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Fluid therapy protocols in people with acute pancreatitis (Protocol)

van Laarhoven S, Di Martino M, Gurusamy KS

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[Intervention Protocol]

Fluid therapy protocols in people with acute pancreatitis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of different fluid therapy protocols (different routes, types of fluids, and rates at which fluid is administered) in people with acute pancreatitis.

BACKGROUND

Please see Glossary of terms (Appendix 1) for a brief description of medical terms.

Description of the condition

The pancreas is an abdominal organ that secretes several digestive enzymes into the pancreatic ductal system, which empties into the small bowel. The pancreas contains regions called islets of Langerhans, which secrete several hormones including insulin (NCBI 2014). Acute pancreatitis is a sudden inflammatory process in the pancreas, with variable involvement of nearby organs or other organ systems (Bradley 1993). The annual incidence of acute pancreatitis ranges from 5 to 30 per 100,000 population (Roberts 2013; Yadav 2006). There has been an increase in the incidence of acute pancreatitis in the last one to two decades in the UK and USA (Roberts 2013; Yang 2008). Acute pancreatitis is the most common gastrointestinal (digestive tract) cause of hospital admission in the USA (Peery 2012). Gallstones and alcohol are the two main causes for acute pancreatitis. Approximately 50% to 70% of acute pancreatitis is caused by gallstones (Roberts 2013; Yadav 2006). This happens when gallstones slip into the common bile duct and obstruct the ampulla of Vater (a common channel formed by the union of the common bile duct and pancreatic duct), which results in obstruction to the flow of pancreatic enzymes and leads to activation of trypsinogen within the pancreas and acute pancreatitis in a proportion of people with common bile duct stones (Sah 2013). Factors associated with higher incidence of acute pancreatitis include increasing age, male gender, and lower socioeconomic status (Roberts 2013).

The clinical manifestation of acute pancreatitis is believed to be caused by activation of inflammatory pathways, either directly by the pathologic insult or indirectly by activation of trypsinogen (an enzyme that digests protein or a protease); this results in formation of trypsin, a protease which can break down the pancreas (Sah 2013). This activation of inflammatory pathways manifests clinically as systemic inflammatory response syndrome in a proportion of people with acute pancreatitis (Banks 2013; Sah 2013; Tenner 2013).

The diagnosis of acute pancreatitis is made when at least two of the following three features are present (Banks 2013):

1. acute onset of a persistent, severe, epigastric pain, often radiating to the back;
2. serum lipase and amylase activity at least three times greater than the upper limit of normal;
3. characteristic findings of acute pancreatitis on contrast enhanced computed tomography (CECT) and, less commonly, magnetic resonance imaging (MRI) or transabdominal ultrasonography.

Depending upon the type of inflammation, acute pancreatitis can be classified into interstitial oedematous pancreatitis (diffuse or occasionally localised enlargement of the pancreas due to inflammatory oedema as seen on CECT) or necrotising pancreatitis (necrosis involving either the pancreas or peripancreatic tissues, or both) (Banks 2013). Approximately 90% to 95% of people with acute pancreatitis have interstitial oedematous pancreatitis, while the remainder have necrotising pancreatitis (Banks 2013). Necrotising pancreatitis may be sterile or infected (Banks 2013). Various theories exist as to how pancreatic and peripancreatic tissues get infected. These include spread from blood circulation, lymphatics, bile, from the small bowel (duodenum) through the pancreatic duct, and movement through the large bowel wall (translocation) (Schmid 1999).

Local complications of acute pancreatitis include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis (Banks 2013). The systemic complications of acute pancreatitis include worsening of pre-existing illnesses such as heart or chronic lung disease (Banks 2013). The mortality rate following an attack of acute pancreatitis is between 6% and 20% (Roberts 2013; Yadav 2006). The mortality rate depends upon the severity of acute pancreatitis.

Acute pancreatitis can be classified as mild, moderate, or severe, depending upon the presence of local or systemic complications, transient organ failure involving one of more of lungs, kidneys, and cardiovascular system (heart and blood vessels) lasting up to 48 hours, or persistent organ failure of these organs lasting beyond 48 hours (Banks 2013). In mild pancreatitis, there are no local or systemic complications or organ failure. In moderately severe acute pancreatitis, there may be local or systemic complications or transient organ failure. In severe acute pancreatitis, there is persistent organ failure (Banks 2013). Severe acute pancreatitis carries the worst prognosis in terms of mortality, while mild pancreatitis has the best prognosis (Banks 2013).

Initial clinical management of acute pancreatitis consists of:

1. replacement of fluid lost or sequestered into third spaces and restoration of electrolyte balance. Current guidelines provide directions for early and vigorous fluid administration (Tenner 2013);
2. nutrition, which may be enteral or parenteral nutrition, particularly in people with severe acute pancreatitis (Al-Omran 2010; Chang 2013; Forsmark 2016).

The presence of any inciting factor, like a common bile duct stone, should be addressed and treated. People with pancreatitis of suspected or proven biliary origin who have associated cholangitis or persistent biliary obstruction are recommended to undergo biliary sphincterotomy and endoscopic stone extraction within 72 hours of presentation (Williams 2017). Percutaneous or endoscopic drainage, based on a step-up approach, are indicated in cases of intra-abdominal collections secondary to necrotising infected pancreatitis (van Santvoort 2010). Minimally invasive step-up approach resulted in fewer adverse events, less organ failure, and lower costs compared to open necrosectomy (Gurusamy 2016a). Very low-quality evidence from a Cochrane Review suggested that the endoscopic, minimally invasive step-up approach resulted in fewer adverse events than the video-assisted minimally invasive step-up approach, but increased the number of procedures required for treatment (Gurusamy 2016a). Endoscopic or surgical drainage may be indicated in large and symptomatic pseudocysts (Gurusamy 2016b).

Description of the intervention

Fluid resuscitation in acute pancreatitis can be administered via the intravenous route or enteral route and can be achieved using blood products, crystalloids, or colloids (Lange 1983; Leese 1991). Colloids are large molecules suspended in a carrier solution and are retained in the intravascular compartment because of their decreased ability to cross the healthy semipermeable capillary membrane; crystalloids are solutions of electrolytes that can easily cross the healthy semipermeable capillary membrane (Myburgh 2013). The common colloids used historically were albumin, hydroxyethyl starch, and gelatin-based solutions (Myburgh 2013). The two commonly used crystalloids are normal saline and Ringer's lactate or Hartmann's solution (Wu 2011).

The commonly used endpoints for guidance for fluid therapy are clinical parameters, blood pressure, heart rate, urinary output, blood urea nitrogen (BUN), hematocrit changes, or central venous pressure (Bortolotti 2014; Wu 2009). This guidance in fluid therapy based on one or more physiological parameter is called goal-directed therapy.

How the intervention might work

Pancreatitis is associated with third-space fluid loss. Third-space fluid loss causes hypoperfusion which results in splanchnic vasoconstriction and decreased blood flow to the pancreas (Takeda 2005). Decreased blood flow precedes reduction in microcirculation of the pancreas, which could be an important factor in the development of necrotising pancreatitis (Cuthbertson 2006). Hypovolaemia also causes poorer perfusion in other organs and can increase multi-organ failure and mortality in people with systemic inflammatory response syndrome (Mofidi 2006; Petrov 2010).

Because of their retention in the intravascular compartment, colloids exert oncotic pressure (osmotic pressure that results in water being pulled into the circulatory system) and maintain the intravascular volume (Myburgh 2013). Cyrstalloids replace the fluid lost from the intravascular compartment.

It is believed that early and rigorous fluid resuscitation may prevent or limit pancreatic necrosis, reduce systemic inflammatory response, prevent multi-organ failure, and preserve pancreas microcirculation (Tenner 2013; Warndorf 2011; Wu 2009; Wu 2011). Supporters of high-rate fluid therapy believe that the earlier replacement of fluid decreases mortality (Gardner 2009), while high-rate fluid therapy has the potential to result in fluid overload, thereby precipitating or worsening heart and lung failure.

Why it is important to do this review

Different types of fluid will affect the patient fluid and electrolyte balance differently (Aggarwal 2014; Haydock 2013; Trikudanathan 2012). Hydroxyethyl starch (a colloid) may increase mortality compared to crystalloids in critically ill people (Perel 2013). Normal saline has a higher chlorine concentration than Hartmann's solution (Semler 2016). Higher chlorine concentration leads to a fall in pH (acidosis); in addition, normal saline lacks bicarbonate which might prevent acidosis by acting as a buffer (Burdett 2003). Acidosis might lead to a more severe inflammatory response and severe pancreatitis (Bhoomagoud 2009; Seyama 2003). In addition, metabolic acidosis due to hyperchloraemia may cause renal vasoconstriction, thereby decreasing the renal blood flow and causing acute kidney injury (Wilcox 1983; Yunos 2012). Thus, there is some uncertainty as to whether normal saline or Hartmann's solution is better for fluid resuscitation in people with pancreatitis.

The rate at which fluid is administered is another controversial issue in fluid resuscitation in people with acute pancreatitis (Loveday 2010): different guidelines suggest different infusion rates and resuscitation protocols (Loveday 2010). For example, American College of Gastroenterology guidelines recommend that fluid is administered at the rate of 250 ml to 500 ml per hour (Tenner 2013); the combined International Association of Pancreatology (IPA) and American Pancreatic Association (APA) working group recommends fluid rates of 5 mL/Kg/hour to 10 mL/Kg/hour, with a possible maximum of 2500 mL to 4000 mL (IAP/APA 2013); and the British guidelines recommend fluid therapy guided by urinary output (British Guidelines 2005). Goal-directed therapy has been shown to be useful in people with major trauma and severe sepsis (Pearse 2005; Rivers 2001). However, its role in acute pancreatitis has not been established.

Existing systematic reviews which include all types of studies highlight the uncertainty around fluid management in people with acute pancreatitis (Aggarwal 2014; Haydock 2013; Trikudanathan 2012). There have been no systematic reviews of randomised controlled trials, or Cochrane systematic reviews on fluid resuscitation strategies in people with acute pancreatitis. Systematic reviews and meta-analyses increase the precision of the treatment effects (i.e. they provide a narrower range of the average treatment effect) (Higgins 2011), and so decrease the risk of a type II error (concluding that there is no difference between treatments when there is actually a difference). Systematic reviews also help in identifying the differences in the treatment effects between studies and allow exploration of the reasons behind these differences. Methods such as multiple treatment comparisons or network meta-analysis allow comparison of several treatments simultaneously, and provide information on the relative effect of one treatment versus another, even when there is no direct comparison. This systematic review will identify the relative effects of different methods of fluid resuscitation and identify any gaps in the research.

OBJECTIVES

To assess the benefits and harms of different fluid therapy protocols (different routes, types of fluids, and rates at which fluid is administered) in people with acute pancreatitis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include studies reported as full text, those published as abstract only, and unpublished data. We will exclude quasi-randomised studies because of the risk of bias.

Types of participants

We will include adults with acute pancreatitis, irrespective of the definition used, severity (mild, moderately severe, or severe acute pancreatitis), and pre-existing comorbidities. However, if there is any evidence of inconsistency (see Data synthesis), we will perform a separate meta-analysis for interventions for mild pancreatitis separately from moderately severe or severe pancreatitis.

Types of interventions

We will include studies comparing different routes of administration, types of fluids (blood products, colloids, or crystalloids, or different types of colloids or crystalloids), and different rates at which fluid is administered, for example high-rate fluid resuscitation versus maintenance-rate fluid resuscitation (approximately

25 ml to 30 ml/Kg/day) (NICE 2017), or goal-directed versus non goal-directed fluid therapy. We will accept cointerventions provided that they are administered equally in all the groups in the trial.

For comparison of type of fluids, we will treat each different type of fluid as a separate intervention, for example, normal saline, Hartmann's solution, hydroxyethyl starch, and albumin.

Types of outcome measures

Primary outcomes

1. Mortality
   i) Short-term mortality (in-hospital mortality or mortality within six months)
   ii) Mortality at maximum follow-up
2. Serious adverse events (within six months). We will accept the following definitions of serious adverse events.
   i) International Conference on Harmonisation - Good Clinical Practice guideline (ICH-GCP 1997): serious adverse events are defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability/incapacity.
   ii) Other variations of ICH-GCP classifications, such as Food and Drug Administration (FDA) classification (FDA 2006) or the Medicines and Healthcare products Regulatory Agency (MHRA) classification (MHRA 2013)
   iii) Organ failure (however reported by authors)
   iv) Infected necrotising pancreatitis (culture proven)
3. Health-related quality of life (using any validated scale)
   i) Short-term (four weeks up to three months)
   ii) Medium-term (more than three months up to one year)
   iii) Long-term (more than one year)

Of these, we will consider short-term mortality, serious adverse events, and short-term health-related quality of life as the most important outcomes.

Secondary outcomes

1. Adverse events (within six months). We will accept all adverse events reported by the trial authors, irrespective of the severity of the adverse event.
2. Measures of decreased complications and earlier recovery (within six months)
   i) Length of hospital stay (including the index admission for acute pancreatitis and any disease-related or intervention-related readmissions including those for recurrent episodes)
   ii) Length of intensive therapy unit (ITU) stay (including the index admission for acute pancreatitis and any disease-related or intervention-related readmissions)
   iii) Requirement for additional invasive intervention such as necrosectomy for pancreatic necrosis, endoscopic or radiological drainage of collections
   iv) Time to return to normal activity (return to pre-acute pancreatitis episode mobility without any additional carer support)
   v) Time to return to work (in those who were employed previously)
3. Costs (within six months)

The choice of the above clinical outcomes is based on the necessity to assess whether the different fluid therapy protocols are effective in decreasing complications, thereby decreasing the length of ITU and hospital stay, decreasing any additional interventions, and resulting in earlier return to normal activity and work, and improvement in quality of life. The cost outcome will provide an indication of resource requirement. We do not regard the reporting of the outcomes listed here as an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will conduct a literature search to identify all published and unpublished randomised controlled trials in all languages. We will translate non-English language papers and fully assess them for potential inclusion in the review as necessary.

We will search the following electronic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL; Appendix 2);
2. MEDLINE (1946 to present; Appendix 3);
3. Embase (1947 to present; Appendix 4); and
4. Science Citation Index (1982 to present) (Appendix 5).

We will also search ClinicalTrials.gov (Appendix 6) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (Appendix 7).

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will contact authors of identified studies and ask them to identify other published and unpublished studies.

We will search for errata or retractions from eligible studies on PubMed and report the date this was done in the review.

Data collection and analysis

Selection of studies

Two review authors (KG and SvL) will independently screen titles and abstracts of all the potential studies we identify as a result of the search, and code them as 'retrieve' (eligible, potentially eligible, or unclear) or 'do not retrieve'. We will retrieve the full text of study reports or publications and two review authors (KG and SvL) will independently screen the full text, identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and characteristics of excluded studies table.

Data extraction and management

We will use an Excel-based data collection form for study characteristics and outcome data, which we will pilot on at least three studies in the review. Two review authors (KG and SvL or MDM) will independently extract the following study characteristics and outcome data from included studies.

1. Methods: study design, total duration of study and run-in period, number of study centres and location, study setting, withdrawals, date of study.
2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria.
3. Interventions: intervention, comparison, and any cointerventions.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

If an outcome is reported at two or more time points within the timeframe of the outcome - for example, 30-day and 90-day mortality are reported - we will use the data that are reported at the latest time point of the outcome. We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus. One review author (MDM) will copy across the data from the data collection form into the Review Manager 5 file. We will double check that the data are entered correctly by comparing the study reports with how the data are presented in the systematic review. A second review author (KG) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (KG and Svl) will independently assess the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement through discussion. We will assess the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We will judge each study to be at either high, low, or unclear risk of bias for each of the domains above, and we will provide a quote from the study report and justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary, e.g. for unblinded outcome assessment, the risk of bias for all-cause mortality may be very different than for a patient reported pain scale. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome, as part of the GRADE methodology.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data (short-term mortality, proportion of participants with adverse events, requirement for additional interventions) as odds ratio, and continuous data (health-related quality of life if the same scale was used, length of hospital stay, ITU stay, time to return to normal activity, time to return to work, and costs) as mean difference or standardised mean difference when different scales are used (e.g. health-related quality of life). We will ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, and we will explain the direction of effect to the reader and report where the directions were reversed if this was necessary. For count outcomes, such as number of adverse events, we will calculate the rate ratio; for time-to-event outcomes, such as mortality at maximal follow-up, we will calculate the hazard ratio.

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

A common way that trialists indicate they have skewed data, is by reporting medians and interquartile ranges. When we encounter this, we will note that the data are skewed and consider the implication of this. If the data are skewed, we will not perform a meta-analysis, but will provide a narrative summary instead.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms.

Unit of analysis issues

The unit of analysis will be individual participants with acute pancreatitis. If we find any cluster-randomised studies unexpectedly, we will include the data in the analysis if results are adjusted for intra-cluster correlation. If we find any cross-over randomised studies, we will include the data prior to the cross-over.
In multi-arm studies, the models account for the correlation between trial-specific treatment effects from the same trial in the context of network meta-analysis, which allows comparison of multiple treatments.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data as indicated (e.g. when a study is identified as abstract only). If we are unable to obtain the information from the investigators or study sponsors, we will impute the mean from the median (i.e. consider median as the mean) and the standard deviation from the standard error, interquartile range, or P values, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will assess the impact of including such studies indicated in a sensitivity analysis. If we are unable to calculate the standard deviation from standard error, interquartile range, or P values, we will impute standard deviation as the highest standard deviation in the remaining studies included in the outcome (though we are aware that this method of imputation will decrease the weight of the studies in the meta-analysis of mean difference, and shift the effect towards no effect for standardised mean difference).

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included studies. We will assess the presence of clinical heterogeneity by comparing effect estimates in mild and moderate or severe acute pancreatitis. Different study designs and risk of bias can contribute to methodological heterogeneity.
We will assess statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study standard deviation (tau^2 and comparing this with values reported in a study of the distribution of between-study heterogeneity (Turner 2012)), and by calculating I^2 (using Stata/SE 14.2). If we identify substantial heterogeneity that is clinical, methodological, or statistical, we will explore and address the heterogeneity in a subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

We will assess the assumption of transitivity by comparing the distribution of the potential effect modifiers (clinical: mild versus moderate or severe acute pancreatitis; methodological: risk of bias, year of randomisation, and duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the network meta-analysis, we will judge the reporting bias by the completeness of the search (i.e. searching various databases and including conference abstracts) and the comparison-adjusted funnel plot (Chaimani 2012).

Data synthesis

Methods for indirect and mixed comparisons

We will conduct network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. We will conduct three network meta-analyses, one each for the route of fluid administration, type of fluid, and rate of fluid. Network meta-analysis combines direct evidence within studies and indirect evidence across studies (Mills 2012). We will obtain a network plot to ensure that the studies are connected by interventions using Stata/SE 14.2 (Chaimani 2013). We will exclude any studies that are not connected to the network. We will perform only direct comparison meta-analysis for such studies not connected to the network.
We will conduct a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3, according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We will model the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and an arbitrarily selected reference group ('basic parameters') using appropriate likelihood functions and links (Lu 2006). We will use binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link for time-to-event outcomes, and normal likelihood and identity link for continuous outcomes. We will use 'intravenous route', 'normal saline', and maintenance fluid rates as the reference groups for the route of fluid, type of fluid, and rate of fluid network meta-analyses respectively. We will use the random-effects model as default but will perform a sensitivity analysis using the fixed-effect model for the network meta-analysis. We will

report the random-effects model for comparison with the reference group in a forest plot if the two models report similar results; otherwise, we will report the more conservative model. For each pairwise comparison in a table, we will report the random-effects model if the two models report similar results; otherwise, we will report the more conservative model.

We will use a hierarchical Bayesian model using three different initial values, employing codes provided by the NICE DSU (Dias 2016). We will use a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors). For the random-effects model, we will use a prior distributed uniformly (limits: zero to five) for between-trial standard deviation but will assume similar between-trial standard deviation across treatment comparisons (Dias 2016). We will use a 'burn-in' of 5000 simulations, check for convergence visually, and will run the models for another 10,000 simulations to obtain effect estimates. If we did not obtain convergence, we will increase the number of simulations for 'burn-in'. If we still did not obtain convergence, we will use alternate initial values and priors employing methods suggested by van Valkenhoef 2012. We will also estimate the probability that each intervention ranks at one of the possible positions using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

We will assess inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We will use the inconsistency models employed in the NICE DSU manual, as we will use common between-study standard deviation (Dias 2014). In addition, we will use design-by-treatment full interaction model and inconsistency factor (IF) plots to assess inconsistency (Higgins 2012; Chaimani 2013). In the presence of inconsistency, we will assess whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the Subgroup analysis and investigation of heterogeneity section.

If there is evidence of inconsistency, we will identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between studies and, when appropriate, limit network meta-analysis to a more compatible subset of studies.

Direct comparison

We will perform the direct comparisons using the same codes and the same technical details. We will use random-effects model by default. For testing the robustness of our findings regardless of which method was chosen, we will conduct sensitivity analyses for primary outcomes using the fixed-effect model. In case of divergence between the two models, we will present the more conservative results; otherwise, we will present only results from the random-effects model.

Presentation of results

We will present the effect estimates with 95% credible intervals (CrIs) for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We will also present the cumulative probability of the treatment ranks (i.e. the probability that the intervention is within the top two, the probability that the intervention is within the top three, etc.) in graphs (SUCRA) (Salanti 2011). We will also plot the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Salanti 2011; Dias 2012b).

We will present 'Summary of findings' tables for the primary outcomes. In the 'Summary of findings' tables, we will follow the approach suggested by Puhan and colleagues (Puhan 2014). First, we will calculate the direct and indirect effect estimates and 95% credible intervals using the node-splitting approach (Dias 2010), i.e. calculate the direct estimate for each comparison by including only studies in which there was direct comparison of interventions and the indirect estimate for each comparison by excluding the studies in which there was direct comparison of interventions. Next, we will rate the quality of direct and indirect effect estimates using GRADE methodology, which takes into account the risk of bias, inconsistency, directness of evidence, imprecision, and publication bias (Guyatt 2011). We will then present the estimates of the network meta-analysis and rate the quality of network meta-analysis effect estimates as the best quality of evidence between the direct and indirect estimates (Puhan 2014). In addition, we will present information on the number of studies and participants, according to the presentation of standard 'Summary of findings' tables.

Subgroup analysis and investigation of heterogeneity

We will to assess the differences in the effect estimates between the following subgroups, using meta-regression for the primary outcomes with the help of the codes provided in the NICE DSU guidance if we include a sufficient number of studies (Dias 2012a). We will use the following trial-level covariates for meta-regression.

1. Studies at low risk of bias compared to studies at high risk of bias
2. People with pre-existing comorbidities compared to those without pre-existing comorbidities
3. Mild versus moderate or severe acute pancreatitis (according to the definition in Atlanta 2012) (Banks 2013)
4. Presence of cointerventions (for example, nutritional supplementation versus no nutritional supplementation)

We will calculate a single common interaction term when applicable (Dias 2012a). If the 95% credible intervals of the interaction term do not overlap zero, we will consider this statistically significant.

Sensitivity analysis

If a trial reports only per-protocol analysis results, we will re-analyse the results using the best-worst case scenario and worst-best case scenario as sensitivity analyses whenever possible. We will also perform a sensitivity analysis using the fixed-effect model.

Reaching conclusions

We will only base our conclusions on findings from the quantitative or narrative synthesis of studies included in this review. We will avoid making recommendations for practice; our implications for research will give the reader a clear sense of the needed focus of future research and remaining uncertainties in the field.

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The methods section of this protocol is based on a standard template used by Cochrane Gastrointestinal and Pancreatic Diseases, modified for network meta-analysis used by the author group.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Glossary of terms

Acidosis: an excessively acid condition of the body fluids or tissues.
Acute: sudden.
Autodigestion: breakdown of the same organ that secretes the substance.
Cholangiopancreatography: fully known as endoscopic retrograde cholangiopancreatography (ERCP); a procedure carried out on the pancreatic and bile ducts using an endoscope and x-rays.
Endoscopic sphincterotomy: endoscopic operation to cut the muscle surrounding the common bile duct and the pancreatic duct.
Endoscopic: with the help of an endoscope, a tube inserted into body (in this context, through the mouth and into the stomach and upper part of the small intestine).
Enteral: through the gut.
Enzyme: substances that enable and speed up chemical reactions that are necessary for the normal functioning of the body.
Epigastric: upper central abdomen.
Epigastric pain: upper central abdominal pain.
Heterogeneity: variability.
Insulin: substance which helps regulate blood sugar.
Interstitial: space in between.
Morbidity: illness (in this context, it means complications).
Mortality: death.
Necrosectomy: removal of dead tissue.
Necrosis: death and decomposition of living tissue usually caused by lack of blood supply but can be caused by other pathological insult.
Necrotising: causing necrosis.
Oedematous: excessive accumulation of serous fluid in the intercellular spaces of tissues.
Pancreatic pseudocysts: fluid collections in the pancreas or the tissues surrounding the pancreas, surrounded by a well-defined wall and containing only fluid with little or no solid material.

Pancreatitis: inflammation of the pancreas.
Pathologic insult: substance or mechanism that causes the condition.
Percutaneous: through the skin.
Peripancreatic tissues: tissues surrounding the pancreas.
Pseudocyst: a fluid-filled cavity that resembles a cyst but lacks a wall or lining.
Radiology guided percutaneous treatments: treatments carried out by insertion of needle from the external surface of the body which are guided by a scan (usually an ultrasound or CT (computed tomography) scan).
Randomisation: using chance methods to assign people to treatments.
Retrograde: moving backwards.
Sepsis: life-threatening illness due to blood infection with bacteria, fungus, or virus.
Step-up approach: initial minimally invasive treatment followed by more invasive treatments if there is no clinical improvement.
Serum: clear fluid that separates out when blood clots.
Transabdominal: through the abdomen.
Transient: temporary.
Tumour necrosis factor-alpha antibody: antibody to tumour necrosis factor-alpha, an intermediary substance in the inflammatory pathway.

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Pancreatitis, Acute Necrotizing] this term only
#2 MeSH descriptor: [Pancreatitis] this term only and with qualifier(s): [Etiology - ET]
#3 MeSH descriptor: [Pancreas] this term only and with qualifier(s): [Abnormalities - AB, Pathology - PA, Physiopathology - PP]
#4 acute near/3 pancrea*
#5 necro* near/3 pancrea*
#6 inflam* near/3 pancrea*
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Fluid Therapy] this term only
#9 MeSH descriptor: [Resuscitation] explode all trees and with qualifier(s): [Methods - MT]
#10 fluid near/3 resuscitation
#11 MeSH descriptor: [Water-Electrolyte Balance] this term only
#12 fluid near/2 balance
#13 fluid near/2 restriction*
#14 MeSH descriptor: [Dehydration] this term only
#15 MeSH descriptor: [Blood Volume] this term only
#16 blood volume index or ITBVI
#17 MeSH descriptor: [Extravascular Lung Water] this term only
#18 Lung Water Index or ELWI
#19 MeSH descriptor: [Stroke Volume] this term only
#20 Stroke Volume Variation or hypervolaemia or hypervolemia
#21 MeSH descriptor: [Central Venous Pressure] this term only
#22 CVP or Swan-Ganz
#23 MeSH descriptor: [Catheterization, Peripheral] explode all trees
#24 preload
#25 MeSH descriptor: [Colloids] this term only
#26 colloid* or crystalloid*
#27 goal near/1 directed
#28 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
#29 #7 and #28

Appendix 3. MEDLINE search strategy

1. Pancreatitis, Acute Necrotizing/
2. Pancreatitis/et [Etiology]
3. Pancreas/ab, pa, pp [Abnormalities, Pathology, Physiopathology]
4. (acute adj3 pancrea*).mp.
5. (necro* adj3 pancrea*).mp.
6. (inflam* adj3 pancrea*).mp.
7. or/1-6
8. Fluid Therapy/
9. exp Resuscitation/mt
10. (fluid adj3 resuscitation).mp.
11. Water-Electrolyte Balance/
12. (fluid adj2 balance).mp.
13. (fluid adj2 restriction*).mp.
14. Dehydration/
15. Blood Volume/
16. blood volume index.mp.
17. ITBVI.mp.
18. Extravascular Lung Water/
19. Lung Water Index.mp.
20. ELWI.mp.
21. Stroke Volume/
22. Stroke Volume Variation.mp.
23. (hypervolaemia or hypervolemia).mp.
24. Central Venous Pressure/
25. CVP.mp.
26. Swan-Ganz.tw.
27. exp Catheterization, Peripheral/
28. preload.mp.
29. Colloids/
30. colloid*.tw.
31. crystalloid*.tw.
32. (goal adj1 directed).mp.
33. or/8-32
34. 7 and 33
35. randomized controlled trial.pt.
36. controlled clinical trial.pt.
37. randomized.ab.
38. placebo.ab.
39. drug therapy.fs.
40. randomly.ab.
41. trial.ab.
42. groups.ab.
43. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. exp animals/ not humans.sh.
45. 43 not 44
46. 34 and 45

Appendix 4. Embase search strategy

1. exp acute hemorrhagic pancreatitis/
2. exp acute pancreatitis/
3. (acute adj3 pancrea*).mp.
4. (necro* adj3 pancrea*).mp.
5. (inflam* adj3 pancrea*).mp.
6. or/1-5
7. Fluid Therapy/
8. exp fluid resuscitation/
9. (fluid adj3 resuscitation).mp.
10. (fluid adj2 balance).mp.
11. (fluid adj2 restriction*).mp.
12. Dehydration/
13. exp blood volume/
14. blood volume index.mp.
15. ITBVI.mp.
16. exp lung extravascular fluid/
17. Lung Water Index.mp.
18. ELWI.mp.
19. exp heart stroke volume/
20. Stroke Volume Variation.mp.
21. exp hypervolemia/
22. (hypervolaemia or hypervolemia).mp.
23. electrolyte balance/
24. Swan Ganz catheter/
25. Swan-Ganz.tw.
26. Central Venous Pressure/
27. CVP.mp.
28. catheterization/
29. heart preload/
30. preload.mp.
31. Colloid/
32. colloid*.tw.
33. crystalloid/
34. crystalloid*.tw.
35. (goal adj1 directed).mp.
36. or/7-35
37. 6 and 36
38. Clinical trial/
39. Randomized controlled trial/
40. Randomization/
41. Single-Blind Method/
42. Double-Blind Method/
43. Cross-Over Studies/
44. Random Allocation/
45. Placebo/
46. Randomi?ed controlled trial*.tw.
47. Rct.tw.
48. Random allocation.tw.
49. Randomly allocated.tw.
50. Allocated randomly.tw.
51. (allocated adj2 random).tw.

52. Single blind*.tw.
53. Double blind*.tw.
54. ((treble or triple) adj blind*).tw.
55. Placebo*.tw.
56. Prospective study/
57. or/38-56
58. Case study/
59. Case report.tw.
60. Abstract report/ or letter/
61. or/58-60
62. 57 not 61
63. 37 and 62

Appendix 5. Science Citation Index search strategy

#1 TS=((acute near3 pancrea*) or (necro* near/3 pancrea*) or (inflam* near/3 pancrea*))
#2 TS=((fluid near/3 resuscitation) or (fluid near/2 balance) or (fluid near/2 restriction*) or blood volume index or ITBVI or Lung Water Index or ELWI or Stroke Volume Variation or hypervolaemia or hypervolemia or CVP or Swan-Ganz or preload or colloid* or crystalloid* or (goal near/1 directed))
#3 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)
4 #3 AND #2 AND #1

Appendix 6. ClinicalTrials.gov search strategy

fluid | Pancreatitis | Phase 2, 3, 4

Appendix 7. WHO ICTRP search strategy

Fluid [title] AND pancreatitis[condition]

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: KSG, SvL, MDM

Designing the protocol: KSG, SvL, MDM

Co-ordinating the protocol: KSG

Designing search strategies: KSG

Writing the protocol: SvL, KSG, MDM

DECLARATIONS OF INTEREST

SvL: none known.

MDM: none known.

KSG: none known.

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Internal sources

- University College London, UK.

The contact author is employed by University College London (UCL). UCL also provided electronic library resources for completing this protocol.

External sources

- No sources of support supplied