DOI: 10.5455/msm.2024.36.77-81
Received: Jan 19 2024; Accepted: Feb 25, 2024

REVIEW

Mater Sociomed. 2024; 36(1): 77-81

Medical, Surgical and Experimental Approaches to Acute Mesenteric Ischemia and Reperfusion

Zoran Matkovic[1], Zoran Aleksic[2,3]

[1]Department of Abdominal Surgery, General Hospital Doboj. Doboj, Bosnia and Herzegovina

[2]Clinic for General and Abdominal surgery, University Clinical Centre of the Republic of Srpska, BanjaLuka. Banja Luka, Bosnia and Herzegovina

[3]Faculty of Medicine, University of Banja Luka. Banja Luka, Bosnia and Herzegovina,

Coresponding autor
Zoran Matkovic, MD. Department of Abdominal Surgery, General Hospital Doboj. Doboj, Bosnia and Herzegovina. Phone: :+387 65 740 459. E-mail : zoranmatna@gmail.com.

ABSTRACT:

Background: Acute mesenteric ishemia(AMI) is a rare but very serious disease with high rate of mortality and morbidity. About 1-2% of all gastrointestinal disease is AMI. Mortality is about 60-80% and depends of time between starting of symptoms and establishing of diagnosis, type AMI, comorbidities. AMI is often in older population with coronary syndrom and atrial fibrilation. AMI may be occlusive(embolisatio arteriae mesentericae superior(AMS), or thrombosis of AMS, mesenterial vein thrombosis) and nonoclusive form(NOMI). NOMI is rising in critical ill patients in shock or sepsis. Pathophysiology of AMI is very complex and significant role in this proces has ischemia and also reperfusion. Reperfusion injury including oxidative stres, inflamation, infection. The best diagnostic approach is CT angiography but after high clinical suspicion on AMI. Patients have sudden, catastrophic abdominal pain, vomitus, bloody diarrhoea. Therapy is multidisciplinary-basic treatment(resuscitation with cristaloids, antibiotic, anticoagulans...), surgical treatment-resection necrotic segments of intestinum without anastomosis or endovascular treatment. In early phases conservative treatment is possible(vasodilatation, thrombolysis). In some countries there are Intestinal Stroke Centers (ISC) in which patients with AMI have better prognosis. Because of progressive nature of AMI(rapide worsening) rare are clinical study,but there are many experimental study on animal models. Most of experimental study investigate protective effects of some supstances on damage on intestinum and remote organs during ishemia and reperfusion**. Objective:** To present literature data of clinical and experimental study, describe experiments on animal models and mention supstances whit promising results in protective strategies during AMI. **Methods:** We analysed Pubmed by using mesh terms such as acute mesenteric ischemia, intestinal injury, reperfusion, experimental study, clinical and therapeutic approach**. Results**: Sudden abdominal pain resists on **o**pioids analgetics**,** high rate of CRP, hyperlactatemia, increase of D dimer is enough for suspicion of AMI. Often is delayed in establishing of diagnosis of AMI. CT angiography has sensitivity of 94%. Pneumatosis is sign of necrosis of intestinal wall. Classical surgical approach is dominant, more than 70%,. Endovascular treatment became often last few years. Experimental studies investigate occlusion of AMS with atraumatic clamp, with schemia and reperfusion in different intervals Most animals models are on wistar male rats. **Conclusion:** AMI has still high rate of mortality. Better diagnostic and therapeutic principles (shorter interval between appearance of symptoms and starting of therapy, multidisciplinary approach, higher percent of endovascular procedures), could decrease mortality. Experimental studies on animal models may be succesfull in development of new clinical, conservative approaches in the early phases of AMI in the future.

Keywords: acute mesenteric ischemia, reperfusion, experimental study.

1. BACKGROUND

Acute mesenteric ishemia (AMI) is a rare but very serious urgent disease with high mortality and morbidity. AMI accounts for 1 do 2% of all gastrointestinal diseases. It is thought that 1 in 100 patients with a clinical picture of acute abdomen actually has AMI. Mortality is between 60 and 80% (1). AMI is a critical and sudden interruption of blood

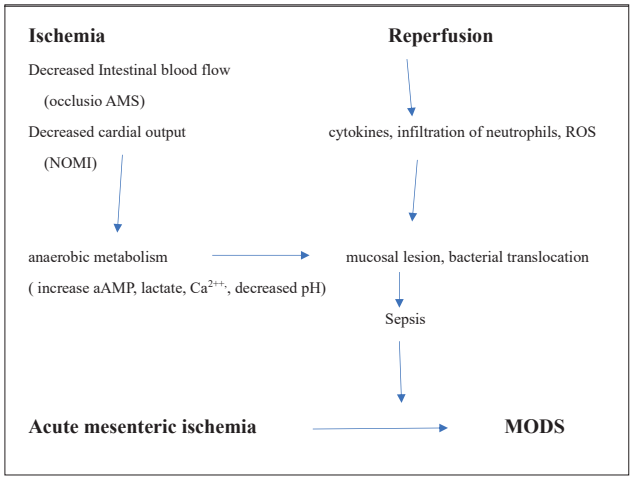

Figure 1. Patophysiologic mechanisms during AMI

flow to the mesentery with funkctional and structural changes in the intestine and distant organs (2). This complex disease most often affects the elderly population with advanced atherosclerosis,with atrial fibrilation, heart failure and other comorbidities.In people over 80 years of age , AMI is a more common cause of acute abdomen than acute appendicitis (3, 4). AMI can be divided into occlusive and non-occlusive forms.(NOMI)

The occlusive form includes:

* Embolization of superior mesenteric artery(AMS) in 40-50% cases.

* Thrombosis of AMS in 25-30% cases.

* Mesenteric venous thrombosis (MVT)in 10-18% cases.(in malignancy, necrotizing pancreatitis, myeloproliferative diseases, protein C and S deficiency, intraabdominal infection,venous trauma).

The non-oclusive form accounts for 20% of all cases of AMI and is found in critically ill patients and in a state of shock, sepsis, where there is hypoperfusion due to the centralization of blood flow caused by the use of vasoconstrictors (5, 6). Despite advances in diagnosis and therapy, AMI remains a highly lethal disease for more than 50 years with perioperative mortality of over 50%. Overal survival has not changed for decades (7). One of the main problems is the delay in establishing a diagnosis and starting treatment. The presentation of the disease is catastrophic pain, the intensity of which does not corespond to the palpation findings. The small intestine is very sensitive to ischemia. The intestine requires about 25% of the minute volume and the pain occurs due to the disproportion between the needs and the amount of available oxygen (8). In anaerobic conditions, pyruvate turns into lactate, which irritates the nerves in the intestines (5, 9, 10). After 6 to 8 hours, there is a reduction in pain due to nerve damage, there is an asymptomatic interval that is temporary and marks the begining of the disaster (11). With the duration of the interruption of circulation, there is a violation of the intestinal barrier and the occurence of bacterial translocation. Endotoxins and bacteria cross the mesenteric lymph nodes and portal vein and s systemic disorder occurs. Necrosis of the intestinal wall occurs after ischemia (11). Initial clinical suspicion that is AMI is very important (12).

The goal is to shorten the time from the onset of symptoms and diagnosis to therapeutic treatment. Every 24-hour delay doubles mortality (2). Survival is about 50% when the diagnosis is made in the first 24 hours, but depends a lot on the AMI subtype. For example: improvement of perfusion and vasospasm in NOMI will enable a favorable outcome in a significant percentage of patients. MVT is considered to have a very poor prognosis. The establishment of blood flow leads to reperfusion, which often causes more damage than that caused by the previous ischemia. The shock wave of oxygen leads to the oxygen paradox (Dual-Hit hypothesis) (13). Bad effects on the organs can be reduced by the action of antioxidants in that phase (14). In the literature this is known as an intestinal ischemia-reperfusion lesion.(IIRI).

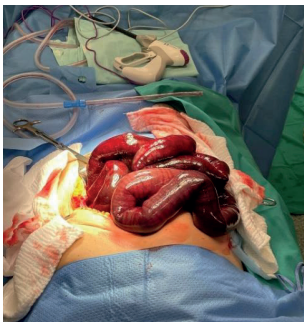

Figure 2. Gangrene of intestinum

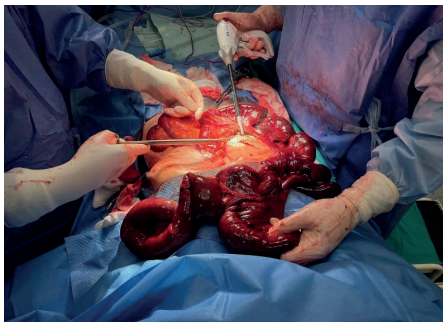

Figure 3. Resection of gangrenous segment of intestinum

In 1986, Parks and Granger were the first to describe the harmful effect of reactive oxygen species created during reperfusion, noting that reperfusion injury is greater than ischemia itself (15). What sets this ischemic reperusion injury apart from the same lesions on other organs(myocardial infarction, cerebrovascular insult, liver and kidney lesions) is the certain occurence of a septic condition due to the already mentioned disruption of the intestinal barrier and bacterial translocation. Multiorgan dysfunction syndrome (MODS) caused by combination of AMI and sepsis is the most common cause of death (16). The mechanism of changes includes oxidative stress, inflammation, the action of the microbiome (17, 18).

Acute mesenteric ischemia MODS

With the interruption of circulation, anaerobic metabolism occurs. The level of adenosine triphosphate decreases, acidity increases, disturbances in the operation of ion pumps occur, which leads to the activation of phospholipase A2 and lipid peroxidation by opening the mitochondrial transition permeable pore (mPTP). Establishment of blood flow leads to the appearance of reactive oxygen species (ROS). These highly reactive substances can directly damage tissue by acting on the level of mitochondria, but they also affect the infiltration of neutrophils through interleukins and adhesive molecules and in the inflamatory reaction, also leading to cell death (15, 16, 18).

Clinical signs and symptoms	abdominal pain(100%) vomitus(48%) blady diarrhoea (31%)
Laboratory parameters	CRP(100 and more), leukocytosis, increase value of D-dimer, hyperlactatemia (2 mmol and more)
New serological biomarkers of AMI	IMA(ischemic modified albumin),I-FABP(Intestinal faty acid protein), D-lactat, L citrulin.
CT angiography (sensitivity 94%), CT scan	aperistalsis, dilation of intestinum, pneumatosis of intestinal wall (19).

Table 1. Diagnostic findings of AMI

Basic(initial) treatment	iv resuscitation,NG tube,urinary cateter, intravenous antibiotics,anticoagulans,opioids analgetics
Classical surgical treatment (about 80%)	exploratory laparotomy, resection of necrotic segments of intestinum without anastomosis.
Endovascular treatment (about 20%)	Embolectomy, thrombolysis, stenting,by pass
Hybrid treatment	Simultaneous work of abdominal surgeon and vascular surgeon ROMS(retrograde open mesenteric stent)

Table 2. Therapeutic approach

Animals models	Male rats (more than 85%of all study), mice, cats, pigs
Type of ischemia	Occlusion of AMS, occlusion AMS and VMS, low flow occlusion, Ligature of AMS (rare), Porcine model (percutaneous or endovascular Embolization of AMS, Murine mode l(segmental vascular occlusion)
Duration of ischemia	30 -90 minuts
Duration of reperfusion	90-120 minuts.

Table 3. Experimental approach. Occlusion of AMS is usually with atraumatic clamp in most studies(25).

Antioxidants	SOD(superoxide dismutase), GSH(glutation), alfa tokoferol, melatonin ,minocycline,curcumin,cysteine, candesartan...
Antiinflammatory and antiapoptotic substances	Ghrelin, dexmedetomidin, levosimendan, flurbiprofen axetil,,methylprednisolone...
Other substances	sevoflurane, sesamin, iloprost, astaxanthin, magniferin, melatonin,sulphoraphane, papaverine, albumin, albendazole,pentoxifilin, nitrat vasodilatators, low molecular weight heparin, nitroindazol, alopurinol, simvastatin, diltiazem, dioscin, ethanol, estradiol, agmantin,glutamin...

Table 4. List of substances with protective effects during AMI.

2. OBJECTIVE

The aim of this article was to present actual literal data of clinical (patophysiology, diagnostic and therapeutic approach of AMI) and experimental study on animals which investigate AMI. Also, we want to mentioned pharmacological supstances applied in experimental study with protecting effects during ishemia and reperfusion injury of mesenterium.

3. MATERIAL AND METHODS

We analysed recent articles on Pubmed ussed mesh terms such as acute mesenteric ischemia, intestinal injury, reperfusion, experimental study, animals models, clinical and therapeutic approach, and remote organs injury.

4. RESULTS

Numerous pharmacological supstances have protective effects on inestinum and remote organs during acute mesenteric ischemia in animal models (30).

5. DISCUSSION

CT angiography is the best diagnostic test for AMI (sensitivity about 94%, specificy 95%) (19). On CT scan we can see absence of peristalsis, thickening and pneumatosis of bowel wall. Pneumatosis is a sure sign of necrosis. Laparotomy is consider as a gold standard, but it si often late. Laboratory parameters are not specific, but can indicate on development of an acute abdominal surgical disease(leukocitosis, increase of CRP, D- dimer, lactate). New serological biomarkers such as ischemia modified albumin (IMA), intestinal faty acid binding protein (I-FABP), D lactate i L citrulin are not yet used in routine practice (Table 1) (20).

Therapeutic principle is mutidisciplinary approach-cooperation of general or abdominal surgeon, vascular surgeon, interventional radiologist, intensivist, according to the recommendations of WSES (World Society of Emergency Surgery). Corcos was initiated the establishment Intestinal Stroke Center in France, 2016 year. Later publications proved improved survival of patients with AMI treated at such centers (22). Generous rehydration is required (1-2 ml ringer lactate/kg/h), due to losses in the intestinal lumen and peritoneal cavity. Correction of metabolic acidosis and hypokalemia is also required, then placement of nasogastric tube, urinar catheter to measure hourly diuresis. Intravenous antibiotics and anticoagulans (bolus of heparin) and finally surgical treatment are applied. Surgical resections are performed without anastomosis, (Damage control surgery) or if ischemic changes are observed, revascularization is performed. A hybdrid treatment is also possible in larger centers- simultaneos work of abdominal and vascular surgeon (Table 2). An alternative to the surgical approach before the occurence of irreversible changes are anticoagulans, thrombolitics, vasoactive drugs.

According to Fuglseth, timely anticoagulant treatment enables recanalization in 80% of cases (6). Understanding of pathophysiological processes and cascade that occurs during ischemia and reperfusion can conntribute to the development of new therapeutic strategies. Due to the nature of the disease, (rapid deterioration in a short time interval) is not possible for ethicals reasons to conduct clinical studies. That is why experimental animal models were developed. Research therapy of AMI involves a pharmacological approach, and in the last ten years, many substances have appeared with some promising results (23). There is also a non pharmacological approach such as pre- and post-condtitioning. Repeated short-term ischemia and reperfusion make the target intestinal tissue and distant organs more resistant to ischemia-reperfusion injury (24).

Experimental animal models

Most of the experiments were conducted on male Wistar rats. The age of the animals was from 6 to 18 weeks, the weight of the animals was from 200 to 350 grams (25, 26). The most common and best described is the superior mesenteric artery occlusion model. The expected period of ischemia is followed by release of the clamp and a period of reperfusion. Reperfusion is recognized by the appearance of pulsations, the establishment of peristalsis and the light-red color of the intestines (26). Microvascular, atraumatic clamps are used for occlusion to avoid endothelial lesions and to adequately evaluate subsequent reperfusion. The duration of occlusion is between 30 and 90 minutes. Reperfusion time is up to 120 minutes. Taking into account the metabolic rate of rats, this corresponds to clinical events in the human organism, where it takes 6 to 8 hours to reach complete ischemia and reperfusion (27). Experiments with complete vascular occlusion were also performed. A porcine model-percutaneous or endovacular embolization is also used. This model is the closest to the clinical event during acute mesenteric ischemia-the flow occlusion is done internally(from the lumen) as an embolus or thrombus does (25, 26, 28). Described works with segmental vascular occlusion (clamping of individual branches) are known as the Murine model (29). The most frequently measured parameters of oxidative stress (SOD, catalase (CAT), glutation (GSH), hydrogen peroxide, superoxide anion radical), markers of inflammation (TNF-alfa, IL1, IL 6)and endothelial dysfunction (Nitric oxide (NO), Intercellular adhaesion molecule-1, (ICAM-1), Vascular Cell adhaesion molecule, (VCAM-1)). Liver enzymes (aspartat aminotranferase (AST), alanin aminotransferase (ALT), TBARS, (thiobarbituric acid reactive substances) were examined (30). Tissue samples (ileum, liver, kidneys, lungs and heart) are used for assesment of apoptosis.

Aplication of substances in experimental studies were as pretreatment, (most common) in the phase of ischemia (rare) and in the start of reperfusion (30). It is considered that lesions of remote organs mostly arises during early phases of reperfusion, about 1 to 6 hours by signaling way Nuclear factor kapa beta (NF-kB). Most often is a lesion of liver because of blood flow from mesenterium through vena porte (31). Regarding patophysiology of AMI it is develope different mechanisms of protection (32). Numerous substances are ussed in experimental conditions, some of them have shown excellent results and were well tolerated. These agents can act on next different mechanisms: antioxidative, antiinflammatory, antiapoptotic, reinforcement of the cell membrane, amplification of energetic resource of the cell (impact on mitochondria) (Table 4) (14, 27, 30-36). List of substances is not final because the effects of other substances are examined on ischemia-reperfusion lesion of mesenterium and remote organ lesions.

6. CONCLUSION

Acute mesenteric ischemia still remain a clinical chalenge because late recognition and delayed therapeutic treatment are very often. Outcome of treatment actualy depends from interval between starting of symptoms and starting of therapy. Surgical approach (laparotomy, resection) have still a dominant role in the treatment, but there are more often endovascular treatment in the last years. In the last decades there are more and more conservative-pharmacological approach in situations where intestinum is still vital. This approacht arrising defence from reperfusion injury and remote organ injury after recovery of circulation. Most of study is experimental and relate on pretreatment by pharmacological agents. In the future we expect wider aplication of conservative treatment on patients with AMI.

- **Author's contribution:** All authors were involved in all steps of preparation this article. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest:** There are no conflicts of interest.
- **Financial support and sponsorship:** Yes, EU Erasmus.

REFERENCES

1. Acosta S, Bjorck M. Modern treatment of acute mesenteric ischemia. Br J Surg. 2014 jan; 101(1): e100-8.
2. Bala M, Kashuk J, Moore EE, Kluger Y, Biffl W, Gomes CA, et al. Acute mesenteric ischemia: guidlines of the World Society of Emergency Surgery. World Journal Emerg Surg. 2017 aug 7; 12: 38.
3. Karkkainen K, JM, Acosta S.Acute mesenteric ischemia (part I) – incidence, etiologies, and how to improve early diagnosis. Best Pract Res Clin Gastroenterol.2017 Feb; 31(1): 15-25.
4. Kase K, Reintam Blaser A, Tamme K, Mandul M, Forbes A, Talving P, Murruste M. Epidemiology of Acute Mesenteric Ischemia.a Population-Based Investigation. World J Surg 2023 Jan; 47(1): 173-181.
5. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia:a clinical review.Arch Intern Med. 2004 May 24; 164(10): 1054-1062.
6. Fuglseth H, Soreide K, Vetrhus M. Acute mesenteric ischemia. British Journal of Surgery. 2023 Aug 11; 110(9): 1030-1034.
7. Sise MJ. Acute mesenteric ischemia. Surg Clin North Am.2014 Feb; 94(1): 165-181.
8. Zheng l, Kelly CJ, Colgan SP. Physiologic hypoxia and oxygen homeostasis in the healthy intestine. A Review in the Theme: Cellular Responses to Hypoxia. Am J Physiol Cell Physiol.2015 Sep 15; 309(6). C350-60.
9. Tilsed JV, Casamassima A, Kurihara H, Mariani D, Martinez I, Pereira J, Ponchieti L, et al.ESTES guidelines: acute mesenteric ischaemia.Eur J Trauma Emerg Surg 2016 Apr; 42(2): 253-270.
10. Memet O, Zhang I, Shen J.Serological bi omarkers for acute mesenteric ischemia.AnnTransl Med.2019;7:394
11. Khun F, Schiergens TS, Klar E.Acute Mesenteric Ischemia. Visc Med.2020 aug;36(4):256-262.
12. Ahmed M.Ischemic bowel disease in 2021. World J Gastroenterol.2021 Aug 7;27(29):4746-4762.
13. Tabriziani H, Ahmad A, Narasimha D, Bergamaschi R,

Frishman WH. A nonsurgical Approach to Mesenteric Vascular Disease.Cardiol rev.2018 Mar/apr;26(2):99-106.
14. Gutierrez-Sanchez G, Garcia-Alonso I, Gutierrez Saenz de Santa Maria J, Alonso-Varona A, Herero de la Parte B.Antioxidant-Based Therapy reduces Early-Stage Intestinal Ischemia-reperfusion Injury in Rats. Antioxidants(Basel).2021 May 27;10(6):853.
15. Parks DA, Granger DN. Contributions of ischemia and reperfusion to mucosal lesion formation. Am J Physiol.1986; 250(6pt1): G749-G753.
16. Akyldiz Hy, Sozuer E, Uzer H, Baykan M, Oz B. Length of necrosis and renal insufficiency predict the outcome of acute mesenteric ischemia. Asian J Surg. 2015 Jan; 38(1): 28-32.
17. Li G, Wang S, Fan Z. Oxidative stress in Intestinal ischemia-reperfusion.Front Med (Lausanne). 2022 Jan 14; 8: 750731.
18. Nadatani Y, Watanabe T, Shimada S, Otani K, Tanigawa T, Fujiwara Y.Microbiome and intestinal ischemia/reperfusion injury.J Clin Biochem Nutr. 2018 Jul; 63(1): 26-32.
19. Nakashima K, Ishimaru H, Fujimoto T, Mizovaki T, Mitarai K, Nakashima K, Matsuoko Y, Uetani M. Diagnostic performance of CT findings for bowel ischemia and necrosis in closed-loop small-bowel obstruction. Abdom imaging.2015 Jun; 40(5): 1097-1103.
20. Treskes N, Persoon AM, van Zanten ARH. Diagnostic accuracy of nowel serological biomarkers to detect acute mesenteric ischemia:a systematic review and meta analysis. Intern Emerg Med. 2017 Sep; 12(6): 821-836.
21. Block TA, Acosta S, Bjorck M. Endovascular and open surgery for acute occlusion of the superior mesenteric artery. J Vasc Surg. 2010 Oct; 52(4): 959-966.
22. Nuzzo A, Corcos O. Management of mesenteric ischaemia in the era of intestinal stroke center. The gut and life saving strategy. Rev Med Interne. 2017 Sep; 38(9): 592-602.
23. Bertoni S, Ballabeni V, Barocelli E, Tognolini M. Mesenteric ichemia-reperfusion: an overview of preclinical drug strategies. Drug Discov Today. 2018 Jul; 23(7): 1416-1425.
24. Abreu MS, Tannuri ACA, Rodrigues RFG, Silva RJD, Gancalves JO, Serafini S. Effects of loca and remote ischemic post-conditioning methods on ischemia-repefusion injury in a young animal model of acute mesenteric ischemia. Acta Cir Bras.2023 Jun1; 38: e381323.
25. Gonzalez LM, Moeser AJ, Blikslager AT. Animal models of ischemia-reperfusion-induced intestinal injury: progress and promise for translational research- Am J Physiol. 2015 jan 15;308(2):G63-75.
26. Wang J, Zhang W, Wu G.Intestinal ischemic reperfusion injury:Recommended rats model and comprehensive review for protective strategies.Biomed Pharmacother. 2021 Jun; 138: 111482.
27. Garcia-Alonso I, Velasco-Oraa X, Cearra I, Iturrizaga-Correcher S, Mar Medina C, Alonso-Varona A.et al. prophylactic treatment of Intestinal Ischemia- reperfusion Injury reduces Mucosal Damage and Improves Intestinal Absorption. J Inflamm Res. 2023 Sep 20; 16: 4141-4152.
28. Walensi M, de Groot H, Schulz R, Hartmann M, Petrat F. Mesenteric ischemia-reperfusion injury:clearly improved hemodinamics but only minor protection of the rat small intestine by(sub) thepautic heparin sodium and enoxaparin doses. J Surg Res. 2013. Jan; 179(1): e57-69.
29. Gubernatorova EO, Perez-Chanona E, Koroleva EP, Jobin C, Tumanov AV. Murine model of Intestinal ischemia-reperfusion injury. J Visc Exp. 2016 May 11; (111): 53881.
30. Soares ROS, Losada DM, Jordani MC, Evora P, Castro-E-Silva O. Ischemia/Reperfusion Injury Revisited:an Overview of the latest Pharmacological Strategies. Int J Mol Sci. 2019 Oct 11; 20(20): 5034.
31. Jin B, Li G, Zhou L, Fan Z. Mechanism involved in acute Liver injury Induced by intestinal ischemia-reperfusion. Front Pharmacol. 2022 May 23; 13: 924695.
32. Hayase N, Doi K, Hiruma T, Matsuura R, Hamasaki Y, Noiri E, et al. Recombinant Thrombomodulin on Neutrophil Extracellular traps in Murine intestinal ischemia-Reperfusion. Anesthesiology.2019 Oct; 131(4): 866-882.
33. Badripour A, Behzadi M, Hasanipour A, Azar PRS, Rahbar A, Abbaslou Z, et al. Albendazol ameliorates inflammatory response in a rat model of acute mesenteric ischemia reperfusion injury. Biomed Pharmacother. 2022 Sep; 153: 113320.
34. Yang I, WU Y, Xu Y, Jia J, Xi W, Deng H, Tu W. Dexmedetomidin resists Intestinal ischemia-reperfusion Injury by inhibiting TL4/MyD88/NF-kB signaling. J Surg Res. 2021 Apr, 260: 350-358.
35. Chang CL, Sung PH, Sun CK, Chen CH, Chiang HJ, Huang TH, Chen YL, TZhen YY, Chai HT, Chung SY, Tong MS, Chang HW, Chen HH, Yip HK. Protective affect of melatonin supported adipose-derived mesenchymal stem cells against small bowel ischemia-reperfusion injury in rat. J Pineal Res. 2015 Sep; 59(2): 206-220.
36. Ricardo-da-Silva FY, Fantozzi ET, Rodrigues-Garbin S, Domingos HV, Oliveira-Filho RM, Vargaftig BB, Riffo-Vasquez Y, Breithaupt-Faloppa AC, Tavares-de-Lima W. Estradiol prevented intestinal ischemia and reperfusion, induced changes in intestinal permeability and motility in male rats. Clinics (Sao Paulo). 2021 Apr 26; 76: e2683.