UNCLASSIFIED

Post-Injury Anti-Bradykinin Therapy with the FDA-Approved Drug Icatibant Fails to Improve Resuscitation Outcomes in a Swine Model of Severe Burn

Caroline Lima PhD[1], Lonnie Grantham MBA[1], James Bynum PhD[2], Evan Ross MD[1]

1. U.S. Army Institute of Surgical Research, San Antonio TX; 2. University of Texas Health Science Center – San Antonio, San Antonio TX

Background

Severe burns ≥20% total burned surface area are near-universally complicated by the formation of large volume interstitial tissue edema that depletes circulating plasma volume, leading to a loss of perfusion pressure and resultant organ injury [1]. The formation of edema is thought to be caused by a generalized capillary leak that is due to pro-inflammatory mediators, including the nonapeptide bradykinin [2].

Bradykinin is a highly vasoactive nonapeptide that is released by enzymatic cleavage from the circulating precursor high-molecular weight kininogen by the enzyme kallikrein in response to stress. Icatibant is a bradykinin B2 receptor antagonist that is FDA-approved for the treatment of angioedema attacks [3].

Hypothesis

We hypothesized that icatibant would reduce edema formation after burn, leading to a reduction in the fluid volumes necessary to maintain urine output.

Materials and Methods

Research was conducted in compliance with Animal Welfare Act, the implementing Animal Welfare regulations, and the principles of the Guide for the Care and Use of Laboratory Animals. The Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by the AAALAC International.

A total of n=30 juvenile female Yorkshire swine weighing approximately 40 kg were randomly assigned to receive a single dose of icatibant (n=10, 0.5 mg/kg x 1), three sequential doses of icatibant (n=10, 0.5 mg/kg x 3), or saline starting 30 minutes after burn and given in 6-hour increments. Animals were maintained under anesthesia with analgesia, underwent a 40% TBSA contact burn followed by administration of the experimental therapy and received goal-directed fluid therapy with lactated Ringer's solution to maintain a urine output between 30-50 mL per hour for 24 hours.

Results

Treatment groups were similar at baseline on shock-relevant characteristics. There were no significant differences between the three treatment groups on weight normalized fluid given over 24 hours, nor weight-normalized urine output over 24 hours. There were no significant differences between the treatment groups on other measures of resuscitation outcomes, including maximum heart rate, minimum blood pressure, minimum cardiac output, maximum arterial lactate, nor plasma creatinine at 24 hours.

Table 1. Baseline Animal and Burn Characteristics

	Saline Control (n=10)	Single Dose Icatibant (n=10)	Triple Dose Icatibant (n=10)
Age (days)	**120** +/- 13	**121** +/- 14	**122** +/- 15
Weight (kg)	**43.0** +/- 1.5	**43.1** +/- 2.1	**43.0** +/- 1.2
Burn Duration (min)	**31** +/- 5	**31** +/- 6	**30** +/- 4
Blood Urea Nitrogen (mg/dL)	**8** +/- 2	**10** +/- 4	**7** +/- 4
Creatinine (mg/dL)	**1.13** +/- 0.17	**1.20** +/- 0.16	**1.09** +/- 0.13

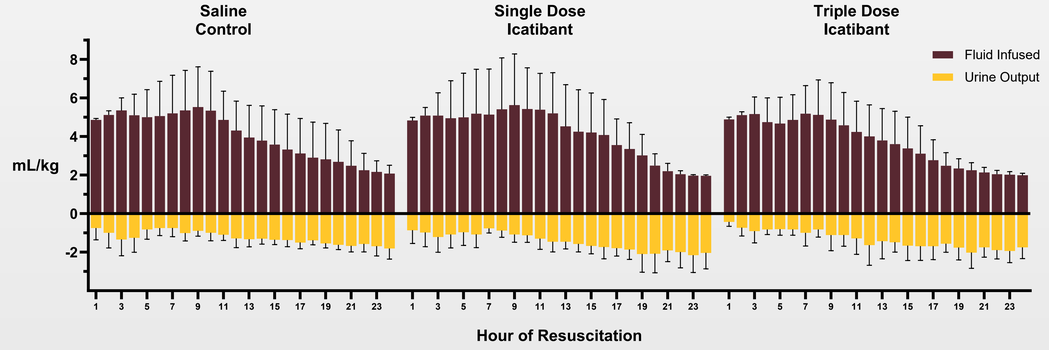


Table 2. Resuscitation Outcomes

	Saline Control (n=10)	Single Dose Icatibant (n=10)	Triple Dose Icatibant (n=10)	p-value
Fluid In (mL/kg/hr)	**3.91** +/- 0.97	**4.04** +/- 1.24	**3.93** +/- 0.92	0.96
Urine Out (mL/kg/hr)	**1.25** +/- 0.19	**1.46** +/- 0.29	**1.33** +/- 0.24	0.17
Maximum Heart Rate (beats/min)	**137.1** +/- 25.7	**138.5** +/- 23.3	**123.8** +/- 13.7	0.26
Minimum Mean Arterial Pressure (mmHg)	**56.0** +/- 6.4	**56.7** +/- 9.9	**55.6** +/- 4.9	0.95
Minimum Cardiac Output (L/min)	**3.5** +/- 0.5	**3.9** +/- 0.6	**3.8** +/- 0.6	0.21
Maximum Arterial lactate (mmol/L)	**13.59** +/- 3.27	**9.77** +/- 3.50	**11.86** +/- 4.60	0.10
Plasma Creatinine (mg/dL)	**1.39** +/- 0.34	**1.38** +/- 0.24	**1.31** +/- 0.22	0.73

For additional results from this study focusing on endotheliopathy, please visit poster MHSRS-26-3723

Discussion

Contrary to our hypothesis, we found that anti-bradykinin therapy with the subcutaneous injection of 0.5 mg/kg icatibant given post-burn does not impact the volumes of intravenous fluid required to maintain urine output after injury.

The dose of icatibant used in this study has previously been shown to occupy 100% of all available B2 receptor binding sites in swine [4].

Either bradykinin is not a driving force behind the development of edema after burn, or 30 minutes after injury is too late to positively impact the clinical course of the resuscitation.

We do not find evidence to support continuing to develop icatibant for use as a post-injury adjunct to severe burn resuscitation.

Conclusion

Post-injury anti-bradykinin therapy with icatibant fails to improve resuscitation outcomes in a swine model of severe burn.

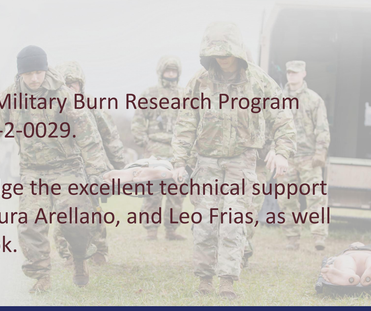
References

1. Wurzer P, Culnan D, Cancio LC, Kramer GC. Total Burn Care (2018).
2. Jonkam CC, Enkhbaatar P, Nakano Y, et al. Shock 2007. 28(6).
3. Lumry WR, Li HH, Levy RJ, et al. Annals of Allergy, Asthma & Immunology 2011. 107(6)
4. Barratt-Due A, Johansen HT, Sokolov A, et al. Shock 2011. 36(5)

Acknowledgements

This work was supported by the Military Burn Research Program under award number HT9425-23-2-0029.

The authors gratefully acknowledge the excellent technical support provided by Kassi McLaughlin, Laura Arellano, and Leo Frias, as well as Belinda Meyers and John Snook.



To learn more, visit: **usaisr.health.mil**