Riboflavin as Migraine Prophylaxis in Children and Adolescents: A Systematic Review of the Literature

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Introduction

Migraine headache is a common condition among children and the prevalence increases into adolescence.

- Migraine headaches are typically unilateral, pulsating, moderate to severe in intensity, made worse by physical activity and can be associated with nausea and vomiting, photophobia, and phonophobia.

- For a clinical problem so prevalent in children and adolescents, there is a disappointing lack of evidence from controlled, randomized, and masked trials” (Lewis et al., 2004, p. 2215).

- Several acute treatments exist for pediatric migraine but there are currently no medications with an FDA approved indication for migraine prophylaxis in children.

- The goal of preventive treatment is to reduce the frequency, severity, and duration of migraine episodes, to improve responsiveness to acute treatment, and to improve functioning and reduce disability.

- A number of supplements have been used for migraine prophylaxis, including riboflavin (vitamin B2), which has been shown in multiple trials to be effective for migraine prophylaxis in adults.

Purpose

- To perform a systematic review of the literature on the use of riboflavin for migraine prophylaxis in the pediatric population including children and adolescents.

- The quality of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group.

Method

- MEDLINE, CINAHL, Evidence Based Medicine Reviews Multifile, Web of Science, and PubMed were accessed through the Pacific University Library.
- Keyword search terms “migraine” and “riboflavin” searched in combination returned 242 articles.
- Search limits: human studies, articles published in English, published from 2000-2011; 139 articles
- Studies of adult patients, duplicates, descriptive reviews, and letters to the editor were excluded.
- Three studies pertaining to the use of riboflavin in children and adolescents for migraine prophylaxis are analyzed in this review.

Results

MacLennan et al. (2008)
- Double-blind randomized controlled trial (RCT), 48 subjects, 5-15 years old, 24 males and 24 females
- Performed in Australia, participants recruited primarily from school newsletters
- Riboflavin 200mg daily vs. placebo for 12 weeks
- No significant decrease in migraine frequency
- No significant decrease in migraine severity
- No significant decrease in migraine duration

Condo et al. (2009)
- Retrospective observational study, 41 participants 8-18 years old, 16 males and 25 females
- Performed in Italy at an outpatient specialty university clinic
- Riboflavin 200mg daily vs. 400mg daily for 3, 4, or 6 months
- Significant decrease in migraine frequency
- Significant decrease in migraine severity
- Increased response to symptomatic treatment
- Males under the age of 12 were most likely to receive benefit

Bruni et al. (2010)
- Double-blind, cross-over RCT, 42 participants, 6-13 years old, 24 males and 18 females
- Performed in the Netherlands, recruited by referral
- Riboflavin 50mg daily vs. placebo for 16 weeks
- No significant decrease in migraine frequency
- No significant decrease in migraine severity
- No significant decrease in migraine duration

Discussion

Limitations of Studies

- Terms “pediatric,” “children,” & “adolescents” not clearly defined
- All studies included patients with other headache types
- MacLennan et al. (2008)
  - Relatively small sample did not meet proposed sample of 56
  - Strict inclusion & exclusion criteria excluded 44 patients and may not represent average migraine patient
  - High placebo response rate, 66%
- Condo et al. (2009)
  - No placebo control group, cannot measure placebo response rate
  - Recommended immediate acute treatment during riboflavin phase
  - No blinding of patients or researchers
  - Included resistant migraine with failure of previous therapy
  - Relatively small sample size
- Bruni et al. (2010)
  - Riboflavin 50mg used despite negative results of MacLennan et al. (2008) at higher dose
  - No upper limit of headaches per month
  - Comparison between groups limited to last 4 weeks of treatment
  - Relatively small sample size

GRADE
- This tool provides a GRADE of the quality of evidence which explains how likely future research is to change the effect or confidence in the effect.

GRADE (Continued)

- A GRADE of high, moderate, low, or very low is assigned to the evidence
  - High Quality: Further research is very unlikely to change our confidence in the estimate of effect
  - Moderate Quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
  - Low Quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
  - Very Low Quality: Any estimate of effect is very uncertain

Table 1: GRADE Table

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Findings</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>GRADE of Evidence by Study Types</th>
<th>GRADE of Evidence by Outcome</th>
<th>Overall GRADE of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riboflavin 200mg</td>
<td>Migraine frequency</td>
<td>RCT</td>
<td>No change</td>
<td>High</td>
<td>-1</td>
<td>0</td>
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<tr>
<td>1 Obs</td>
<td>Migraine severity</td>
<td>RCT</td>
<td>No change</td>
<td>High</td>
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<tr>
<td>1 Obs</td>
<td>Migraine duration</td>
<td>RCT</td>
<td>No Change</td>
<td>High</td>
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</table>

GRADE of Recommendations

- Migraine Frequency
  - Starting GRADE High for RCTs, Low for Obs. study
  - RCTs downgraded for study quality & consistency
  - End GRADE Low

- Migraine Severity
  - Starting GRADE High for RCTs, Low for Obs. study
  - RCTs downgraded for study quality & consistency
  - End GRADE Low

- Migraine Duration
  - Starting GRADE High for RCTs
  - RCTs downgraded for study quality & consistency
  - End GRADE Moderate

- Overall GRADE is Low which suggests further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Conclusion

- There is currently low quality evidence supporting the use of riboflavin as migraine prophylaxis in children and adolescents and only a weak recommendation can be made for its use.

- Future research should:
  - Utilize high quality RCTs with large sample size in cross-over or parallel group design
  - Test riboflavin 200mg, 300mg, 400mg daily, or higher dose, alone or in combination
  - Consider investigating the use of a weight based dose in the pediatric population
  - Investigate potential difference between diagnostic criteria of migraine used clinically and in research