# 60th Medical Group (AMC), Travis AFB, CA

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

## FINAL REPORT SUMMARY

**(Please type all information. Use additional pages if necessary.)**

**PROTOCOL #:** FDG20160013A **DATE:** 25 July 2017

**PROTOCOL TITLE:** Analysis of Serum Concentrations of Tranexamic Acid Given by Alternate Routes in Swine (*Sus scrofa*) During Controlled Hemorrhage.

**PRINCIPAL INVESTIGATOR (PI) / TRAINING COORDINATOR (TC):** Maj Erik DeSoucy

**DEPARTMENT:** SGSE **PHONE #:** 423-7400

**INITIAL APPROVAL DATE:** 21 July 2016 **LAST TRIENNIAL REVISION DATE:** N/A

**FUNDING SOURCE:**

1. **RECORD OF ANIMAL USAGE:**

| Animal Species: | Total # Approved | # Used this FY | Total # Used to Date |
|---|---|---|---|
| *Sus scrofa* | 16 | 16 | 16 |

2. **PROTOCOL TYPE / CHARACTERISTICS:** (Check all applicable terms in **EACH** column)

| | | |
|---|---|---|
| ___ Training: Live Animal | _X__ Medical Readiness | ___ Prolonged Restraint |
| ___ Training: non-Live Animal | ___ Health Promotion | ___ Multiple Survival Surgery |
| __X_ Research: Survival (chronic) | ___ Prevention | ___ Behavioral Study |
| ___ Research: non-Survival (acute) | ___ Utilization Mgt. | ___ Adjuvant Use |
| ___ Other ( ) | _X__ Other (Treatment ) | ___ Biohazard |

3. **PROTOCOL PAIN CATEGORY (USDA):** (Check applicable) ___ C _X_ D ___ E

4. **PROTOCOL STATUS:**

***Request Protocol Closure:**

___ Inactive, protocol never initiated

___ Inactive, protocol initiated but has not/will not be completed

_X__ Completed, all approved procedures/animal uses have been completed

5. **Previous Amendments:**
List all amendments made to the protocol. **IF none occurred, state NONE. Do not use N/A.**

**For the Entire Study Chronologically**

| Amendment Number | Date of Approval | Summary of the Change |
|---|---|---|
| 1 | 11 Aug 16 | Personnel, procedures |
| 2 | 18 Aug 16 | Animal use, procedures |
| 3 | 25 Aug 16 | Biosample |
| 4 | 7 Sept 16 | Personnel, biosample |

6. **FUNDING STATUS:** Funding allocated: $32,813.00 Funds remaining: $ 5,813.00

7. **PROTOCOL PERSONNEL CHANGES:**

Have there been any personnel/staffing changes (PI/CI/AI/TC/Instructor) since the last IACUC approval of protocol, or annual review? _X_ Yes ___ No

If yes, complete the following sections (Additions/Deletions). For additions, indicate whether or not the IACUC has approved this addition.

**ADDITIONS:** (Include Name, Protocol function - PI/CI/AI/TC/Instructor, IACUC approval - Yes/No)

| NAME | PROTOCOL FUNCTION | IACUC APPROVAL |
|---|---|---|
| Maj Erik DeSoucy | PI | Yes |
| Dr. Guillaume Hoareau | AI | Yes |

**DELETIONS:** (Include Name, Protocol function - PI/CI/AI/TC/Instructor, Effective date of deletion)

| NAME | PROTOCOL FUNCTION | DATE OF DELETION |
|---|---|---|
| None | | |

8. **PROBLEMS / ADVERSE EVENTS:** Identify any problems or adverse events that have affected study progress. Itemize adverse events that have led to unanticipated animal illness, distress, injury, or death; and indicate whether or not these events were reported to the IACUC.

LCMS analysis was delayed due to calibration and training issues. Sample analysis was delayed from October 2016 to June 2017 when the final samples were run.

There were two complications which required early euthanasia of animals. Animal P1757 underwent protocol on 19 September 16 and had to be euthanized on 23 September 16 for what appeared to be a painful left groin hematoma. Animal P1753 underwent protocol on 26 September 16 and had to be euthanized the same day due to severe hyperkalemia after the protocol completed. These events were known to the attending veterinarian, but not reported to the IACUC.

9. **REDUCTION, REFINEMENT, OR REPLACEMENT OF ANIMAL USE:**

**REPLACEMENT (ALTERNATIVES):** Since the last IACUC approval, have alternatives to animal use become available that could be substituted in this protocol without adversely affecting study or training objectives?

None

**REFINEMENT:** Since the last IACUC approval, have any study refinements been implemented to reduce the degree of pain or distress experienced by study animals, or have animals of lower phylogenetic status or sentience been identified as potential study/training models in this protocol?

None

**REDUCTION:** Since the last IACUC approval, have any methods been identified to reduce the number of live animals used in this protocol?

None

10. **PUBLICATIONS / PRESENTATIONS:** (List any scientific publications and/or presentations that have resulted from this protocol. Include pending/scheduled publications or presentations).

Accepted for poster presentation 13 September 2017 at American Association for the Surgery of Trauma.

11. **PROTOCOL OBJECTIVES:** (Were the protocol objectives met, and how will the outcome or training benefit the DoD/USAF?)

We were able to characterize the pharmacokinetics of tranexamic acid (TXA) given via intravenous (IV), intraosseous (IO) and intramuscular (IM) route in a hemorrhagic shock state. We have identified similar characteristics between IV and IO dosing which supports the use of IO route when IV access is not available. The pharmacokinetics of IM TXA demonstrated a similar half-life to IV administration, but a marked decrease and delay to peak concentration. However, all routes achieved a serum adequate concentration as defined by previous studies in humans. Additional pharmacodynamic studies in a model with coagulation profile similar to humans would help determine whether IM TXA is a viable adjunct to traumatic hemorrhage.

12. **PROTOCOL OUTCOME SUMMARY:** (Please provide, in "ABSTRACT" format, a summary of the protocol objectives, materials and methods, results - include tables/figures, and conclusions/applications.)

Objectives: Define the pharmacokinetics of tranexamic acid given by IV, IO and IM routes.

Methods: 15 Yorkshire swine were anesthetized, hemorrhaged 35% of their blood volume, equilibrated and randomized to IV, IO, or IM administration of TXA. Serum samples were taken at T0, 5, 10, 15, 30, 60, 120, 180, 240, and 300. High performance liquid chromatography mass spectroscopy was used to determine the concentration of TXA in the serum at these time points.

Results: There were no significant differences in baseline measurements or hemorrhage percentage between groups and all were in a congruent state of class III shock. Serum sample analysis showed all three routes achieved a serum concentration of >10µg/mL within 10 minutes of administration which was maintained over 240 minutes. The IV and IO routes had much higher initial peak serum concentrations. There were no injection site changes noted at necropsy.

Conclusion: While there were significant differences in the peak serum concentration of TXA when comparing IV and IM administration, IM did reach a minimum concentration which in vitro has been shown to inhibit fibrinolysis. As expected, the IM route performed like a depot injection with greater concentrations still present at time 120min. Additional research is needed to determine the efficacy of TXA given by this route.

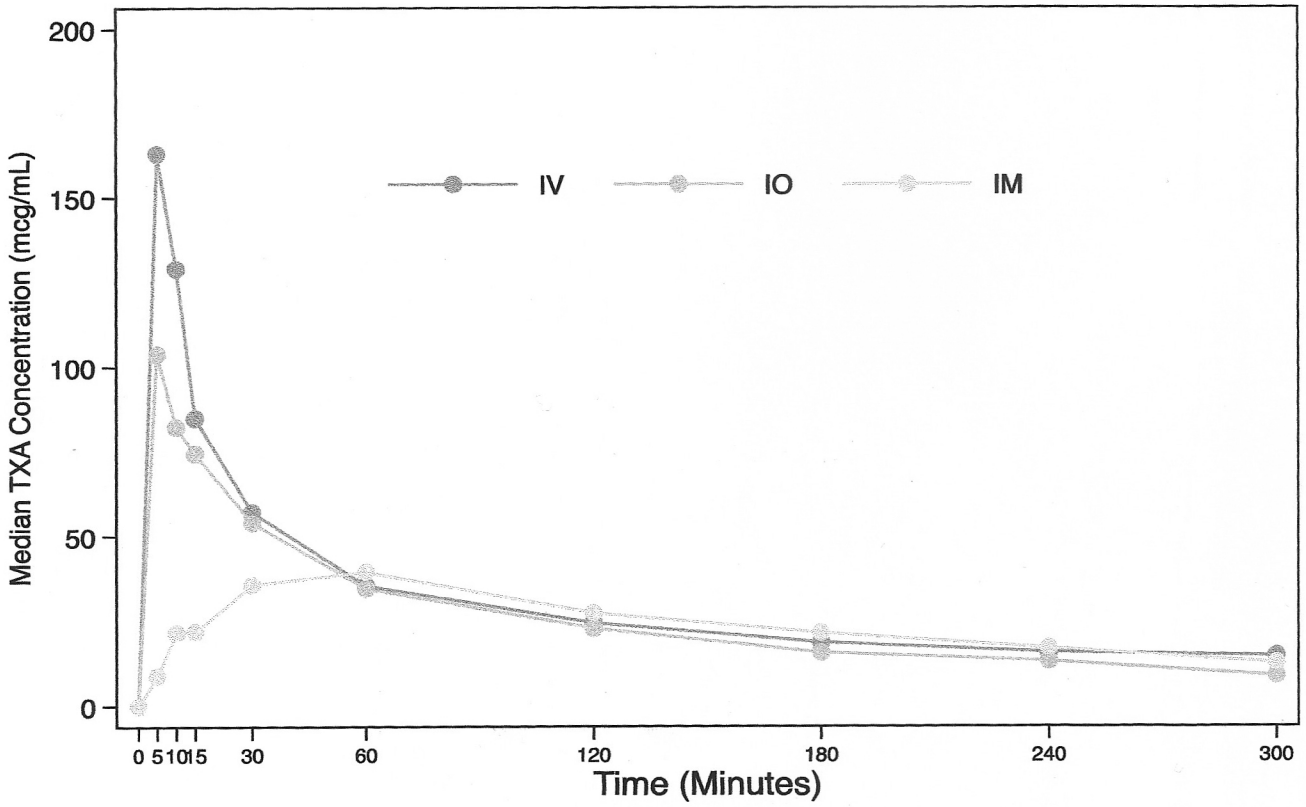


**Figure 1: TXA serum concentration over time given via IV, IO and IM routes during shock**

| | IV | IO | IM |
|---|---|---|---|
| Cmax (mcg/mL) | 185.2 | 103.8 | 39.4 |
| Time to Cmax (min) | 7.5 | 5 | 60 |
| Half-life (min) | 158.5 | 126.8 | 160.9 |
| Area Under Curve | 10080 | 7781 | 7812 |

**Table 2: Pharmacokinetic profile of TXA via IV, IO and IM routes.**

(PI / TC Signature)

1AUG17

(Date)

**Attachments:**
Attachment 1: Defense Technical Information Center (DTIC) Abstract Submission

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**Grant Number:**_____
**From:__SG Grant**_____
****If you utilized an external grant, please provide Grant # and where the grant came from. Thank you.**