WORKSHEET for Evidence-Based Review of Science for First Aid -

Worksheet author(s)
Shenefelt

Date Submitted for review: 9/16/09 (search rerun)

Clinical question.
"Does irrigation of eyes exposed to a toxin with water compared to other substances 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: Identified as revision, but in fact a 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).

1. MEDLINE/PubMed (NLM -US)
   a) MeSH, Major topic and subheading
      i. Eye AND Injuries AND chemically induced AND Toxic Actions AND Irrigation/methods OR Irrigation/adverse effects OR Irrigation/complications OR Irrigation/contraindications OR Irrigation/methods OR Irrigation/mortality OR Irrigation/statistics and numerical data OR Irrigation/trends AND Emergency Treatment OR first aid n= 14806
      ii. Eye AND Injuries AND chemically induced AND Toxic Actions AND Irrigation/methods AND Emergency Treatment OR first aid n= 14635
      iii. Eye AND Injuries AND chemically induced AND Emergency Treatment OR “first aid” n= 7920
      iv. Eye AND Injuries AND chemically induced AND Emergency Treatment n= 71
      vi. Relevant to question LOE1-5, n= 3 (Merle 2005, Langefeld 2003, Kompa 2002)
      b) Text Words
         i. Irrigation, eye, injury, toxin, water, emergency treatment, first aid n=0
         ii. Chemical injury, ocular, burns, emergency treatment (limited to RCT) n=0
         iii. Chemical injury, ocular, burns, emergency treatment (limited to CT) n=0
         iv. Chemical injury, ocular, burns, emergency treatment n=4
         v. Chemical eye injury AND irrigation AND emergency treatment n=7
         vi. Chemical eye injury AND irrigation AND emergency treatment limits: Comparative Study n=3
         vii. Relevant to question LOE1-5, n= 2 (Langefeld 2003, Kompa 2002)

2. TOXLINE/TOXNET (NLM -US)
   a) Text words
      i. Eye Injuries, chemically induced, first aid n=2
      ii. Chemical injury, ocular burns, emergency treatment n=2
      iii. “Diphtherine” n=15
      iv. Relevant to question LOE1-5, n= 3 (Mathieu 2005, Rihawi 2006, Gerasimo 2001)

3. Cochrane Collaboration (UK)
   a) Database of Systematic Reviews
      i. Chemical injury, ocular burns, emergency treatment n=2
         1. Relevant to question LOE1-5, n= 0
   b) Central Register of Controlled Trials
      i. Chemical injury, ocular burns, emergency treatment n=5
      ii. Relevant to question LOE1-5, n= 1 (Langefeld 2003)

4. Embase (Elsevier)
   a) ('eye'/exp OR 'eye') AND ('eye injuries'/exp OR 'eye injuries') AND ('toxin'/exp OR 'toxin') AND ('eye irrigation'/exp OR 'eye irrigation') Limits: All Years, Priority Journals n=0
   b) ('eye'/exp OR 'eye') AND ('injury'/exp OR 'injury') AND chemical AND ('emergency'/exp OR 'emergency') AND treatment limits: All Years, Priority Journals n=14
      i. Relevant to question LOE1-5, n= 2 (Rihawi 2006, Kompa 2002)
   c) chemical AND injury AND burn AND ('emergency'/exp OR 'emergency') AND ('first aid'/exp OR 'first aid') Limits:
      All Years, Priority Journals n=2
   d) Relevant to question LOE1-5, n= 0

5. Scirus (Elsevier)
   a) Chemical injury, ocular burns, emergency treatment. Limits: All Years, Abstracts and Articles n= 354
i. Relevant to question LOE1-5, n = 0

6. Database of Abstracts of Reviews of Effects (NIHR – UK)
   a) Chemical injury, ocular burns, emergency treatment, first aid. (all words, no limits) n=0
   b) Eye injuries, chemically induced, emergency treatment (all words, no limits) n = 0
   c) “Ocular”, “burns”, and “first aid” (all words, no limits) n=0
   d) Eye and burns (all words, no limits) n=1
   i. Relevant to question LOE1-5, n = 0

7. AHA Endnote Master Library (24MAR08)
   a) Key Words
      i. Irrigation + eye + toxin n=0
      ii. Chemical + eye + first aid n=0
      iii. Chemical + eye + burn n=0
      iv. Eye + burn n=10
   v. Relevant to question LOE1-5, n = 1 McCulley 1990

8. Google Scholar
   a) Chemical injury, ocular burns, first aid n = 4,180
   b) Chemical injury, ocular burns “first aid” n= 568
   c) “Ocular burns”, “first aid” n=36

9. Worksheet 258 (Judge/Holstege 2005)
   b) Relevant to 2010 question LOE1-5, n = 1 (Kompa 2002)

• State inclusion and exclusion criteria

Inclusion criteria: Humans, animals, all years, all languages, peer-reviewed journals, all ages, comparative study with water.

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


Summary of evidence

<table>
<thead>
<tr>
<th>Evidence Supporting Clinical Question</th>
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<tbody>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Fair</td>
</tr>
<tr>
<td>Poor</td>
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<tr>
<td>Kompa 2002</td>
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<td>Kompa 2005</td>
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<table>
<thead>
<tr>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>A = conjunctival inflammation</td>
</tr>
<tr>
<td>B = conjunctival ischemia</td>
</tr>
<tr>
<td>C = corneal swelling</td>
</tr>
<tr>
<td>D = osmolarity</td>
</tr>
<tr>
<td>E = opacity</td>
</tr>
<tr>
<td>F = radioactive decontamination</td>
</tr>
<tr>
<td>G = intraocular pH</td>
</tr>
<tr>
<td>H = penetration</td>
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<tr>
<td>I = buffer capacity</td>
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<td>J = other</td>
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</tbody>
</table>

| Italics = animal study     |

A = conjunctival inflammation B = conjunctival ischemia C = corneal swelling D = osmolarity E = opacity F = radioactive decontamination G = intraocular pH H = penetration I = buffer capacity J = other

Italics = animal study
Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th>Good</th>
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McCulley 1990<sup>ABCE</sup>

Gerasimo 2001<sup>FH</sup>

Evidence Opposing Clinical Question

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Kompa 2002<sup>22</sup>

Rihawi 2006<sup>DGJ</sup>

Spöler 2008<sup>DEH</sup>

Gerasimo 2001<sup>FDH</sup>

Outcomes – Please use the same outcomes as defined for the Evidence Supporting table above

**REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:** (please include implementation considerations including at a minimum training, environment and availability):

Studies in this review involved chemical and animal model laboratory experiments (in vitro, in vivo, ex vivo) thus limiting them to a LOE 5. As most studies had at least some of the relevant quality assessment items, methodological quality was considered fair.

Sample sizes were small, but typical for the literature. One study (Gerasimo 2001) was not published in a peer-reviewed journal and gave the impression of bias, but was considered of sufficient value to include. Osmolarity, corneal swelling, and penetration were objectively measured in several studies, but there were no standard criteria for assessing the efficacy of the various rinsing solutions (10 in all), against water. Rinsing times varied from 5-30 minutes. Most of the articles included multiple experiments with various solutions, intent, and outcome. Only those with direct relevance to the question were included in the summary below.

Immediately after burning rabbit eyes (n = 10) with a concentrated HF solution (3.0 ml), magnesium chloride (MgCl<sub>2</sub>); normal saline; a divalent ion mixture, and water were used as rinsing solutions. Injuries were followed for 46 days. Clinically scored ocular signs were confirmed by histologic examination. All interventions were shown to have equal effect. Although slight improvement occurred, none of the treatments induced recovery that was significantly better than no treatment at all (McCulley 1990; 674). This outcome can be attributed to the unique ability of concentrated solutions of HF to quickly penetrate through the cornea, causing a severe, progressively caustic effect that spreads and deepens, dissolving and destroying tissue. This rapid penetrating ability of HF was recently confirmed using optical coherence tomography (OCT). This non-invasive, non-contact, high resolution imaging method demonstrated full penetration of the rabbit cornea with HF is complete within 4 minutes (Spöler 2008; 551). In the same study, rinsing excised rabbit eyes (n=4) burned with a standardized amount of HF solution (25 ml of 2.5%), for 15 minutes with 1L of either tap water, 1% calcium gluconate solution or a commercially available HF rinsing solution (Hexafluorine<sup>®</sup>, Laboratories Prevor,
FR) was shown to limit structural damage to the anterior half of the cornea at 15 minutes. However, rinsing severe burns with tap water or calcium gluconate was not shown to prevent ongoing damage from continued penetration of HF into the eye after rinsing ended. These findings were in contrast to those of the commercially available HF rinsing solution which stopped further penetration as illustrated by OCT image sequences and photographs of the burnt corneas (Spöler 2008; 552).

A series of experiments compared the buffer capacity of emergency eye-wash products and the correlation between corneal swelling and osmolarity in burned porcine eyes. The ability of solution to absorb additional alkali or acid while maintaining its pH between 5 & 8 is thought to be important as irreversible damage of intraocular structures may occur once the pH of the aqueous humor exceeds 11 (Grant 1950, Paterson 1975). The buffer capacity of tap water, normal saline (NaCl 0.9%), Lactated Ringer’s Solution (LR), ophthalmic balanced salt solution (BBS, Aqsià™ Bausch & Lomb, UK), phosphate buffer, and an amphoteric solution (Previrin, containing Diphoterine® - Prevor, DE) were measured with microelectrode. Tap water, NaCl 0.9%, LR, and BBS, were found to have low to no buffer capacity, making phosphate buffer and the amphoteric solution “suitable for first aid treatment in terms of buffer capacity”(Kompa 2002; 310). To measure the correlation between corneal swelling and osmolarity, 4 N NaOH was used to burn the corneas of enucleated pig eyes for 60 seconds (n=32). Four groups of 8 eyes each were rinsed with tap water (0.5 l) or with NaCl of different osmolarities for 5 minutes. Corneal edema immediately after burning and during irrigation was measured. Results demonstrated that the lower the solution’s osmolarity, the stronger the swelling reaction of the cornea. This suggests that irrigation with hypoosmolar solutions cause corneal swelling due to osmosis, allowing the rinsing solution to penetrate and dilute the burning agent. Tap water, by virtue of its low osmolarity (0 mOsm/l) was more effective than saline solution in this regard. Hyperosmolar (amphoteric, phosphate buffer) solutions cause less cornea edema and may only chemically neutralize a caustic agent because of their high buffer capacities (Kompa 2002; 310). In another study comparing tap water and isotonic saline, rabbit corneas (n=16) were burned with 2 N NaOH. The maximum pH rise following rinsing with tap water (1.5 l) showed a significant delay in comparison to saline solution. This delay was attributed to corneal edema caused by the (hypoosmolar) tap water which enlarged the diffusion barrier, diluted the toxin, and inhibited elevated intracorneal pH levels. Investigators concluded that irrigation with (isosmolar) saline solution was less efficacious than tap water for emergency rinsing of caustic burns of the eyes (Kompa 2005;469). Another investigation of rinsing solution effect on pH in the aqueous humor compared tap water, isotonic physiological saline solution (NaCl 0.9%, Braun Melsungen), isotonic phosphate buffer solution (PBS), borate buffer eye wash solution (Cederoth, Sweden), and amphoteric solutions (Diphoterine® Laboratories Prevor, FR and Previn, Prevor, DE). After burning with 2 N NaOH, enucleated rabbit eyes (n=35) were grouped. Five eyes from different animals each received 15 min of rinsing (66 ml/min) with a different solution. One group of eyes were not treated. Continuous measurement of pH was accomplished with a microelectrode inserted in the anterior chamber of the eye. Borate and the amphoteric solutions were significantly (>0.001) more effective in lowering pH compared with untreated eyes and with eyes treated with water, saline and PBS. Rinsing with tap water had an intermediate position on the scale of efficiency (Rihawi 2006; 852). Finally, a laboratory study also using enucleated porcine eyes exposed in vitro for 3 min to 20 microliters of Cobalt-60 (Co-60) compared water to an amphoteric solution (Diphoterine). Three irrigation protocols were used; a single water or amphoteric solution lavage of 150mL over 30 min. begun at 3, 10, & 90 min following exposure; 3 separate 150 mL lavages; and bathing in an eyewash device with 100 mL over 1-5 min. The distribution of radioactivity penetration was measured in the cornea, aqueous, and vitreous humor and in residual lavage fluid. A single water or amphoteric solution lavage delayed 90 minutes had little effect. A delay of 10 minutes showed a trend for the amphoteric solution as superior to water. There was little difference between water and the amphoteric solution after a 3 minute delay (Gerasimo 2001; 204). Three successive lavages with 3 min delay showed significantly (>0.05) more radioactivity removed with the amphoteric solution versus water, as did bathing the cornea for 1 and 5 minutes after a 3 min delay in an eyewash device (Gerasimo 2001;205).

**Citation List**


[Comments: LOE -S, Quality- Fair, Level- Neutral and Opposing, Summary - Three laboratory studies using enucleated pigs eyes conducted in French Army Laboratory for Radiological Control. Unclassified defense paper published by U.S. Department of Commerce National Technical Information Service. Compilation report, part of a symposium, not published in a peer-reviewed journal. Enucleated pigs eyes exposed in vitro for 3 min to 20 microliters of Cobalt-60 and then decontaminated with water or an amphoteric solution (Diphoterine®) using various protocols. When rinsing eyes exposed to a radiologic agent after a delay of three minutes, there is little difference between a single lavage using an amphoteric solution (Diphoterine®) when compared to water (Neutral). When rinsing eyes exposed to a radiologic agent after a delay of three minutes using successive lavage and corneal bathing, an amphoteric solution (Diphoterine®) is more effective than water}
(Opposing). Animal model laboratory experiments limited methodological quality to a LOE 5, fair (without randomized controls). Paper left the impression of potential bias as 2 of 2 references cite the unpublished papers of same 4 authors and 2 of 5 authors affiliated with manufacturer of Diphoterine aka Previn in Germany. Diphoterine® is a water-based decontamination solution that neutralizes both acids and bases. It is used to decontaminate occupational skin/eye splashes and is classified and approved as a medical device in Europe, Canada, Australia, and Brazil (Laboratories Prevor, FR - MeSH Unique ID C472007). Funding unknown.]


[Comments: LOE - 5, Quality - Fair, Level -Supporting and Opposing, Summary - Four experiments comparing properties of common rinsing solutions; buffer capacity, osmolarity, correlation between corneal swelling and osmolarity (porcine corneas) and tolerance (healthy human volunteers, no water comparator). Tap water, NaCl 0.9%, LR, BBS, have low to no buffer capacity, making phosphate buffer and an amphoteric solution suitable for first aid treatment in terms of buffer capacity (opposing). When initially rinsing eyes exposed to a caustic, solutions with low osmolarities penetrate the burned cornea and prevent further damage by diluting and removing the toxic agent. Tap water, by virtue of its low osmolarity is more effective than saline solution (supportive). Animal model laboratory experiments limited methodological quality to a LOE 5, fair (without randomized controls). Funding unknown.]


[Comments: LOE - 5, Quality - Fair, Level -Supporting, Summary - Four groups of 4 rabbit corneas each were burned with sodium hydroxide and then rinsed with 0.5 L or 1.5 L of saline solution or tap water. Irrigation with different solutions affected the maximum pH levels reached. Rinsing with 1.5 L of tap water significantly delayed maximum rise of pH. Thus, irrigation with tap water is more effective at lowering pH than saline solution (supportive). Animal model laboratory experiments limited methodological quality to a LOE 5, fair (without randomized controls). Funding unknown.]


[Comments: LOE - 5, Quality - Fair, Level -Neutral, Summary - Extensive paper containing a number of laboratory experiments in rabbits to clarify the mechanism of injury, severity of clinical signs, potential therapeutic agents, and toxicity of HF burns. Regarding the worksheet question, when rinsing eyes exposed to 3.0 M HF hydrofluoric acid and immediately rinsed with either tap water, normal saline, or isotonic MgCl2 (1 L over 30 minutes at room temperature) “slight improvement occurred, but none of these treatments induced recovery that was significantly better than no treatment at all” (neutral). This outcome was attributed to “a clearly dose related response to increasing acid strength” (Neutral). Animal model laboratory experiments limited methodological quality to a LOE 5, fair (without randomized controls). Funding unknown.]


[Comments: LOE - 5, Quality - Fair, Level -Opposing, Summary - “In chemical eye burns we generally recommend a prompt rinsing with agents of high neutralizing capacity as emergency treatment. In our experiments on the most severe eye burns a period no less than 15 min was required to return the pH to normal... with a quantity no less than 1,000 ml of one of the high activity therapeutic solutions such as Diphoterine, Previn and Cederroth Eye Wash Solution. These solutions, with their varying osmolarities, can equalize the destructiveness of the substance that causes the burn on the eye’s surface in a better way than phosphates or physiological saline solution, which did not show any therapeutic activity in the model of severe alkali eye burns used in this study. Rinsing with tap water had an intermediate position on the scale of efficiency, but was much less effective in this experiment than the amphoteric or buffering solutions.” (Opposing) Animal model laboratory experiments limited methodological quality to a LOE 5, fair (without randomized controls). Funding: German Academic Exchange Service (DADD), Aachen Center of Technology Transfer in Ophthalmology (research and study), Cederroth Inc. and Prevor Inc. (rinsing solutions). Authors declare no proprietary rights or financial interest in the products named in the article.]


[Comments: LOE - 5, Quality - Fair, Level -Opposing, Summary - “Enucleated rabbit eyes (stored at 4° C) were used within 12 hours of animals’ death. 25 s. after burning with HF, eyes were rinsed (66.7 ml/min, 1000 ml total) for 15 min. with tap water, 1% calcium gluconate solution and a commercially available HF rinsing solution. Treatment control = untreated HF burns. Photos of globes were recorded after rinsing at 15, 30, 45, 60 and 75 min. to evaluate the effectiveness of different rinsing solutions on the burn. “There is clear evidence... that Hexafluorine is an effective antidote in first aid treatment to prevent further tissue damage, and that water rinsing is the least effective treatment.” Animal model laboratory experiments limited methodological quality to a LOE 5, fair (without
randomized controls). Funding: Author disclosure- study partially supported by Prevor, manufacturers of Hexafluorine, who financed the rinsing solutions and other materials but did not otherwise influence the study (Prevor required evaluation of Hexafluorine under a new EU regulatory framework). Personal costs and equipment were financed by the Aachen Centre of Technology Transfer in Ophthamology and by the Institute of Semiconductor Electronics of the RWTH Aachen University.]