Clinical question.
In patients with frostbite, does the use of an anti-inflammatory, when compared with usual care, improve outcome?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy

State if this is a proposed new topic or revision of existing worksheet: New topic

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).


Related articles: (25 hits)

PubMed “frostbite” as [MeSH terms] OR [all fields] AND “ibuprofen” [all fields]: 6 hits

PubMed “frostbite” as [MeSH terms] OR [all fields] AND “prostaglandins” [terms] 7 hits

Cochrane Database for systematic reviews: “frostbite” (0 hits), “cold injury” (0 hits), “non-steroidal anti-inflammatory drugs” (6 hits, none relevant)

EMBASE: search using text words 'nonsteroid antiinflammatory agent'/exp AND 'frostbite'/mi AND [english]/lim AND [abstracts]/lim AND [1974-2008]/py

search using: (‘frostbite'/syn) AND (‘ibuprofen'/exp/dd_dt): 49 hits, 30 excluded

Search using 'frostbite'/mi AND [english]/lim AND [abstracts]/lim AND 'nonsteroid antiinflammatory agent'/exp: 34 hits, 10 excluded

AHA EndNote X.1 master library; search using text word “frostbite”: 8 hits, 7 excluded

Review of references from articles; Manual search of articles in Wilderness Emergency Medicine: 8 hits, 5 excluded. Manual review of articles cited in web-based publication eMedicine.com:

Forward search using GoogleScholar with terms ‘frostbite” AND “nonsteroidal anti-inflammatories’: 27 hits, 25 excluded.

State inclusion and exclusion criteria

Included: controlled trials, animal or human studies, all ages, case reports, case series, english

Excluded articles:
Review articles
Not true frostbite (e.g., chilblains, pernio, trenchfoot, hypothermia, cryoinjury, frostnip);
Steroidal anti-inflammatories;
Alternative therapies (e.g., HBO, rewarming, surgery, vasodilators, calcium channel blockers, anticoagulants, sympatholytics)

Number of articles/sources meeting criteria for further review: 14

Animal RCT – 8
Case series – 4
Prospective cohort study - 1
Diagnostic case-controlled study - 1.
### Summary of evidence

#### Evidence Supporting Clinical Question

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<td>Heggers 1987(β)(A)</td>
<td>Robson 1981 (C)</td>
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<td>Berg 1999 (B)</td>
<td>Ozyazgan 1998 (C)</td>
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<td>Purkayastha 2002 (A)</td>
<td>Talwar 1972 (A, D)</td>
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Outcomes – Please define outcomes for this question, place them after letters below and use letters to identify studies which evaluate this outcome

A = extent of tissue loss or damage  
B = microscopic/vascular perfusion  
C = levels of inflammatory mediators/eicosanoids  
D = Edema formation  
E = no outcome described

*Italics = Animal studies*

### Evidence Neutral to Clinical question

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<td>Bilgic 2008 (E)</td>
<td>Foray 1992 (E)</td>
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Outcomes

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*Italics = Animal studies*
## Evidence Opposing Clinical Question

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**Goldberg 1994 (A)**

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**Level of evidence**

### Outcomes

- **A** = extent of tissue loss or damage
- **B** = microscopic/vascular perfusion
- **C** = levels of inflammatory mediators/eicosanoids
- **D** = edema formation
- **E** = no outcome described

*Italics = Animal studies*
Over the past 2 decades, the use of a NSAID – particularly ibuprofen – has become a component of many frostbite treatment protocols for backcountry, alpine rescue and outdoor emergency care organizations. Research to this potential benefit dates back to the early 1970’s, consists primarily of animal controlled trials, and suffers from lack of a consistent model of frostbite injury, small group sizes, and often from confounding factors such as timing of intervention or failure to limit the number of simultaneous interventions. In addition, much of what we believe to know about the pathophysiology of frostbite injury is inferred from burn studies. Case series in general do not describe outcomes. One prospective cohort study shows a benefit to topical aloe vera plus ibuprofen, but the study groups are poorly matched. There are no studies looking at prehospital use of ibuprofen or other NSAIDs for frostbite injury. More recent advances in treatment of severe frostbite injury using tPA may pose a potential contraindication to use of NSAIDs prior to rewarming and evaluation of perfusion. Thus, the use of NSAIDs, including aspirin, prior to hospital evaluation, is not recommended.

Acknowledgements:

Citation List


Study Comments: This is an animal study of frostbite using rats treated with a-Trinositol, a metal chelator with anti-inflammatory properties and compared with a control group treated with saline, using an outcome of edema formation as an indirect indicator of microvascular permeability. Of interest this study looked at administration of trinositol both pre and post rewarming and found that administration both pre and post thawing resulted in less edema than when administered only post thawing. Group sizes were small (control = 5, post treatment = 5, pre + post treatment = 9). LOE 5.


Summary – Case series of 7 patients with frostbite (five 2nd degree, two 3rd degree) treated with an inpatient protocol that included rapid rewarming at 40°C, ibuprofen 12 mg/kg po daily, ASA 100 mg po daily, pentoxifylline 500 mg in low molecular weight dextran daily for 5 to 7 days. No outcomes from this protocol were described. LOE 4 neutral.


Conclusions: Tissue plasminogen activator improved tissue perfusion and reduced amputations when administered within 24 hours of injury. This modality represents the first clinically significant advancement in the treatment of frostbite in more than 25 years.


Study Comments: This was an animal study using a rat skin frostbite model to investigate the effects of 4 different nonsteroidal antiinflammatories on “exudative responses” (i.e., edema formation as a result of vascular damage) to cold injury. Indomethacin is the only NSAID used that is currently available/in use in the USA. Outcome was assessed by injecting a blue dye IV and measuring the amount of dye exuded into frostbitten tissues (micrograms dye/lesion) at 30 or 60 minutes. Each group of 5 rats received 2 doses of their respective anti-inflammatory either IV or intragastrically 1.5 and 1 hour prior to injection of Evans Blue dye and prior to freezing injury. A control group received IV and IG normal saline.
The authors found that exudate was significantly decreased (p<.01) at 3.5 – 4.5 hrs post freezing injury by indomethacin and one other NSAID. Indocin was not effective in reducing exudative response in the first 1-2 hours post injury. LOE 5


**Summary** - A case series of 1261 frostbite victims describing treatment protocols, which include rapid rewarming in a 36°C water bath and “systemic nonsteroidal anti-inflammatories”. Outcomes not described, multiple confounders not identified. Neutral evidence, LOE 4.


**Summary** – This was an animal model of frostbite injury using rabbits, with the control group(n=9) receiving no treatment, one group (n=9) receiving treatment with a thromboxane inhibitor immediately after injury and a third group(n=9) receiving treatment 4 hours post injury. The authors found no difference between control or treatment groups in terms of tissue survival, but 8 of 27 animals died during the experiment, reducing the study power. LOE 5.


**Summary**: This is a “review” that essentially restates the methods, findings and discussion related to the two studies presented in Hegger 1987. No new material is presented. LOE 5 neutral.


**Summary and Comments**: This paper presents results of two studies that are identified in the evidence tables as Heggers 1987 “α” or “β”. In the first (“α”) study an animal model of frostbite injury using rabbit earflaps was used to evaluate the effects of treatment with topical methylprednisolone, aspirin, aloe vera cream and methimazole(n=4 per group) versus a control group (n=4) without treatment and using an outcome of tissue survival measured by planimetry. Treatment immediately followed rapid rewarming in a water bath and continued for 96 hours. The authors describe “statistically significant improvement” in tissue loss for each of the 4 treatment groups as compared to the control group, most notably for the groups receiving methimazole or aloe vera, but the study group numbers were small, and this appears to be the same experiment reported by Raine in 1980 Surgical Forums (see below) which is authored by 2 of the same authors in this paper. LOE for first study is 5, supporting, but this specific paper is not being added to the evidence tables.

The second (“β”) study involved patients admitted with frostbite over a 3 year period. It appears that patients were not randomized and either admitted to the Burn Center (n= 56) or to “other services” (n=98). The Burn Center group was treated with a protocol that included rapid rewarming if needed in a water bath, wound care including topical aloe vera, and oral ibuprofen 12 mg/kg/day. Patients in the “other services” group were not treatment with any specific protocol but appear to not have received either topical aloe vera or systemic ibuprofen. The authors found that frostbite patients treated with the aloe vera/ibuprofen protocol had much less tissue loss compared to the “other services” group (67.9% vs 32.7%), reduction in morbidity (7.0% vs. 32.7% amputation) (p<0.001) and a reduction in hospital stay. This study was flawed in that groups were not matched in terms of size or the degree of frostbite (a third of the protocol group had only 1st degree frostbite, which usually does not result in tissue loss, while only 10% of the “other services” conventional treatment group had 1st degree frostbite; a fourth of the protocol group had 3rd degree frostbite versus nearly 40% of the “other services” group.). LOE 2 (study used concurrent control group without true randomization), supporting.


**Summary**: This is a case series of 38 consecutive patients with frostbite injuries treated with a protocol that included application of topical aloe vera to wounds and oral aspirin, 325 mg q 6h for 72 hours. Results of treatment with this protocol...
were reported as “all patients healed without major tissue loss of the affected areas.” Patients included in this series included 16 with first degree frostbite (which normally does not produce tissue loss), 19 patients with 2nd degree frostbite, and only 3 patients with 3rd degree frostbite. LOE 4.


Summary: This was an animal study of frostbite injury using a total of 21 rabbits (10 control animals not subjected to frostbite and 11 subjected to frostbite of the earflaps), with the goal of measuring and comparing levels of thromboxane A2 (as B2), Prostaglandin I2 (as 6-keto-prostaglandin F1α), PMNs and mast cells in frostbitten vs uninjured tissue. No intervention was attempted but results provide support for frostbite treatment and study protocols using thromboxane and prostaglandin inhibitors. LOE 5


Summary - Animal model of frostbite in rats, with control group allowed to rewarm at room temperature and treatment groups rewarmed at 37 – 39°C in a tea decoction. Treatment groups also received a variety of other interventions including aspirin, pentoxifylline and topical silver sulfadiazine. Outcome was tissue necrosis as measured by hind paw volume. LOE 5, fair supportive study (confounding interventions).


Summary: Animal study of frostbite using rabbit earflaps, 5 groups with 4 rabbits per group. All frostbite tissue was allowed to rewarm at room temperature. Treatment groups received 1) topical methylprednisolone 2) topical aloe vera 3) oral methimazole and 4) oral ASA all immediately following rewarming and continuing for 96 hours. Outcome was tissue survival as the percent of total area frostbitten that survived. Tissue survival was greatest in the methimazole group but no treatment group was statistically greater than another. The authors concluded that their results suggest that substances that block the production of prostaglandins and thromboxane may be beneficial in preserving tissue in a frostbite injury.

This study is part of the proceedings from an ACS forum held in 1980. It appears to be the same animal study reported by Heggars in 1987 (above) in which they claim statistically significant improvement for each of the 4 treatment groups as compared to the untreated control group. LOE 5.


Summary: This is a case series of 10 frostbite injury patients who underwent aspiration of blister fluid immediately following rapid rewarming and “where possible” prior to rewarming. Aspirate underwent analysis for a variety of properties, including measurement via radioimmune assay of prostaglandins E2 (vasodilating/antiaggregating properties), F2α and thromboxane B2 (vasoconstricting and platelet aggregating properties). The authors report that levels of prostaglandin F2α and thromboxane B2 were found to be markedly elevated compared to normal, and the levels of prostaglandin E2 were found to be slightly depressed compared to normal serum values, which has been previously reported with burn blister fluid studies. Normal serum values are never presented, and the values that were tabulated from the aspirated blisters have a very wide range of values (for instance, for Pg F2α, 3 patient samples were reported as <0.5 mg/ml, while one sample at the extreme contained 66.9 ng/ml). Measurements for Pg E2 and thromboxane B2 likewise had a wide range of values, and no mean or median values are documented. The authors conclude that their data suggests that the arachidonic acid metabolites PgF2α and thromboxane B2 may cause the progressive vascular changes seen in tissue following cold injury and that it may be possible to prevent the progressive injury by sing local and/or systemic antiprostaglandin or antithromboxane agents. LOE 4.

Summary: This was an animal study of frostbite using rabbit limbs to determine the effect of treatment with three different NSAIDS on tissue loss following frostbite injury. There were 4 groups of 10 rabbits, including a control group and 3 groups treated with either indomethacin, oxyphenbutazone or xanthinol nicotinate. Treatment was initiated following freezing injury, (within 2 hours of injury) and continued for 5 days. Outcomes were determined by the amount of tissue loss as graded by the authors at “various intervals” on a scale of 0 to 5. Outcome was also measured by the amount of limb edema as determined through a volume displacement plethysmograph. The authors found that tissue loss was significantly reduced for all three treatment groups compared to the control group; The indomethacin group was noted to have slightly greater amounts of edema. Compared to the control group. It is unclear when the observations of tissue loss and edema were noted for how long. LOE 5.


Comments: The protocol for treating frostbite in this study included use of ibuprofen 400 – 600 mg 4 times daily for all patients, but the study authors note “Based on the suggestions of others and our own concerns, we will be evaluating beginning aspirin therapy on postinjury day 1 and continuing it for several weeks in lieu of both warfarin and ibuprofen.” The early success of TPA for treatment of frostbite may have implications for use of ibuprofen and other eicosanoids for patients with frostbite in the prehospital setting.


Summary: Animal study of frostbite using rabbit hindlimbs and combining slow versus rapid rewarming with pharmacological interventions including IA reserpine, PGE1 or normal saline, using tissue loss as graded numerically as an outcome. Study groups of 5 animals each. Results suggest (p<0.5) that with slow rewarming, infusion of PGE1 may be of benefit compared to no treatment. The authors conclude the data suggests a clinical application for PGE1 in frostbite where rapid rewarming is not possible. LOE5