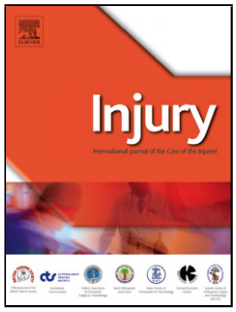
Accepted Manuscript



Title: The impact of hemocoagulase for improvement of coagulation and reduction of bleeding in fracture-related hip hemiarthroplasty geriatric patients: a prospective, single-blinded, randomized, controlled study

Author: Meiguang Qiu Xuming Zhang Hongru Cai Zhixian Xu Hao Lin

PII: S0020-1383(16)30772-0
DOI: http://dx.doi.org/doi:10.1016/j.injury.2016.11.028
Reference: JINJ 6999

To appear in: *Injury, Int. J. Care Injured*

Accepted date: 26-11-2016

The impact of hemocoagulase for improvement of coagulation and reduction of bleeding in fracture-related hip hemiarthroplasty geriatric patients: a prospective, single-blinded, randomized, controlled study

Running title: Hemocoagulase Improves Hip Hemiarthroplasty Coagulation

Meiguang Qiu (PhD), Xuming Zhang (BS)*, Hongru Cai (PhD), Zhixian Xu (PhD), Hao Lin (MM)

Department of Surgery, Fujian Provincial Hospital Emergency Center; Provincial Clinical College of Fujian Medical University; Fujian Provincial Emergency Medicine Institute, Fuzhou, China

***Corresponding author:**

Xuming Zhang

Department of Surgery, Fujian Provincial Hospital Emergency Center; Provincial Clinical College of Fujian Medical University; Fujian Provincial Emergency Medicine Institute, Fuzhou, China

Tel: +86-020-62787191

Fax: +86-021-64085875

Email: zhanjunshisci@163.com

Abstract

Background: Uncontrolled bleeding is associated with poor outcomes and mortality in geriatric patients undergoing hemiarthroplasty. Hemocoagulase agkistrodon is a hemocoagulative, anti-hemorrhagic enzyme complex from *Deinagkistrodon acutus* snake venom. This study aimed to investigate the efficacy of hemocoagulase agkistrodon on coagulation and bleeding outcomes in fracture-related hemiarthroplasty.

Patients and methods: This was a prospective, single-blinded, randomized controlled trial carried out between October 2013 and September 2014 in 96 geriatric patients undergoing hemiarthroplasty for unilateral femoral neck fracture. Patients were administrated hemocoagulase agkistrodon (n=48) or normal saline (n=48). Intraoperative blood loss, transfusion volume and rate, and drainage were assessed. Hemoglobin (Hb) and coagulation parameters (prothrombin time [PT], thrombin time [TT], plasma fibrinogen [FIB], and activated partial thromboplastin time [aPTT]) were recorded preoperatively and 30 min and 1, 3, and 5 days after surgery. Complications were followed up for 4 weeks.

Results: Compared to controls, hemocoagulase patients exhibited lower intraoperative blood loss (P<0.01) and postoperative blood loss, total drainage, mean transfusion volume, and transfusion rates (*all* P<0.05), with lower aPTT at 30 min (P<0.05). No significant differences in postoperative FIB were observed. Controls exhibited significantly higher PP and TT on day 1, and Hb on days 1, 3, and 5 (P<0.05). No serious complications were reported.

Conclusions: Hemocoagulase reduced blood loss and transfusion in fracture-related hip hemiarthroplasty without increasing short-term adverse event rates. In geriatric

populations, hemocoagulase could be used for limiting bleeding and related complications.

Keywords: hemocoagulase; blood loss; femoral neck fracture; hemiarthroplasty; bleeding; coagulation; geriatric populations

Trial registration: This trial is registered in the *Chinese Clinical Trial Register* (no. ChiCTR-TRC-14004379)

Introduction

Hip fractures are a common condition, particularly in geriatric populations, and are associated with significant morbidity and mortality.[1] It is suggested that the incidence of hip fractures will double by 2040.[1] Elderly patients are at high risk of mortality after hip surgery.[2] Bleeding and transfusion as well as the presence of significant comorbidities, surgical trauma and postoperative anemia have been suggested as risk factors in patients undergoing hemiarthroplasty following hip fracture.[3-5] Several studies have revealed that postsurgical anemia in hip fracture patients increased morbidity, prolonged hospital stays, increased readmission rate, and raided overall mortality.[6-9]

Allogeneic blood transfusion (ABT) has been associated with adverse events.[3-5] There are, however, widely discrepant clinical guidelines for transfusions between facilities resulting in a lack of clear consistency in the global efforts to weigh the benefits of avoiding perioperative anemia with inherent risks of transfusion.[10-17]

The need for allogenic transfusion can be minimized by several means, including autologous blood donation of the patient's own blood prior to surgery, hypotensive

anesthesia, and perioperative blood salvage.[18-21] However, there has been growing safety concerns with some of these methods, particularly in elderly patient populations that are already at high risk for deep vein thrombosis (DVT) and pulmonary embolism.[22] This has prevented the widespread acceptance of IV antifibrinolytics in clinical the settings.

Hemocoagulase is a hemocoagulative, anti-hemorrhagic enzyme complex that is present in the venom of the *Bothrops Jararaca* or *Bothrops atrox* snake, and it may be useful in improving coagulation and preventing bleeding.[23] Intrasvascular injections of hemocoagulase agkistrodon, a factor isolated from the venom of the Chinese moccasin snake (*Deinagkistrodon acutus*) in China, is a single component thrombin that has already successfully passed phases I and II clinical trials and has been demonstrated to have positive intraoperative and postsurgical effects on hemostasis and coagulation in humans.[24] Hemocoagulase agkistrodon positively impacts hemostatic and coagulative function and has been recently approved for commercial use as a pharmaceutical agent during abdominal surgery.[25-27]

While hemocoagulase efficacy is well demonstrated in patients undergoing abdominal surgery, its safety and efficacy in patients undergoing cementless hemiarthroplasty after femur neck fracture has not yet been characterized. This study aimed to evaluate intraoperative and postoperative blood loss and coagulation factors in patients undergoing cementless hemiarthroplasty. We hypothesized that intravascular hemocoagulase administration has the potential to reduce intraoperative and postoperative blood loss.

Patients and Methods

Study design

This was a prospective, single-blinded, randomized, controlled study (level of evidence: Level 1) carried out between October 2013 and September 2014 at our hospital. The intent was to enroll up to 100 geriatric subjects (aged ≥65 years) undergoing fracture-related hip hemiarthroplasty. Consecutive eligible subjects were asked to provide written informed consent prior to participation, or (if unable to provide consent due to medical status) written informed consent was obtained from the patient's legally authorized representative. Subjects were randomized (1:1) to receive either hemocoagulase treatment (hemocoagulase group) or normal saline (control group) based on an automated randomization system that allocated patients into groups according to their enrollment number. Randomization occurred 10-15 h before surgery, i.e. just before beginning the hemocoagulase (or placebo) regimen. A single-blind methodology was used: study and clinical staff were aware of group assignments, while patients were blinded. This methodology was used to ensure the safety of the medication for the patients, and to avoid the occurrence of accidents. The study was reviewed and approved by the Regional Ethics Committee of our hospital.

Eligibility criteria

Inclusion criteria were: 1) geriatric patients aged ≥65 years; 2) clinical indication for hip hemiarthroplasty because of femoral neck fracture; 3) able to walk unassisted prior to fracture; 4) unilateral fracture confirmed by conventional radiography; and 5) no significant confounding comorbidities, such as another trauma.

Exclusion criteria were: 1) medical history of osteoarthritis in the hip joint; 2) pathologic fractures due to other comorbidities; 3) bilateral fractures; 4) fracture of the intertrochanteric region; 5) history of cardiac, pulmonary, renal, and/or hepatic

disorders; 6) were prescribed NSAIDs within 7 days before surgery; 7) medical history of coagulation disorders including prior DVT or pulmonary embolism; or 8) abnormal clotting including abnormal prothrombin time (PT) and/or platelet counts. Subjects that declined to complete the operation were withdrawn.

Hip hemiarthroplasty procedures

Patients were administered standard spinal or general anesthesia. Hip hemiarthroplasty procedures were performed by a single surgical group (chief surgeon and three attending surgeons) via the posterior approach with the patient positioned in the lateral decubitus position. Uncemented prostheses were implanted (Bipolar heads; Mobile Cup; DePuy, USA) with similar diameter as the femoral head. Postoperative administrations of 2 g × 3 of intravenous (IV) cefazolin were administered within the first 24 h. An intra-articular drain was inserted and removed after 48 h. All patients received 10 mg of oral Rivaroxaban at 24 h and every 24 h thereafter for at least 14 days. Early mobilization and return to weight bearing was recommended as soon as the patient was able to tolerate it. The duration of the operations and type and dosage of anesthesia were recorded.

Intravenous hemocoagulase

Intravenous hemocoagulase (Bangtin; Jinzhou Aohong Pharmaceutical Co., Ltd.; China) at a dose of 1 U was administered to each participating patient on the night before surgery (10-15 h preoperative) and repeated in equivalent volumes at 30 min preoperative and 12 h postoperative. An additional 1 U of hemocoagulase dissolved in 10 ml of NaCL was administered by intra-articular injection at the incision site upon closing. For the control group, equivalent volumes of normal saline were administered at the same intervals and by the same administration routes.

Bleeding and transfusion

Hemoglobin (Hb) levels were assessed preoperatively (at admission) and monitored throughout operative procedures. Notably, while transfusion is widely performed at Hb 8-9 g/dl in healthy patients and 10 g/dl in patients with severe cardiac disease,[25,26] adherence to the institutional policy for restrictive transfusion necessitated transfusion at <8g/dl or 10 g/dl for symptomatic patients (extreme weakness, chest pain, extreme paleness, or major bleeding) with destabilizing vital signs (tachycardia, heart rate >100, systolic blood pressure [SBP] <90mmHg), history of heart disease (coronary, valvular, and arrhythmia), or cerebrovascular disease.

Data collection

Demographic and medical information were collected for all enrolled subjects including, gender, age, body mass index (BMI), fracture Garden stage (I, II, III, IV, or unclassified), and cause of injury.

Intraoperative blood loss was measured by weighing the swabs and recording the amount of fluid returned to the suction apparatus, minus the amount of saline used for washing. After preparation of the femoral canal and insertion of an uncemented prosthesis, an estimate of blood loss from the femoral canal was made using the technique described by Bannister et al.[28] A small surgical swab was inserted fully into the femoral canal and left for 2 minutes. This swab was used to stabilize bleeding from the femur. Four swabs were subsequently inserted in a similar fashion, each for one minute. These swabs were then weighed, and the difference between the wet weight and the dry weight gave a fair estimate of the blood loss from the femoral canal during the procedure. A recording of the blood pressure was obtained and used to estimate femoral canal blood loss. At the end of surgery, an intra-articular drain was inserted and was used to record postoperative blood loss by measuring the total

drainage at 48 hours.[29] Allogenic transfusion volume and rate and drainage were also assessed. Hb levels and coagulation parameters (prothrombin time [PT], thrombin time [TT], plasma fibrinogen [FIB], and activated partial thromboplastin time [aPTT]) were recorded preoperatively and postoperatively at 30 min and days 1, 3, and 5. Additionally, follow-up Hb measurements were made upon clinical suspicion of low Hb and for patients with Hb concentrations approaching, but not reaching, the transfusion threshold or following transfusion.

Complications and short-term adverse events

The condition of the wound site (skin necrosis, hematoma, and infection) and occurrence of imaging-confirmed (ultrasound and/or spiral computer tomography) DVT and pulmonary embolism were recorded for 4 weeks after each operation.

Statistical analysis

Continuous data are presented as means ± standard deviations and were analyzed using the Student t test. Categorical data are presented as frequencies and were analyzed using the chi-square test. Two-sided *P*-values <0.05 were considered statistically significant. All data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the patients

Of the total 225 consecutive patients with proximal femoral fracture screened for enrollment, 100 were determined to be eligible and provided consent. Of the 100 enrolled subjects, four patients (two in each group) were withdrawn due to declining the operation (Figure 1). No significant differences in age, body mass index (BMI), Garden stage, or cause of injury were observed between the two groups (Table 1).

Surgical characteristics, bleeding, and transfusion

Surgical time, anesthesia duration and dose, and implant types were not significantly different between the two groups (Table 1). Compared to controls, significantly lower levels of intraoperative blood loss (225.16±67.74 vs. 277.95±96.05 ml, $P<0.01$), total 0-48 h drainage (200.64±58.95 vs. 267.27±96.95ml, $P=0.04$), allogeneic transfusion rates (31.2% vs. 56.3%, $P=0.01$), and mean transfused volume (0.87±1.42 vs. 1.62±1.63 units, $P=0.02$) were observed in hemocoagulase patients (Table 2).

Pre- and postoperative hemoglobin levels

Similar preoperative Hb levels were observed in both groups (109.45±11.12 vs.107.58±10.55 g/l, $P=0.39$), followed by similar levels in hemocoagulase patients vs. controls at 30 min postoperative (94.45±11.45 vs. 87.04±8.45 g/l, $P=0.06$), but significantly higher levels on postoperative days 1, 3, and 5; (87.47±6.35 vs. 79.81±4.15 g/l, $P<0.01$; 84.54±6.62 vs. 80.06±4.70 g/l, $P<0.01$; and 86.00±6.80 vs. 82.87±6.25 g/l, $P=0.02$, respectively) (Table 2).

Coagulation factors

Mean PT and TT levels on day 1 were significantly lower in the hemocoagulase group compared to controls (12.61±0.86 vs. 12.77±0.61 s, $P=0.02$; 14.19±0.91 s vs. 14.90±1.23 s, $P<0.01$). Mean APTT levels at 30 min were lower in the hemocoagulase group compared to controls (35.23±3.11 vs. 36.74±3.69 s, $P=0.03$). Mean FIB levels were not significantly different between the two groups at any time point (Table 3).

Complications and short-term adverse events

No cases of severe complications or short-term adverse events including DVT, pulmonary embolism, or poor wound condition requiring medical treatment (such as necrosis, infection, and hematoma) were observed in either group.

Discussion

This study strongly suggests that a hemocoagulase regimen administered IV could reduce overall bleeding and transfusion rates compared to controls, without significant comorbidities. Furthermore, improved hemoglobin levels and coagulation factors were observed in the subacute period following surgery in patients treated with hemocoagulase. Though no significant short-term adverse events were observed in either group, these findings strongly suggest that similar efficacy may be observed in future studies, particularly in geriatric populations.

In this study, preoperative and postoperative administration of hemocoagulase was shown to effectively reduce postoperative blood loss and transfusion rates after hemiarthroplasty. Furthermore, hemocoagulase administration is relatively easy to perform, suitable for these patients, and does not interfere with normal standard of care procedures. Compared to other hemostasis drugs and physical hemostasis to stop bleeding in surgical procedures, hemocoagulase may provide a viable and less disruptive alternative.[27] A number of prior studies have demonstrated that hemocoagulase, a snake venom serine proteinases (SVSP), has several bioactive functions that affect various physiological processes including blood coagulation, fibrinolysis, and platelet aggregation.[22,27] As a result, SVSPs have been used in studies of molecular mechanisms involved in hemostasis control and, more recently, as therapeutic agents in various thrombotic and hemostatic pharmaceutical agents.[30] In particular, injectable hemocoagulase agkistrodon has been used as a coagulating agent, with minimal risk of thrombus formations such as those associated with adverse events with the use of tranexamic acid.[31,32] There have, however, been isolated reports of safety incidents associated with hemocoagulase use in orthopedic

and other surgeries, though these conditions are rare and the vast majority of patients achieve good outcomes.[24,33] Notably, this study reported no evidence of safety events related to typical intravascular hemocoagulase regimen after hemiarthroplasty surgery.

The findings of this study are underpinned by a strong mechanistic rationale. It is well established that hemocoagulase inhibits the induction and release of factor XIII (fibrin stabilizing factor), resulting in the retention of soluble fibrin polymers and reduced bleeding and clotting times as a result of coagulation at the bleeding site.[34] Therefore, the hemostatic effect of hemocoagulase is present centrally at the point of injury, avoiding large-scale intravascular coagulation and potential adverse effects such as thrombotic formations. Notably, this study observed that coagulation parameters, in particular FIB, were similar throughout the subacute period following surgery, and that PT was more similar during follow-up (days 3 and 5). Although the safety of hemocoagulase in this patient population has not been thoroughly established, no thrombotic complications or other short-term adverse events were detected in this clinical trial, and these findings suggest the stable and predictable effect of hemocoagulase regimens, which may be applicable to diverse patient populations in the future.

These findings are consistent with previous studies indicating that hemocoagulase can markedly reduce blood loss and transfusion rates. Kadar *et al*.[35] retrospectively assessed 1,484 patients (mean age of 82±10.3 years) with hip fractures and analyzed the probability of receiving allogenic blood transfusion within 72 hours of admission; they reported that patients typically evidenced a mean Hb drop of 2.87±1.37 g/dL and that about 59% of them received transfusions within 10 days of admission. Similarly, Kumar *et al*.[36] estimated in 127 patients (mean age 78 years) that patients experienced

a mean drop in Hb of 0.7g/dL following intracapsular fractures, and that the mean postoperative drop in Hb was 1.61 g/dL for hemiarthroplasty.[36] These findings are highly consistent with this study, which indicates a mean perioperative drop in Hb of 2.34±1.05 g/dL in patients treated with hemocoagulase and 2.47±0.43 g/dL in controls. Notably, this study also suggests greater reduction in allogeneic transfusion rates in patients receiving hemocoagulase compared to controls (31.2% vs. 56.3%, P=0.01). These findings strongly suggest that the perioperative administration of hemocoagulase minimized blood loss to 119.42±66.31 ml, a decrease of 21.8% compared to the control group. These findings, in line with prior studies, show that hemocoagulase can markedly reduce blood loss and transfusion rates in geriatric patients undergoing fracture-related hip surgery.

An important consideration in the introduction of any new treatment is the likely cost of the intervention. In our hospital the cost of hemocoagulase is 6$/U, while blood costs 60$/U. The amount of blood transfused in the hemocoagulase group was less than that in the control group, by almost 1 unit of blood (60$), and for this result 4U hemocoagulase (16$) was used. Therefore, this suggests that hemocoagulase treatment also makes economic sense as it may reduce the cost of treatment. In our hospital this is likely to be a saving of approximately 44$ per patient.

It is worth noting that cement less prostheses were used for treating the patients in this study. While bone cement provides ideal fixation strength, it does have some shortcomings such as long surgical time and large surgical trauma. And during the process of the prosthesis cement fixation, the patients are prone to have decreased blood pressure, cardiac arrest, formation of deep vein thrombosis and pulmonary embolism, which are known as bone cement implantation syndrome (BCIS). The non-cemented prosthesis used in this study was forged with titanium alloy, showing

excellent biocompatibility. It could also be directly fixed on the patient's own bone tissue. In our experience this meant that the surgical time was shorter, and surgical trauma was smaller, and the surgery was relatively safe. The adverse effect from intraoperative bone cement injection, and the various difficulties and excessive bone destruction from postoperative revisions and could be also avoided.[37,38]

The present study suffers from some limitations. First, it was single-blinded. Nevertheless, since it is one of the first, if not the first, trial in this population of patients, we wanted the medical staff to be fully aware of the treatment taken by the patients in order to respond as best as possible to any eventual threat or thrombotic event. While randomization and blinding reduce the possible effects of biases on study results, these findings are still limited by the possibility of selection bias and population selection. There might be an apparent discrepancy between blood loss and blood transfusion. In this study, the statistical analysis was performed based on the visible hemorrhage amount. The non-visible amount (including subcutaneous, muscle, and joint cavity) is almost impossible to estimate accurately. Therefore, the actual hemorrhage amount would be much more than our measurements. Meanwhile, the patients in the study were old with relatively low preoperative hemoglobin levels and even a small blood loss could significantly decrease hemoglobin levels, which would then meet the criteria for transfusion (based on hemoglobin levels and/or symptoms). Incomplete information on potential risks of hemocoagulase (including adverse effects and effectiveness) still limit the study population due to safety considerations. Thus, the preliminary evidence generated by this study should be further tested in future studies with a larger sample size to verify the efficacy and safety of varying doses and administrations of hemocoagulase. Notably, this study also did not incorporate routine imaging and diagnostic testing to rule out DVT, pulmonary

embolism, and other effects not apparent based on clinician symptoms alone. The follow-up period was short, and complications might have been observed if it had been longer, and we cannot exclude the possibility that the patients consulted other hospitals for minor symptoms. More rigorous methods could be used, beyond the scope of typical clinical practice, to test the effects of hemocoagulase. Additionally, no complications were observed, but may be present in larger, more diverse populations, necessitating future confirmatory trials.

Conclusions

In this study, a hemocoagulase regimen markedly reduced blood loss and transfusion rates compared to normal saline. These findings are initial evidence that hemocoagulase agkistrodon has good hemostatic and coagulative function, and is safe after hip hemiarthroplasty. Further research, however, is necessary to determine the efficacy and safety in populations with significant comorbidities, as well as the optimal dose and administration routes.

Conflicts of interest

The authors declare they have no conflicts of interest.

Acknowledgements

None.

References

1. Beaupre LA, Cinats JG, Senthilselvan A, Lier D, Jones CA, Scharfenberger A, et al. Reduced morbidity for elderly patients with a hip fracture after implementation of a perioperative evidence-based clinical pathway. *Qual Saf Health Care* 2006; **15**: 375-9.

2. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int* 2009; **20**: 1633-50.

3. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *JAMA* 2009; **302**: 1573-9.

4. Holt G, Smith R, Duncan K, Finlayson DF, Gregori A. Early mortality after surgical fixation of hip fractures in the elderly: an analysis of data from the scottish hip fracture audit. *J Bone Joint Surg Br* 2008; **90**: 1357-63.

5. Richmond J, Aharonoff GB, Zuckerman JD, Koval KJ. Mortality risk after hip fracture. *Journal of orthopaedic trauma* 2003; **17**: 53-6.

6. Bhaskar D, Parker MJ. Haematological indices as surrogate markers of factors affecting mortality after hip fracture. *Injury* 2011; **42**: 178-82.

7. Gruson KI, Aharonoff GB, Egol KA, Zuckerman JD, Koval KJ. The relationship between admission hemoglobin level and outcome after hip fracture. *Journal of orthopaedic trauma* 2002; **16**: 39-44.

8. Hagino T, Ochiai S, Sato E, Maekawa S, Wako M, Haro H. The relationship between anemia at admission and outcome in patients older than 60 years with hip fracture. *J Orthop Traumatol* 2009; **10**: 119-22.

9. Landi F, Russo A, Danese P, Liperoti R, Barillaro C, Bernabei R, et al. Anemia status, hemoglobin concentration, and mortality in nursing home older residents.

J Am Med Dir Assoc 2007; **8**: 322-7.

10. Vochteloo AJ, Borger van der Burg BL, Mertens B, Niggebrugge AH, de Vries MR, Tuinebreijer WE, et al. Outcome in hip fracture patients related to anemia at admission and allogeneic blood transfusion: an analysis of 1262 surgically treated patients. *BMC Musculoskelet Disord* 2011; **12**: 262.
11. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. *Vox Sang* 2010; **98**: 56-64.
12. Halm EA, Wang JJ, Boockvar K, Penrod J, Silberzweig SB, Magaziner J, et al. The effect of perioperative anemia on clinical and functional outcomes in patients with hip fracture. *J Orthop Trauma* 2004; **18**: 369-74.
13. Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. *Transfusion* 2009; **49**: 227-34.
14. Engoren M, Mitchell E, Perring P, Sferra J. The effect of erythrocyte blood transfusions on survival after surgery for hip fracture. *J Trauma* 2008; **65**: 1411-5.
15. Johnston P, Wynn-Jones H, Chakravarty D, Boyle A, Parker M. Is perioperative blood transfusion a risk factor for mortality or infection after hip fracture? *Journal of orthopaedic trauma* 2006; **20**: 675-9.
16. Halm EA, Wang JJ, Boockvar K, Penrod J, Silberzweig SB, Magaziner J, et al. Effects of blood transfusion on clinical and functional outcomes in patients with hip fracture. *Transfusion* 2003; **43**: 1358-65.
17. Carson JL, Duff A, Berlin JA, Lawrence VA, Poses RM, Huber EC, et al. Perioperative blood transfusion and postoperative mortality. *JAMA* 1998; **279**: 199-205.

18. Imai N, Dohmae Y, Suda K, Miyasaka D, Ito T, Endo N. Tranexamic acid for reduction of blood loss during total hip arthroplasty. *J Arthroplasty* 2012; **27**: 1838-43.

19. Chareancholvanich K, Siriwattanasakul P, Narkbunnam R, Pornrattanamaneewong C. Temporary clamping of drain combined with tranexamic acid reduce blood loss after total knee arthroplasty: a prospective randomized controlled trial. *BMC Musculoskelet Disord* 2012; **13**: 124.

20. McConnell JS, Shewale S, Munro NA, Shah K, Deakin AH, Kinninmonth AW. Reduction of blood loss in primary hip arthroplasty with tranexamic acid or fibrin spray. *Acta Orthop* 2011; **82**: 660-3.

21. Zufferey P, Merquiol F, Laporte S, Decousus H, Mismetti P, Auboyer C, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? *Anesthesiology* 2006; **105**: 1034-46.

22. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; **344**: e3054.

23. Joshi SA, Gadre KS, Halli R, Shandilya R. Topical use of Hemocoagulase (Reptilase): A simple and effective way of managing post-extraction bleeding. *Ann Maxillofac Surg* 2014; **4**: 119.

24. Wei JM, Zhu MW, Zhang ZT, Jia ZG, He XD, Wan YL, et al. A multicenter, phase III trial of hemocoagulase Agkistrodon: hemostasis, coagulation, and safety in patients undergoing abdominal surgery. *Chin Med J (Engl)* 2010; **123**: 589-93.

25. Carless PA, Henry DA, Carson JL, Hebert PP, McClelland B, Ker K. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2010: CD002042.

26. Young SW, Marsh DJ, Akhavani MA, Walker CG, Skinner JA. Attitudes to blood transfusion post arthroplasty surgery in the United Kingdom: a national survey. *Int Orthop* 2008; **32**: 325-9.

27. Xu C, Wu A, Yue Y. Which is more effective in adolescent idiopathic scoliosis surgery: batroxobin, tranexamic acid or a combination? *Arch Orthop Trauma Surg* 2012; **132**: 25-31.

28. Bannister GC, Young SK, Baker AS, Mackinnon JG, Magnusson PA. Control of bleeding in cemented arthroplasty. *J Bone Joint Surg Br* 1990; **72**: 444-6.

29. Garneti N, Field J. Bone bleeding during total hip arthroplasty after administration of tranexamic acid. *J Arthroplasty* 2004; **19**: 488-92.

30. Serrano SM. The long road of research on snake venom serine proteinases. *Toxicon* 2013; **62**: 19-26.

31. Stocket K, Todd P, Bier M. *Medical use of snake venum protein*. Boston: CRC Press; 1990.

32. Montori VM, Guyatt GH. Progress in evidence-based medicine. *JAMA* 2008; **300**: 1814-6.

33. Wei JM, Zhu MW, Zhang ZT, Jia ZG, He XD, Wan YL, et al. The effects of hemocoagulase agkistrodon on its hemostatic and hemoagglutinant function, on abdominal incision and safety in surgical patients, a multicenter clinical study. *Chinese Journal of New Drugs* 2007; **16**: 19-.

34. Lu HM, Li CL, Dong JC, Zhang CL, Zhou XY. [Hemostatic effect of hemocoagulase agkistrodon and its mechanism]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 2008; **16**: 883-5.

35. Kadar A, Chechik O, Steinberg E, Reider E, Sternheim A. Predicting the need for blood transfusion in patients with hip fractures. *Int Orthop* 2013; **37**: 693-700.

36. Kumar D, Mbako AN, Riddick A, Patil S, Williams P. On admission haemoglobin in patients with hip fracture. *Injury* 2011; **42**: 167-70.

37. Ahn J, Man LX, Park S, Sodl JF, Esterhai JL. Systematic review of cemented and uncemented hemiarthroplasty outcomes for femoral neck fractures. *Clin Orthop Relat Res* 2008; **466**: 2513-8.

38. Figved W, Opland V, Frihagen F, Jervidalo T, Madsen JE, Nordsletten L. Cemented versus uncemented hemiarthroplasty for displaced femoral neck fractures. *Clin Orthop Relat Res* 2009; **467**: 2426-35.

Figure legend

Figure 1. Patient flowchart. Patients were blinded to group assignments.

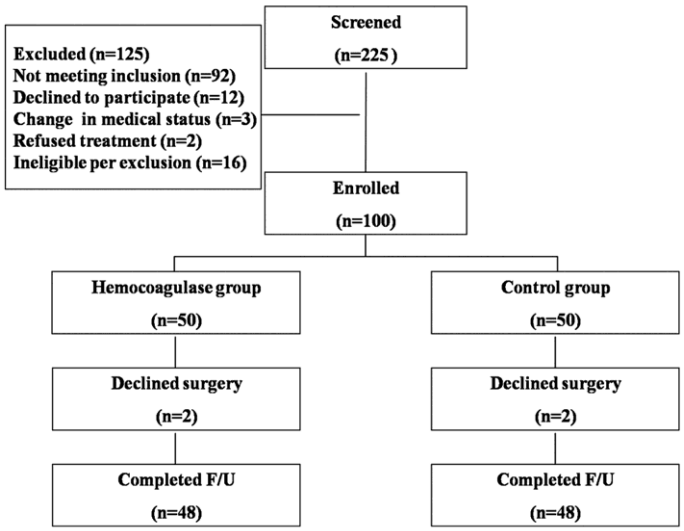


Table 1. General demographic and medical characteristics of enrolled patients receiving hemocoagulase or placebo

Patient characteristics	**Hemocoagulase (*n* = 48)**	**Placebo (*n* = 48)**	***P***
Age (years)	83.0±7.6	82.6±8.5	0.30
Women, *n* (%)	34 (70.8)	36 (75)	0.36
Body mass index (kg/m^2)	21.3±3.7	22.1±4.2	0.22
Garden stage, *n* (%)			0.40
III	18 (37.5)	16 (33.3)	
IV	30 (62.5)	32 (66.7)	
Cause of injury, *n* (%)			0.83
Slip down	35 (72.9)	36 (75)	
Fall down	9 (18.8)	7 (14.6)	
Traffic accident	4 (8.3)	5 (10.4)	

Values are given as mean and standard deviation (mean±SD) for continuous variables and counts and percentages for categorical variables.

Table 2. Surgical characteristics, bleeding, and transfusion data for enrolled patients receiving hemocoagulase or placebo

Parameter	**Hemocoagulase (*n* = 48)**	**Placebo (*n* = 48)**	***P***
Duration of operation (min)	73.29±7.40	71.89±7.59	0.36
Type of anesthesia, n (%)			0.24
Spinal	46 (95.8)	47 (97.9)	
General	2 (4.2)	1 (2.1)	
Intraoperative blood loss (ml)	225.16±67.74	277.95±96.05	<0.01
0-48 h drainage volume (ml)	200.64±58.95	267.27±96.95	0.04
Transfusion (units)	0.87±1.42	1.62±1.63	0.02
Patients transfused postoperatively, *n* (%)	15 (31.2)	27 (56.3)	0.01
Preoperative hemoglobin (g/L)	109.45±11.12	107.58±10.55	0.39
Hemoglobin Postoperative (30 min)	94.45±11.45	87.04±8.45	0.06
Hemoglobin (Day 1)	87.47±6.35	79.81±4.15	<0.01
Hemoglobin (Day 3)	84.54±6.62	80.06±4.70	<0.01
Hemoglobin (Day 5)	86.00±6.80	82.87±6.25	0.02

Values are given as mean and standard deviation (mean±SD) for continuous variables and counts and percentages for categorical variables.

Table 3. Coagulation parameter data for patients receiving hemocoagulase or placebo

Parameter	**Hemocoagulase (*n* = 48)**	**Placebo (*n* = 48)**	***P***
Preoperative PT(s)	12.86±1.09	13.03±1.01	0.77
Postoperative PT(s)			
PT (30 min)	13.13±1.07	13.38±1.02	0.77
PT (Day 1)	12.61±0.86	12.77±0.61	0.02
PT (Day 3)	12.45±0.95	12.81±0.72	0.25
PT (Day 5)	12.79±o.91	12.85±0.65	0.12
Preoperative TT(s)	16.06±1.62	15.83±1.42	0.47
Postoperative TT(s)			
TT (30 min)	16.37±1.37	16.71±1.99	0.32
TT (Day 1)	14.19±0.91	14.90±1.23	<0.01
TT (Day 3)	15.70±1.26	15.93±1.20	0.35
TT (day 5)	15.73±1.00	15.83±1.35	0.58
Preoperative APTT (s)	35.67±3.92	34.68±3.85	0.21
Postoperative APTT (s)			
APTT (30min)	35.23±3.11	36.74±3.69	0.03
APTT (Day 1)	34.12±4.17	35.67±3.62	0.06
APTT (Day 3)	34.30±3.36	35.70±2.84	0.07
APTT (Day 5)	36.70±2.81	36.05±2.61	0.24
Preoperative FIB (g/L)	3.13±0.62	3.0752±0.59	0.61
Postoperative FIB (g/L)			
FIB (30 min)	4.59±1.42	4.47±1.34	0.68
FIB (Day 1)	4.90±1.14	4.75±1.06	0.48

FIB (Day 3)	5.16±1.02	5.07±1.00	0.66
FIB (Day 5)	5.52±0.89	5.38±0.89	0.42

Values are given as mean and standard deviation (mean±SD) for continuous variables and counts and percentages for categorical variables.

PT: prothrombin time; TT: thrombin time; aPTT: activated partial thromboplastin time; FIB: fibrinogen.