Novel Preoperative Pharmacologic Methods of Preventing Postoperative Sore Throat

POST

• Sore throat and hoarseness after general anesthesia (GA) with tracheal intubation occurs in 30–70% of patients
• Usually is self-limiting
• Rated as one of the TOP 10 most undesirable postoperative outcomes

Etiology:
– Mechanical injury during intubation
– Mucosal damage from endotracheal cuff
– Dehydration of the muccosa

POST

• Postoperative Care Time
  – 14 minute longer stay in PACU
  – 25 minute longer stay in the Ambulatory Care Unit
  – 51 minute later discharge from operative facility

• Reducing POST should
  – Decrease length of stay
  – Increase patient satisfaction

POST

• Non-pharmacologic factors to decrease POST
  – Care during laryngoscopy
    – Cuff pressure inflated to no more than 20–30 cm H2O
    – Laryngeal mask airway

• Pharmacologic interventions
  – Local anesthetics or corticosteroids to the cuff of endotracheal tube (ETT)

POST

• The PICO question:
  Population: Adult patients requiring endotracheal intubation
  Intervention: What is the efficacy of topical preoperative non-local anesthetic, non-steroid pharmacologic agents
  Comparison: Reducing the incidence of POST
  Outcome: The search for evidence (1990 to 2012)

• Research Criteria
  – Non-local anesthetic and non-steroid pharmacologic treatments administered topically prior to intubation

• Excluded
  – Sources examining combinations of drugs
  – Supraglottic airway use
  – Surgeries involving the oropharynx
  – Pediatrics
POST

- 117 potential evidence sources —
  - 11 meeting inclusion criteria
- All sources were Random Controlled Trials (RCT)
  - Ketamine ................. 4
  - Benzydamine gargle ........ 3
  - Aspirin .................. 1
  - Desmopanethol ............. 1
  - Amyl-m-cresol ............. 1
  - Licorice .................. 1
  - Magnesium ................. 1

- A total of 1078 subjects participated in the 11 investigations with study sample sizes ranging from 37 to 378 (median sample size of 58)
- There was subject withdrawal in 6 investigations
- All of the studies used blinded observers
- Subject blinding
  - None in 3 investigations
  - Questionable in one
  - Not reported in one
- A placebo was used in all of the studies except for one

POST

- Endotracheal intubation performed by:
  - Experienced staff anesthesiologist
  - Experienced anesthesiology resident
  - Not reported in one investigation
- Endotracheal tube size
  - 7.0–7.5 female
  - 8.0–8.5 male

- Intubation attempts limited to 1 or 2
- ETT cuff pressure 10–25 cm H2O
- Not always monitored or reported
- Other
  - Backing on extubation
    - 2 studies excluded these subjects
  - Suctioning of the posterior pharynx prior to extubation
  - Oropharyngeal airway insertion prior to extubation
  - Heat and moisture exchanger sometime used

POST

- Anesthesia
  - Intravenous induction
  - Nondepolarizers
  - Opioids often administered (not always described)
    - Fentanyl 2 mcg/kg
    - Post-op opioid administration was not reported

POST

- Postoperative Evaluation
  - All of the investigators reported the incidence of POST
  - All directly asked the subjects about POST rather than asking general questions about their postoperative condition
  - Severity was usually assessed in the post anesthesia care unit (often as "0 h") and 2 to 24 hrs postoperatively.
  - Severity was usually assessed using a 4 point visual or verbal analog scale anchored with 0 as no POST and 3 as severe POST with hoarseness or other voice changes
    - One group assessed severity using a 7-point scale and another using a 100-point scale
    - None of the investigators offered data describing the reliability or validity of the instruments used to measure POST

POST

- Ketamine
  - 4 group of investigators examined the effect of gargling 30 mL of water or saline containing 40-50 mg of ketamine
  - This is an N-methyl-D-aspartate (NMDA) receptor antagonist
    - Investigators have suggested NMDA receptors are found not only in the central nervous system, but also in the peripheral nerves
    - Moreover, experimental studies point out that peripherally administered NMDA receptor antagonists are involved with antinociception and anti-inflammatory cascade
    - This treatment probably resulted in the most promising results in reducing POST
• **Ketamine**
  - The incidence of POST early (in the post anesthesia care unit) and late (measured at 24 h) postoperatively was dramatically reduced.
  - For example: A group reported the incidence of POST at 24 h postoperatively was cut from 48% to 4%.
  - No authors reported side or systemic effects due to the ketamine.
  - It is not likely the results were due to systemic effects of the ketamine.

• **Subjects (N = 22)** gargled 40 mg of ketamine for 30 seconds.

• **Serum ketamine and norketamine levels were measured for five subjects at intervals up to 103 min after gargling.**
  - The authors reported both levels were below those described to produce analgesia.

• **Benzydamine**
  - It is a topical anti-inflammatory with local anesthetic properties.
  - Widely available outside of the United States.
  - May act on the prostaglandin system.
  - Has been used for mucositis due to radiation treatment.
  - Others reportedly used the drug treating lesions due to endotracheal intubation.
  - Benzydamine was examined as a 22.5 mg gargle and as an oral spray in 2.16 and 7.5 mg doses.
  - The higher doses were generally more effective in reducing the incidence of POST.
  - While the treatment was usually well tolerated, two subjects in a study complained of oral numbness and a distorted sense of taste.

• **Sodium azulene sulfonate**
  - Derived from azulene, a chamomile extract, and available in Japan.
  - The authors reported:
    - Anti-inflammatory effects when used to treat chronic gastritis and ulcers.
    - They theorized that gargling with sodium azulene sulfonate might be a simple, effective way to prevent POST.
    - No side effects were reported.
    - Azulene is absorbed only in the small intestine and local tissue reactions are likely rare at the concentration used in the study.
    - Investigators (Japan) reported significant reduction of POST immediately postoperatively and at intervals up to 24 hours after surgery.
    - Notably at 24 h postoperatively, no subjects reported POST in the treatment group while 45% of subjects reported POST in the group receiving the placebo.

• **Aspirin**
  - Widely used anti-inflammatory has been used in a gargle to relieve pain due to oral lesions.
  - Gargling with 30 mL of distilled water containing 350 mg of aspirin was reported to significantly reduce the incidence of POST.
  - While the subject was in the post anesthesia care unit at 2 hours, but not at 4 and 24 h postoperatively.
  - No side effects were reported.
  - The widely used anti-inflammatory has been used in a gargle to relieve pain due to oral lesions.

• **Dexpanthenol**
  - Applied topically is reported to have anti-inflammatory properties.
  - Acts as a moisturizer, improving skin hydration.
  - Subjects who preoperatively sucked on Pastilles containing 200 mg of dexpanthenol.
  - Investigators reported significantly less POST at all intervals up to 24 h when compared to both placebo and oral benzydamine spray.
  - The investigators theorized a greater positive effect would have been observed if a larger dose was administered (six rather than two pastilles).
  - The drug is marketed for topical but not for oral use in the United States.

• **Licorice**
  - Licorice contains a number of ingredients.
  - Many of these including glycyrrhizin, liquiritin, and glabridin are reported to have anti-inflammatory and anti-allergen, peripheral and central antitussive properties, and ulcer-healing properties, respectively.
  - Subjects gargled with 0.5 g of licorice in 30 mL of water.
  - The incidence of POST was reported to be reduced by more than half at all evaluation intervals.
  - Subjects all underwent lumbar laminectomy in the prone position.
  - No severe side effects were reported.
The researchers noted N, preoperatively Ketamine 50 mg Subjects Number Hours Comments

A similar reduction Hours Serum magnesium levels in subjects in the treatment group were unchanged compared with the control However They Ketamine 40 mg However - Comments The researchers Investigators 14% of Number There 17 (74%)

Amyl-m-cresol

- The researchers noted these lozenges have been used successfully to treat patients with oral inflammatory diseases and before oral surgery and suggest amyl-m-cresol produces an anti-inflammatory effect.
- Investigators examined the use of a lozenge commercially only available over-the-counter outside of the United States (Strepsils lozenges, Kingston-upon-Thames, UK) containing amyl-m-cresol
- 14% of subjects complained of POST in the PACU compared with 33% of subjects receiving a placebo (P < 0.05)
- A similar reduction was seen 24 h postoperatively
- The lozenges were well tolerated by all subjects.

**RESULTS**

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**POST**

Magnesium

- The researchers indicated the mechanism of action of magnesium for reducing inflammation is thought to be via reducing the release of mediators of inflammation including histamine, leukotrienes, and thromboxanes. Magnesium may also antagonize NMDA receptors.
- They theorized the effect of magnesium was due to direct contact of magnesium ions with the pharyngeal wall
- There was a significantly decreased incidence of POST when subjects sucked on a lozenge containing magnesium --- preoperatively at 2 h and 4 h, but not immediately or 24 h postoperatively
- Preoperatively at 2 and 4 h but not immediately or 24 h postoperatively
- Subjects reported no local or systemic side effects.

<table>
<thead>
<tr>
<th>Evidence source</th>
<th>n</th>
<th>Intervention</th>
<th>Controla</th>
<th>POST incidence in treatment group</th>
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<tbody>
<tr>
<td>Rudra et al. (2008)</td>
<td>40</td>
<td>Ketamine 50 mg (in 30 mL saline) gargled for 30 s, 5 min prior to induction of general anesthesia</td>
<td>Saline gargle</td>
<td>N = 20 4 h 17 (85%) 8 h 15 (75%) 24 h 12 (60%) 6 h 8 (40%) 8 h 7 (35%) 24 h 5 (25%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>N = 20 4 h 15 (75%) 8 h 12 (60%) 24 h 10 (50%)</td>
<td></td>
<td>No significant difference in age, height, weight, gender and duration of surgery between groups Unable to blind subjects, only mention of observer blinding ETT cuff pressure and monitoring intermittently No, OG, HME, ETT tube lubrication, NMB used, incidence of coughing prior to extubation not reported</td>
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<td>Sheela et al. (2010)</td>
<td>40</td>
<td>Ketamine 50 mg (in 30 mL saline) gargled for 30 s, 5 min prior to induction of general anesthesia</td>
<td>Drinking water gargle</td>
<td>N = 20 4 h 15 (75%) 8 h 12 (60%) 24 h 10 (50%)</td>
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<td>No significant difference between groups in gender, weight, duration of surgery. Smoking history not reported Method of sample size determination not reported Unable to blind subjects, only mention of observer blinding ETT cuff pressure and monitoring not reported NG, OG, HME, oral airway used; coughing prior to extubation not reported</td>
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Investigators examined the effects of gargling solutions on postoperative sore throat (SPT) incidence. The study included two groups: one gargled solutions and the other did not. The solutions included saline, tap water, and various medications.

- **Sodium Benzydamine**: Gargled solutions of sodium benzydamine were compared to saline for their effect on SPT incidence. The study found a significant reduction in SPT incidence when sodium benzydamine was gargled.

- **Aspirin 350 mg**: A 350 mg aspirin paste was administered in 30 mL saline and gargled for 30 s, 5 min prior to induction of general anesthesia. This treatment significantly reduced SPT incidence.

- **Dexpanthenol Gargle**: Gargling solutions of dexpanthenol were compared to saline. The results showed a significant reduction in SPT incidence when dexpanthenol was gargled.

- **Mineral Water Gargle**: Gargling with mineral water significantly reduced SPT incidence compared to saline gargling.

- **Distilled Water Gargle**: Gargling with distilled water also significantly reduced SPT incidence.

In summary, the study concluded that gargling solutions can significantly reduce the incidence of postoperative sore throat, with sodium benzydamine, aspirin paste, dexpanthenol, and mineral water showing the most effective results.

**POST**

- Postoperative sore throat, a usually self-limiting complication, continues to be an important concern for the surgical patient undergoing endotracheal intubation.

- Steps should be taken to help lessen the risk of POST including:
  - avoiding a preoperative antihistamine if feasible
  - avoiding trauma during laryngoscopy and intubation
  - using an appropriate ETT size
  - perhaps lubricating the cuff of the ETT with a water soluble jelly
  - using the appropriate ETT cuff pressure and monitoring the cuff pressure
  - avoiding the use of a non– or organic-based tube if possible
  - carefully suctioning the oropharynx prior to extubation
  - and taking steps to reduce the risk of the patient coughing or bucking prior to extubation

**POST**

- Despite taking these steps, patients may suffer POST
- Local anesthetics and steroids might be considered to help decrease the incidence of POST
- Would be attractive to have an inexpensive, quick, convenient, and easy-to-administer medication that the patient could take immediately prior to induction of general anesthesia to help decrease this complication

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<td>Li et al. (2010)</td>
<td>34</td>
<td>Librox containing amphotericin B 0.6 mg and 45% dextrose prior to induction of general anesthesia</td>
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<td>Hortepcan et al. (2012)</td>
<td>35</td>
<td>Librox containing 600 mg magnesium citrate salt, 45% dextrose prior to induction of general anesthesia</td>
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*Evidence table indicates only the group's characteristics, not the controls.*  

- **ETT, endotracheal tube; HME, heat and moisture exchanger; NG, nasogastric tube; POST, postoperative sore throat; VAS, visual analog scale**

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<td>Agur et al. (2009)</td>
<td>35</td>
<td>Librox containing 0.5 g (in 30 mL water) gargled 45 min prior to induction of general anesthesia</td>
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POST

- Of the medications found for this review, preoperative ketamine and aspirin gargle are probably the most promising for providers practicing in the United States.
  - However, before these agents are recommended for general use, large multicenter trials should be done exploring not only efficacy but also dose-response relationships and potential side effects.
- For those medications not available in the United States (Sodium azulene sulfonate), studies should continue and we should be aware of work being done with these agents.
  - Hopefully these drugs will be approved for use in the United States if found to be safe and effective.