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Title	Management of severe frostbite using iloprost, alteplase and heparin: a Yukon case series
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Reviewer 1	Dr. Christopher Evans
Institution	Department of Emergency Medicine, Queen's University, Kingston, Ont.
General comments (author response in bold)	Thank you for the opportunity review this article. The management of frostbite injuries is poorly researched and there has been little change in the practice of this type of injury for many years. The authors should be commended for their efforts to improve the care of frostbite patients in the Yukon as they have clearly dedicated substantial effort to this patient population. I found this article to be interesting and novel, and I think most emergency physicians, some family physicians and some surgeons will as well. Clearly the conclusions can be drawn are limited by the study design (which the authors acknowledge) and it is difficult to separate out how the purported effectiveness of their treatment is related to the medications versus the aggressive wound care, supportive care, and general in hospital management the patients received. The article is a good fit for CMAJ Open as it has a uniquely Canadian flavour to it that readers will appreciate. **Thank you!** My main suggestion for revision would be to include in the results and conclusions of the abstract as well as the final paragraph of the discussion, specific comment on the rates of adverse effects with both altepase and iloprost. The rates of adverse events were significant and deserve emphasis, particularly as the study is not randomized, and many readers will be unfamiliar with these medications in the setting of frostbite. Until such data is available it will be particularly important for practitioners and patients to have a good sense of the balance between benefit and harm with the use of these medications. (pages 15 and 19)
Reviewer 2	Dr. Ken Zafren
Institution	
General comments (author response in bold)	This paper will be useful for other hospitals trying to improve care of frostbite. You have built on the 2 cases you originally published and have nicely described how the steps you took to develop an efficient protocol. **Thank you!** Abstract Results. 4/21The sentence should begin with “Twenty-two” rather than Arabic numerals (page 4) 4/26 By “on average” do you mean that this was the mean? Please specify mean or median. 4/27 same point: mean or median **These were mean values. Corrected throughout the text, table and figure. The median values were not significantly different from the mean except for duration of cold exposure.** Introduction 5/24 60°N latitude is so standard that it does not need parenthetical explanations.

	25-26 should just say -40°C (page 5) Methods Yukon Frostbite Protocol 6/22 should say “intravenously.” (in spite of usual usage) 6/25 should say “intravenously” (page 6) Exclusion 73-9 Please state your predetermined exclusion criteria in the Methods section. You can discuss the patient who was excluded in the Results section. (pages 6 and 10) **Included in the “Participants” subsection of the “Methods” as per Editor’s suggestion.** 7/16 Delete “over the years.” (page 7) Figure 1 8/23 Please use generic name for Mepitel (page 9) **“Non-adherent silicone dressing”** 9/16 (and 9/19) It is enough to say that there was no significant correlation. The p-values are distracting. If they are important, you should present them in a figure. (page 10) 9/23 should say “that takes place every year…” (page 10) Table 1 Averages should be called “means” and should be presented as mean±SD (page 11) **Standard deviation calculated and included for all means throughout the table and text.** 10/30 should read “freeze-thaw-refreeze” (page 11) Figure 2 Good figure (page 13) **Formatting changed as per Editor’s suggestion.** Figure 3 Good figure (page 14) 13/4 “Although” is the formal written word. 13/14 should say “two of whom had adverse reactions…” 13/16 delete “traumatic” 13/16 Start a new sentence and say “Both required blood transfusions.” (page 15) 13/18 change averages to mean±SD (page 15) **Standard deviation calculated and included for all times in that paragraph.** Table 2 14/5-11 Treatment regimen seems ambiguous. There is clearly overlap with rapid

	rewarming and other treatments. Could you perhaps make 2 columns with drug treatments – with and without rapid rewarming? (page 17) **This is an interesting issue. None of the patients who had rewarming outside of the hospital required amputations. All but one of those 9 patients where Grade 2 and 3. Given that the rewarming outside of the hospital was uncontrolled it is not possible to draw clear conclusions from this. It does raise the question of whether rapid rewarming is as important in the iloprost/alteplase era as it was prior. Frankly, we suspect warm ischemia time to be a more crucial factor than the method and speed or rewarming. Perhaps a larger trial could answer this question.** **We tried making two columns but all the numbers below seemed to fall under the "without rewarming" column. We indicated the number of patients with rapid rewarming and those with passive rewarming, separated by a "/". We also clarified the wording in the Result section (Page 15).** Table 2 14/32 There were only 2 "other" adverse drug reactions. You could put the reasons in parentheses or make an extra line, using one line for each reason (page 17) **We changed the word "Other" to "Bleeding" and changed the number of patients from 2 to 1. The other patient had a perforated duodenal ulcer that was not believed to be related to iloprost but the scheduled ibuprofen the patient was receiving for 5 days. We discussed this in the Interpretation section (Page 19).** **We also removed the word "Other" in Table 1 (Page 11) under "Predisposing event" and changed "Work" to "Work/Labour" to combine the two patients together. This change is also reflected in Figure 3 (Page 14).** Table 2 14/37-47 With 5 patients, there is no reason to use percentages for alteplase dosing and adverse reactions. (page 17) Table 2 14/46-47 "drug reactions" and delete "overall" (page 17) Figure 4 Figure 4 could be deleted, but I would favor keeping it, since it shows that the improvement in time occurred in the first 2 years. Delete "average" from the caption. Please add an explanation in the caption that no iloprost was given in 2016. You should add all of the individual data points. You should add 2016 to the x-axis (and keep it to scale). This will flatten the curve slightly. (page 18) Interpretation. 16/7 You cannot demonstrate efficacy in a case series. You compare and contrast your results with other published case series and RCTs in the next paragraph. The place to say that your case series suggests that iloprost, etc. have efficacy is after the 2nd paragraph. (page 19) 16/10 Delete "of note." It's either notable or not. Convince the reader. 16/11 Delete "notable." (same comment) (page 19) 16/15 Please make it clear that these numbers refer to risk without iloprost. (page

	19) 16/21 Please start a new paragraph with “In our series… (page 19) 16/23 Delete “Interestingly.” It is your job to convince your readers that something is interesting. (page 19) 16/25 What were Juopperi’s findings? Give your readers enough information to evaluate whether your findings were consistent with other studies. (page 19) 16/26-28 This sentence is not logical. Increased risk is not the same as being at risk. Please rewrite. (page 19) 16/34-35 Delete this sentence. It is identical to a previous sentence. (page 19) 16/44-45 Please rewrite for clarity: Because iloprost was well tolerated we decided to err on the side…” You can delete “by our patients.” (page 19) 17/5 Please find another way to describe the risks associated with alteplase than “notable.” You could say: “Because use of alteplase carries a significant risk, it should be reserved for patients at high risk of amputation.” (page 20) 17/7 Delete “thus.” This is not a logical syllogism. (page 20) 17/8 should say “is only available through the Health Canada Special Access Program.” (page 20) 17/9 Delete “only.” (page 20) 17/11 Rewrite for clarity: Because there is limited evidence regarding the use of epoprostenol… we recommend continuing to use iloprost…” (page 20) 17/17 Rewrite for clarity (“due to” is ambiguous). “Because there was no control group, our case series…” (page 20) 17/21 should say: compared to (page 20) 17/22 rewrite: “controlled trial comparing the digit salvage rates with iloprost alone, alteplase alone, and a combination of both. (page 20) 17/24-25 revise: “whether there are enough cases… such a study.” (page 20) 17/25 Should say “ further limitation of our study is that it was retrospective. Also, grading of frostbite relies on…” (page 20) **Sentence removed to avoid repetition with the first sentence of the paragraph.** Conclusion The conclusions in the abstract and the main text need not be identical, but should be aligned. It is often easiest to make them identical. Please revise the conclusions. I suggest using the conclusion I the main paper, but adding the

	specifics from the conclusion in the abstract. (We believe the education of the healthcare providers involved, a defined protocol algorithm with visual grading system, and pre-printed orders have contributed to improved frostbite care at our institution.) (page 20 [and page 4] 17/32 “comparable with the literature” is ambiguous. You could say: “digit salvage rate comparable with the best published results. (page 20) 17/34 You don’t discuss “warm ischemia” in the paper. The easiest solution would be to delete the reference to warm ischemia time. However, this is a useful concept. Perhaps you can explain warm ischemia time and how decreasing time to treatment shortens warm ischemia time. (page 19) 17/35-36 This is a weak conclusion. You should strengthen it. How about “… all Grade 4 injuries is a safe and effective regimen that can be achieved, even at a rural or remote centre. (page 20)
Reviewer 3	Dr. Rachel M. Nygaard
Institution	Department of Surgery, Hennepin Healthcare
General comments (author response in bold)	This is a well-written manuscript detailing the authors' experience treating frostbite injury at a single center. Notably, they treat frostbite injured patients with iloprost in addition to commonly used modalities. The methods and results are detailed and the discussion puts the authors results in context of the current literature. I was interested to see the presentation of temperature with injury timing - while, not surprising, this is rarely detailed in most frostbite studies. The authors show great benefit, especially for grade 2 and 3 injury with 100% salvage. **Thank you!** Interestingly, the authors note a 73% adverse drug reaction for iloprost - were these patients that didn't get alteplase or heparin? **16 patients out of 22 (73%) had adverse drug reactions to iloprost.** **These 22 are all the patients in the study, including those that did and did not get alteplase/heparin. All 22 patients received iloprost. Only grade 4 would qualify to also receive alteplase/heparin and 5 of 7 cases did. One excluded from thrombolysis due to a delayed presentation and the other due to trauma. All 5 of the alteplase patients had adverse effects from the iloprost. Separating those patients out from the 22 patients leaves 17 iloprost only (ie no alteplase/heparin) patients who then had a lower (65%) adverse reaction rate.** **The adverse drug reactions listed in the table are common iloprost adverse effects.** How many were also in those with drug/alcohol use as a factor associated with their injury? (don't need to add this to the manuscript, I'm simply curious if you know offhand). **Looking at the 7 patients whose presentation was alcohol-related or were chronic users, 5 had adverse effects. Recognizing our small numbers, it would not appear that the alcohol group responded differently.** I have just a couple questions that I believe will be easy to add and improve the manuscript.

	1. What are your contraindications for iloprost? You note 2 patients with freeze-thaw cycles - did they get iloprost and not, I'm assuming, alteplase? **All the patients in our study received iloprost. Neither of the patients with freeze-thaw-refreeze cycles received alteplase. One because they had a Grade 2 injury and we only add alteplase if they are Grade 4. The other was a Grade 4, but they had significant trauma which precluded giving thrombolysis.** **We use the contraindications from the iloprost product monograph: pregnancy, lactation, active peptic ulcers, trauma (relative contraindication), intracranial hemorrhage, severe coronary heart disease or unstable angina, myocardial infarction within the last 6 months, acute or chronic congestive heart failure and severe arrhythmias.** 2. What is your timing of initiation of heparin? For grade 4 frostbite patients, do you initiate iloprost, alteplase, and heparin simultaneously or do you complete one and then start the other? **This is a good question and frankly we have tied ourselves in knots looking through the literature to answer if iloprost and alteplase help or hinder each other. Should a vasodilator be given first to enhance thrombolytic delivery? Based on your groups' work demonstrating that the less warm ischemic time the better we have thus far decided to make sure they get alteplase as soon as possible and run both iloprost and alteplase at the same time. We initiate heparin within 30 minutes of the alteplase and again influenced by your group, we will likely move to a low molecular heparin in the future.** 3. Do you use any imaging to assess perfusion or doppler for pulses prior to initiation of alteplase or iloprost? **Not consistently. We do not have nuclear medicine (nearest bone scan is 1000 km away as the crow flies!). We have tried CT angiography and MR with limited success. We recently had a trial of ICG fluorescence in our hospital for other reasons, but we did try it on frostbite patients and we think it would be a good option if a quantitative method could be developed.** Unfortunately, iloprost isn't available in the United States, but it would be a benefit for patients that have contraindications to alteplase. I applaud the authors on their work and strong addition this manuscript will make to the frostbite literature. **Thank you!**