An assessment of the effects of pressure infusion with the novel LifeFlow device on blood

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AN ASSESSMENT OF THE EFFECTS OF PRESSURE INFUSION WITH THE NOVEL LIFEFLOW DEVICE ON BLOOD

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14. ABSTRACT-
Background: To improve survival for hemorrhagic shock treatment, guidelines emphasize two patient care priorities: (1) immediate hemorrhage control and (2) early resuscitation with whole blood or blood products. The LifeFlow device is designed to rapidly infuse blood products. However, the effects of using this device compared to pressure-bag systems remains unclear. We hypothesize there will be no laboratory-measured difference with the blood when infused through the LifeFlow versus the current standard pressure bag system.
Methods: Two units of fresh whole blood were obtained from a sus scrofa model. One unit was "infused" using the LifeFlow with the other unit used as a control through a standard pressure bag system into an empty bag. The "before" measurements were obtained from blood samples from a standard fresh whole blood collection bag. The blood was "infused" into a whole blood bag devoid of storage solution from which the "after" measurements were obtained.
Results: This study utilized 22 clinically healthy sus scrofa. Blood units were primarily obtained from a left subclavian central line (50.0%). The median time to acquire and administer a unit of blood was similar for both the LifeFlow device (8.4 minutes and 8.1 minutes) and the pressure bag (8.7 minutes and 7.4 minutes). No significant differences were found in the total time to acquire or administer blood between the two devices. The median volume of blood acquired was 500 mL for both groups. While no significant differences in blood parameters were observed between the two devices, significant differences were noted when comparing pre- and post-transfusion values within each device. For the LifeFlow device, an increase in hemoglobin and chloride levels, as well as a decrease in thromboplastin time and glucose levels, were observed. With the pressure bag, only a decrease in blood urea nitrogen was observed.
Conclusions: In comparing the LifeFlow to the pressure bag, there were no significant differences noted in the total time to acquire or administer a whole unit of blood. However, there were differences with several laboratory parameters of unclear clinical significance.

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1.0 EXECUTIVE SUMMARY

The novel LifeFlow device, was developed by 410 Medical, as a non-battery-operated method for rapid infusion of crystalloid and blood products. Hemorrhage is the leading cause of potentially survivable death on the battlefield. Early infusion of blood products prehospital has been shown to reduce mortality. The current standard for infusion prehospital is the use of a pressure bag or gravity. Pressure bags are limited because the pressure applied decreases as the bag empties. The LifeFlow uses a pull-push method in a hand squeeze device. Preliminary data demonstrates substantially faster infusion rates that are sustained over the entire bag of crystalloid. Currently, there is no data assessing the use of this device by medics who would be the primary end-user in a prolonged field care (PFC) setting. It remains unclear whether this device has an acceptable range of effects on blood after rapid infusion through the LifeFlow versus the currently used pressure bag system. We are yoking this effort to an approved study so no new animals will be required to support this effort. In this effort, we will assess for hemolysis and other measures of blood cell damage using this device compared to a pressure bag system in a large animal model. This protocol will be attached to "Emergency skills training using the pig (sus scrofa) model" (FWH20190004AT) protocol in order to obtain the units of blood necessary to complete the study. A member of the study team will obtain 2 units of blood into standardized blood collection bags. We will aim to collect 1-2 units of blood per pig; to meet our goal of 40 units of blood total we will use anywhere between 20-40 pigs. We will use either peripheral access or central venous access for capture of the blood into the bag. Both procedures are standard procedures that are described in "Emergency skills training using the pig (sus scrofa) model" (FWH20190004AT) protocol.

2.0 INTRODUCTION

Catastrophic hemorrhage is a leading cause of potentially preventable death in prehospital settings.[1,2] Recently published data demonstrated that early administration of blood products near the point-of-injury (POI) is lifesaving.[2] To improve survival from life-threatening bleeding, treatment guidelines emphasize immediate hemorrhage control and early resuscitation with whole blood or blood products.[1,3] Rapid correction of hemorrhagic shock by early delivery of blood transfusion at POI through the intravenous (IV) or intraosseous (IO) increases the odds of survival.[4,5] Significant progress has been made on techniques for achieving better hemostasis in the field, but these advantages are not available to civilian trauma patients. Furthermore, less attention has been directed at developing rapid, precise, and portable methods of blood transfusion in hemorrhagic shock.

Current methods of delivery of blood products include gravity infusion and pressure bag infusions, and mechanical rapid infusers. Gravity infusion delivers blood at a rate as slow as 5ml/min, which is insufficient for the rapid correction of shock.[6] Incorporating the use of a pressure bag may increase the flow speed, however, it requires constant re-inflation, positional adjustment, a method for elevated hanging, does not allow for controlled delivery rates, and carries the risk of air embolism.[6] Powered rapid infusers are commonly used but are unavailable at the POI or during transport.[7] Furthermore, these devices are often challenging to operate, are large, complex, and with limitations with smaller IV catheters or IO access.[6] Per the guidelines of Tactical Combat Casualty Care (TCCC), if the preferred cold-stored O whole blood with low titer (LTOWB) is not available a recommended alternative is warm fresh whole blood (WFWB).[3] Data collected from special operations units have demonstrated success with WFWB.[8-10] Therefore, a rapid infusion device that can be used without power is a needed technology.

The LifeFlow is a novel, handheld, hand-powered device that uses a syringe-based method for the rapid infusion of blood, blood products, and cold or warm blood. The LifeFlow utility in rapidly administering a defined amount of fluid sufficient to reverse acute shock in a wide variety of conditions.[11] Studies have shown that the LifeFlow is capable of more rapid and controlled delivery of blood products than commonly used techniques through the IV and IO routes.[12,13] Other studies have been performed using various crystalloid and blood infusion methods in pigs.[6,12,14,15] LifeFlow has many advantages including

its lightweight, non-battery-operated characteristics and rapid infusion capabilities with a relatively low cost. However, it remains unclear if this new infusion method has any determining effects on blood degradation.

Goal of this Study

We sought to determine the effects on warm fresh whole blood (WFWB) infused through the LifeFlow device versus the pressure bag method using a sus scrofa model.

3.0 METHODS, ASSUMPTIONS AND PROCEDURES

Ethics

The 59th Medical Wing Institutional Animal Care and Use Committee reviewed and approved protocol FWH20210118AR. Our study was performed in conjunction with another sus scofra model project for training resident physicians that is approved under a separate protocol.

Animal Welfare

Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for Care and Use of Laboratory Animals, National Research Council. The facility's Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by Association for the Assessment and Accreditation of Laboratory Animal Care. Animal welfare was directed under the supervision of the attending veterinarian and supporting surgical staff.

Prior to starting study interventions, the general health of the animals was evaluated to ensure they were clinically healthy and free from endo- and ectoparasites. Animals were then sedated with ketamine (4.4mg/kg IM), telazol (2.2mg/kg IM) and glycopyrrulate (0.04-0.4 mg/kg IM) prior to induction. After sedation, animals were endotracheally intubated with appropriately sized cuffed endotracheal tube. Vital signs, O2 saturation, end tidal carbon dioxide, blood pressure, continuous ECG and body temperature were monitored throughout study procedures. Following completion of study procedures, animals were euthanized using IV pentobarbital, 100 mg/kg by the attending veterinarian, veterinary technician, or qualified surgical technician under the direction of the attending veterinarian.

The sus scofa model was chosen due to the availability of such models within the government laboratories, of the available models, represents the best hemorrhage model.16 Other large animals such as goats and primates are not available within our government laboratory. Additionally, our team has extensive experience with this animal model for hemorrhage. Moreover, by yoking our study to another large animal study, we were maximally adhering to the Department of Defense instructions to minimize the number of animals consumed.

Blood Unit Acquisition

Trained study team members (FM, MM, DS, JM) ensured that all animals met the minimum weight requirement of 70 kgs prior to acquiring units of blood. Metrics including length, weight, sex, and location of IV placement of each subject was recorded. Study team members acquired two units of blood per animal through an established central vein access port placed by an emergency medicine trainee as part of their routine training (Supplemental Figure 1). Time to acquisition of blood into blood bag and weight was recorded for each unit collected. Pre-infusion samples were acquired using an 18-gauge needle and transferred to dated lab tubes for pre-infusion analysis. The remaining unit of blood was then

infused through standard intravenous (IV) tubing using either the LifeFlow or pressure bag (pressure maintained between 300-400mmHg) into a whole blood bag devoid of storage solution. Time to complete infusion of blood into a new whole blood bag was recorded. Post-infusion samples were then allocated using an 18-gauge needle and transferred to dated lab tubes for post-infusion analysis.

Blood Analysis

After collection, pre- and post-infusion samples were transferred to an adjacent laboratory for analysis. The blood samples were processed according to established protocols that assessed various hematological, coagulation, and biochemical parameters.

Statistical Analysis

Data were compiled into Microsoft Excel 365 (Microsoft Corporation, Redmond, Washington) by the research team and then exported to SAS version 9.4 (SAS Institute, Cary, North Carolina) for analysis. We summarized categorical variables using frequencies and percentages, normally distributed continuous variables as means and standard deviations, and non-normal continuous variables as medians and interquartile ranges. To determine whether there were changes from pre- to post-infusion for each device separately, we used paired t-tests (and its nonparametric equivalent, the Wilcoxon signed rank test). We also compared the devices (LifeFlow vs. pressure bag) before and after infusion to examine whether any blood parameters differed between the two devices at either time point. We considered $p<0.025$ significant due to a Bonferroni correction for multiple comparisons. Our sample size was limited to the number of animals available for enrollment from the study we were yoking our study to, with the primary limitation being weight requirements set forth by the IACUC.

4.0 MAJOR EVENTS/MILESTONES/SUCCESS

We successfully met the following milestones as stated in our SOW:

Milestone #1: Obtain IRB and IACUC approval:

IACUC Approval – 8 Sep 2021

Milestone #2: Staff training for enrollment

We successfully training all staff on protocol and procedures to execute study.

Milestone #3: Data collection

Our trained staff was able to collect data while utilizing the lifeflow device for Twenty-two clinically healthy *sus scrofa.*

Milestone #4: Data analysis

We successfully completed our data analysis on blood obtained for this study.

Milestone #5: Publication, dissemination

We have published our manuscript and presented at multiple conferences listed below in section presented our findings at below listed in section 9.

Milestone #6: Submission of closure documents

We successfully complete the study and submit final report requirements such as DTIC manuscript upload, final progress report, ST final report, and fulfilled our requirements with programmatic reporting.

5.0 RISK ASSESSMENT

5.1 Risk Analysis:

The primary risk currently lies within acquisitions for device purchase. The device we have

tested is already FDA cleared for use and currently available on the open market.

5.2 Technical Challenges

When conducting this study, the only challenge encountered by the study team was that not all animals met the 70kgs requirement prior to acquiring units of blood which decreased our overall data collection number due to frequency in pigs weighing less than what we are required thus, not allowing enrollment.

6.0 TRANSITION PLAN

6.1 Military Relevance

Hemorrhage is the leading cause of potentially survivable death on the battlefield. The Tactical Combat Casualty Care (TCCC) and the Advanced Resuscitative Care (ARC) guidelines from the Joint Trauma System (JTS) recommend the use of whole blood or balanced blood component therapy as the volume expander of choice after major hemorrhage.1,3 Current methods for infusion at or near the point of injury (POI) or during transport are inadequate. The LifeFlow has significant potential for filling this technological gap.

6.2 Transition Strategy

We have transitioned this knowledge product by way of a peer-reviewed publication in an open access journal, publication on the DTIC website, wide dissemination on social media, and shared our findings with leadership within the Joint Trauma System and the Committee on Tactical Combat Casualty Care.

7.0 RESULTS

Twenty-two clinically healthy sus scrofa were utilized for this study. Most of the animal subjects were male (72.7 %). The average length and weight of animal subjects were 157 cm and 76.6 kg, respectively. The blood units were primarily acquired from a left subclavian (50.0 %) central line [Supplemental Table 1]. The median time to acquire a unit of blood for the LifeFlow group was 8.4 minutes and for the pressure bag group was 8.7 minutes. The median time to administer a unit of blood with the LifeFlow was 8.1 minutes and for the pressure bag was 7.4 minutes. No differences were observed in total time to acquire one unit of blood or total time to administrate blood for LifeFlow and pressure [Table 1]. Median volume of blood acquired for both groups was 500 mL.

Blood parameters were compared between the two devices, but no significant differences were found. However, when the blood parameters were compared within the device, pre- and post- transfusion, significant differences arose [Table 2, Table 3]. For pre- and post-infusion with the LifeFlow device, an increase in hemoglobin (pre- 8.0 g/dL to post- 8.5 g/dL, P=0.002) and chloride (pre- 82.0 mEq/L to post- 86.0 mEq/L, P=0.001) were observed [Table 4]. A decrease in thromboplastin time (pre- 43.8 seconds to post- 36.2 seconds, P=0.008) and glucose (pre- 441.0 g/dL to post- 421.0 g/dL, P=0.004) [Table 3, Table 4]. With the pressure bag, only a decrease in blood urea nitrogen was observed (pre- 7.5 mg/dL to post- 6.5 mg/dL, P=0.009).

8.0 CONCLUSION/DISCUSSION

Discussion

The blood parameter results of this study showed that when comparing the LifeFlow to the pressure bag, there were minimal statistically significant differences before or after infusion with the two methods. We noted no clinically relevant differences. However, significant differences were observed before and after infusion in certain variables within the LifeFlow group and within the pressure bag group. Our study only looked at a small number of variables, all of which were laboratory-based and not focused on clinical outcomes since the animals were part of a terminal study. Although the LifeFlow device is designed and marketed for its rapid infusion capabilities, it slightly underperformed in transfusion time compared to the traditional pressure bag though this was non-significant. The reduced transfusion time in the LifeFlow device supports previous findings that compared rapid and pressure bag infusion, which also found pressure bag to have a greater rate of infusion than the rapid infusion device [2].

Technological advancements also play a crucial role in addressing hemorrhage-related mortalities. The development of portable transfusion systems has been introduced to facilitate rapid transfusions in austere environments17. It is also important to consider the context of large-scale combat operations, where availability and feasibility of different devices may be limited in remote environments.18,19 A recently published study found that combat medics viewed the LifeFlow device as beneficial due to its ease of use and rapid rate of transfusion. This is in keeping with other studies published using this device which showed generally positive results.20,21 However, concerns of its durability, and incompatibility with blood warmers suggests that improvements maybe needed including miniaturization and durability.22 They also felt the device had more value during en route care than the POI based on the current design. Thus, this study serves as a validation of this device as a tool that is likely at least as safe as the currently used pressure bag option for rapid infusion.

Our study has several limitations. First, we only assessed laboratory values and did not seek out any "patient-centered outcomes". However, this would be challenging due to the required sample size and the most significant support needed to perform such large animal studies. Second, our samples were obtained from the blood donation bag and a bag devoid of preservatives, it is unclear how this may have affected the results, though the results do not suggest that major changes occurred. Third, the equipment is all hand-powered and manually adjusted, which may have affected the delivery rate among the two modalities. Fourth, we only tested one unit of blood per animal per device which may limit the generalizability to the massively hemorrhaging patient where multiple units will be used. This was due to limitations in the funding for the study and as such, we had to yoke this study to another approved study. Removal of additional blood could jeopardize the other study that we were utilizing resources from. Lastly, we used a large animal model that does have physiological differences in response to hemorrhage and resuscitation and may not directly translate to human use.

Conclusions

In comparing the LifeFlow to the pressure bag, there were no significant differences noted in the total time to acquire or administer a whole unit of blood. However, there were differences with several laboratory parameters of unclear clinical significance.

9.0 DELIVERABLES

All presentations and publications have been cleared by 59 CIRS and Public Affairs

9.1 Publications:

Manuscript submission to Military Medicine Journal

Mancha, F., Martinez, M., Mireles, M., Sifuentes, D., Mendez, M., Maddry, J., Schauer, S., "Comparative Analysis of Whole Blood Infusion Effects: Assessing LifeFlow versus Pressure Bad in a Sus Scrofa Model" Military Medicine, 2023. http://dx.doi.org/10.1111.trf.17325

9.2 Presentations :

Mancha, F., Tapia, A., Maddry, J., Schauer, S., "An assessment of the effects of pressure infusion with the novel LifeFlow device on porcine (Sus Scrofa) blood" **SURF conference, June 2022**

Mancha, F., Tapia, A., Maddry, J., Schauer, S., "An assessment of the effects of pressure infusion with the novel LifeFlow device on porcine (Sus Scrofa) blood" **SOMA conference, Raleigh, May 2022**

10.0 COST

The grant received from the Department of Defense RESTORAL program funds were all expended. Cost was on target and appropriate.

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FIGURES AND TABLES:

Supplemental Table 1. Animal characteristics

Variable	Value
Length, cm	157.0 (8.41)
Weight, kg	76.59 (4.07)
Male sex	16 (72.7%)
IV location	
Left Subclavian	11 (50.0%)

Left Femoral	8 (36.4%)
Right Femoral	5 (22.7%)
Right Subclavian	4 (18.2%)

Values are mean (standard deviation), count (percentage), or median [interquartile range]. (n=22)

Table 1. Study Procedure Times

Procedure times	LifeFlow	Pressure bag
Time to blood acquisition, minutes	8.4 [7.2-16.2]	8.7 [4.9-12.7]
Volume of blood acquired, mL	500.0 [436.5-500.5]	500.0 [473.0-506.5]
Time to blood administration, minutes	8.1 [4.8-10.9]	7.4 [5.2-11.0]

Values are mean (standard deviation), count (percentage), or median [interquartile range]. There were no significant differences between the LifeFlow and pressure bag in time to blood acquisition, volume of blood acquired, or total time to blood administration.

Table 2. Comparison of Complete Blood Count with Differential

	LifeFlow			Pressure bag		
Variable	**Pre-infusion**	**Post-infusion**	**p-value**	**Pre-infusion**	**Post-infusion**	**p-value**
WBC	12.85 (3.59)	12.72 (3.28)	0.6126	12.78 (3.84)	12.44 (3.87)	0.0386
RBC	4.40 (0.56)	4.57 (0.52)	0.1218	4.38 (0.65)	4.36 (0.67)	0.7361
Hgb	8.0 [7.3-8.9]	8.5 [7.6-9.1]	0.0022*	8.1 [6.8-9.0]	8.1 [6.9-9.1]	0.7701
Hct	26.9 [24.4-30.0]	28.7 [25.4-30.2]	0.0332	27.8 [24.0-30.5]	27.3 [22.9-29.9]	0.6598
Plts	309.7 (112.9)	298.6 (109.8)	0.0637	303.9 (101.2)	296.8 (100.6)	0.1403
Neut	30.22 (11.80)	30.12 (11.95)	0.6389	31.74 (12.76)	31.56 (12.72)	0.4608
Lymph	60.27 (12.67)	60.99 (11.83)	0.4647	60.63 (11.90)	60.63 (12.22)	0.9873
Mono	2.6 [2.2-3.7]	3.3 [2.1-3.9]	0.1361	2.5 [1.9-3.7]	2.6 [1.9-3.7]	0.3728
Eos	1.8 [0.6-6.3]	1.8 [0.6-5.8]	0.4688	1.1 [0.6-5.7]	1.3 [0.5-5.1]	0.7007
Baso	0.4 [0.2-0.5]	0.3 [0.2-0.5]	0.4088	0.3 [0.3-0.5]	0.4 [0.3-0.5]	0.2820

Values are mean (standard deviation), count (percentage), or median [interquartile range].
P-values are for differences between pre- and post-infusion for each device.

Table 3. Coagulation and D-dimer

	LifeFlow			Pressure bag		
Variable	**Pre-infusion**	**Post-infusion**	**p-value**	**Pre-infusion**	**Post-infusion**	**p-value**
PT	15.8 [15.5-16.5]	15.8 [15.2-16.5]	0.0991	16.2 [15.4-16.9]	16.3 [15.5-17.5]	0.6294
PTT	43.8 [25.9-55.6]	36.2 [22.7-51.6]	0.0080*	33.8 [22.6-46.6]	32.8 [21.9-43.8]	0.3252
Fib	138.3 (35.71)	131.8 (33.53)	0.2709	130.7 (36.13)	127.1 (32.33)	0.4295
D-dimer	2.0 [1.7-3.0]	2.1 [1.7-3.0]	0.2692	2.0 [1.5-2.5]	1.9 [1.4-2.7]	0.3778

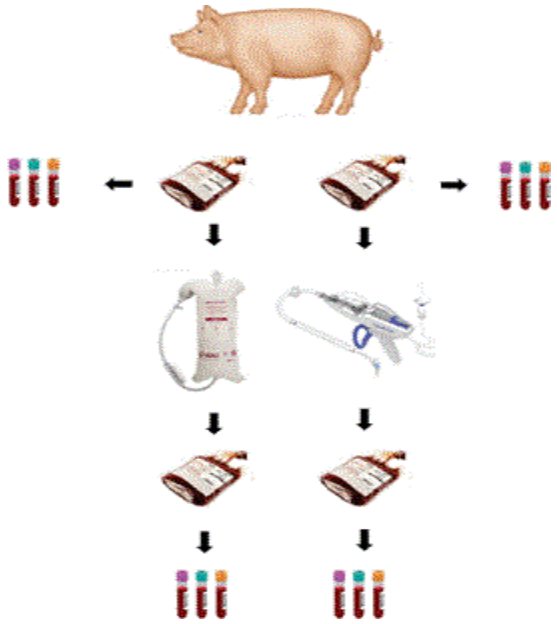
Values are mean (standard deviation), count (percentage), or median [interquartile range].
P-values are for differences between pre- and post-infusion for each device.

Table 4. Clinical Chemistry Panel Comparison

	LifeFlow			Pressure bag		
Variable	**Pre-infusion**	**Post-infusion**	**p-value**	**Pre-infusion**	**Post-infusion**	**p-value**
K	2.67 (0.36)	2.82 (0.32)	0.0327	2.82 (0.36)	2.75 (0.38)	0.1314

CL	82.0 [77.0-86.0]	86.0 [79.0-88.0]	0.0013*	86.0 [81.0-87.0]	86.0 [82.0-87.0]	0.1602
CO2	20.43 (2.30)	21.29 (1.80)	0.1428	20.86 (2.19)	20.14 (3.13)	0.5347
GLU	441.0 [412.3-553.3]	421.0 [386.5-438.3]	0.0044*	422.0 [396.5-454.0]	429.0 [400.8-481.0]	0.6372
BUN	7.0 [5.0-8.0]	7.0 [5.8-8.0]	0.6133	7.5 [5.0-8.3]	6.5 [5.0-8.0]	0.0098*
CRE	1.1 [0.9-1.4]	1.1 [0.9-1.4]	0.4453	1.2 [1.0-1.4]	1.1 [1.0-1.4]	0.0469
CAL	7.9 [7.4-8.5]	8.0 [7.6-8.3]	0.2298	8.0 [7.6-8.3]	7.9 [7.0-8.1]	0.4653
LDH	438.8 (97.80)	442.0 (101.6)	0.8409	405.1 (84.97)	394.3 (90.94)	0.3773
MAG	2.1 [1.5-2.4]	2.1 [1.4-2.4]	0.1094	2.1 [1.6-2.4]	2.1 [1.4-2.4]	0.2188

Values are mean (standard deviation), count (percentage), or median [interquartile range].
P-values are for differences between pre- and post-infusion for each device.



Supplemental Figure 1.

12.0 LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

KEYWORDS: hemorrhage, blood, prehospital, medic, rapid, infusion, shock, resuscitation

Abbreviations/Acronyms:

Pig (sus scrofa)

Prolonged field care (PFC)

Point-of-injury (POI)

Intravenous (IV)

Intraosseous (IO)

Tactical Combat Casualty Care (TCCC)

O whole blood with low titer (LTOWB)

Warm fresh whole blood (WFWB)

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Jessica Mendez (JM)

Microsoft Excel 365 (Microsoft Corporation, Redmond, Washington)

SAS version 9.4 (SAS Institute, Cary, North Carolina)