# Crystalloids vs. colloids for fluid optimization in patients undergoing brain surgery

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# Abstract

BACKGROUND This randomised, double-blinded, single-centre study prospectively investigated the impact of goal directed therapy and fluid optimization with crystalloids or colloids on perioperative complications in patients undergoing brain surgery.

METHODS 80 patients were allocated into two equal groups to be optimised with either crystalloids (n=40) or colloids (n=40). Invasive hemodynamic monitoring and optimization with fluids and vasoactive drugs were used to adjust and maintain mean arterial pressure and cerebral oxygenation within the baseline values (± 20%) and stroke volume variation (SVV) ≤13. Postoperative complications from different organ systems were monitored during the first 15 days after surgery. Hospital stay and mortality were also recorded.

RESULTS Crystalloid group received significantly more fluids (p = 0.003) and phenylephrine (p = 0.02) compared to colloid group. This did not have any significant impact on intraoperative or postoperative complications, hospital stay or mortality, where no differences between groups were observed.

CONCLUSIONS Either crystalloids or colloids could be used for fluid optimization in brain surgery. If protocolised perioperative haemodynamic management is used, the type of fluid does not have significant impact on the outcome.

CLINICAL TRIAL REGISTRATION: Identified as NCT03249298 at www.clinicaltrials.gov KEY WORDS: Brain surgery, fluid optimization, haemodynamic management


# Introduction

Proper intravenous fluid therapy has effect on perioperative care and long-term postoperative outcome. Perioperative fluid therapy, guided by flow based haemodynamic monitors, can improve outcome. Optimization of hemodynamic and oxygen delivery by using a goal-directed therapy (IV fluids and/or vasoactive infusions), guided by objective monitoring, could be more personalised approach (1, 2, 3).

Recent studies showed that haemodynamic management should be tailored to the cardiovascular physiology and the clinical situation of each individual patient, the so called personalised haemodynamic management (4). It improves outcome of the surgery (better wound healing, shorter hospital stay, less surgical site infections, cardiovascular and pulmonary complications) (5).

It is unclear whether crystalloid or colloids fluids or a combination should be used for goal directed therapy to optimise patient outcome and what is the clinical impact of this technique (5, 6, 7, 8)

Brain oedema prevention and optimization of cerebral perfusion and oxygenation are main goals of anaesthetic technique during brain surgery (9, 10). Optimal neuroprotective strategies include appropriate patient positioning, management of systemic and cerebral haemodynamic, maintenance of fluid,

electrolyte and coagulation balance, and postoperative prevention and treatment of pain, postoperative nausea and vomiting (8, 9).

The optimal volume status during brain surgery is not known. There are two main dilemmas regarding fluids, the use of liberal or restrictive protocol and the type of fluid used. Fluid therapy may augment both cardiac output and cerebral blood flow. Fluid overload may result in poor neurological outcome, but it is still uncertain if fluid restriction is favourable or damaging to post-craniotomy neurological outcome. There is also concern regarding possible negative impact of colloids on coagulation that can cause bleeding and worsen outcome perioperatively (10, 11, 12).

Stroke volume variation (SVV) is one of the dynamic haemodynamic parameters that predicts intraoperative fluid responsiveness also in brain surgery (13, 14). The goal is to maintain systemic and cerebral haemodynamic variables (cardiac output, arterial blood pressure, cardiac rhythm, cerebral blood flow) (8, 9). In our previous study we showed that type of anaesthesia for brain surgery does not have impact on haemodynamic stability and the occurrence of postoperative complications (8). But the question arised if the type of fluid used for managing systemic and cerebral haemodynamic variables does have any impact on the postoperative outcome.

Thus, we hypothesized that routine use of goal-directed therapy for craniotomy is more important for prevention of postoperative complications than the type of fluid (crystalloid or colloids) used for haemodynamic optimization.

The aim of our study was to investigate the impact of perioperative haemodynamic management with crystalloids or colloids on perioperative complications, hospital stay and mortality in brain surgery.

# Materials And Methods

Prospective, randomised, double-blind, single-centre study, with two parallel group, was conducted at the University Medical Centre Ljubljana, Department of Anaesthesiology and Surgical Intensive Care and Department of Neurosurgery in years 2016- 2018 (trial registry: NCT03249298 at www.clinicaltrials.gov). The study was approved by the National Medical Ethics Committee of the Republic of Slovenia. All the procedures were performed in accordance with the declaration of Helsinki. The CONSORT recommendations for reporting randomized trials were followed. Written informed consent was obtained from all subjects participating in the trial.

80 patients, aged 18-80 years, ASA (American Society of Anaesthesiologists) Class 1-3 and GCS (Glasgow coma score) of 15, scheduled for elective craniotomy, were included in the study.

Exclusion criteria were (a) unwillingness to give a written informed consent, (b) cardiac arrhythmia (c) hemodynamic unstablity or shock (d) and coagulation disorder.

All patients were visited by a member of our team a day prior to surgery to seek an informed consent and to answer any question. Patients were able to freely withdraw from the trial.

Using a computer-generated list, the patients were randomised into two groups by the fourth author, not involved in patient care. The first author enrolled the patients and informed them about the participation in the study. The surgeon and the anaesthesiologist were blinded to the type of fluids used.

In the operating room standard monitoring was instituted. An arterial catheter was placed in the radial artery for continuous blood pressure monitoring. Advanced pulse contour cardiac output monitoring using the EVA 1000/FloTrac device (Edwards Lifescience, CA, USA) and near infrared spectroscopy oximetry (NIRS) monitoring (Medtronic, MN, USA) were applied.

Patients were premedicated (midazolam 7,5 mg po). Antibiotic prophylaxis with intravenous cefazolin 2g in 100 ml of 0.9% NaCl was invariably used in all patients.

Anaesthesia was induced with propofol 1-2 $mgkg^{-1}$ (Propoven, Fresenius Kabi AG, Bad Homburg, Germany). Before intubation all patients received remifentanil 0.5-1 $\mu gkg^{-1}$ (Ultiva, GlaxoSmithKline) and rocuronium 0.6 $mgkg^{-1}$ (Esmeron, MSD, NY, USA).

Patients were intubated and mechanically ventilated (oxygen-air mixtures, I/E ratio 1:2, tidal volume 8 $mlkg^{-1}$, peak inspiratory pressure 35 cm $H_2O$). The goal was to reach normal values of partial pressure of carbon dioxide in arterial blood ($paCO_2$) and normal values of partial pressure of oxygen in arterial blood. Anaesthesia was maintained by continuous infusion of propofol 4–6 mg $kg^{-1}h^{-1}$. Remifentanil was adjusted according to the degree of surgical manipulation (0.1–2 $\mu g\ kg^{-1}min^{-1}$) and was increased when mean arterial pressure and heart rate increased over 30% from baseline. The depth of anaesthesia was measured with bispectral index (BIS) and maintained from 40 to 60. This is according to hospital policy, since total intravenous infusion was used in order to prevent intraoperative awareness.

Haemodynamic management was followed by study protocol. Intraoperative basal fluid replacement was realized with continuous infusion 2-4 $ml^{-1}kg^{-1}h^{-1}$ of balanced crystalloid regimes (Sterofundin, B. Braun Melsungen AG). Additional boluses of 250 ml fluid were given when stroke volume variation (SVV) measured by EVA 1000/FloTrac system rose above 10% (a sustained change during the previous 5 minutes) or in the case of a positive response to previous fluid challenge until normal SVV value (13 or less). Colloid group (CO) received colloid solution (Voluven 130/0.4 6%; Fresenius Kabi AG, Bad Homburg, Germany) and crystalloid group (CR) balanced crystalloid (Sterofundin). If mean arterial pressure (MAP) or cerebral oxygenation (ScO2) after fluid boluses were still < 20% from the baseline values with normal SVV values, vasoactive drugs were given (ephedrine 5-10 mg (0.5% Ephedrine, UMC Ljubljana Pharmacy, Slovenia) or phenylephrine 50 µg (0.01%, UMC Ljubljana Pharmacy, Slovenia)) to maintain MAP and/or ScO2 ± 20% from the baseline values. Bradycardia (heart rate (HR) < $40min^{-1}$) was treated with atropine 0.5 mg. If MAP and/or HR increased over 30% from baseline, the infusion of remifentanil was increased by 0.1 $\mu g\ kg^{-1}min^{-1}$. Any adverse haemodynamic events (increase of MAP and/or HR over 30% from baseline) that did not respond to higher remifentanil infusion rate, were managed with urapidil or metoprolol, as appropriate. Blood loss was replaced with colloids (CO group) or crystalloids (CR group) until a reduced PRBC transfusion trigger (haemoglobin level < 90 $gl^{-1}$) was reached. Haemodynamic

parameters were recorded continuously in 5-min intervals (from induction to discharge from the postanaesthesia care unit (PACU)). If needed, rotational tromboelastometry (ROTEM) was performed to detect early coagulopathy and to predict blood transfusion requirements (15). During dura closing piritramide 0.1 $mg/kg^{-1}$ (Dipidolor, Janssen-Cillag GmbH, Neuss, Germany), metamizole 2,5 g (Analgin, Stada AG, Bad Vilbel, Germany) and ondansetron 4 mg were given to the patients.

Propofol infusion was stopped at the last skin suture. Remifentanil infusion was stopped after the removal of the Mayfield head holder.

Postoperatively intravenous infusion of piritramide was started as patient-controlled analgesia (PCA). The definition of operation duration was the time from the application of the Mayfield head holder to its removal. Duration of anaesthesia was measured from induction to extubation. The time from anaesthetics cessation to tracheal extubation was also recorded. All the patients were extubated in the operating theatre and then transferred to the PACU, where they stayed for not more than 2 hours. Afterwards they were admitted to the Department of Neurosurgery intensive care unit (ICU).

Standard postoperative monitoring generally used in these procedures was implemented. Oxygen was administered via a Venturi mask and titrated to the lowest level needed to achieve arterial oxygen saturation greater than 96%. During the hospital stay the main investigator (JMB) visited the patients daily to check the postoperative complications and the fluid loading.

# Measurements

The following data were collected: demographics, duration of surgery and anaesthesia, the consumption of intraoperative drugs, fluid balance and haemodynamic parameters, the length of hospital stay and postoperative complications during 15 days after surgery.

Postoperative complications were defined as any unintended changes in body function or well-being, such as hypertension (systolic blood pressure 30% higher than the baseline level), postoperative nausea with vomiting, pain (visual analogue scale (VAS) > 3), infection, pulmonary, cardiovascular and neurological events, reoperation and death.

The primary outcome measure was the difference in the consumption of the fluid used for haemodynamic optimization.

The secondary outcome measures included the incidence of postoperative complications, the length of hospital stay, perioperative haemodynamic variables, fluid balance, and serum safety control markers (lactate, haemoglobin, coagulation status).

# Statistical analysis

The appropriate sample size was calculated from our previous pilot study of two independent groups (20 patients optimised with colloids and 20 patients treated with standard non-optimised approach) using a

priori two-tailed t-test power analysis. The difference in the mean colloid consumption between the groups was used for the effect size calculation and the sample size determination. For a significance level of 5% ($\alpha = 0.05$) and a power of 90% ($\beta = 0.1$), the calculated minimum sample size was 36. To compensate for possible withdrawals, 40 patients were included in each group. Two patients from each group were excluded for further analysis because of technical reasons (Figure 1).

The two-tailed t-test with unequal variances or the Chi-square test were used to test the differences in demographic data, duration of the procedure and anaesthesia, drug consumption, fluid balance, haemodynamic parameters, postoperative complications and hospital stay.

The means of continuous variables are presented, and categorical data are summarized as counts. A p-value of less than 0.05 was considered statistically significant. Data were analysed by SPSS 13.0 software package (IBM Corp., Armonk, NY, USA).

# Results

80 patients, 40 in the CO group and 40 in CR group (Figure1), scheduled for brain surgery, were included in the study. There were sixty-nine primary operations and 7 reoperations. No significant differences were found between the groups regarding their demographics, underlying pathology, position during surgery and duration of procedure (Table 1). Neither there were any significant differences in perioperative variables that could have influence on the outcome and the length of hospital stay (Table 2). CR group received statistically significant more fluids and phenylephrine, but there were no differences in fluid balance and the levels of serum safety serum markers (Table 2).

Table 1

**Baseline demographics and surgical procedure**

| | CR (N=38) | CO (N= 38) | p value |
|---|---|---|---|
| Age (years) | 54 ± 14 | 55 ± 16 | 0,69 |
| Weight (kg) | 79 ± 16 | 76 ± 15 | 0,45 |
| Gender (M/F) | 17/21 | 14/24 | 0,32 |
| ASA (I/II/III) | 8/19/11 | 7/24/7 | 0,46 |
| First operation/reoperation | 33/5 | 36/2 | 0,43 |
| Pathology | 35/0/3 | 35/2/1 | 0,22 |
| Tumour /Vascular/Adenoma | 24 | 22 | 0,48 |
| Patient position | 13 | 12 | 0,63 |
| Supine | 1 | 2 | 0,50 |
| Lateral | 0 | 2 | 0,49 |
| Sitting | 33/5 | 33/5 | 0,82 |
| Prone | 35/3 | 37/1 | |
| Localization supratentorial/infratentorial | 195±60 | 209±101 | |
| Type of surgery craniotomy/endoscopic | 242±64 | 247±105 | |
| Duration of procedure (min) | | | |
| Duration of anaesthesia (min) | | | |
| The results are expressed as mean ± SD or number of patients. | | | |
| The differences between groups were not significant (p>0,05). | | | |
| Abbreviations: | | | |
| ASA, American Society of Anaesthesiologists | | | |

Table 2
**Intraoperative and postoperative variables and outcome**

| Group | CR | CO | p |
|---|---|---|---|
| **Intraoperative data** | | | |
| Propofol (mg) | 1355±451 | 1307 ± 766 | 0,74 |
| Remifentanil (mg) | 15 ± 8 | 13 ± 8 | 0,25 |
| Total loss of blood (ml) | 311 ± 262 | 461 ± 486 | 0,09 |
| Urine volume (ml) | 996 ± 510 | 772± 655 | 0,99 |
| Total fluids (ml) | 2250±1000 | 2122± 758 | 0,53 |
| Blood transfusion | 17±107 | 73±203 | 0,14 |
| Fresh frozen plasma | 13±78 | 61±185 | 0,14 |
| Fluid optimization boluses | 5/6/2/14 | 8/13/6/9 | 0,16 |
| (1/2/3/>3 times) | 1120±816 | 653±365 | 0,003* |
| Consumption of optimization fluid | | | |
| Intraoperative hypotension | 9/7/6/8 | 6/7/3/6 | 0,88 |
| (1/2/3/>3 times) | | | |
| Vasoactive drugs | 6/4/4//3/11 | 6/5/1/5/5 | 0,41 |
| (1/2/3/>3 times/infusion) | 874±1632 | 210±530 | 0,02* |
| Phenylephrine (mcg) | 8±10 | 7±13 | 0,64 |
| Ephedrine (mg) | | | |
| Urapidil (mg) | 3 ± 10 | 3± 8 | 0,88 |
| Metoprolol (mg) | 0,13±0,8 | 0,13±0,8 | 1 |
| Atropine (mg) | 0,07±0,2 | 0,08±0,2 | 0,7 |
| Tromboelastometry (Rotem) (normal/pathological) | 33/5 | 33/4 | 0,57 |

The results are expressed as mean ± SD or number of patients;

The differences between groups are significant with p <0.05).

POMS: postoperative morbidity score

| Group | CR | CO | p |
|---|---|---|---|
| **Intraoperative data** | | | |
| Lactate (mmol/l) | 1,1±0,4 | 0,88±0,5 | 0,10 |
| Haemoglobin (g/l) | 120±13 | 115±12 | 0,08 |
| Postoperative data (24 h) | 37/1/0 | 34/0/4 | |
| Arterial pressure (normal/low/high) | | | |
| Postoperative CT of the head (good/oedema/haematoma/other) | 30/6/1/1 | 28/6/4/0 | 0,41 |
| Total fluids (ml) | 1693±520 | 1772±684 | 0,57 |
| Urine volume (ml) | 1382±660 | 1297±735 | 0,59 |
| Lactate (mmol/l) | 1,1±0,4 | 0,95±0,4 | 0,25 |
| Haemoglobin (g/l) | 123±17 | 119±13 | 0,29 |
| POMS (15 days) | 23 | 23 | 0,41 |
| No difference (comparing to score before surgery) | 1 | 0 | |
| Death | | | |
| Wound infection | 1 | 0 | |
| Inflammation | 0 | 1 | |
| Pulmonary (pneumonia/embolism) | 0/0 | 0/2 | 0,70 |
| Neurological complications (minor/major) | 13/0 | 12/0 | |
| Hospital stay (days) | 9 ± 4 | 9 ± 5 | |
| The results are expressed as mean ± SD or number of patients; | | | |
| The differences between groups are significant with p <0.05). | | | |
| POMS: postoperative morbidity score | | | |

# Discussion

Historically anaesthesiologists observed patients and act according to clinical changes. If decision to give fluid bolus or vasoactive drugs is based only on low blood pressure, one could easily overlook the need for fluid and give just vasoactive drugs and vice versa. Namely, liberal fluid approach can prolong hospital stay and lead to oedema, on the other hand restrictive fluid regime is correlated with postoperative complications (16,17,18,19). That is extremely important in neurosurgery, where infusing

too much fluid can result in brain oedema and hypoperfusion. Non-invasive haemodynamic monitoring is therefore important to control brain perfusion. According to the results of Luo and co- workers goal directed fluid therapy significantly reduces the consumption of colloids and crystalloids compared to the group, where therapeutic decisions were left at the discretion of the attending anesthesiologist and intensivist (20).

Feldheiser and colleagues showed that colloids have longer intravenous effect and enable better haemodynamic stability and flow measurement (5). This can explain why in our study the crystalloid group received more fenilefrine.

Our first goal was to achieve the desired SVV with fluid optimisation. Vasoactive drugs were used only if hypotension persisted (21). Hypotension occurred more often in crystalloid group, but non-significant. These patients needed more fluid, and even when optimised, they still needed fenilefrin to achieve desired perfusion pressure. This was the reason why crystalloid group needed more fenilefrin, even though number of fenilefrin interventions did not vary between the groups.

Lactate is a measurement of adequate tissue perfusion and was not significantly raised in our groups. Wu and co-workers showed that for supratentorial brain tumor resection, fluid boluses targeting lower SVV are more beneficial than a restrictive protocol, and result in lower lactate, brain biomarkers and postoperative neurological events (22).

The incidence of intraoperative events that needed intervention (fluid and/or vasoactive drugs) did not differ between our groups. Intraoperative stabile patients did not need any intervention with fluid bolus or vasoactive drugs for haemodynamic optimisation.

Optimal brain perfusion prevents brain ischemia and oedema in patient undergoing neurosurgical procedure. Haemostasis is also essential to prevent worse outcome caused with haematoma. Colloids could have impact on coagulation. It was shown by Lindroos and colleagues that HES induced a slight disturbance in fibrin formation and clot strength (23).

We used ROTEM to exclude possible side effects of colloids on haemostasis.

We also showed that fluid optimisation with crystalloids is safe. Even though their consumption was larger compared to colloids. The amount of colloids needed for optimisation was 41 % lower, which was less then described in the literature (23,24). Obviously, good outcome with no postoperative neurological complications in both our groups showed that technique and haemodynamic management are more important than the type and volume of fluid. Same results were shown by Xia and co-workers. They showed that goal-directed colloid therapy was not superior to goal-directed cristalloid therapy for brain relaxation, cerebral oxygenation or cerebral metabolism, although less fluid was needed to maintain the target SVV in the colloid group (25). Fluids and vasoactive drugs should be applied according to haemodynamic measurements (4). Every patient should receive as much fluid as needed at appropriate time (26).

Conclusions: Our study showed that either crystalloids or colloids could be used for fluid optimization in brain surgery. If protocolised perioperative haemodynamic management is used, the type of fluid does not have significant impact on outcome.

Future studies in this area should focus on the development of broad goal directed strategies in perioperative fluid therapy rather than trying to find the best type of fluid.

# Declarations

AUTHORS' CONTRIBUTION

JMB is the first author who designed and conducted the study, analysed the data, reviewed the data analysis, wrote the manuscript, approved the final version of the manuscript, and is responsible for archiving the study files; BV and PM helped design the study, ASV conducted the study, reviewed the data analysis, wrote the manuscript and approved the final version of the manuscript;

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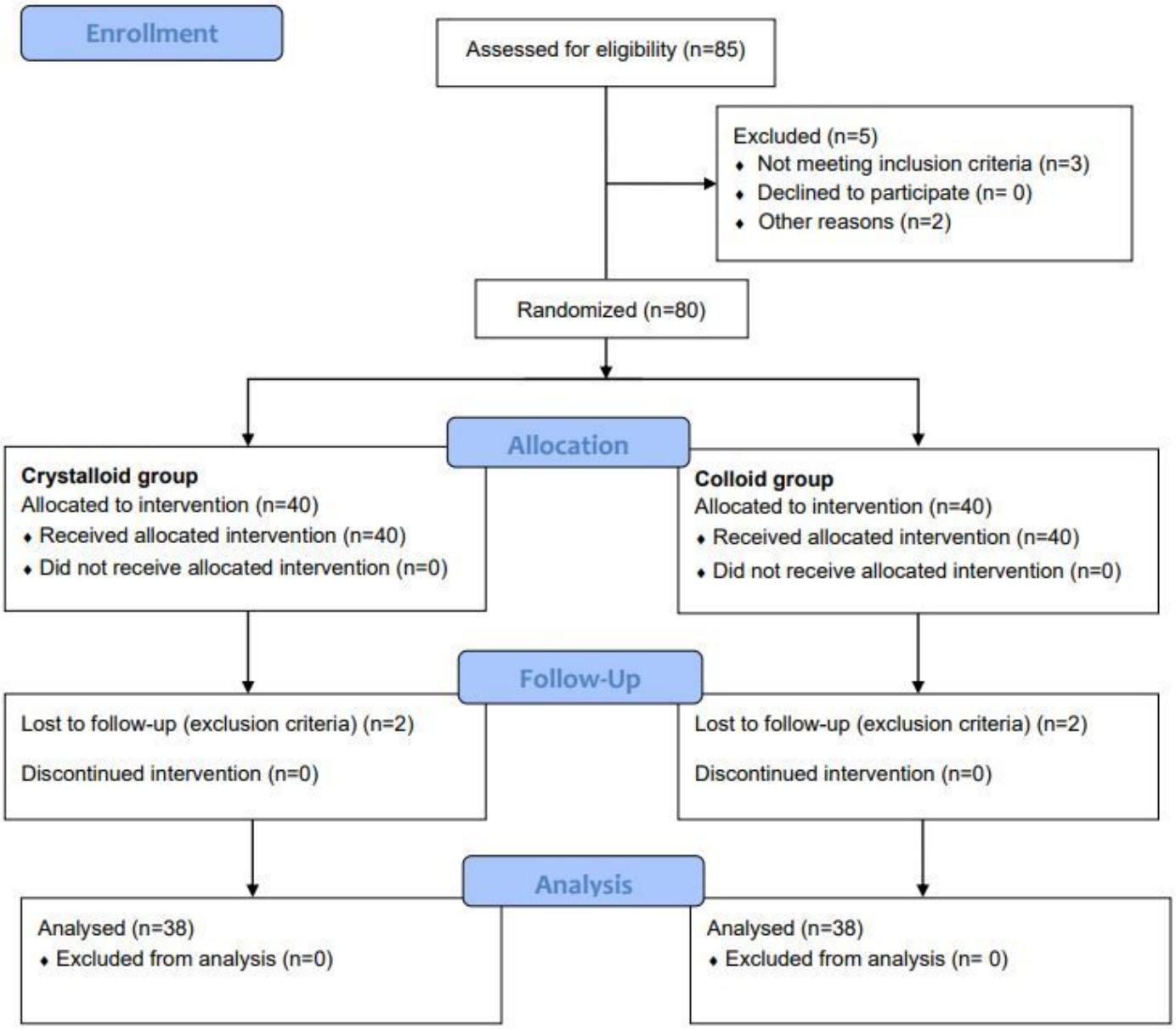
# Figures




## Figure 1

Flow diagram of the study