Impact of Haloperidol as Adjunct Therapy in Patients with Intractable Migraine

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Disclosure

• No financial or conflict of interest to disclose
Objectives

1. Discuss pathophysiology of migraine and dopamine involvement

2. Review current literature for the utilization of haloperidol in the treatment of migraine

3. Evaluate efficacy of haloperidol use in patients with intractable migraine
BACKGROUND
Prevalence

- 3 billion individuals worldwide have migraine
- 25% of U.S. households estimated to have ≥ 1 member with migraine
- Prevalence higher in women between ages 15-49
- Often observe treatment failure despite optimal analgesic regimens
Dopamine Involvement

- D₂ receptors have been associated with hemodynamic responses with migraine
- D₁ receptors can induce cranial vasodilation
Haloperidol

• First generation antipsychotic

• Dopamine receptor antagonist (mainly D₂)

• Available dosage forms: oral, IV, IM

• Theorized benefit for migraine – D₂ receptor blockade and reduction of intracranial vasospasms
Impact of Haloperidol as Adjunct Therapy in Patients with Intractable Migraine
Purpose

• To assess the efficacy of haloperidol as adjunctive therapy to dihydroergotamine (DHE) per the Raskin Protocol in patients with intractable migraine
Design

• Retrospective, cohort study
  – December 1\textsuperscript{st}, 2017 to March 1\textsuperscript{st}, 2020

• Comparative groups:
  – Haloperidol with DHE vs. DHE

• Patients matched in a 1:1 ratio based on:
  – Age and gender
  – Total amount of DHE, metoclopramide, and glucocorticoid used
## Study Population

### Inclusion Criteria
- Age $\geq 18$ years
- Intractable migraine per ICHD-3 definition
- Length of stay $\geq 24$ hours
- Received DHE per the Raskin Protocol

### Exclusion Criteria
- Pregnancy
- QTc $\geq 450$ms
- Parkinson disease
- Sepsis
- Dementia with Lewy bodies
- Uncontrolled hypertension
Study Outcomes

• Primary
  – Mean reduction in pain score

• Secondary
  – Hospital length of stay
  – Time to significant pain relief
  – Pain reduction ≥ 50% from admission
  – Rescue medication and opioid usage
  – 7-day readmission rate
Study Outcomes

• Safety
  – Any adverse effects associated with haloperidol

• Subgroup analysis
  – Mean pain reduction of oral vs. IV haloperidol
Statistical Analysis

• Sample size calculation:
  – 70 patients for 60% decrease in numeric rating scale
  – Power of 80% and significance level of 5%

• Continuous data – Unpaired Student’s t-test
• Discrete data – Chi-squared or Fisher’s exact test
• SPSS version 24.0
RESULTS
Participants

- Total number of patients screened: n = 158

- Post-match final cohort: n = 70
  - Haloperidol with DHE: n = 35
  - DHE: n = 35
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Haloperidol + DHE (n = 35)</th>
<th>DHE (n = 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yrs±</td>
<td>45.0 (36.5 – 53.0)</td>
<td>42.0 (36.5 – 53.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>31 (88.6)</td>
<td>31 (88.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI – kg/m²±</td>
<td>32.7 (27.2 – 34.0)</td>
<td>33.1 (27.3 – 35.6)</td>
<td>0.87</td>
</tr>
<tr>
<td>Metoclopramide Doses – no. ±</td>
<td>1.0 (0 – 4.5)</td>
<td>1.0 (0 – 3.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>Admission Pain Score – no. ±</td>
<td>8.0 (7.0 – 9.0)</td>
<td>8.0 (7.0 – 9.0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

± median (IQR)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Haloperidol + DHE (n = 35)</th>
<th>DHE (n = 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHE Dosage – mg.±</td>
<td>7.0 (5.0 – 10.0)</td>
<td>6.5 (4.0 – 9.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Magnesium Used – no. (%)</td>
<td>35 (100.0)</td>
<td>24 (68.6)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Valproic Acid Used – no. (%)</td>
<td>13 (37.1)</td>
<td>18 (51.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Prednisone Dosage – mg.±</td>
<td>133.0 (6.3 – 200.0)</td>
<td>200.0 (0 – 2500.0)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

± median (IQR)
Baseline Haloperidol Characteristics

- Dosage forms
  - Oral (15), IV (12), oral and IV (8)
- Median time to first haloperidol administration
  - 10.5 hrs (IQR 6.1 – 18.9 hrs)
- Median dose of haloperidol
  - 2 mg (IQR 2.0 – 5.0 mg)
Dopamine Antagonists Continued Inpatient

<table>
<thead>
<tr>
<th>Medication – no. (%)</th>
<th>Haloperidol + DHE (n = 35)</th>
<th>DHE (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (2.9)</td>
<td>6 (17.1)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2 (5.7)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Brexipiprazole</td>
<td>0</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>1 (2.9)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>3 (8.6)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
</tbody>
</table>
Primary Endpoint

- Mean reduction in pain score
  - Haloperidol with DHE vs. DHE
  - 4.7 vs. 5.4, $p = 0.31$
### Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Haloperidol + DHE (n=35)</th>
<th>DHE (n=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Hospital Stay, hr.</td>
<td>82.5</td>
<td>77.5</td>
<td>0.60</td>
</tr>
<tr>
<td>Pain Reduction ≥ 50% Achieved, no.</td>
<td>32</td>
<td>31</td>
<td>1.00</td>
</tr>
<tr>
<td>Doses of non-opioid Rescue Medications, no.</td>
<td>4.3</td>
<td>2.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Total MME± Used, mg.</td>
<td>14.3</td>
<td>11.2</td>
<td>0.67</td>
</tr>
<tr>
<td>Time to Significant Pain relief, hr.</td>
<td>44.1</td>
<td>49.3</td>
<td>0.56</td>
</tr>
<tr>
<td>7-day Readmission, n.</td>
<td>3</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

± MME – morphine milligram equivalence
Safety Endpoint

• Adverse events include:
  – Dizziness, drowsiness, dystonia, akathisia, etc.

• No adverse effects associated with haloperidol were observed
Oral vs. IV Haloperidol

- Oral = 15, IV = 10
- Median dose (mg):
  - Oral, 2.0 (IQR 1.0 – 5.5)
  - IV, 3.0 (IQR 2.0 – 4.5)
- Mean pain reduction
  - Oral vs. IV
  - 5.2 vs. 4.2, p = 0.32
Conclusion

• Use of haloperidol as adjunctive therapy to DHE did not provide additional statistically significant pain relief
Strengths

1. Premier trial to evaluate haloperidol with DHE
2. Oral and IV form of haloperidol analyzed
3. Adequate balance of baseline characteristics
4. Sample size met pre-determined power
Limitations

1. Potential for unmeasured confounding
2. Limited generalizability
3. Haloperidol not started on admission
4. No standardization of dose or route of administration
5. High prevalence of resistant migraine
6. Lower dose of haloperidol than previously studied
HALOPERIDOL IN THE ACUTE TREATMENT OF MIGRAINE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Background and Methods

• Objective – To assess the efficacy of IV haloperidol in the treatment of acute migraine
• Population – Adults with acute or prolonged migraine attack
• Intervention:
  – Haloperidol 5mg IV once
  – Placebo (normal saline)
• Primary outcome: Numeric pain score reduction

Results

• N = 40 patients
  – Haloperidol (20) vs. placebo (20)

• Baseline pain score:
  – 7.7 vs. 7.2

• Post-intervention pain score:
  – 2.2 vs 6.3, p<0.0001

• Common haloperidol-associated adverse effects:
  – Motor agitation (9) and sedation (9)
A RANDOMIZED CONTROLLED TRIAL OF INTRAVENOUS HALOPERIDOL VS. INTRAVENOUS METOCLOPRAMIDE FOR ACUTE MIGRAINE THERAPY IN THE EMERGENCY DEPARTMENT

Background and Methods

- **Objective** – Assess the efficacy of haloperidol in acute migraine
- **Population** – Adults with typical migraine headache
- **Intervention:**
  - Haloperidol 5mg IV once
  - Metoclopramide 10mg IV once
- **Primary outcome:** Numeric pain score reduction per 100 mm visual analogue scale (VAS)

Results

- N = 64
  - Haloperidol (33) vs. metoclopramide (31)
- Numeric pain score reduction:
  - 57 mm vs. 49 mm, p>0.05
- Rescue medication use:
  - 3% vs. 26%, p<0.02
- Adverse effects:
  - Sleepiness and nausea, (~67%)
Summary and Recommendation

• Low-dose haloperidol did not show increased pain relief efficacy when added to DHE

• Several limitations may contribute to non-significant results

• Considerations for future trials to assess efficacy of:
  1. Earlier time to haloperidol administration
  2. Higher dose of haloperidol
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