Efficacy of New Hemostatic Agents, WoundStat™ and Combat Gauze ™, under Coagulopathic Condition

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Introduction

Previous studies identified WoundStat (WS) and Combat Gauze (CG) as the most effective hemostatic agents for controlling arterial bleeding in normal subjects. These agents have potential utility for treating combat wounds.[1,2]

Based on blood loss and survival results, WS was found to be the most effective hemostatic agent available with 100% survival rate followed by CG with 80% survival rate with no difference in efficacy between the two products in the subjects with competent coagulation function (Fig. 1).

Successful *in vitro* tests indicated WS treatment can restore normal clotting time in coagulopathic blood.[3] The inherent tissue sealant properties of WS clay [4] (when mixed w/ blood) also suggested an efficacy advantage for WS to treat coagulopathic bleeding over CG, which only promotes clotting activities of normal blood.

Therefore, the efficacy of WS along with CG was tested in an extremity hemorrhage model under coagulopathic condition.

Objectives

To determine the efficacy of WS and CG to control external bleeding in coagulopathic animals and to compare their effectiveness with a placebo control (gauze).

To determine whether the potential benefit of WS for treating coagulopathic bleeding (if proven to be effective) outweighs the serious side effects of this agent (see the safety poster).

Methods

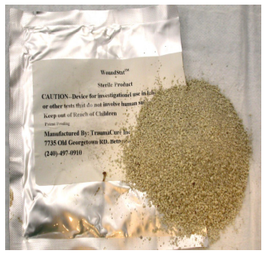
- Anesthetized pigs (n=42) were cannulated; laparotomy and splenectomy were performed, and the abdominal incisions were closed by suturing.
- The right femoral artery was isolated and prepared for injury, the left artery was cannulated for controlled hemorrhage.
- Dilutional hypothermic coagulopathy was then induced by ~50% isovolemic blood exchange with Hextend (25 °C) and external cooling setting pigs' core temp at 32.5±.5 °C.
- A 6 mm arteriotomy was then made in the femoral artery and free bleeding was allowed for 30 sec.
- A test agent, WS (n=15), CG (n=15) or control gauze (n=12) was then applied to the wounds and compressed with the aid of lap sponge for 2 min (twice if needed).
- Fluid resuscitation (500 ml Hextend and up to 10 liter LR at 100 ml/min) was administered and titrated to a MAP of 65 mmHg.
- Animals were monitored for 180 min or until death; survival animals were CT scanned to assess blood flow in the treated vessels.
- Local tissues including femoral vessels, nerve, and muscle were then collected for histology, and the animals were euthanized.

Results

Combat Gauze (CG)

Surgical gauze + kaolin

WoundStat (WS)



Smectite (Aluminum Phyllosilicate)

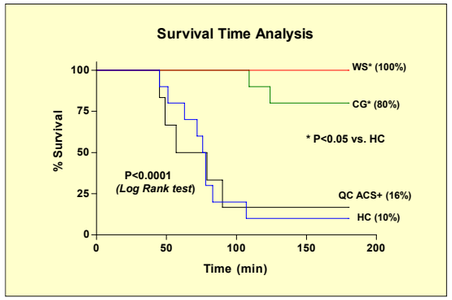


Figure 1. Percent survival and survival times of pigs with normal coagulation function after injury and treatment with new hemostatic agents.

Cell Counts and Clotting Time Measurements in Hemodiluted Blood

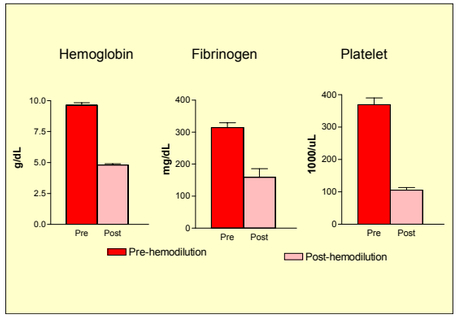


Figure 2. Cell counts and fibrinogen concentration changes after 50% isovolemic hemodilution.

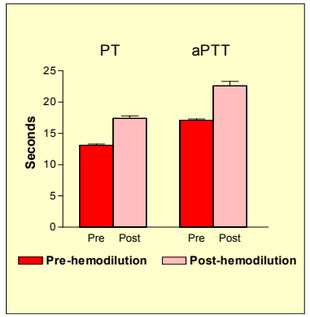


Figure 3. Prothrombin (PT) and activated partial thromboplastin time (aPTT) following dilutional coagulopathy.

Clotting Effects of CG and WS in Coagulopathic Pigs (*In Vivo*)

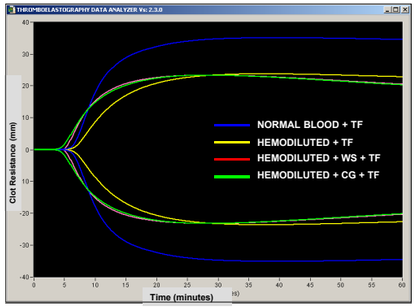


Figure 4. Clotting profiles of pigs' blood before hemodilution (NORMAL), after in vivo hemodilution and after successful treatment with WS or CG. Clotting was induced with addition of Ca++ and tissue factor (TF) to citrated blood.

Hemostatic Activity of CG and WS *In Vivo*

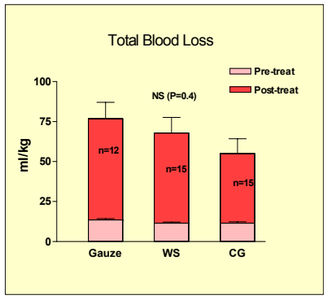


Figure 5. Pre-treatment and post-treatment blood loss volumes in differently treated groups.

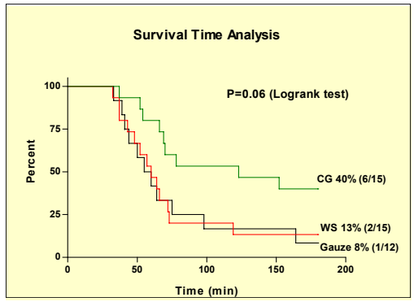


Figure 6. Percent survival and survival times of coagulopathic pigs (dilutional and hypothermia) after injury and treatment with new hemostatic agents.

Clotting Effects of CG and WS in Blood (*In Vitro*)

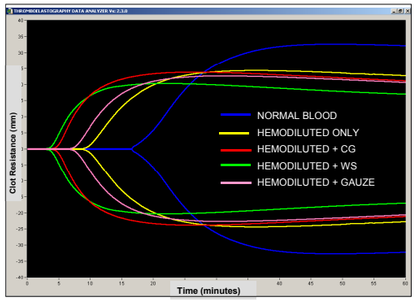


Figure 7. Clotting profiles of pigs' blood before hemodilution (NORMAL), after hemodilution only, and after in vitro treatment with different hemostatic agents. Spontaneous clotting was initiated by addition of Ca++ to citrated blood.

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Summary

- Isovolemic hemodilution (50%) with Hextend decreased hemoglobin and fibrinogen by half, but lowered the platelet count by approximately three quarters(72%, Fig. 2).
- Coagulopathy development was confirmed based on 33% prolongation of PT and aPTT (Fig. 3) and concurrent changes in TEG parameters (47% delay in K-time, 19% and 34% decreases in α angle and MA , respectively).
- No significant change occurred in the TEG parameters following successful *in vivo* treatments with CG or WS (Fig. 4).
- Pretreatment blood loss was ~12 ml/kg with no difference among groups. Post-treatment blood loss varied from 44 ml/kg (CG) to 63 ml/kg (gauze), but the differences were not statistically significant (Fig. 5).
- The percent survival and average survival time of the CG-treated group were numerically higher than the other groups, but the differences were not significant (Fig 6).
- *In vitro* treatment of coagulopathic blood (drawn from pigs after hemodilution) with WS or CG improved the clotting rate of the samples (Fig. 7). The R-time and K-time were shortened (60% and 25%, respectively), the α angle was increased (23%), but MA (max. clot strength) was not affected.
- No differences were seen between hemostatic ability of WS and CG; both products were more effective than regular gauze.

Conclusion

- In this model of coagulopathy, which may be different from Acute Traumatic Coagulopathy, neither WS nor CG was found to be effective in securing hemostasis.
- There was essentially no difference between WS and regular gauze in spite of tissue sealant properties of WS (an unexpected finding).
- The current efficacy and safety studies do not support the use of WS for wound treatment particularly when an equally effective and safer agent such as CG is available.
- There is a continued need for hemostatic agents that can function independently from the coagulation status of the patient and being able to control coagulopathic bleeding.

References

1. Kheirabadi BS, Edens JW, Terrazas IB, et al. Comparison of new hemostatic granules/powders with currently deployed hemostatic products in a lethal model of extremity arterial hemorrhage in swine. *J Trauma*. 2009;66:316-328.
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3. Moskowitz KA, Manly DA, Mackman N. Effect od topical hemostatic agents on clotting times in a whole blood model of dilutional coagulopathy. J Thromb Haemstasis. 2009;7(suppl 1), PP-TH-678.
4. Ward KR, Tiba MH, Holbert WH, et al. Compariosn of new hemostatic agent to current combat hemostatic agents in a swine model of lethal extremity arterial hemorrhage. J Trauma. 2007;63:276-284.