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CASE STUDY

Topical Yunnan Baiyao administration as an adjunctive therapy for bleeding complications in adolescents with advanced cancer

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Abstract
Purpose Yunnan Baiyao (White Medicine from Yunnan, YNB) is a Chinese herbal medicinal powder used to stop bleeding and improve circulation in traumatic injuries. We describe the use of YNB in adolescents with cancer as an adjunct to uncontrolled bleeding in the palliative care setting.
Methods Through a retrospective chart review of all patients receiving integrative medicine consultations at the Integrative Therapies Program at Columbia University from January 1, 2007 to January 31, 2012, we describe the outcome of patients treated with YNB for management of uncontrolled bleeding.
Results Four patients were identified who received topical YNB for uncontrolled bleeding; patients included two males and two females with diagnoses of solid tumors (n=3) and Burkitt's lymphoma (n=1). Mean age was 15.5 years (range 15–17). Fifty percent had life-threatening bleeding from the tumor site and 50 % experienced uncontrollable epistaxis. All patients received preceding therapy with packed red blood cells and platelet transfusions, topical thrombin, and oral aminocaproic acid. Two patients used YNB in the inpatient setting, and all four patients used YNB as outpatients. In all patients, bleeding control improved with the addition of YNB to conventional hemostatic interventions. Two patients using YNB in their home reported control of bleeding episodes. There were no adverse events reported.
Conclusions YNB may be an efficacious agent for uncontrolled bleeding in conjunction with conventional hemostatic agents in adolescents with advanced cancer. It is well accepted by patients. YNB may be especially valuable in the outpatient setting to prevent the recurrence of hemorrhage.

Keywords Palliative care · Yunnan Baiyao · Hemorrhage · Hemostasis · Chinese herbs

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Introduction

Yunnan Baiyao (White Medicine from Yunnan, YNB) is a Chinese herbal medicinal powder formulated in 1902 and is most commonly applied to stop bleeding and improve circulation in traumatic injuries. YNB is a blend of seven herbs that includes *Panax notoginseng*, *Ajuga forrestii Diels*, *Dioscoreae Parviflora Ting*, *Herba Inulae Cappae*, *Herba Geranii* and *Herba Erodii*, *Rhizoma Dioscoreae*, and *Rhizoma Dioscoreae Nipponicae*. Approximately 40 % of the YNB is the dried root extract of *P. notoginseng,* referred to as San Qi [1]. Each of the components of the YNB is harvested in the Yunnan and Guangxi provinces of China.

According to the traditional Chinese medicine (TCM) theory, the clinical effects of YNB's main ingredient, *P. notoginseng*, are attributed to the seemingly conflicting and simultaneous actions of arresting bleeding while also promoting normal blood flow within the vessels, thereby resolving blood stasis. As a result of these combined actions, *P. notoginseng* can promote circulation, stop abnormal bleeding, and reduce healing time. Due to *P. notoginseng*'s hemostatic abilities, YNB is most commonly administered internally in patients at risk or experiencing internal bleeding or topically for external hemorrhage and wound care. Along with being a topical and oral haemostatic,

YNB is used for swelling and pain caused by falls, contusions, sprains, and chest, abdominal, and joint pain [2].

YNB's components and precise mechanism of action have not been well described. Microchemical analysis of YNB has revealed a predominance of polysaccharide structure and the presence of calcium within the mixture, which may add to the procoagulation effect [3]. Early studies have suggested YNB causes the release of rat and guinea pig platelet alpha granules in vitro [4, 5]. This reaction was more apparent in platelet-rich rat plasma than washed guinea pig platelet samples, suggesting that plasma components in platelet-rich plasma may play a role in YNB's mechanism for hemostasis [4, 5]. Animal models have suggested that saponins, plant-derived chemical compounds from *P. notoginseng*, may contribute to the accelerated coagulation effect, considering that bleeding times are similar between *P. notoginseng* and its saponin extract [6]. In addition, it has been suggested that the organic nanofibers present in YNB may facilitate platelet activation, rapid clot formation, and wound sealing [7].

Research on *P. notoginseng* has reported both hemostatic and anticoagulant properties similar to the theoretical TCM mechanisms [8, 9]. Trauma models on rat tails showed a significant shortening of bleeding times with topical *P. notoginseng* and *P. notoginseng* saponin extract compared to control and placebo [6, 10]. A similar significant effect was observed when comparing topical YNB and *P. notoginseng* in a different rat tail model [1]. Despite the hemostatic properties shown in animal models, *P. notoginseng* also appears to inhibit platelet activation through multiple mechanisms. Extracted saponins from *P. notoginseng* have demonstrated a dose-dependent inhibition of in vitro and in vivo ADP-platelet activation in both rat platelet-rich plasma and washed rat platelets [11]. Studies of notoginseng saponins have measured in vitro inhibition of shear-induced platelet aggregation in rats as well [12]. Given the conflicting biochemical and clinical effects, the mechanisms of *P. notoginseng* and its saponins remain to be elucidated in both animal and human studies.

Animal models evaluating the hemostatic properties of YNB have shown preliminary support for the herbal powder and its components. YNB solution significantly decreased clotting time when compared to saline control, starch, and starch with calcium comparisons in rabbit and human blood [13]. When given enterally, YNB also significantly decreased the blood clotting time in rabbits in a dose-dependent pattern and caused significant decreases in liver laceration bleeding times in rats against starch controls [14]. Topical YNB, *P. notoginseng*, and *P. notoginseng* saponin extract all significantly reduced bleeding times in small studies using bleeding rat tail trauma models [1, 6, 10]. Recent animal experimental models have also investigated the anti-inflammatory effects of YNB in inflammatory bowel disease and rheumatoid arthritis [15, 16].

Research of YNB in human subjects is limited, though literature searches are restricted as the majority of YNB research is in published Chinese literature. One human clinical study evaluated the hemostatic effect of YNB in a small double-blinded, placebo controlled trial (N=87) for the prevention of intraoperative blood loss in adults undergoing bimaxillary orthognathic surgery [17]. YNB was administered orally for 3 days prior to surgery. Total blood loss in the treatment group was significantly lower as compared to the control group (p=0.009) and no allergic reactions, thromboembolic events, or other side effects were reported. Two Chinese studies reported that oral YNB administration decreased intraoperative bleeding during cervical open-door laminoplasty and during transurethral resection of the prostate with similar side effect rates versus controls [18, 19]. However, further trials are needed to determine the safety, efficacy, and indication of YNB use.

Bleeding is a common, yet often poorly controlled complication of cancer. We report four cases of pediatric cancer patients experiencing bleeding complications who were treated with topical YNB in the palliative care setting.

Methods

Institutional review board (IRB) approval was obtained from the Columbia University Medical Center IRB. Cases were identified through the Integrative Therapies Program of Columbia University patient records. For each case report, the sequence of medical interventions is presented longitudinally.

Case Examples

Patient #1

The patient was a 15-year-old adolescent male with recurrent synovial sarcoma of the left mandible and oral cavity. He was initially treated with an ifosfamide/doxorubicin chemotherapy regimen, complete gross total excision, and radiation therapy. The tumor recurred locally in the mandible and in the intraoral cavity despite repeat surgery and several chemotherapy regimens including clinical trials of sorafenib and trabectedin (Yondelis®). The tumor progressed, but overall Karnofsky status was excellent. He entered a phase I clinical trial of aflibercept (VEGF-trap), and shortly thereafter, developed severe pain and bleeding from the intraoral mass as well as bleeding from fungating mandibular nodal masses and a large fungating preauricular mass. He required a previous hospital admission for control of pain and hemorrhage; PT/PTT, fibrinogen, and platelet count were within normal limits at that time.

The patient had an increase in bleeding from the preauricular tumor site and was transferred to CUMC from an outside emergency department. The patient was seen by the Interventional Neuroradiology Department and underwent embolization of the facial arteries and the left lingual artery to block blood supply to the tumors. Bleeding of the sites continued after embolization, and when a dressing change was attempted, the preauricular tumor became detached from the base and bleeding increased. After handheld electrocautery was unsuccessful, hemostasis was achieved with thrombin/gel packs, Floseal™ hemostatic matrix (Baxter, Zurich, Switzerland), gauze, and elastic wrap bandage. The patient was intubated, transferred to the Pediatric Intensive Care Unit (PICU) on a ventilator, and received five units of packed red blood cells (PRBCs). Following extubation and discontinuation of ventilator support, the patient continued to experience intermittent bleeding which was initially managed with oral vitamin K, oral aminocaproic acid, and application of thrombin-soaked gauze. Breakthrough bleeding continued and YNB was added to the regimen. The patient was instructed to open the capsules of YNB, crush the contents, dip a sterile sponge into the YNB powder and apply it directly to the intraoral mass as needed; bleeding was initially controlled after three topical administrations of the powder. Throughout this admission, the patient continued use of topical YNB with reported relief of bleeding.

The patient was discharged home with 3 % bismuth tribromophenate and petroleum-impregnated gauze, fluffy gauze, protective plastic mastoid cup over the preauricular mass, aminocaproic acid swishes, and topical YNB. For palliative treatment of the intraoral mass, the patient also received radiation therapy to the head/neck and intraoral region and an additional brief course to the supraorbital skull, jaw, and humerus. The patient continued to experience intermittent bleeding from the intraoral and preauricular mass that was managed well at home with YNB. Due to patient preference, aminocaproic acid use was limited at this time. The patient and his family used YNB throughout the hospice course, requested multiple refills of the prescription, and reported that YNB was especially successful in ameliorating the bleeding from the tumor site. Ultimately, the patient succumbed to his illness, but did not have any further unmanageable bleeding episodes at home.

Patient #2

The patient was a 15-year-old female who presented with a 20-cm right axillary and chest wall synovial sarcoma. Her course was complicated by deep vein thrombosis of the right upper extremity at the time of presentation which was managed with enoxaparin. The patient was treated on the Children's Oncology Group study ARST0332 group D (grade 3, stage 4 metastatic) with ifosfamide, doxorubicin, and radiation therapy (http://www.cancer.gov/clinicaltrials/search/view?cdrid=483702&version=HealthProfessional). After the first course of chemotherapy, she was emergently admitted to the hospital with bleeding from the chest wall tumor site; she required multiple platelets and PRBC transfusions, and enoxaparin was held. During her third cycle of chemotherapy, she redeveloped bleeding from the chest wall tumor site that was initially uncontrolled despite holding pressure and application of topical thrombin to the wound. After continued bleeding, hemostasis was achieved with deep pressure for over an hour and 8 units of PRBCs, 12 units of platelets, and 2 units of fresh frozen plasma.

At discharge a few days later, topical YNB was initiated as an adjunctive therapy to assist with preventing hemorrhage and controlling recurrent bleeding at home. YNB was to be applied as needed with a sponge to any recurrent sites of bleeding until hemostasis was achieved. When she returned to care, the patient reported two bleeding episodes at home that were quickly controlled with repeated topical application of YNB. The patient reported no side effects from the YNB.

The patient went on to undergo tumor resection that required complete axillary and brachial artery bypass. She did well initially, but the arterial graft failed and due to persistent severe arterial bleeding, she underwent an emergency forequarter amputation. She remained stable for a year after her amputation, but thereafter, her disease recurred and she succumbed to the sarcoma 8 months following relapse.

Patient #3

The patient was a 15-year-old male with vertically transmitted HIV-associated Burkitt's lymphoma who developed recurrent epistaxis related to chemotherapy-associated thrombocytopenia. Due to progressive disease, he was admitted to the hospital for reinduction chemotherapy including intravenous etoposide, ifosfamide, rituximab, carboplatin, and intrathecal methotrexate. He required transfer to the PICU because of the acute onset of volume-refractory hypotension and bilateral pulmonary effusions with polymicrobial sepsis.

During this admission, he developed profuse epistaxis which persisted over several days. He received 18 total units of platelets to keep his platelet count above 50,000/mm^3 and was administered vitamin K and topical thrombin. Both nares were packed by the Otolaryngology service, and the patient received intravenous aminocaproic acid, oxymetazoline hydrochloride nasal spray, and saline nasal spray. He continued to require platelet transfusions. After 5 days of continued epistaxis despite these measures, the nasal packing was removed and YNB mixed with petroleum jelly was applied to the nasal membrane. Shortly after direct YNB application, the bleeding resolved. He was instructed to

apply the herb with a cotton swab topically two times daily for 1 week for bleeding prophylaxis. Upon his hospital discharge, the YNB was discontinued as no bleeding episodes were experienced thereafter.

Patient #4

A 17-year-old female with relapsed alveolar rhabdomyosarcoma with therapy-related myelodysplasia treated as per ARST0921 with vinorelbine and cyclophosphamide was admitted for the management of epistaxis during the first cycle of chemotherapy (http://www.cancer.gov/clinicaltrials/search/view?cdrid=687113&version=Patient). Previous therapy included vincristine, ifosfamide, doxorubicin, cyclophosphamide, dactinomycin, and Cixutumumab and radiation therapy to the abdomen/pelvis and neck/mediastinum, but the patient unfortunately relapsed 6 months later.

The patient developed uncontrolled bleeding from her right nare at home with no other signs of bleeding. In the outpatient setting, the patient was anemic and thrombocytopenic at presentation and received 6 units of platelets and 2 units PRBCs. The nare was packed, and topical thrombin was applied, but hemostasis was not achieved. YNB powder mixed with petroleum jelly was then applied topically to the nasal membrane. Hemostasis was achieved within 15 min of one application. The patient was hospitalized and received additional 12 units of platelets for thrombocytopenia secondary to chemotherapy. The patient was discharged on topical YNB to be used with petroleum jelly and aminocaproic acid tablets for any consequent bleeding and went home on hospice care. No other bleeding episodes were reported.

Safety evaluation

After patient #3 was diagnosed with a nasal fungal infection after YNB use, our institution sent sample of YNB for fungal culture. The YNB specimen was potassium hydroxide negative and no fungal growth was found after 43 days. No infection risks were identified within the specimen. The petroleum jelly was obtained from individually sealed packages provided by the hospital, limiting the possibility (although not eliminating) as a contributor to the fungal infection. The packaging of petroleum jelly was not available for laboratory analysis.

Discussion

Uncontrolled bleeding can be a recurrent medical challenge for many patients with cancer despite blood product transfusion support and other conventional hemostatic therapies including topical thrombin or oral aminocaproic acid. Our case series suggests that as an adjunct to conventional therapies, YNB may provide a clinical benefit and relief to patients with persistent bleeding.

Due to the limited clinical studies available, the safety of YNB is a consideration for the pediatric oncology patient. YNB is a patented Chinese herbal medicine approved by the Chinese State Food and Drug Administration, and any YNB for patient use should be purchased from a reputable manufacturer (17). The cost of YNB varies. One dose may range between 0.08 and 0.20¢. None of our patients who received YNB experienced a drug interaction, adverse event, or side effect secondary to the herbal powder, and fungal cultures sent by our institution have showed no infection risk. To our knowledge, there have been no reports of pro-thrombotic or adverse events in humans with YNB in the literature. However, our search is limited since the majority of research on YNB is published in the Chinese medical literature. Due to the unclear mechanism of YNB, careful consideration should be used for patients with hereditary bleeding disorders.

All patients in this series received multiple transfusions and additional therapy directed against hemorrhage, such that YNB was used as an adjunctive therapy to reduce the risk of additional bleeding, and the exact contribution of YNB to hemostasis cannot be determined. Due to the fact that YNB is a compilation of multiple ingredients, it is likely that multiple mechanisms may be responsible for its hemostatic effect. It is difficult to predict whether YNB could have an antagonistic, complementary, or synergistic effects with other hemostatic agents based on the currently available research. Pharmacologic studies can elucidate these interactions between YNB and other hemostatic agents as well as determine its safety in patients receiving other hemostatic therapy.

YNB may be effective against refractory superficial bleeding in high-risk individuals, such as the cases described here. In all patients, bleeding control improved with the addition of YNB to conventional hemostatic interventions. Further clinical trials to better explore the mechanism of YNB and *P. notoginseng* and their role as an adjunctive therapy for hemostasis should be considered.

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Conflict of interest No authors have financial relationships with the sponsoring organization of this research. We have full control of all primary data and agree to allow the journal to review data if requested.

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