Trials

STUDY PROTOCOL

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The effect of Colchicine IN Sepsis (COLINS): a study protocol for a randomized, double-blind, placebo-controlled trial

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Abstract

Background Sepsis is a life-threatening condition with high mortality rates of up to 40% due to multiple organ dysfunction. Systemic inflammatory response plays a key role in the pathophysiology and progression of this disease. Therefore, anti-inflammatory drugs can be considered as augmentation therapy for the management of the early phase of inflammation in septic patients, along with appropriate antimicrobial therapy and source control. Experimental studies suggest the beneficial effects of colchicine in animal septic models. However, the clinical effects of colchicine in the setting of sepsis have not been investigated yet.

Methods This prospective, double-blinded, placebo-controlled, randomized trial will be conducted at Imam Reza Hospital, the largest northwest referral hospital, in Tabriz, Iran. A total of 44 patients aged 18 to 80 years with sepsis diagnosis will be randomized 1:1 to receive colchicine 1 mg daily or placebo for 10 days. The primary outcome is interleukin-6 (IL-6) changes from the baseline through day 4. Sequential organ failure assessment (SOFA) and qSOFA scores will be evaluated at baseline, day 4, and day 10. Patients will be assessed regarding the need for supplemental oxygen, mechanical ventilation, and vasopressor from the randomization through day 4 and day 10.

Discussion The Colchicine IN Sepsis (COLINS) trial will be the first to investigate colchicine's efficacy versus placebo in sepsis patients. The results of this trial will be a step forward in treating patients with sepsis.

Trial registration Clinical trial ID: IRCTID: IRCT20231017059748N1. Registration date: 21 October 2023. https://irct.behdasht.gov.ir/trial/73232.

Keywords Sepsis, Colchicine, IL-6, COLINS, Anti-inflammatory, Clinical trial

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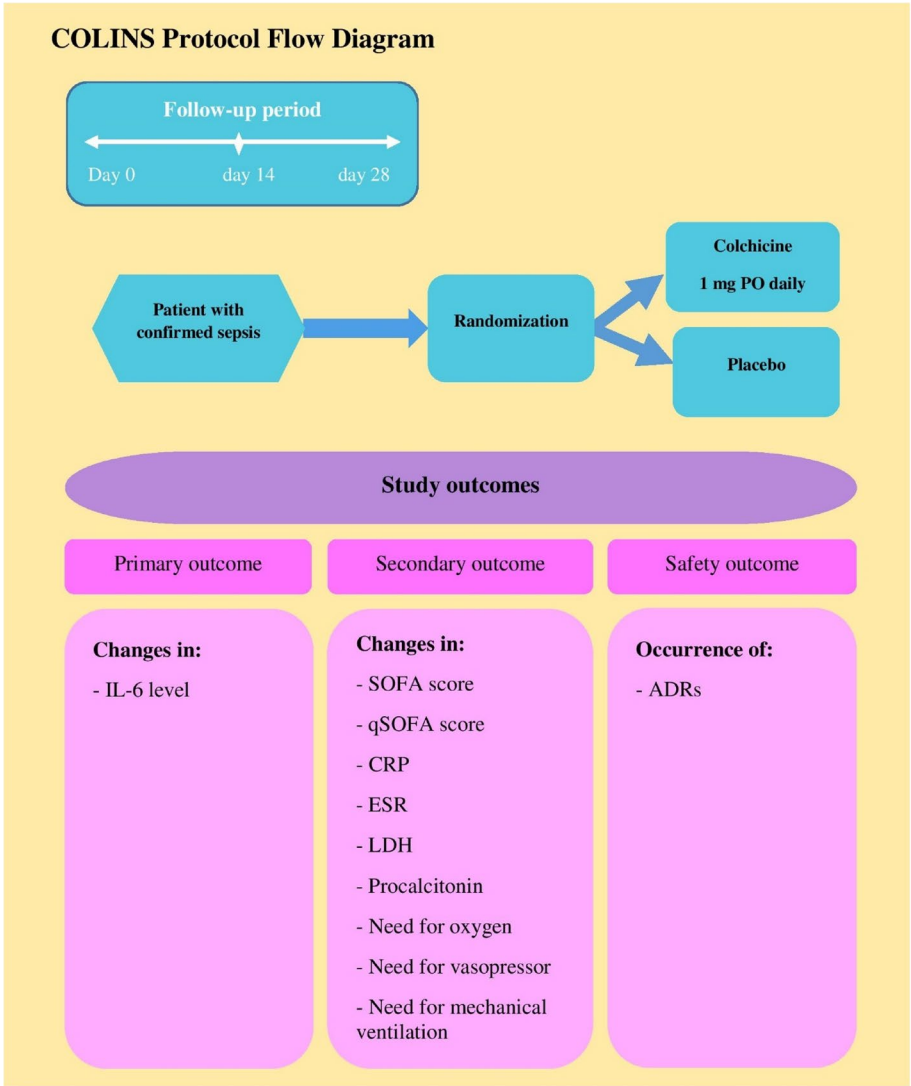
Graphical Abstract



Background

Sepsis is a syndrome of impaired tissue perfusion and oxygenation caused by dysregulated host response to infection eventually leads to life-threatening acute organ dysfunction [1, 2]. Septic shock is a severe form of sepsis characterized by hypotension, oliguria, metabolic acidosis, and tissue hypoxia due to vasodilatation and increased capillary permeability [3]. The mortality rate of sepsis and septic shock is reported 25 to 30% and 40 to 70%, respectively [4]. The incidence of sepsis in the USA is 750,000 cases per year, and this rate increases in the older population [5]. Sepsis treatments include volume resuscitation, antibiotics, vasopressors, and organ support. Even with early initiation of therapy, most septic patients develop multiple organ failure and death [6]. Systemic inflammatory response plays a key role in the pathophysiology and progression of this disease. Therefore, anti-inflammatory drugs can be considered as augmentation therapy in the early phase of inflammation in septic patients, along with appropriate antimicrobial therapy and source control [7–9]. Corticosteroids are one of the most widely investigated anti-inflammatory class drugs in sepsis. The results of clinical trials showed beneficial effects with low doses of these drugs in septic shock [10]. Also, several drugs (such as pentoxifylline, statins, intravenous immune globulin, and ibuprofen)

have been studied in sepsis patients with the goal of systemic inflammation reduction [11–14].

Colchicine, an ancient alkaloid-based drug with well-documented anti-inflammatory effects, is FDA-approved for gout, familial Mediterranean fever, and prevention of stable ischemic heart disease [15]. Currently, this drug is used as an off-label for a wide range of diseases including Behçet's syndrome, pericarditis, calcium pyrophosphate crystal arthritis, postpericardiotomy syndrome, Sweet syndrome, and vasculitis [15–22]. The suggested mechanisms for the anti-inflammatory effects of colchicine include preventing activation, degranulation, and migration of neutrophils and monocytes, inhibition of NF-κB, tumor necrosis factor (TNF)-α, interleukin (IL)−6, and IL-1β [15, 23]. Recently, experimental studies have suggested the beneficial effects of colchicine on animal septic models. Kenig et al. study showed that low-dose colchicine can alleviate sepsis-induced liver damage in mice [24]. Also, the study conducted by Liu et al. revealed that colchicine significantly attenuated acute lung injury in mice following sepsis via inhibition of STAT3 phosphorylation [25].

However, the clinical effects of colchicine in the setting of sepsis have not been investigated yet. The COLINS trial will be the first to investigate colchicine's efficacy versus placebo in patients with sepsis. The results of this trial will be a step forward in treating patients with sepsis.

Methods and design

Study design

COLINS is a prospective, double-blinded, placebo-controlled, randomized clinical trial evaluating colchicine's efficacy versus placebo in patients with sepsis diagnosis. Patients will be enrolled for the trial at Imam Reza Hospital, the largest northwest referral hospital affiliated with Tabriz University of Medical Sciences, Tabriz, Iran. This study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (IR.TBZMED.PHARMACY.REC.1402.002), and an ethical consent form will be completed for all participants before the study. This clinical trial was registered in the IRCT platform center with ID (IRCT20231017059748 N1). The COLINS study protocol diagram will be demonstrated in Fig. 1 which follows the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines [26].

Eligibility criteria

Any patients diagnosed with sepsis will be assessed for enrollment within 24 h of the sepsis onset. Inclusion criteria include suspected or confirmed infection as ordering of blood cultures and the use of at least one antibiotic drug, 18 to 80 years of age, and completing a written consent form. The exclusion criteria include hypersensitivity to colchicine or other components of the formulation, severe hepatic failure (Child–Pugh score B or C), severe renal failure (eGFR < 15 mL/min/1.73 m^2), end-stage renal disease, malignancy, pregnancy, lactation, and concomitant use of P-glycoprotein inhibitors or strong CYP3 A4 inhibitors in the presence of hepatic or renal impairment.

Interventions

Participants will be randomized 1:1 to receive colchicine 1 mg daily or placebo for 10 days. All patients will receive standard treatments for sepsis at the clinical team's discretion according to local protocols. These treatments include fluid resuscitation, vasopressor, antibiotics, mechanical ventilation, blood transfusion, and nutrition. All nurses will be guided to report any adverse reactions such as diarrhea, nerve system, hepatic, hematologic, neuromuscular, and skeletal events as soon as possible during the colchicine use. Colchicine may be administered without regard to meal. Colchicine will be gavage through a nasogastric tube in intubated patients.

Adherence

FP will explain the trial protocol in detail to the nurses and participants. Medication packages with a unique intervention code will be delivered to the patient's nurse. On the 10 th day of the study, the remaining medications will be returned to the researchers to evaluate adherence to the treatment. The patient will be considered non-adherent to treatment if less than 90% of the medications have been used.

Outcomes

The primary outcome is changes in the IL-6 levels from the baseline to day 4. IL-6 will be assessed in plasma samples preserved frozen at −80 °C, using a validated human cytokine ELISA kit.

Secondary outcomes include changes in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alanine transaminase (ALT), aspartate aminotransferase (AST), cell blood count, lactate dehydrogenase (LDH), procalcitonin, SOFA, and qSOFA scores, need for supplemental oxygen, need for mechanical ventilation, and need for vasopressor from the randomization through day 10.

Safety

Gastrointestinal events including nausea, vomiting, and diarrhea are the most common adverse reactions associated with colchicine that will be monitored during the trial period. Other adverse effects including leukopenia, thrombocytopenia, hepatotoxicity, neuropathy,

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				
Time point	**$-t_1$**	**t_0**	**t_1**	**t_2**	**t_3**	**t_4**	**t_5**
Enrolment							
Eligibility screen	X						
Informed consent	X						
Demographic and clinical data	X						
Allocation		X					
Interventions							
Colchicine 1 mg daily			◆—	—	—◆		
Placebo 1 tablet daily			◆—	—	—◆		
Assessments							
IL-6			X	X			
Procalcitonin			X	X			
CRP			X	X	X		
ESR			X	X	X		
LDH			X	X	X		
SOFA score			X	X	X		
qSOFA score			X	X	X		
Full blood count			X	X	X		
Liver function test			X	X	X		
Albumin			X	X	X		
Blood pressure			X	X	X		
O_2 saturation			X	X	X		
Survival status						X	X
Heart rate			X	X	X		
Respiratory rate			X	X	X		
Body temperature			X	X	X		

Fig. 1 COLINS study protocol diagram. $-t_1$, 1-day pre-allocation; t_0, allocation; t_1, baseline; t_2, 4 days after allocation; t_3, 10 days after allocation; t_4, 14 days after allocation; t_5, 28 days after allocation. IL-6, interleukin-6; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; SOFA, sequential organ failure assessment; qSOFA, quick sequential organ failure assessment

myopathy, and rhabdomyolysis will also be reported to researchers.

Sample size

The sample size calculation was based on the IL-6 levels as the primary outcome. According to the Karimi et al. trial and presuming a significance level of 0.05 and a power of 80%, the sample size for this outcome was calculated to be 38 cases total with 19 patients in each group [27]. The G*power software was used to calculate the sample size. The sample size would surge to at least 44 patients in practice, considering the attrition rate of 20%. At the end of the trial, the power of the study will be recalculated, and if the power is weak, the study will continue until reaching a statistically acceptable power.

Recruitment and baseline assessment

Patients who meet the inclusion criteria will be included in the COLINS trial. The white blood cells (WBC), creatinine, CRP, LDH, ESR, procalcitonin, and IL-6 levels will be evaluated at baseline.

Participants enrolled in the COLINS study will be randomized to receive either an oral colchicine 1 mg tablet or an identical placebo tablet once daily for 10 days. The placebo tablets will consist of starch, lactose, and a microcrystalline cellulose filler.

Randomization and blinding

Eligible participants will be randomized 1:1 to the colchicine or placebo group. Randomization will be conducted through online random allocation using a blocked randomization method with random block sizes of 4 and 6. The sequentially numbered, opaque sealed envelopes (SNOSE) method will be applied for allotment concealment [28]. PS will be responsible for generating the allocation sequence. The medical team including AM, HS, AG, and RAA will enroll participants, and FP will allocate patients to interventions by opening a sealed opaque

envelope with ordered serial numbers. HH devised the main conceptual ideas and supervised the trial.

All researchers involved directly in the trial and participants will be blinded to treatment status during the study period. The placebo is identical in color, appearance, and consistency to the colchicine tablet.

Outcome measurements

Baseline sepsis workup and blood sampling will be carried out before the first dose of colchicine or placebo.

Participants' baseline clinical and demographic data will be documented in data-collecting forms. The patients will be visited daily during the hospitalization period. Blood samples will be taken at baseline, fourth, and tenth days. The SOFA and qSOFA scores will be assessed in baseline, day 4, and day 10. IL-6 and procalcitonin will be measured in cryopreserved plasm samples frozen at −80 °C. IL-6 plasma levels will be assessed by the enzyme-linked immunosorbent assay (ELISA) kit. Also, the plasma levels of procalcitonin will be quantified by procalcitonin ELISA test kit. Patients will be evaluated regarding ADRs and MACEs during the study period.

Statistical analysis

The data will be analyzed by SPSS version 22 (SPSS Inc., Chicago, IL, USA, 2013). The mean and standard deviation or median and interquartile range will be used to describe quantitative data. Qualitative data will also be reported with numbers and percentages.

The independent samples *t*-test will be performed for between-group comparisons of quantitative variables. Also, paired *t*-tests or Wilcoxon will be used for within-group comparisons. Qualitative variables will be compared between two groups with the chi-square test or Fisher's exact test. Multivariable repeated measures will be performed to adjust the effect of confounding factors and covariates.

Trial steering and data monitoring committees

Due to the single-center nature of the study, the research team will be responsible for steering and monitoring the trial. Patients will be under continuous monitoring, and any adverse events will be recorded by the investigators. The head investigator (HH) is responsible for the design and conduct of the trial, organizing committee meetings, and publication of study results. Day-to-day trial support will be provided by a core group, including the principal investigator, an infectious disease specialist, a biostatistician, an anesthesiologist, and a clinical pharmacist, responsible for the trial progression, adherence to the protocol, patient safety, and consideration of new information relevant to the research question. A data monitoring committee is not required during the trial period since there is a low risk of adverse events. Tabriz University of Medical Sciences will afford organizational support. An independent clinical event committee consisting of an anesthesiologist, clinical pharmacists, and a biostatistician will provide an independent expert review of critical endpoints reported by investigators to adjudicate clinical events and determine whether the endpoints meet the protocol-specific criteria periodically. All serious adverse effects will be reported to the Research Ethics Committee of Tabriz University of Medical Sciences and documented.

Discussion

This trial is a prospective, double-blinded, placebo-controlled, randomized clinical trial designed to evaluate the efficacy and safety of colchicine in patients with sepsis.

Sepsis is a condition with a high mortality rate of up to 30% and systemic inflammation has a key role in the progression of this syndrome. The binding of surface epitopes on microorganisms to host recognition receptors such as toll-like receptors (TLR) stimulates the release of NF-κB and cytokines (e.g., TNF-α, IL-6, and IL-10). Cytokine release can lead to endothelium injury, increased vascular permeability, and end-organ damage through upregulation of adhesion molecules in neutrophils and endothelial cells [9]. Multiple organ dysfunction in patients with sepsis can result in circulatory shock, respiratory failure, and hepatic and renal dysfunction [9]. Therefore, early control of systemic inflammation with an anti-inflammatory drug may help better manage, along with appropriate antimicrobial therapy and source control.

Corticosteroids are the most widely investigated anti-inflammatory drugs in sepsis. A meta-analysis study found that systemic corticosteroids can hasten the resolution of shock and increase vasopressor-free days [29]. However, corticosteroid has no clear mortality benefit in patients with sepsis. Based on the international sepsis guidelines recommendation, hydrocortisone can be considered in septic shock patients with ongoing vasopressor requirement at doses of 50 mg intravenously every 6 h [30].

Meta-analyses of clinical randomized trials showed a mortality benefit with polyclonal intravenous immune globulin compared to placebo [31–34]. This benefit was greatest with intravenous immune globulin enriched by IgA or IgM [33, 34]. However, the main limitation of all meta-analyses was heterogeneity. Therefore, intravenous immune globulin is not recommended in sepsis, and well-designed randomized clinical trials are needed to definitive conclusions [35].

Pentoxifylline is another drug with anti-inflammatory properties that is investigated in sepsis. The

possible mechanisms for its effectiveness in sepsis include decreasing erythrocyte aggregation, inhibition of neutrophil adhesion and activation, and modulation of endotoxin-induced pro-inflammatory cytokines release [36]. Staubach et al. conducted a randomized, double-blind, placebo-controlled study for the evaluation of pentoxifylline effects in 51 patients with severe sepsis. It improved the multiple organ dysfunction score and the ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration (PaO2/FiO2), without a beneficial effect on the 28-day mortality [11].

Some randomized clinical trials proposed the beneficial anti-inflammatory effects of statins in sepsis via suppression of TLR-4 and TLR-2 upregulation. However, meta-analyses of randomized trials showed no benefit from statin in septic patients [12, 37–44].

Karimi et al. conducted a randomized trial to evaluate the effect of nanocurcumin on the clinical outcomes of critically ill patients with sepsis [27]. The results of this trial showed that the use of nanocurcumin for 10 days can decrease serum levels of procalcitonin ($p = 0.002$), TNF-α ($p = 0.026$), and IL-6 ($p = 0.012$) compared to placebo. Also, the duration of mechanical ventilation and the SOFA score were lower in the intervention group compared to the placebo group [27]. However, there was no significant difference between the two groups in terms of the duration of the intensive care unit stay and mortality rates.

Several potential anti-inflammatory therapies such as ibuprofen and deltibant have been investigated in patients with sepsis that have proven ineffective [14, 45].

As mentioned in the introduction, colchicine is indicated in many inflammatory diseases. Recently, it was investigated during the COVID-19 pandemic to reduce systemic inflammation. The proposed mechanisms for the anti-inflammatory effects of colchicine in COVID-19 include preventing activation, degranulation, and migration of neutrophils and monocytes, inhibition of pyrin domain-containing protein 3 (NLRP3) inflammasome activation, decreasing TNF-α, IL-6, and IL-1β levels, and inhibition of superoxide anion production [46]. An umbrella review of published meta-analyses showed a reduction in mortality rate with colchicine in early mild to moderate COVID-19 [47].

Recently, two experimental studies have shown the beneficial effects of colchicine in animal septic models. In the Kenig et al. study, the mice in the intervention group received colchicine at doses of 0.02 mg/kg daily by gavage for 5 days and were assessed for end-organ damage, cytokine levels, blood counts, and liver pathology. This study showed that low-dose colchicine can alleviate sepsis-induced liver damage in mice through liver pathology improvement and pro-inflammatory cytokine (TNFα and IL1-β levels) reduction [24]. Another study by Liu et al. showed that colchicine significantly attenuated acute lung injury in mice with sepsis via NLRP3 suppression and thereby STAT3 phosphorylation inhibition [25].

There is no randomized clinical trial investigating the effects of colchicine in the setting of sepsis. The COLINS trial will be the first to investigate colchicine's efficacy versus placebo in patients with sepsis.

Conclusion

Considering the proposed anti-inflammatory mechanisms of colchicine in sepsis and the available evidence on the effectiveness of this drug in experimental animal models, the present study aims to investigate its effects in patients with sepsis. The results of the COLINS trial will be a step forward in treating patients with sepsis.

Trial status

This protocol (version 1.0) was registered at irct.behdasht.gov.ir on October 21, 2023 (IRCT20231017059748N1). The recruitment has not yet started and is expected to begin on February 10, 2025, with an estimated study completion date of May 30, 2025.

Abbreviations

ALT	Alanine transaminase
AST	Aspartate aminotransferase
COLINS	Colchicine IN Sepsis
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
IL	Interleukin
LDH	Lactate dehydrogenase
NLRP3	Pyrin domain-containing protein 3
SOFA	Sequential organ failure assessment
TLR	Toll-like receptors
TNF-α	Tumor necrosis factor-α

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08901-y.

Supplementary Material 1: SPIRIT checklist

Acknowledgements

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Authors' contributions

HH, the principal investigator, created the initial concept and designed and supervised the trial. AM, HS, AG, and RAA will evaluate patients' eligibility and collect data. PS will be involved in the data analysis and interpretation. HH and FP are responsible for providing the manuscript draft.

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role in the study design, data collection, management, analysis, interpretation of the data, reporting of the results, and report submission.

Data availability

The protocol is part of FP's Ph.D. thesis. All primary and secondary outcome data will be reported at the end of the trial. The participant-level information will be available through the corresponding author upon reasonable request.

Declarations

Ethics approval and consent participate

This study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (IR.TBZMED.PHARMACY.REC.1402.002), and then registered in www.irct.ir with the clinical trial ID of IRCT20231017059748 N1. The research protocol is designed under the Declaration of Helsinki and later revisions of ethical principles for medical research. All respective institutional review boards and regulatory authorities reviewed and approved the protocol before registration. The researchers will explain the trial protocol and any related modifications in detail to patients, their trustees, or their guardians. At the beginning of the study, a modified version of the World Health Organization's (WHO) informed consent form template will be used to obtain written informed consent for participation by HH. Ethical consent forms will be completed for all participants before the study. Also, consent for participants' biological specimen collection will be obtained for the quantification of procalcitonin and IL-6 serum levels.

Consent for publication

There will be no personal identifying information published.

Competing interests

The authors declare that they have no competing interests.

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