammatory agents in the study of Tohidinezad F et al. (2020)[12], as well as pexelizumab in the study of Verrier ED et al. (2004)[14], it was found that the results of the intervention were effective in preventing IRI with an RRR that varied from 14% to 85%.

In addition to looking at the effectiveness of therapy with RRR, it can also be seen how many patients need to be treated (NNT) or the minimum number of patients who need intervention to prevent one incident of IRI. In the NAC intervention, where poor outcomes were more common in the intervention group, there were 11 outcomes, but with the interpretation of the number needed to harm (NNH) or the minimal number of patients who were given intervention to create one IRI event. In addition, the NNT in the MP intervention in the studies of Volk T et al. (2003)[9] and Hasegawa et al. (2019)[10] could not be determined due to the same outcome between the control and intervention groups. Then, in the TM intervention in the study of Volk T et al. (2003)[9], it was found that NNT was in 11 patients. Meanwhile, the MP intervention in Aldrighetti L et al. (2006)[11] study and Pulitano C et al. (2007)[13] Found that the NNT was 3 and 2, respectively. Then, the NNT in the anti-inflammatory intervention in the study of Tohidinezad F et al. (2020)[12] Known to be up to 25 patients. Finally, the NNT in the pexelizumab intervention in the Verrier ED et al. (2004)[14] The study reached 40 patients.

Apart from seeing how effective it is on the clinical incidence of IRI, there is also an analysis to see how the effect of the intervention is on IL-6 levels in the body. Several studies reporting the results of the IL-6 intervention group and the control group can be seen in Table 6. In El-Hamamsy et al.'s (2006)[8] Study, the differences in preoperative and postoperative IL-6 levels of the intervention and control groups were not significantly different. However, in the studies of Hasegawa Y et al. (2020)[10], Aldrighetti L et al. (2006)[11], and Pulitano C et al. (2007)[13], it was found that the difference in IL-6 levels between the intervention and control groups postoperatively was significantly different, where IL-6 levels were higher in the control group.

Table 6. The Effect of Anti-inflammatory Therapy on IL-6 Levels.

No	Author (year)	IL-6 Level before Surgery (pg/mL)		p-value	IL-6 Level after Surgery (pg/mL)		p-value
		Intervention	Control		Intervention	Control	
1	El-Hamamsy, et al (2006)	5.9	3.9	>0.05	161.3	184.3	>0.05
2	Hasegawa Y, et al (2020)	2.5	2.9	0.905	10	60	<0.0001*
3	Aldrighetti, et al(2006)	1	1	>0.05	34	88	0.034*
4	Pulitno C, et al (2007)	1	1	0.81	23	61	0.001*

e. Applicability

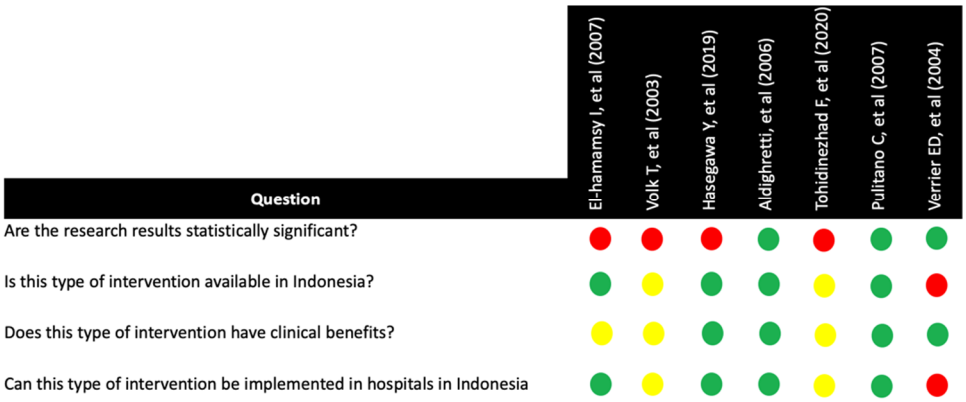
The applicability of the included studies is shown in **Table 7**. The assessment is based on questions about applying interventions in clinical situations and conditions in Indonesia and on case illustrations. Thus, the questions set are whether the research results are statistically significant, whether the type of intervention has clinical benefits, whether the type of intervention is available in Indonesia, and whether the type of intervention can be implemented in hospitals in Indonesia.

The study of El-Hamamsy I et al. (2007)[8] found that the study's results were not statistically significant, and it was not known whether there were any clinical benefits. However, the interventions are available in Indonesia and can be implemented in hospitals. Then in the studies of Volk T et al. (2003)[9] and Tohidinezhad F et al. (2020)[12], it is also known that there are non-significant research results and clinical benefits, availability of interventions, and unclear effectiveness. Meanwhile, in the study of Hasegawa Y et al. (2006)[10], it was found that the research results were not significant. However, the clinical benefits of the intervention were known to be helpful. Interventions are also available and able to be implemented in Indonesia. Then there are studies by Aldighretti L et al. (2006)[11] and Pulitano C et al. (2007)[13], which are equally statistically significant, clinically beneficial, and interventions are available and capable of being implemented in hospitals in Indonesia. Then there is a study by Verrier ED et al. (2004)[14] whose research is statistically significant and clinically helpful but is unavailable and cannot be implemented in Indonesia.

DISCUSSION

Of the seven literatures included in this study, none of them describe the role of anti-inflammatory agents specifically in patients with PAD receiving reperfusion therapy. Anti-inflammatory agents are known to be useful clinically to reduce inflammation in the body. Based on the results of a literature search in randomized controlled studies in humans, it is known that the anti-inflammatory agents that can be used sequentially from the most effective are methylprednisolone (MP), Pexelizumab, TM, and NAC. MP is the first recommendation as an anti-inflammatory agent to prevent IRI events because it can prevent IRI events by 75-85%, with the number of patients needing treatment to prevent one IRI event <5. In addition, MP significantly reduced IL-6 levels objectively compared to patients who did not receive MP before reperfusion. MP works as an anti-inflammatory by suppressing the synthesis of cyclooxygenase (COX)-2, which causes a decrease in prostaglandins, restores vascular permeability, suppresses the migration of fibroblasts and polymorphonuclear leukocytes (PMN), controls the rate of protein synthesis, and stabilizes lysosomes at the cellular level. MP preparations are easy to obtain in Indonesia, and

Table 7. Applicability of the studies.



its intravenous administration before reperfusion therapy can also be administered in hospitals in Indonesia. The dose that can be given to patients is 500 mg intravenously before the reperfusion procedure begins. However, it is also necessary to pay attention to the side effects of giving MP that can arise, such as the risk of infection, the risk of hyperglycemia, and the symptoms of dyspepsia.[10–15]

Furthermore, pexelizumab is the second agent that is effective in preventing IRI. Pexelizumab is a human monoclonal antibody known to inhibit complement C5. It is also known that the complement system is also activated during inflammation and plays an essential role in apoptosis. C5 is known to cleave into C5a and C5b. C5a can be an anaphylatoxin and proinflammatory mediator.

In comparison, C5b can form C5b-9, which forms the membrane attack complex (MAC). MAC then plays a role in thrombosis, inflammation, and tissue damage through osmotic lysis. Pexelizumab has a significant role in inhibiting the conversion of C5 to C5a and C5b. Based on the author's analysis, pexelizumab reduced a person's risk of experiencing IRI by 27%, with the number of patients who needed to be treated to prevent one incident of IRI by 40 patients. Also, objectively, pexelizumab significantly reduced serum complement levels compared to the group that did not receive pexelizumab. However, unfortunately, pexelizumab is not yet available in Indonesia as a monoclonal antibody preparation. The use of monoclonal antibodies in Indonesia itself is still more often used in malignancy or chronic inflammation cases to suppress the body's immune system. An example is tocilizumab which has a mechanism as an IL-6 receptor inhibitor.[14–16]

Another agent that can also reduce the risk of ischemic injury is TM. As an aminosteroid, TM is known to have fewer gene regulatory effects than MP, and its effectiveness has been proven in subarachnoid hemorrhage. The mechanism of action of TM is an inhibitor of lipid peroxidation and is cytoprotective. So to measure its effectiveness, we can see the formation of malondialdehyde (MDA), a marker of inflammation due to lipid peroxidation. MDA release is known to be significantly reduced in patients administered TM. The risk of IRI in patients receiving TM can be reduced by 18%, and the number of patients who need to be treated with TM to prevent one IRI event is 11 patients. Although effective, TM preparations are unavailable in Indonesia, so they cannot be applied.[9,17]

Finally, an agent known to reduce the risk of IRI is N-acetylcysteine (NAC). NAC is known to have anti-inflammatory effects because it acts as a precursor of glutathione (GSH). NAC also affects signaling pathways in cells and reduces cytokine production early in the inflammatory response. In addition, NAC also protects cellular membranes through sulfhydryl groups and maintains endothelial function. Although NAC is theoretically beneficial, in tracing studies, it is ineffective in preventing IRI. IL-6 levels were also not significantly different between the groups that received NAC and the groups that did not receive NAC. On the other hand, NAC is a drug readily available in Indonesia, and administration of NAC before reperfusion therapy can be carried out in hospitals in Indonesia. It is possible that NAC has no role in inhibiting the pathogenesis of IRI events and does not affect IL-6 levels directly.[8,18]

CONCLUSION

Administration of anti-inflammatories before reperfusion is effective in preventing IRI. Treatment with methylprednisolone 500 mg intravenously before reperfusion therapy reduces the risk of IRI by 74-85%. Treatment with intravenous pexelizumab at a bolus dose of 2 mg/kg followed by a continuous infusion of 0.05 mg/kg 24 h <10 minutes before reperfusion therapy reduced the risk of IRI by 27%. Treatment with 10 mg/kg of Tirilazad-Mesylate before reperfusion therapy reduced the incidence of IRI by 18%. NAC therapy before reperfusion was ineffective in reducing the risk of IRI.

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