Octreotide Safety and Efficacy in Pediatric Non-variceal Upper Gastrointestinal Bleeding, A Randomized Controlled Trial

Bahador Mirrahimi (✉ Mirrahimi@sbmu.ac.ir)
  Shahid Beheshti University of Medical Sciences   https://orcid.org/0000-0001-7276-8770

Pejman Rohani
  Shahid Beheshti University of Medical Sciences School of Medicine

Omid Moradi
  Shaheed Beheshti University of Medical Sciences

Azin Hemmati
  Shahid Beheshti University of Medical Sciences School of Pharmacy

---

Research article

Abstract

Background: Octreotide as somatostatin analogue decrease the production of gastrointestinal (GI) peptides. Its consumption in pediatric population has been limited to control of bleeding episodes with variceal origin. In this randomized controlled trial, we aim to assess octreotide as an add-on therapy to conventional regimen of proton pump inhibitors in controlling upper GI bleeding in pediatric population.

Methods: In a prospective randomized controlled clinical trial, in Mofid Children's Hospital, Tehran, Iran, pediatric patients with age of 0 to 15 years diagnosed with acute non-variceal upper GI bleeding allocated to receive Octreotide or placebo and pantoprazole concomitantly. Medication administration initiated after patient's stabilization. Patients with hepatic failure, liver stigma, coagulopathy thrombocytopenia etc. were excluded. Demographic, clinical and preclinical data were recorded in prepared sheets. All patients were followed until therapy discontinuation.

Results: Forty-three patients with the mean age of 4.98 ± 3.79 years with confirmed non-variceal upper GI bleeding included to the study. Most patients had no specific etiology for their bleeding episode. Patients in intervention and control group received pantoprazole in comparable doses. No differences in baseline hemoglobin values was observed but final hemoglobin values were higher in intervention group. No differences in bleeding duration observed. In regard of adverse drug reaction due to octreotide infusion, none was observed in any patient.

Conclusions: Our study demonstrated that octreotide does not alter bleeding duration but need for transfusion in non-variceal upper GI bleeding but it may have effect on amount of blood loss.

Trial registration: The study was registered in Iranian Registry of Clinical Trial by the code of IRCT20120415009475N6.

Background

Upper gastrointestinal bleeding (UGIB) is an uncommon but life-threatening condition in pediatric population. UGIB encompasses origin of the bleeding site from esophagus to Treitz ligament [1]. Mortality rate for pediatric UGIB ranges from 5–15% or more in developing countries based on diverse properties of population which experience different associated conditions with UGIB, like acute variceal hemorrhage [1–3]. Octreotide is somatostatin synthetic peptide analog which mimics pharmacologic activity of somatostatin with advantages in pharmacokinetics parameters. Its potency and longer half-life in comparison to somatostatin lead to somatostatin replacement by octreotide [4]. The mechanism of actions of octreotide and its pharmacologic activity is by decreasing production of gastrointestinal peptides like gastrin, cholecystokinin, secretin and others via binding to G protein receptors [5, 6]. With limited experience in treatment of pediatric UGIB, it is being used widely in acute variceal bleeding treatment and also variceal rebleeding prevention. It has been used less frequently to manage UGIB by other etiologies. Most clinical trials involving octreotide have been performed in adults population [7]. In regard of octreotide efficacy in pediatric population few reports exist and based on our knowledge no

clinical trial has been performed by this date on octreotide efficacy in pediatric non-variceal UGIB [8, 9]. In this randomized clinical trial, we evaluate octreotide efficacy in the treatment of non-variceal UGIB in coadministration with a proton pump inhibitor in pediatric population.

Methods

In this prospective randomized double blinded placebo controlled clinical trial, gathered data form 43 patients analyzed. We enrolled Patients with acute non-variceal UGIB by the age of zero to 15 years between February 2019 to December 2019 in Mofid Children's Hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. Study was done in accordance with the declaration of Helsinki and was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran and registered in Iranian Registry of Clinical Trials (IRCT20120415009475N6, Registered 14 September 2019, https://www.irct.ir/trial/10069). Written informed consents were obtained from Legal guardian of all patients before enrollment. Patients were randomly selected and divided into two groups of test and control. Randomization was performed by Sealed Envelope randomization and online databases for clinical trials, London, United Kingdom. The study was designed as a double blinded clinical trial and both the administrator and analyzer were blinded. All of octreotide and placebo vials were labeled to not to be distinguishable from each other. The inclusion and exclusion criteria for enrollment were as followed. All patients with approved non-variceal UGIB, normal Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, Bilirubin serum level and stable hemodynamic, Age from zero to 15 years enrolled to the study. Patients with variceal UGIB, hepatic impairment (defined as child-pugh category C) [10], hepatic stigma, symptomatic hepatosplenomegaly, coagulopathy, platelet count less than 30000 cell/mcL and unstable hemodynamic despite maximum hydration and blood transfusion if indicated were excluded from the study. Patients were first examined for hemodynamic status and fluid or blood transfusion requirement. Stabilized enrolled patients received pantoprazole by dose of 1 mg/kg/hr for gastric pH of 6 or more for at least 24hr and octreotide by dose of 1–2 mcg/kg/hr, concomitantly. Collecting required demographic, clinical, preclinical data were performed under supervision of a clinical pharmacist. The recorded demographic data were included age, sex, weight, height for all patients. Also, clinical data about patients chief complaints and reason for referring to the hospital, physician diagnosis of non-variceal UGIB, underlying disease and conditions, coagulation profile, gastrointestinal problems, endoscopic results. All preclinical data include complete blood count, liver function and enzymes tests were recorded. Daily pantoprazole and octreotide dose as long as ongoing therapy were recorded. All patients were investigated for time bleeding discontinuation, rebleeding and length of therapy. All statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS) version 20.0 software. Mean and standard deviation were used to expressed continuous variables and numbers and percentage for categorical variables. Paired t-test were used for comparison of the quantitative data and the chi-square test for qualitative ones. p-values less than 0.05 were considered to be statistically significant.

Results

In this study 43 patients included 26 males and 17 females were recruited. The mean age of patients was 4.98 ± 3.79 years. In regard of distribution of gender, age and other demographic data there were no statistically significant differences between two groups of the study. Demographic values of recruited patients were represented in Table 1. Non-variceal acute gastrointestinal bleeding (AGIB) was confirmed for all patients by a pediatric gastroenterologist diagnosis. All of the patients were hemodynamically stable during the study. Hematemesis, melena and coffee grounded vomiting were the three most frequent chief complaints of the patients. There were no statistically significant differences between patient's complaints at first presentation between two intervention and control group. Most of the GI bleeding occurred in patients with no past medical history. Patients with past history of receiving chemotherapy or non-steroidal anti-inflammatory drugs and with diagnosis of AGIB were in the following. No significant differences observed in patient's past medical history distribution between two groups. (p = 0.052). seventeen in the study undergone endoscopic procedure. Normal GI mucosa observed in eight patients and six patients were diagnosed by gastritis. Antral ulcer, gastric ulcers and duodenitis were diagnosed in three patients. No differences were observed in endoscopic findings between two groups (p = 0.381). In only one patient of the study in intervention group GI bleeding despite receiving treatment by pantoprazole and octreotide did not stopped. Only one patient deceased who were undergoing chemotherapy for treatment of hematologic malignancy in intervention group. Baseline hemoglobin values was not different between two groups (p = 0.080) but after seven days of treatment hemoglobin drops was significantly more in control group (p = 0.014). Figure 1 demonstrate hemoglobin values in two groups of the study. Patients in two groups received pantoprazole by comparable dose. None of the patients in two group have any kind of coagulopathy. Mean INR of recruited patients were 1.08 ± 0.22. In control group patient received more packed red blood cells for correcting severe anemia in bleeding condition but this value was not statistically significant between two groups (p = 0.863). Figure 2 demonstrate mean octreotide dosing in intervention group in ten days of treatment. Time of GI bleedig resolving was not different between two groups (p = 0.99). In regard of adverse drug reaction (ADR), no patients who received octreotide showed any ADR consistent with serious conditions such as hypersensitivity reactions, cholelithiasis, pancreatitis or hyperglycemia. ADR due to alteration in heart rate and rhythm such as QTc prolongation or any kind of arrythmias did not occurred in patients who received octreotide. Hepatomegaly, splenomegaly and rise in hepatic aminotransferases were not seen in any patients.

Discussion

Octreotide as a peptide could alter various aspects of physiologic pathways in gastrointestinal tract and has a valuable therapeutic role as an add-on therapy in the pharmacotherapy of a variety of gastrointestinal disorders. In adults, approved octreotide indications are included vasoactive intestinal peptide tumors, therapy worked in management of esophageal varices bleeding, secretory or chemotherapy-induced diarrhea, excessive ileostomy losses, gastroenteropancreatic neuroendocrine tumors, and pancreatitis [11–13]. In pediatric population data about using octreotide are mostly included in indication such as secretory diarrhea or variceal GI bleeding [8, 14] and no clinical trial have

investigated safety and efficacy of octreotide in pharmacotherapy of AGIB in pediatric population without esophageal varices. In eighteen months survey all patients who admitted to the hospital with diagnosis of AGIB undergone endoscopic procedure. All the patients with variceal bleeding and whom undergone surgical procedures were excluded from the study. Patients with the mean age of 61.2 ± 15 years of age were randomly assigned to receive 50 mg ranitidine every eight hours alone or 100 mcg octreotide every eight hours subcutaneously, concomitantly with ranitidine. Based on pathologic data from endoscopy, there were no differences between two groups [15]. Blood transfusion and hospital length of stay were not different in two groups. In our study in pediatric population as there is no data on octreotide usage in pediatric population many data came from adult studies. But based on pharmacokinetic data in children it is known that octreotide clearance is more rapid in comparison data from adult studies and we should use it as intravenous infusion but not bolus doses. In limited retrospective studies in children it was shown than octreotide may be beneficial in controlling non-arterial bleeding in children and variceal GI bleeding but not bleeding from mucosal ulcers [16]. In a prospective non randomized clinical study for determining safety and efficacy of octreotide in controlling acute upper GI bleeding all patients with acute bleeding received octreotide for a 5 days course. Twenty-two patients had non-variceal bleeding confirmed by endoscopic evidences. In contrast to our study GI bleeding did not stopped in about one third of the patients [17]. Patients population, dosing and length of the therapy in two groups were different. In a study in three children with chronic hepatic impairment octreotide was efficacious in controlling bleeding from portal hypertension, unknown origin or arteriovenous malformations. These three children received octreotide by the dose of 4 to 8 mcg/kg/day which lead to bleeding cessation and hemoglobin rise in first week [18]. In hour study we did not observed hepatic impairment from octreotide consumption or significant rise in hepatic aminotransferases. In critically ill patients GI bleeding is more frequent than non-critically ill patient [19] but acute GI bleeding with clinical symptoms (hemodynamic instability, decrease in hemoglobin for 2 g/dL or more and blood transfusion) is less frequent. In developing countries GI bleeding occurred as a result of GI varices, mostly. Proton pump inhibitors (PPI) are the mainstay of treatment of non-variceal GI bleeding. In studies on octreotide administration concomitantly by a PPI, time of the bleeding cessation was not different as in our study.

In our study patients who received octreotide, received less blood transfusion in contrast to patients who only received pantoprazole but this difference was not statistically significant. And also, patients who received octreotide showed statistically significant less hemoglobin value in comparison to patients who did not received. This difference is more valuable when we compared baseline hemoglobin values which was not different. In a study conducted in Alberta pediatric hospital from January 1998 to December 2004, octreotide was consumed for different purposes in children [20]. In 21 patients who received octreotide, eleven patients received octreotide for massive GI bleeding. Cause of GI bleeding in these patients included esophageal and gastric varices, portal hypertension and gastropathy. Octreotide was administered in these patients by the dose of 2.2 ± 1 mg/kg/hr and tapered to the half dose after 24 hours and discontinued after bleeding stopped. In this retrospective study cardiovascular and hyperglycemia were the most common ADR in this study. In our study in Mofid hospital as a prospective randomized clinical trial we did not observed any ADR related to octreotide consumption in pediatric

patients. In one patient in our study in child who were admitted to the hospital by hypertension under treatment by labetalol we recorded data of hypertension which was not distinguishable that this hypertension was octreotide ADR or from patient's uncontrolled hypertension. An important point in octreotide safety of usage in pediatric population is that, most of the ADR reported in studies are observed in patients who received octreotide for longer duration in comparison to our study. For example, in Alberta study patients received octreotide for the duration of 7 to 90 days which were more than our study which patients received octreotide for only ten days. Another issue in investigating octreotide safety in pediatric use for treatment of AGIB is larger population seizes and multicenter randomized control trials. There was also some limitation to our study. First low sample size, second single centered study design, third, not monitoring for ADR after patients were discharged and fourth, not performing diagnostic endoscopy procedure for all patients.

Conclusions

From data of our study, octreotide showed no effect on decrease of bleeding duration in patients with non-variceal AGIB. Octreotide decrease the need for blood transfusion and hemoglobin value was significantly higher in patients who received octreotide. Safety issues for octreotide usage in pediatric population which diagnosis of non-variceal AGIB showed no serious ADR which lead to drug use cessation. Because of octreotide pricing, safety and efficacy which is not completely observed in pediatric patients it is also notable that, drug utilization evaluation study about octreotide use in pediatric population could be performed from data from this study. Also, it is recommended that multicentered, prospective randomized trials could be performed to evaluate safety and efficacy of octreotide in pediatric population with more sample size.

Abbreviations

Upper gastrointestinal bleeding (UGIB), Serum glutamic oxaloacetic transferase (SGOT), Serum glutamic pyruvic transaminase (SGPT), Statistical package for the social Sciences (SPSS), Acute gastrointestinal bleeding (AGIB), Adverse drug reactions (ADR), Proton pump inhibitors (PPI).

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, and all participant or written informed consents was obtained from all participant or their legal guardian.

Consent for publication

No personal data of any participant will be published.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare none.

Funding

Authors contributions

Conceptualization, Mirrahimi B, Rohani P; Methodology, Mirrahimi B; Statistical analysis, Mirrahimi B; Investigation and Data curation, Mirrahimi B Hemmati A; Original draft writing, Moradi O, Hemmati A; Review and editing, Mirrahimi B, Rohani P, Moradi O; Supervision, Mirrahimi B, Rohani P.

References

1. Owensby S, Taylor K, Wilkins T. Diagnosis and management of upper gastrointestinal bleeding in children. J Am Board Fam Med 2015;28(1):134-45.

2. Houben CH, Chiu PW, Lau JY, Lee KH, Ng EK, Tam YH, et al. Duodenal ulcers dominate acute upper gastrointestinal tract bleeding in childhood: a 10-year experience from Hong Kong. J Dig Dis 2008;9(4):199-203.

3. Cochran EB, Phelps SJ, Tolley EA, Stidham GL. Prevalence of, and risk factors for, upper gastrointestinal tract bleeding in critically ill pediatric patients. Crit care med 1992;20(11):1519-23.

4. Anthony L, Freda PU. From somatostatin to octreotide LAR: evolution of a somatostatin analogue. Curr Med Res Opin 2009;25(12):2989-99.

5. Chaudhry R, Singh B, Subhas P. Octreotide In Gastroenterology. Med J Armed Forces India 1997;53(4):293-4.

6. Sadowski DC. Use of octreotide in the acute management of bleeding esophageal varices. Can J Gastroenterol 1997;11(4):339-43.

7. Alhazzani W, Win LL, Howden CW, Leontiadis GI. Somatostatin or somatostatin analogues for acute non-variceal upper gastrointestinal bleeding. Cochrane Database of Systematic Reviews. 2011(10).

8. Al-Hussaini A, Butzner D. Therapeutic applications of octreotide in pediatric patients. Saudi J Gastroenterol 2012;18(2):87-94.

9. Puri K, Caldwell RL, Molleston JP. Role of Octreotide in Pediatric Gastrointestinal Bleeding Secondary to Angiodysplasia in Children With Right Heart Failure. J Pediatr Gastr Nutr 2018;66(2):e41-e4.

10. Child CG, Turcotte JG. Surgery and portal hypertension. Major problems in clinical surgery 1964;1:1-85.

11. Battershill PE, Clissold SP. Octreotide. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in conditions associated with excessive peptide secretion. Drugs 1989;38(5):658-702.

12. Chaudhry R, Singh B, Subhas P. OCTREOTIDE IN GASTROENTEROLOGY. Med J Armed Forces India 1997;53(4):293-4.

13. Stajich GV, Ashworth L. Octreotide. Neonatal netw 2006;25(5):365-9.

14. Meier R, Dierdorf R, Gyr K. [Somatostatin analog (octreotide) in clinical use: current and potential indications]. Schweizerische medizinische Wochenschrift. 1992;122(25):957-68.

15. Archimandritis A, Tsirantonaki M, Tryphonos M, Kourtesas D, Sougioultzis S, Papageorgiou A, et al. Ranitidine versus ranitidine plus octreotide in the treatment of acute non-variceal upper gastrointestinal bleeding: a prospective randomised study. Curr Med Res Opin 2000;16(3):178-83.

16. Siafakas C, Fox VL, Nurko S. Use of octreotide for the treatment of severe gastrointestinal bleeding in children. J Pediatr Gastr Nutr. 1998;26(3):356-9.

17. Kullavanuaya P, Manotaya S, Thong-Ngam D, Mahachai V, Kladchareon N. Efficacy of octreotide in the control of acute upper gastrointestinal bleeding. J Med Assoc Thai 2001;84(12):1714-20.

18. El-Shabrawi MH, Kamal NM. Medical management of chronic liver diseases (CLD) in children (part II): focus on the complications of CLD, and CLD that require special considerations. Paediatric drugs 2011;13(6):371-83.

19. Green DS, Abdel-Latif ME, Jones LJ, Lui K, Osborn DA. Pharmacological interventions for prevention and treatment of upper gastrointestinal bleeding in newborn infants. The Cochrane database of systematic reviews 2019;7:Cd011785.

20. Al-Hussaini A, Butzner D. Therapeutic applications of octreotide in pediatric patients. Saudi J Gastroenterol 2012;18(2):87-94.

Tables

Table 1. Demographic and clinical values of recruited patients.

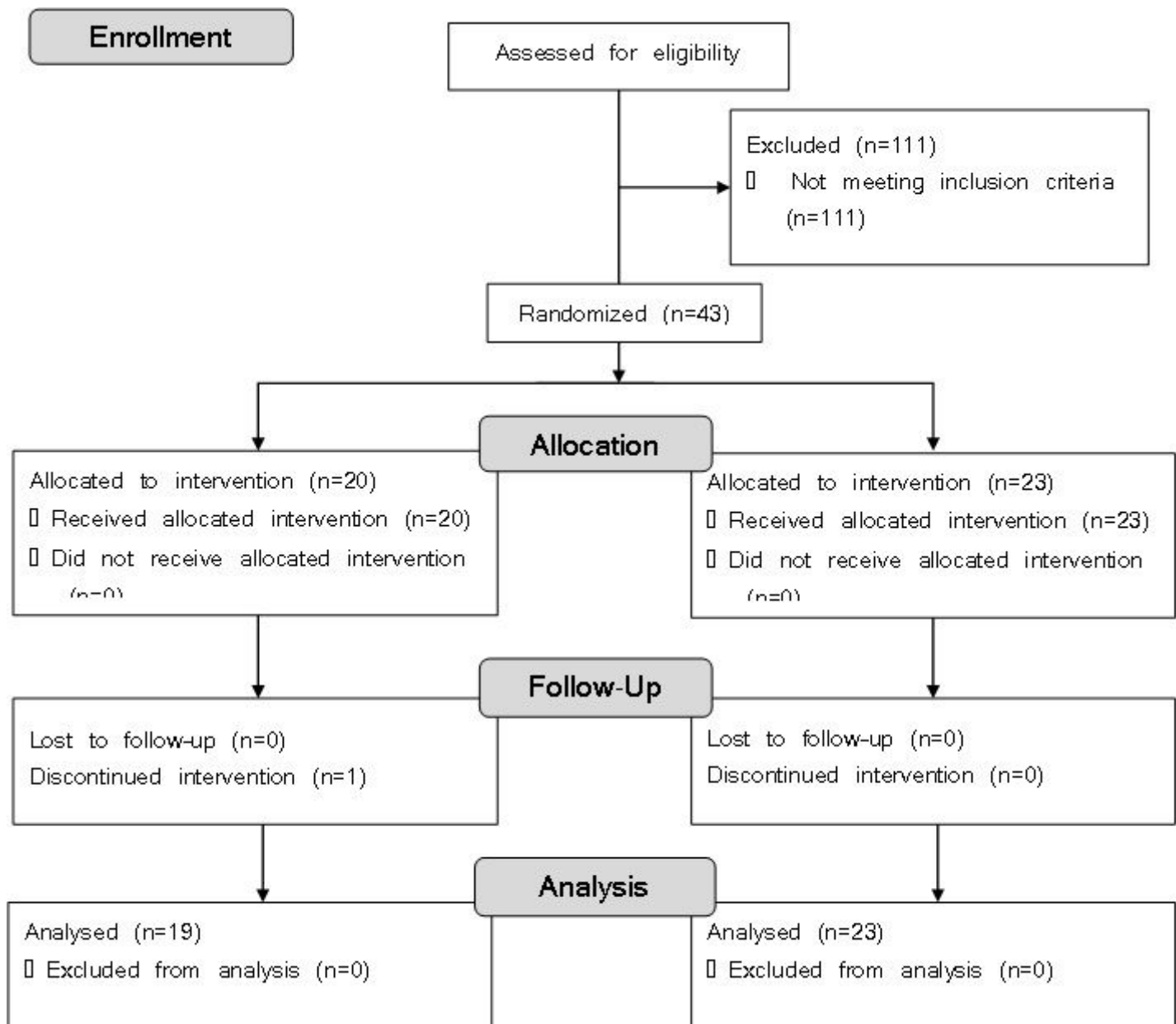| Value		Intervention group	Control group	p-value
Gender	Male	9	8	0.500
	Female	11	15	
Age (years)		5.71 ± 4.18	4.24 ± 3.27	0.386
Weight (kg)		16.9 ± 97.10	17.11 ± 20.46	0.215
Height (cm)		111.29 ± 50.17	114.18 ± 89.90	0.604
Past medical history	None	4	15	0.053
	Chemotherapy	5	0	
	NSAID usage	2	3	
	Prior GI bleeding	1	2	

Figures

Figure 1

Study flow diagram. The diagram illustrates the study enrollment and disposition of trial participants
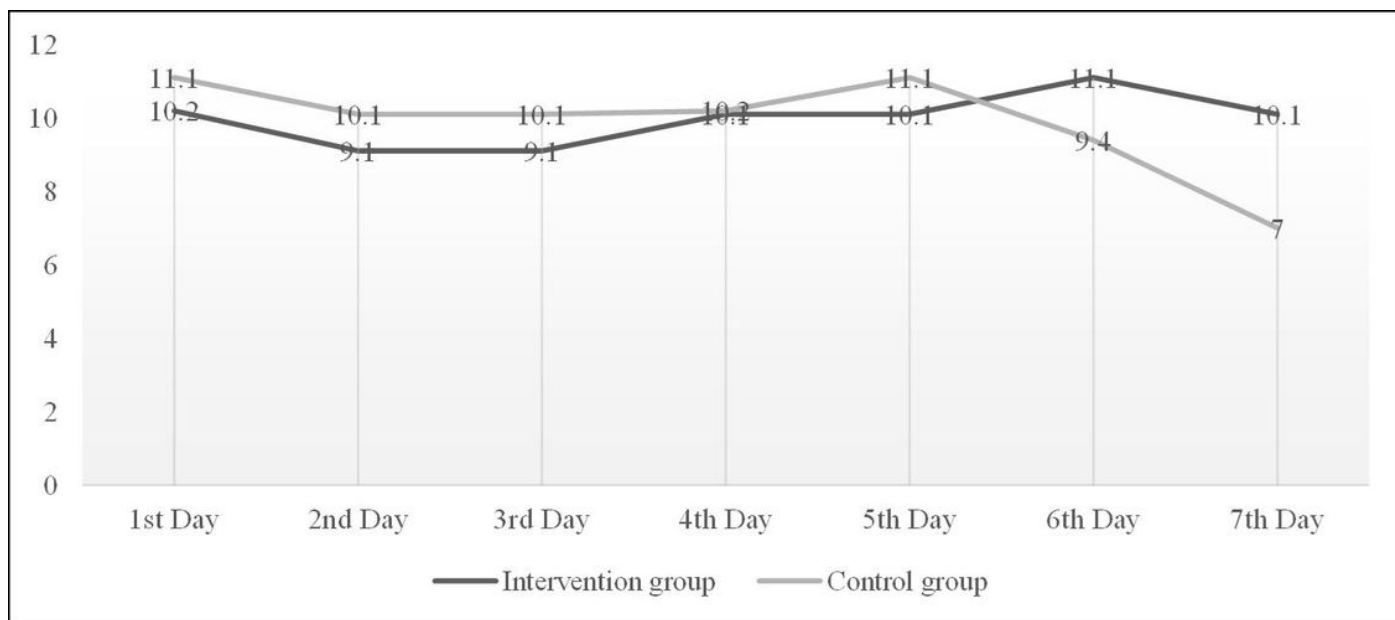
Figure 2

Hemoglobin values trend in intervention and control group

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc