AGI Grade-guided Chaiqin Chengqi Decoction Treatment For Predicted Moderately Severe And Severe Acute Pancreatitis (CAP Trial): Study Protocol of a Randomised, Double-blind, Placebo-controlled, Parallel-group, Pragmatic Clinical Trial

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Abstract

Background: Acute pancreatitis (AP) is the common digestive disease with a potentially high risk of mortality. Traditional Chinese medicinal formula chaiqin chengqi decoction (CQCQD) has been used for the management of AP in West China Hospital for decades. CQCQD for AP (CAP) trial tests whether the administration of CQCQD will improve the efficacy of the present comprehensive treatments for predicted moderately severe and severe AP.

Methods: This is a single-centre, randomised, controlled, double-blind, two-arm pragmatic clinical trial. Eligible patients with a clinical diagnosis of AP will be randomly allocated on a 1:1 basis to CQCQD or placebo control administration based on conventional standard therapy for AP. The administration of CQCQD and placebo are guided by Acute Gastrointestinal Injury (AGI) grade-based algorithm. The primary outcome measure will be the duration of respiratory failure within 28 days after onset. Secondary outcome measures include occurrence of new-onset organ failure and new-onset persistent organ failure, receipt of new organ support therapy, duration of gastrointestinal decompression, requirement of prokinetic agents, duration of fasting, incidence of local complications, requirement for drainage or necrosectomy, hospital length of stay, intensive care unit (ICU) length of stay, cumulative levels of C-reaction protein (CRP) on day 1, 2, 3, 5, 7, 14, 21, 28 after admission, in-hospital cost, all-cause mortality, five-level EuroQol five-dimensional (EQ-5D-5L) questionnaire and so on. Follow-up will be scheduled on 6, 12, and 26 weeks after enrolment.

Discussion: The results of this study may provide high-quality evidence of the efficacy of CQCQD in the management of AP.

Trial registration: Chictr.org.cn Registry (ChiCTR2000034325). Registered on 2 July, 2020. https://www.chictr.org.cn/showproj.aspx?proj=55591

Background

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas [1]. The common causes of AP such as gallstones, alcohol, hypertriglyceridaemia, endoscopic retrograde cholangiopancreatography (ERCP) and various drugs trigger self-digestion of acinar cells and induce local and systemic inflammation. It has an increasing prevalence with the overall incidence of over 34 affected cases per 100,000 person-years [2]. Most of the patients are uneventful and recover from mild disease, or pull through local complication or transient organ failure defined as moderately severe acute pancreatitis (MSAP). Approximately 15–20% of patients manifesting persistent organ failure (POF) are defined as severe acute pancreatitis (SAP) [3], which are at risk of multiple organ dysfunction and the mortality can be up to 50% mortality risk [4, 5]. Despite the global socioeconomic burden of disease, currently, there is no specific and effective therapeutic agents available to treat AP [6]. According to published guidelines [7, 8], supportive measures, such as fluid therapy, organ support, analgesia, nutritional supplementation, remain the primary management for AP patients.

Traditional Chinese Medicine (TCM), which are abundant of multiple-target biologically active substances, have been broadly used in many countries and regions. Gastrointestinal dysmotility or dysfunction/failure, one of common and complex complications in AP [9–11], is widely accepted as an important role in the pathogenesis of systemic inflammation and multiple organ failure (MOF) [12–14]. Most of TCM herbal formulas, such as dachengqi decoction (DCQD) [15, 16], qingyi decoction [17, 18], and rhubarb [19, 20], are used as an important “gut-centred” therapeutic strategy in the early treatment of AP [21]. Based on the TCM theory, we summarized in our clinical practice that AP is attacked by the invasion of “heatevil” to the organs, and treatment of AP requires “clearing heat, removing toxin and purgation” [22, 23]. Chaiqin chengqi decoction (CQCQD) has been modified from DCQD and used to treat AP in our hospital for over 30 years [24, 25]. The comprehensive approach integrated by Traditional Chinese and Western Medicine improved clinical outcomes and reduced the mortality of SAP to 19.6% [26]. Our previous studies demonstrated that CQCQD can restore intestinal motility or ameliorate systemic inflammation via the toll-like receptor 4 (TLR4) and nucleotide-binding domain-like receptor protein 3 (NLRP3) pro-inflammatory pathways in AP models [23, 27].

Systematic review and meta-analyses of observational studies and trials with small sample size have demonstrated the effectiveness of TCM in improving the clinical outcomes of AP [28, 29]. Owing to the lack of sufficient strength of the current evidence, we designed a randomised, double-blind, placebo-controlled, parallel-group trial to provide high quality evidence of the efficacy of CQCQD for patients with AP (CAP trial). Aiming to restoration or maintenance of gastrointestinal function, Acute Gastrointestinal Injury (AGI) grade-based algorithm will be used to guide the administration of CQCQD [11]. Our trial protocol, informed consent and other documents were submitted to the Biomedical Research Ethics Committee of West China Hospital of Sichuan University in February 2020. After revisions, ethical approval was obtained on 22 June, 2020. The trial was registered with an identifier (ChiCTR2000034325) at chictr.org.cn on 2 July, 2020.

Methods/design

Study design

This study is a single-centre, double-blind, two-arm, pragmatic, placebo-controlled randomised trial. Patients with AP will be recruited through Department of Integrated Traditional Chinese and Western Medicine, West China Hospital, Sichuan University. Eligible patients will be randomly assigned to the treatment or control group with the ratio of 1:1. The study flowchart is shown in Fig. 1, and the trial schedule is shown in Table 1.

Table 1 Study schedule of CAP trial

			STUDY PERIOD									
	Enrolment	Allocation	Post-allocation							Follow-up period		
TIMEPOINT	<12h	day_0	day_1	day_3	day_5	day_7	day_{14}	day_{21}	day_{28}	$week_8$	$week_{12}$	$week_{26}$
ENROLMENT												
Eligibility screen	X											
Informed consent	X											
Allocation		X										
INTERVENTIONS												
CQCQD			←	—	—	—	→					
Placebo			←	—	—	—	→					
Data collection												
Laboratory test			X	X	X	X	X	X	X	X		X
EQ-5D-5L						X	X	X	X	X	X	X
ASSESSMENTS												
Organ failure									X			X
Cumulative CRP			X	X	X	X	X	X	X			
Major complications			X	X	X	X	X	X	X			X
Health status and infection									X			X

CQCQD, chaiqin chengqi decoction; EQ-5D-5L, five-level EuroQol five-dimensional questionnaire; CRP, C-reactive protein

This protocol follows the recommendations of Pragmatic Explanatory Continuum Indicator Summary Framework-2 (PRECIS-2) criteria (Additional file 1) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Additional file 2) [30–32]. The Consolidated Standards of Reporting Trials (CONSORT) has been used as frameworks of methodology to design this protocol [33].

Study population

CAP trial focuses on eligible patients with predicted MSAP and SAP and admitted within 72 hours of the onset. A patient will be considered eligible if he/she meets the inclusion criteria and does not meet any of the exclusion criteria.

Inclusion criteria

Patients will be included if they fulfil all the following criteria:

1. Meet the diagnostic criteria of AP [3], which fulfil two of the following three items: typical symptoms and signs of abdominal pain, elevated serum amylase and/or lipase at least three times the upper limit of normal, AP characteristic image findings.

2. Aged between 18 to 75 years, male or female.
3. Admitted to our centre within 72 hours from the disease onset.

4. Written informed consent obtained.
Exclusion criteria

Patients with any of the following conditions will be excluded:

1. Known pregnant or lactating at admission.

2. The presence of severe organ failure identified using Sequential Organ Failure Assessment (SOFA) scoring by a score of > 3 for individual organs (respiratory, cardiovascular, or renal systems) at admission [34].
3. The predicted mild acute pancreatitis (MAP) defined as Harmless Acute Pancreatitis Score (HAPS) > 2 at admission [35].
4. Known malignant tumour or having radiotherapy and chemotherapy within 6 months.
5. Known gastrointestinal perforation, bleeding, and mechanical ileus at admission.
6. Acute attack of chronic pancreatitis.
7. Known history of neoplasm in duodenal or biliopancreatic systems.
8. Known history of pancreatic resection.
9. Known undergoing other clinical trials.
10.Known taken traditional Chinese herb orally before enrolment.

Recruitment procedures

Patients admitted to Emergency Department of West China Hospital will be primarily screened via the symptoms of abdominal pain and onset time by research nurses. The patients with a diagnosis of AP will be admitted to our centre for further recruitment. Research assistants will continue the enrolment process by screening eligible patients according to the inclusion and exclusion criteria.

Randomised and blinding methods

After the completion of screening measurements and the acquisition of signed consent, eligible participants will be randomised in a 1:1 ratio to either the treatment or control group. The randomization code will be automatically created by computer using Analytics Software & Solutions software (SAS, version 9.3, SAS Institute Inc, USA). Patients will be randomised using sequentially numbered, opaque sealed envelopes, which is the most accessible and straightforward method of maintaining allocation concealment. A group of independent assessors will interview the patients and perform the screening. All the patients, researchers, statistician in this clinical study will be blinded to the treatment assigning and unaware of the actual medications.

Study herbal formulation

The prescription of CQCQD was developed by this research team and standardised to contain 13 Chinese Medicines, the contents of which can be found in Table 2.

Table 2
The ingredients list of standardised Chinese herbal medicine prescription of CQCQD

Ingredients	Latin name	Plant name	Weight (g)
Dahuang	*Rhei Radix et Rhizoma*	*Rheum palmatum* L.	15
Houpo	*Magnoliae Officinalis Cortex*	*Magnolia officinalis* Rehd. et Wils.	15
Zhizi	*Gardeniae Fructus*	*Gardenia jasminoides* Ellis	15
Zhuyechaihu	*Bupleuri Radix*	*Bupleurum chinese* DC.	15
Huangqin	*Scutellariae Radix*	*Scutellaria baicalensis* Georgi	15
Chuanxiong	*Chuanxiong Rhizoma*	*Ligusticum chuanxiong Hort.*	15
Honghua	*Carthami Flos*	*Carthamus tinctorius* L.	10
Zhishi	*Aurantii Fructus Immaturus*	*Citrus aurantium* L.	15
Yanhusuo	*Corydalis Rhizoma*	*Corydalis yanhusuo* W. T. Wang	15
Muxiang	*Auklandiae Radix*	*Aucklandia lappa* Decne.	15
Chishao	*Paeonia Radix Rubra*	*Paeonia veitchii* Lynch	15
Gancao	*Glycyrrhizae Radix et Rhizoma*	*Glycyrrhiza uralensis Fisch.*	3
Mangxiao	*Natrii Sulfas*	$Na_2SO_4 \cdot 10H_2O$	30

Due to the absence of a positive control drug for AP and the difficulty in preparing a placebo for the decoction, we will utilize a low-dose arm administering 10% CQCQD of similar colour and odour by adding dextrin and colorant, which intend to mimic placebo group as a control [36].

The raw herbal drugs with the quality certificates will be supplied by Chengdu Kangmei Pharmaceutical Company Limited, Co., Ltd., China. Quality-controlled decoctions will be prepared by Pharmacy of West China Hospital using the Good Manufacturing Practice (GMP) standards, according to the 2005 Edition of the Chinese Pharmacopoeia. High-performance liquid chromatography-mass spectrometry (HPLC-MS) method is used for the quality control of CQCQD. The study decoction preparations will be transported to the inpatient ward and dispensed by two individual research assistants. Researchers will provide the study decoction solution for free. Study investigators and subjects do not know which decoction preparation will be used.

Administration of randomised drugs guided by AGI-based algorithm

AGI grade has been widely used to assess the gastrointestinal injury in patients with acute critically illness [11, 37]. Evidence has shown AGI grading system is useful for identifying the severity of GI dysfunction/failure in AP [38]. In our study, the participants will receive randomised drugs guided by AGI-based algorithm (Fig. 1).

1. Initiation: If Bedside Index of Severity in Acute Pancreatitis (BISAP) score or Glasgow criteria system (GCS) < 2 at allocation [39, 40], the patients will empirically receive CQCQD or placebo 200ml oral intake (or intragastric infusion) and enema, 3 times a day. If the patients have BISAP/GCS score ≥ 2 at allocation, they will be required to receive urethral catheterization to monitor intra-abdominal pressure (IAP) every 4 hours, which is the key index in AGI grade. The dosage and frequency of decoction is determined by AGI grading as the following criteria: (1) if AGI grade = 1, 200 mL CQCQD or placebo are administered orally (or intragastrical infusion) and enema, 3 times a day; (2) if AGI grade = 2, CQCQD or placebo are given 100mL orally (or intragastrical infusion) and 200 mL enema, every 6 hours; (3) if AGI grade = 3, CQCQD or placebo are given 100mL orally (or intragastric infusion) and 200mL enema, every 4 hours; (4) if AGI grade = 4, CQCQD or placebo are given 100mL orally (or intragastric infusion) and 200mL enema, every 2 hours. If the patient with BISAP/GCS score ≥ 2 at allocation rejects the urethral catheterization, the initial administration of randomised drug is in accordance with AGI grade 1 and will be reassessed the conditions for further judgement.

2. Continuation: AGI grade is evaluated daily at 7–8 am by the researchers. The dosage and frequency of CQCQD or placebo are determined by the corresponding AGI grade at the time points.
3. Termination: CQCQD or placebo is administrated for at least 5 days and no more than 14 days. IAP monitoring will be terminated if it is less than 15 mmHg for consecutive two days. CQCQD or placebo will be terminated, if AGI grade < 1 for consecutive two days, or normally oral refeeding without discomfort. Other conditions will be determined by clinical treatment leaders and principal investigators.
4. The upgrade principle for patients with AGI grade 1 initially or who reject the urethral catheterization: (1) the aggravation of abdominal distension and constipation; (2) the occurrence of new organ dysfunction; (3) the deterioration of the original organ function; (4) Other conditions will be assessed and determined by clinical treatment leaders and principal investigators.

Withdrawal criteria

The patients are withdrawal if they meet any of the following criteria:

1. Having manifestations of gastrointestinal perforation, bleeding, mechanical ileus, severe haemorrhoids, and anal fissure which require restricted fast and enema.

2. Quitting voluntarily.
3. Adverse medical events occurring during the study such as severe hypernatremia, intolerance to critically worsening conditions, or other reasons as judged by the investigators, which might make the patient unlikely to complete the study.

Conventional treatment regimen

All patients will receive standard treatment according to recently published guidelines [7, 8], including fluid therapy, nutritional supplement, routine medical treatment like proton pump inhibitor, analgesia and antibiotics as indicated, organ supportive therapy and ERCP if necessary. Nasogastric and annal tube will be used for patients with intra-abdominal hypertension (IAH) or abdominal compartment syndrome (ACS). For patients with persistent ACS or new organ failure develops, percutaneous drainage of ascites

and the surgical abdominal decompression will be considered [41, 42]. When pancreatic infection occurs, either a surgical or endoscopic step-up approach considering the location of the necrotic collection and the technical availability will be applied.

During the hospitalization, the patients are not allowed to use other Chinese Medicine and alternative therapy (e.g., herbal extract injection, acupuncture, abdominal ultra-sound therapy). Drugs for inhibitory gastrointestinal motility (e.g., catecholamines, sedatives) and prokinetics (e.g., neostigmine, domperidone, metoclopramide, erythromycin) are not used routinely, unless the patients presenting AGI grade 4 or other critical conditions suggested by clinical treatment leaders and principal investigators in aiming to ensure the safety of the patients. All the additional drugs or therapies must be recorded in case report form (CRF) in details.

Endpoints

Primary outcome measurements

Referring to the existing study results and expert recommendations [6, 25, 26, 43], the duration of respiratory failure within 28 days after admission will be served as the primary outcome in CAP trial.

Secondary outcome measurements

▯ Secondary outcomes during the index admission

1. The occurrence of new-onset organ failure and new-onset persistent organ failure (SOFA score for respiratory, cardiovascular, or renal system ≥ 2 points). New-onset is defined as events that occur after randomization and not present 24 hours before randomization.

2. Daily visual analogue scale (VAS) score of pain [44].
3. Duration of IAH and ACS.
4. Duration of gastrointestinal decompression.
5. Duration of fasting.
6. The requirement of anal tube.
7. The requirement of prokinetic agents.
8. The receipt of respirator support and renal replacement therapy.
9. Local pancreatic injury by contrast-enhanced computed tomography (CECT) on day 7 and 14.
10. Cumulative levels of C-reaction protein (CRP) on day 1, 2, 3, 5, 7, 14, 21, 28 after admission.
11. Length of intensive care unit (ICU) stay.
12. In-hospital cost.
13. Duration of systemic inflammatory response syndrome (SIRS).
14. Daily pancreatitis activity scoring system (PASS) score within 1st week after enrolment [45].
15. Levels of Albumin, Procalcitonin, Interleukin-6 (IL-6), Neutrophils count on day 0, day 3, day 5, day 7, and day 14.

▯ Secondary outcomes within 26 weeks after enrolment

1. Infective pancreatic necrosis.

2. The requirement for catheter drainage or necrosectomy.
3. Self-report health situation by five-level EuroQol five-dimensional (EQ-5D-5L) [46].
4. All-cause mortality.
5. Length of hospital stay.
6. Potential safety signals.

Sample size estimation

Based on our previous study [17, 26], we assumed a reduction in duration of respiratory failure of 2 days in the treatment group. Assuming that the significance level is 0.05 and study power is 0.8 (two-sided $\alpha = 0.05$, $\beta = 0.2$), we projected a sample size of 111 patients in each group using Power Analysis & Sample Size software (PASS statistic software, version 11.0.7, NCSS). Considering a 10% dropout, a total of 248 patients will be recruited in this trial with 124 patients for each group.

Adverse events and safety assessment

Adverse events (AEs) are defined in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Events. The common aberrations in symptoms, signs, and laboratory values due to the severity of the underlying disease and the impact of standard therapies will not necessarily constitute an AE unless they require significant intervention or are of concern in the investigator's clinical judgement. If severe adverse events (SAEs) happen that threaten the patients' safety, researcher should stop the study at once, cancel the blinding, take any measures to rescue the patients' life who occurs SAE.

All details of any AE/SAE will be documented and reported during the treatment and the follow-ups. Furthermore, SAE will be reported to the principal investigator and the ethics committee immediately to decide whether the patient should withdraw from the trial.

Data collect and management

The researchers involved will received the restricted training to make sure of the study process in details. Data collection will use a CRF and include source-verifiable data from patient records. CRF will be anonymized and contain no individual patient-identifiable information. Paper copies of the CRF will be stored in a locked cabinet in the Chief Investigator's office in West China Hospital. All data will be input by the primary investigator or nominated investigators approved by the primary investigator, and a double check will be done by the research coordinator.

According to the study schedule shown in Table 1, data will be collected during the index admission and 26 weeks after enrolment. If a participant wishes to discontinue the study drug or the treating physician believes a participant should discontinue the study drug due to medical conditions, the investigator will communicate with the participant and the treating physician to obtain the reasons and record in CRF. Further follow-up will still be performed unless the participant withdraws the trial. Patients who are discharged and re-admitted within 4 weeks will be regarded as a re-admission for the same episode of

care and will be in the same arm as their original allocation. Data of re-admission elsewhere will be collected at follow-up typically at 4 weeks. The study blinding will only be broken in a medical emergency when the treating physician believes that the administration of the study drug is associated with the emergency.

Statistical analysis

Data cleaning and statistical analysis will be performed by a statistician blinded to the whole trial process using the latest version of SAS software. The data will be analysed based on full analysis set (FAS), per-protocol set (PPS) and safety set (SS). The FAS analysis is the basic principle of intention-to-treat (ITT), including all the enrolment patients in the trial. Analysis will follow ITT principles with patients analysed according to randomization and irrespective of actual use or compliance with the algorithm. The PP analysis is the subset of FAS, which just includes patients who finish the trial completely. The SS analysis is the set of patients who receive the treatment and have safety assessment. Missing values will be addressed by multiple imputation, having appropriately explored the missingness mechanism, and in accordance with good practice.

The results of data will be expressed as means with ranges, medians with interquartile ranges, or numbers of patients with percentages. Endpoints will be assessed using an appropriate linear model adjusted for baseline value, age, sex, aetiology, and disease course. The comparison between the individualized CQCQD and control group is the primary interest in this study. Interim analysis was not planned in CAP trial. The detailed analysis strategies for secondary outcomes and subgroup analyses by the severity of AP (severe and non-severe), age (dichotomized at 60 years old) and aetiologies of AP (hyperlipidaemic and non-hyperlipidaemic) will be compared using appropriate summary statistics (according to its distribution). Statistical tests will be two-sided, and P values < 0.05 will be considered as significant.

Discussion

Over the past 30 years, the Chinese herbal formula CQCQD has been widely used as an adjunctive therapy of conventional comprehensive treatment for AP in China. Both basic and clinical observational studies have revealed its anti-inflammatory role and protective function for organs in AP [23, 47, 48]. The CAP trial was designed to investigate the efficacy of CQCQD potentially alleviating gastrointestinal and respiratory failure, which are potentially lethal complications inducing substantial morbidity and mortality of AP. The results of the CAP trial would potentially provide high-quality evidence of CQCQD in the treatment of AP.

The CAP trial is conducted at Department of Integrated Traditional Chinese and Western Medicine, Sichuan Provincial Pancreatitis Centre, West China Hospital, Sichuan University, which is one of the largest single tertiary referral centres admitting over 1800 cases of AP annually. The distinctive treatment of integrated TCM and Western Medicine by multiple-discipline team (MDT) in our AP centre has been formed for a long history of over 30 years [24, 49]. The treatment system qualifies the trial, but limited the

performance of the multi-centre study. Therefore, the CAP trial was designed as a single centre study in order to assure the homogeneity of the study.

Quality control for CQCQD plays a vital role in the trial. Hundreds of characteristic phytochemicals contained in compound formula poses a challenge for developing robust quality assessment metrics. In previous study [50], we successfully constructed a multi-strategy based analytical method and identified potential quality-markers (Q-markers) based on drug properties and effect characteristics. Because of a pragmatic clinical trial, the preparation of decoction is performed by Pharmacy of West China Hospital according to standard operating procedures (SOPs). Despite qualified materials used for CQCQD preparation, the quality of CQCQD will be assessed by appropriate content range of Q-markers. This feasible platform lays the solid foundation for the CAP trial.

Outcome determination is of great importance for the trial. The recent evidence-based study suggested that trials in participants with AP should consider complications or health-related quality of life, but not mortality, as primary outcomes [6]. In the CAP trial, duration of respiratory failure will be served as the primary endpoint. Respiratory failure constitutes a high proportion of organ failure in AP [4, 26]. In Zangfu theory of TCM, the lung and the large intestine are interior-exteriorly related. Based on this theory, the method “purging the bowel” could potentially treat pulmonary disease such as acute respiratory distress syndrome (ARDS) and respiratory failure. The CAP trial will employ AGI guided algorithm for CQCQD administration in aiming to shorten the duration of respiratory failure in early stage as a primary endpoint for SAP. Most of the secondary endpoints are registered within the index admission and follow up patients for six months.

In conclusion, the CAP trial is the first randomised controlled trial in high quality to evaluate the efficacy of CQCQD in early administrating gastrointestinal dysfunction to alleviate respiratory failure and other major clinical outcomes of AP.

Trial Status

The current protocol is version 1, dated December 10, 2019. The trial started to recruit the patients on August 1, 2020 and anticipate to complete on June, 2023.

Abbreviations

AP: Acute pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; MSAP: Moderately severe acute pancreatitis; POF: Persistent organ failure; SAP: Severe acute pancreatitis; TCM: Traditional Chinese medicine; MOF: Multiple organ failure; DCQD: Dachengqi decoction; CQCQD: Chaiqin chengqi decoction; TLR4: Toll-like receptor 4; NLRP3: Nucleotide-binding domain-like receptor protein 3; CAP: CQCQD for AP; AGI: Acute Gastrointestinal Injury; PRECIS-2: Pragmatic Explanatory Continuum Indicator Summary Framework-2; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; CONSORT: Consolidated Standards of Reporting Trials; SOFA: Sequential Organ Failure Assessment;

MAP: Mild acute pancreatitis; HAPS: Harmless Acute Pancreatitis Score; GMP: Good Manufacturing Practice; HPLC-MS: High-performance liquid chromatography-mass spectrometry; BISAP: Bedside Index of Severity in Acute Pancreatitis; GCS: Glasgow criteria system; IAP: Intra-abdominal pressure; IAH: Intra-abdominal hypertension; ACS: Abdominal compartment syndrome; CRF: Case report form; VAS: Visual analogue scale; CECT: Contrast-enhanced computed tomography; CRP: C-reaction protein; ICU: Intensive care unit; SIRS: Systemic inflammatory response syndrome; PASS: Pancreatitis activity scoring system; IL-6: Interleukin-6; EQ-5D-5L: Five-level EuroQol five-dimensional; AEs: Adverse events; SAEs: Severe adverse events; FAS: Full analysis set; PPS: Per-protocol set; SS: Safety set; ITT: Intention-to-treat; MDT: Multiple-discipline team; Q-markers: Quality-markers; SOPs: Standard operating procedures; ARDS: Acute respiratory distress syndrome

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the ethics committee of West China Hospital, Sichuan University (Ethnic number: 2020107). The design of this trial is in accordance with the Declaration of Helsinki (Version Edinburgh 2000).

Before enrolment, the consents for this study are obtained from each patient or his/her next of kin with full information regarding the possible adverse effects of the experimental drug and potential consequences. They will be told about the equal chance of allocation to any one of the two groups before signing the informed consent. Meanwhile, they will be given enough time to decide whether they join in the trial or not. Lastly, patients will be included voluntarily by signing the written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Final data of the trial that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors were involved in the study design, read, discussed, revised, and approved the final manuscript. CZ and YX contributed equally to this study as co-first authors. XQ, DL, YX and HW contributed the conception and design of the trial. CZ, DL and XQ drafted the manuscript. ZP, LJ and LL planed randomised and the statistics analysis. CZ, CF, HY, HC and TQ participated in recruitment and data collection. DD contributed to quality control of study drug. YX, GJ, JT, LZ, LL, JK in charge of the treatment of patients.

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References

1. Forsmark CE, Vege SS, Wilcox CM. Acute Pancreatitis. N Engl J Med. 2016;375(20):1972–81.
2. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol. 2019;16(3):175–84.
3. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102–11.
4. Guo Q, Li A, Xia Q, Liu X, Tian B, Mai G, et al. The role of organ failure and infection in necrotizing pancreatitis: a prospective study. Ann Surg. 2014;259(6):1201–7.
5. Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut. 2019;68(6):1044–51.
6. Moggia E, Koti R, Belgaumkar AP, Fazio F, Pereira SP, Davidson BR, et al. Pharmacological interventions for acute pancreatitis. Cochrane Database Syst Rev. 2017;4(4):Cd011384.
7. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology. 2018;154(4):1096–101.
8. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400-15; 16.
9. Andersson R, Andersson B, Andersson E, Axelsson J, Eckerwall G, Tingstedt B. Acute pancreatitis–from cellular signalling to complicated clinical course. HPB (Oxford). 2007;9(6):414–20.
10. Capurso G, Zerboni G, Signoretti M, Valente R, Stigliano S, Piciucchi M, et al. Role of the gut barrier in acute pancreatitis. J Clin Gastroenterol. 2012;46(Suppl):46–51.

11. Reintam Blaser A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 2012;38(3):384–94.
12. de Jong PR, González-Navajas JM, Jansen NJ. The digestive tract as the origin of systemic inflammation. Crit Care. 2016;20(1):279.
13. Klingensmith NJ, Coopersmith CM. The Gut as the Motor of Multiple Organ Dysfunction in Critical Illness. Crit Care Clin. 2016;32(2):203–12.
14. Leaphart CL, Tepas JJ 3. The gut is a motor of organ system dysfunction. Surgery. 2007;141(5):563–9. rd. .
15. Wan MH, Li J, Huang W, Mukherjee R, Gong HL, Xia Q, et al. Modified Da-Cheng-Qi Decoction reduces intra-abdominal hypertension in severe acute pancreatitis: a pilot study. Chin Med J (Engl). 2012;125(11):1941–4.
16. Zhang MJ, Zhang GL, Yuan WB, Ni J, Huang LF. Treatment of abdominal compartment syndrome in severe acute pancreatitis patients with traditional Chinese medicine. World J Gastroenterol. 2008;14(22):3574–8.
17. Chen W, Yang X, Huang L, Xue P, Wan M, Guo J, et al. Qing-Yi decoction in participants with severe acute pancreatitis: a randomized controlled trial. Chin Med. 2015;10:11.
18. Zhang JW, Zhang GX, Chen HL, Liu GL, Owusu L, Wang YX, et al. Therapeutic effect of Qingyi decoction in severe acute pancreatitis-induced intestinal barrier injury. World J Gastroenterol. 2015;21(12):3537–46.
19. Wan B, Fu H, Yin J, Xu F. Efficacy of rhubarb combined with early enteral nutrition for the treatment of severe acute pancreatitis: a randomized controlled trial. Scand J Gastroenterol. 2014;49(11):1375–84.
20. Zhou Y, Wang L, Huang X, Li H, Xiong Y. Add-on effect of crude rhubarb to somatostatin for acute pancreatitis: A meta-analysis of randomized controlled trials. J Ethnopharmacol. 2016;194:495–505.
21. Petrov MS. Gastric feeding and "gut rousing" in acute pancreatitis. Nutr Clin Pract. 2014;29(3):287–90.
22. Li J, Zhang S, Zhou R, Zhang J, Li ZF. Perspectives of traditional Chinese medicine in pancreas protection for acute pancreatitis. World J Gastroenterol. 2017;23(20):3615–23.
23. Wen Y, Han C, Liu T, Wang R, Cai W, Yang J, et al. Chaiqin chengqi decoction alleviates severity of acute pancreatitis via inhibition of TLR4 and NLRP3 inflammasome: Identification of bioactive ingredients via pharmacological sub-network analysis and experimental validation. Phytomedicine. 2020;79:153328.
24. Liu XB, Jiang JM, Huang ZW, Tian BL, Hu WM, Xia Q, et al. Clinical study on the treatment of severe acute pancreatitis by integrated traditional Chinese medicine and Western medicine. Sichuan Da Xue Xue Bao Yi Xue Ban. 2004;35(2):204–8.
25. Jin T, Jiang K, Deng L, Guo J, Wu Y, Wang Z, et al. Response and outcome from fluid resuscitation in acute pancreatitis: a prospective cohort study. HPB (Oxford). 2018;20(11):1082–91.

26. Shi N, Liu T, de la Iglesia-Garcia D, Deng L, Jin T, Lan L, et al. Duration of organ failure impacts mortality in acute pancreatitis. Gut. 2020;69(3):604–5.
27. Zhang CL, Lin ZQ, Luo RJ, Zhang XX, Guo J, Wu W, et al. Chai-Qin-Cheng-Qi Decoction and Carbachol Improve Intestinal Motility by Regulating Protein Kinase C-Mediated Ca(2+) Release in Colonic Smooth Muscle Cells in Rats with Acute Necrotising Pancreatitis. Evid Based Complement Alternat Med. 2017;2017:5864945.
28. Lu X, Xiao W, Kang X, Yu J, Fan Z. The effect of Chinese herbal medicine on non-biliogenic severe acute pancreatitis: a systematic review and meta-analysis. J Ethnopharmacol. 2014;155(1):21–9.
29. Wang Q, Guo Z, Zhao P, Wang Y, Gan T, Yang J. Chinese herbal medicines for acute pancreatitis. Cochrane Database Syst Rev. 2005(1):CD003631.
30. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
31. Dai L, Cheng CW, Tian R, Zhong LL, Li YP, Lyu AP, et al. Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018: Recommendations, Explanation and Elaboration (SPIRIT-TCM Extension 2018). Chin J Integr Med. 2019;25(1):71–9.
32. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.
33. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
34. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286(14):1754–8.
35. Lankisch PG, Weber-Dany B, Hebel K, Maisonneuve P, Lowenfels AB. The harmless acute pancreatitis score: a clinical algorithm for rapid initial stratification of nonsevere disease. Clin Gastroenterol Hepatol. 2009;7(6):702–5. quiz 607.
36. Zhou Q, Chang B, Chen XY, Zhou SP, Zhen Z, Zhang LL, et al. Chinese herbal medicine for obesity: a randomized, double-blinded, multicenter, prospective trial. Am J Chin Med. 2014;42(6):1345–56.
37. Hu B, Sun R, Wu A, Ni Y, Liu J, Guo F, et al. Severity of acute gastrointestinal injury grade is a predictor of all-cause mortality in critically ill patients: a multicenter, prospective, observational study. Crit Care. 2017;21(1):188.
38. Ding L, Chen HY, Wang JY, Xiong HF, He WH, Xia L, et al. Severity of acute gastrointestinal injury grade is a good predictor of mortality in critically ill patients with acute pancreatitis. World J Gastroenterol. 2020;26(5):514–23.
39. Imrie CW, Benjamin IS, Ferguson JC, McKay AJ, Mackenzie I, O'Neill J, et al. A single-centre double-blind trial of Trasylol therapy in primary acute pancreatitis. Br J Surg. 1978;65(5):337–41.
40. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57(12):1698–703.

41. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190–206.
42. Siebert M, Le Fouler A, Sitbon N, Cohen J, Abba J, Poupardin E. Management of abdominal compartment syndrome in acute pancreatitis. J Visc Surg. 2021.
43. Mukherjee R, Nunes Q, Huang W, Sutton R. Precision medicine for acute pancreatitis: current status and future opportunities. Precis Clin Med. 2019;2(2):81–6.
44. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain. 1986;27(1):117–26.
45. Buxbaum J, Quezada M, Chong B, Gupta N, Yu CY, Lane C, et al. The Pancreatitis Activity Scoring System predicts clinical outcomes in acute pancreatitis: findings from a prospective cohort study. Am J Gastroenterol. 2018;113(5):755–64.
46. Oppe M, Devlin NJ, van Hout B, Krabbe PF, de Charro F. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. Value Health. 2014;17(4):445–53.
47. Guo J, Xue P, Yang XN, Lin ZQ, Chen Y, Jin T, et al. The effect of Chaiqin Chengqi Decoction on modulating serum matrix metalloproteinase 9 in patients with severe acute pancreatitis. Chin J Integr Med. 2013;19(12):913–7.
48. Wu W, Guo J, Yang XN, Lin ZQ, Huang z Z, Xia Q, et al. Effect of Chaiqinchengqi decoction on serum amyloid A in severe acute pancreatitis patients. Asian Pac J Trop Med. 2012;5(11):901–5.
49. Li L, Jin T, Wen S, Shi N, Zhang R, Zhu P, et al. Early Rapid Fluid Therapy Is Associated with Increased Rate of Noninvasive Positive-Pressure Ventilation in Hemoconcentrated Patients with Severe Acute Pancreatitis. Dig Dis Sci. 2020;65(9):2700–11.
50. Liang G, Yang J, Liu T, Wang S, Wen Y, Han C, et al. A multi-strategy platform for quality control and Q-markers screen of Chaiqin chengqi decoction. Phytomedicine. 2021;85:153525.

Figures

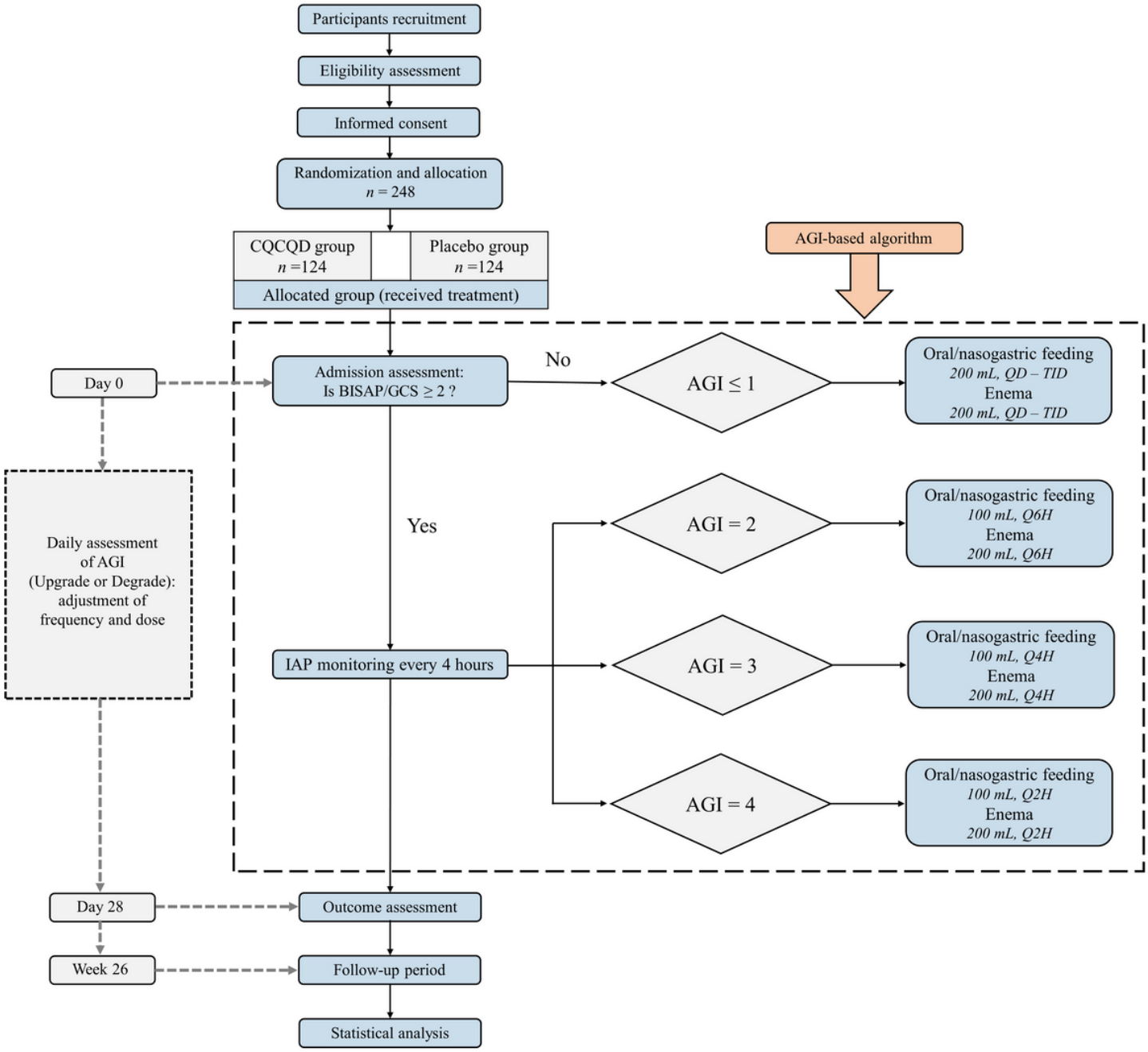

Figure 1

Study flowchart. CQCQD, Chaiqin chengqi decoction; AGI, acute gastrointestinal injury; BISAP, bedside index of severity in acute pancreatitis; GCS: Glasgow criteria system; IAP: intra-abdominal pressure; QD: once daily; TID: three times a day; Q6H: every 6 hours; Q4H: every 4 hours; Q2H: every 2 hours.

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