



VCA West Los Angeles Animal Hospital Clinical Study Announcement



YUNNAN BAIYAO STUDY AT VCA WEST LOS ANGELES ANIMAL HOSPITAL

March 2014

Dear Colleagues,

The Oncology Service of VCA West Los Angeles Animal Hospital is conducting a clinical trial involving the administration of oral Yunnan Baiyao to dogs with visceral or cardiac hemangiosarcoma has an effect on coagulation as evaluated by thromboelastography (TEG).

Yunnan Baiyao is a Chinese herbal medication (neutraceutical) commonly prescribed to patients with hemangiosarcoma by oncologists. Although the exact ingredients are proprietary and closely guarded, some known ingredients include steamed and raw Sanqi (Panax Notoginseng). Yunnan Baiyao is manufactured in the Yunnan province of China by the Yunnan Baiyao group and is sold in 3 forms: powder, capsule and patch form. The capsule form is the most common form used in veterinary medicine. The capsule is available in a package of 16 250 mg capsules; the instructions are typically to give 1-2 capsules every 8 to 12 hours. The small red tablet in the middle of the blister packet is equal in potency to the rest of the capsules and is to be reserved for emergencies (severe hemorrhage). There is little known pharmacologic data on Yunnan Baiyao or when peak plasma concentration is reached, however it is meant to be dosed at 60-75 mg/kg at least once every 24 hours. Yunnan Baiyao is thought to slow down/stop hemorrhage and promote healing. It is given prophylactically to hemangiosarcoma patients as well as to patients actively having small bleeding episodes. It has been shown to decrease both bleeding and clotting times in rabbits. In vitro, using guinea pig platelets, it also has been shown to release platelet constituents.



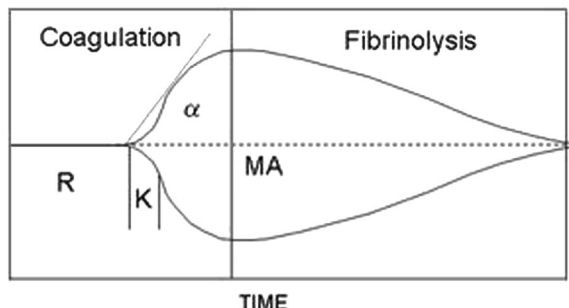
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**Medical Oncology Service
VCA West Los Angeles Animal Hospital**

1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
Ph 310-473-2951 | Fx 310-979-5400



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Normal parts of the coagulation cascade assessed via TEG (thromboelastography).

Thromboelastography (TEG) allows a full assessment of hemostatic function of whole blood by evaluating cellular and plasma components during initiation, amplification and propagation of clot formation as well as during fibrinolysis. TEG assesses overall hemostatic function by evaluating the following properties of blood clots: clot formation, strength, stability and resolution. It allows cage side, clinically relevant information regarding coagulopathy. A recent study showed 67% of dogs with neoplasia had abnormal TEG values; approximately 50% of the dogs with malignant neoplasia were hypercoagulable and 17% were

hypocoagulable. There was also a significant increase in PT and D-dimer formation, and a decrease in platelet count in this same population of dogs with malignant neoplasia. One study found that patients with distant metastasis had increased fibrinogen levels and d-dimer levels. Another study showed that approximately 50% of hemangiosarcoma patients were in DIC at presentation, with thrombocytopenia and increased FDP's. Most cancer patients are hypercoagulable; hemangiosarcoma patients by virtue of the endothelial cell based disease tend to bleed although they are hypercoagulable.

Purpose:

To evaluate the effect of Yunnan Baiyao on coagulability in dogs with hemangiosarcoma using TEG.

Study Design:

Prospective double blinded placebo controlled randomized clinical study with 20 dogs total, 10 in each group. Group 1 consists of 10 dogs with either visceral (splenic or hepatic) or cardiac hemangiosarcoma receiving Yunnan Baiyao at a dose of 60 mg/kg/day rounded down to nearest capsule size and divided into 3 equal doses for once every 8 hours dosing. Dogs will receive Yunnan Baiyao for the 21 day study period. Group 2 consists of 10 dogs with visceral or cardiac hemangiosarcoma not receiving Yunnan Baiyao matched for stage with Group 1. Enrollment into treatment groups would be randomized. The patient population would not include dermal, subcutaneous, renal, retroperitoneal or any other "unique forms. Dogs who receive surgery for their hemangiosarcoma will still be included in the study; if possible, an additional TEG would be obtained pre-operatively. Otherwise, the TEG would be obtained at the start of Yunnan Baiyao therapy. All

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dogs would be diagnosed by either cytological or histopathologic means or, if not possible, (auricular HSA) by postmortem histopathology (sent to Antech). All dogs would be on a doxorubicin protocol (25-30 mg/m²) every 3 weeks at the discretion of the clinician, paid for by the owner. The owner will either go home with Yunnan Baiyao or placebo, but will be blinded as to which one. The Yunnan Baiyao will be compounded into 250 mg capsules; the placebo will be compounded by the same pharmacy and will appear identical. The Yunnan Baiyao will be provided free of charge to the owner, as well as the TEG, PCV/TP and coagulation profiles. Blood will be drawn for a PCV/TP, TEG (testing performed by VCAWLAH) and the plasma will be frozen for batch analysis of PT/PTT, fibrinogen, D-dimers and platelet count (VCA Antech, Inc) at day zero (before Yunnan Bai Yao), day 7 and day 21. If possible, for all dogs undergoing surgery, pre-surgical assays will also be performed. A questionnaire will be sent home with the hemangiosarcoma patients recording any episodes of weakness, lethargy or pallor consistent with a bleeding event. The patients will be followed to assess disease progression and long-term survival effects (potentially for another study). A potential secondary outcome could include the effect of stage on coagulation with Yunnan Baiyao.

Exclusion criteria:

Patients on any form of steroidal or non-steroidal medication, patients who have received chemotherapy prior to inclusion, dogs on any anticoagulant including Plavix, heparin or Coumadin, and patients with a comorbid known clotting disorder (Von Willebrands, etc.). They can be on any medications after the 3 week time period.

If you have potential patients or have questions regarding the study, please contact Drs. Chretien and Oakley at 310-473-2951 or via email at john.chretien@vca.com or christine.oakley@vca.com.

Sincerely,

John Chretien, DVM, DACVIM (Oncology)

Christine Oakley, DVM

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