RCT
Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

A. Citiation: Kurian A, Reghunadhan I, Thilak P, Soman I, Nair U. Short-term Efficacy and Safety of Topical β-Blockers (Timolol Maleate Ophthalmic Solution, 0.5%) in Acute Migraine: A Randomized Crossover Trial. JAMA Ophthalmol. 2020;138(11):1160-1166. doi:10.1001/jamaophthalmol.2020.3676
B. Link to PubMed Abstract: https://pubmed.ncbi.nlm.nih.gov/33001159/
C. First date published study available to readers: 11/1/2020
D. PubMed ID: 33001159
E. Nominated By: Jim Stevermer
F. Institutional Affiliation of Nominator: MO – University of Missouri-Columbia
G. Date Nominated: 10/12/2020
H. Identified Through: JAMA Ophthalmol
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 10/22/2020
K. Potential PURL Review Form (PPRF) Type: RCT

A. Abstract: **Importance: Oral β-blockers used for the prevention of migraine headache are not effective for the treatment of acute pain. Small case series have suggested that topically applied β-blockers may be useful in the management of acute migraine pain, warranting evaluation with randomized clinical trials.**

Objective: To evaluate the short-term efficacy and safety of topically applied timolol maleate ophthalmic solution, 0.5%, compared with topically applied placebo eyedrops in the treatment of acute migraine attacks.

Design, setting, and participants: In this randomized, masked placebo-controlled crossover trial conducted from May 27, 2015, to August 28, 2017, 50 patients with migraine were randomized to receive either timolol eyedrops, 0.5%, or a placebo eyedrop (carboxymethyl cellulose, 0.5%). After a 3-month treatment period, patients completed a 1-month washout period and were crossed over to receive the opposite treatment for a final 3 months. Analysis was performed on a modified intent-to-treat basis.

Intervention: After random assignment, patients were instructed to use 1 drop of the assigned medication in each eye at the earliest onset of migraine.

Main outcomes and measures: The main outcome measure was reduction in pain score with treatment. The primary end point was reduction of pain score by 4 points, or to zero, 20 minutes after instillation of the eyedrop.

Results: Of the 50 patients, 42 (84%) were females and the mean (SD) age was 27.3 (11.3) years. Of a total of 619 migraine attacks, 284 (46%) were treated with timolol, 271 (44%) were treated with the placebo, and 64 (10%) occurred during the washout period when no study medications were used. Seven patients (14%) withdrew after randomization. A total of 233 of the timolol-treated migraine attacks (82%) were associated with a reduction in pain score by 4 points, or to zero, at 20 minutes compared with 38 of the placebo-treated attacks (14%), with a difference of 68 percentage points (95% CI, 62-74 percentage points). A generalized estimating equation analysis revealed that pain score reduction at 20 minutes was greater in the timolol group compared with the placebo group by a mean (SE) of 4.63 points (0.34) (P < .001).

Conclusions and relevance: This randomized crossover trial supports consideration of timolol eyedrops in the acute treatment of migraine. Further research is warranted to determine if the improvements observed are sustained for a longer follow-up and with larger groups.

B. Pending PURL Review Date**:** 7/6/2021

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. Number of patients starting each arm of the study?
25 patients randomized to each group. 20 patients were analyzed in Group A and 23 analyzed in Group B.

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
Patients at least 12 years old, clinical diagnosis of migraine, not taking any antimigraine medications for at least 1 month

C. Intervention(s) being investigated?
allocated to group A (treatment group: timolol maleate, 0.5%, plus hydroxypropyl methylcellulose, 0.3%, eyedrops; 1 drop of 0.5% timolol ophthalmic solution contains 0.25 mg of the drug)

D. Comparison treatment(s), placebo, or nothing?
group B (control group: placebo eyedrops; carboxymethyl cellulose, 0.5%, eyedrops, which are artificial tears often used over the counter for treatment of dry eye disease)

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)

7 months.

F. What outcome measures are used? List all that assess effectiveness.
The primary end point was reduction of the pain score by 4 points, or to zero, 20 minutes after instillation of the eyedrop. The secondary end point was nonuse of an oral rescue medication. A reduction in pain score to 0 or of at least 4 points on the pain scale when measured at 2 minutes, without the use of any oral rescue medication, was considered a potentially clinically relevant outcome.

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.
A total of 233 of the timolol-treated migraine attacks (82%) were associated with a reduction in pain score by 4 points, or to zero, at 20 minutes compared with 38 of the placebo-treated attacks (14%), with a difference of 68 percentage points (95%CI, 62-74 percentage points). A generalized estimating equation analysis revealed that pain score reduction at 20 minutes was greater in the timolol group compared with the placebo group by a mean (SE) of 4.63 points (0.34) ($P < .001$).

H. What are the adverse effects of intervention compared with no intervention?
No adverse events were seen.

I. The study addresses an appropriate and clearly focused question.
(select one) Well covered

Comments:

J. Random allocation to comparison groups:
(select one) Well covered

Comments:

K. Concealed allocation to comparison groups:
(select one) Well covered

Comments: cross over trial

L. Subjects and investigators kept “blind” to comparison group allocation:
(select one) Well covered

Comments:

M. Comparison groups are similar at the start of the trial:
(select one) Well covered
Comments: cross over trial design

N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential sources of bias. (select one) Adequately addressed
Comments:

O. Were all relevant outcomes measured in a standardized, valid, and reliable way?

(select one) Well covered
Comments:

P. Are patient oriented outcomes included? If yes, what are they?
Yes migraine pain scores.

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
Looks like a total of 7 people were excluded (7 with no post-baseline measurements) likely not to impact results much as patients were crossed over.

R. Was there an intention-to-treat analysis? If not, could this bias the results? How?
Yes, it was modified with only those who had post-baseline data available.

S. If a multi-site study, are results comparable for all sites?
n/a

T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?
n/a

U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.
Patients in primary care or neurology.

V. In what care settings might the finding apply, or not apply?
Primary care or neurology offices.

W. To which clinicians or policy makers might the finding be relevant?
As above

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions:

For up-to-date citations, use style modified the AMA style. For example:
Norton JM, Bavendam TG, Elwood W, et al. Research needs to understand self-management of lower urinary tract symptoms: summary of NIDDK workshop. *J Urol*. 2018;199(6):1408-1410. doi:10.1016/j.juro.2017.11.079

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham,Mass: UpToDate; 2009. Available at: https://www.uptodate.com/login. {Insert date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at https://www.dynamed.com/. Last

updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

Management

- Response to acute medication is patient-specific and several medications may need to be trialed before successful management is achieved.
- Advise the patient to use acute medication as early as possible during migraine attack (while pain is still mild), unless at risk for medication overuse headache.
- For mild-to-moderate migraine attacks, simple analgesics are recommended, including (Strong recommendation):
  - aspirin 900-1,000 mg orally (tablet or effervescent)
    - consider avoiding during pregnancy and do not use during third trimester
  - ibuprofen 400 mg orally
  - acetaminophen 1,000 mg orally
  - naproxen 500-550 mg orally (immediate-release tablet)
  - diclofenac potassium 50 mg orally (tablet or powder for oral solution)
- For moderate-to-severe migraine attacks, triptans are recommended. (Strong recommendation)
  - First choice is sumatriptan 50-100 mg orally.
  - If sumatriptan is not effective, other triptans should be offered, such as almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan.
  - Exercise caution to minimize use of adverse events associated with triptans.
    - Limit triptan use to ≤ 9 days/month to avoid medication overuse headache.
    - Potential adverse effects to the fetus in animal studies, but evidence in humans is limited. Consider in pregnant women with severe migraine if potential benefits outweigh harms.
  - Contraindications to use of triptans include:
    - ischemic heart disease, previous myocardial infarction, coronary vasospasm, cerebral or peripheral vascular disease, or severe or uncontrolled hypertension
    - use within 24 hours of using another triptan or an ergot derivative (due to possibility of additive vasoconstriction)
- For patients with nausea and/or vomiting:
  - give adjunct metoclopramide 10 mg or prochlorperazine 10 mg orally or parenteral administration. (Strong recommendation)
  - consider nonoral routes of administration such as injection, nasal spray, and orally disintegrating tablets.
- Avoid routine use of oral opioids, including codeine, due to lack of superiority to other acute medications, risk of abuse/dependence, potential medication overuse headache, and withdrawal concerns. (Strong recommendation)
- Discuss a rescue therapy plan with patients with severe migraine attacks whose regular acute medication does not consistently provide adequate headache relief.
  - For patients presenting to the emergency department, consider (Weak recommendation):
    - IV metoclopramide 10-20 mg.

        - IV prochlorperazine 10 mg.
        - Subcutaneous sumatriptan 6 mg (however, avoid in patients who have had ergotamine, dihydroergotamine, or a triptan within the past 24 hours).
    - For patients who normally take nonsteroidal anti-inflammatory drugs (NSAIDs), consider triptans as rescue therapy.
    - For patients who normally take triptans, medications from another drug class are recommended as rescue therapy, including:
        - NSAIDs.
        - dopamine antagonists.
        - dihydroergotamine (Weak recommendation), however may not be used within 24 hours of triptans.
        - corticosteroids .
        - opioids and opioid-containing combination analgesics. (Weak recommendation)
            - Consider as rescue medication only if triptans and/or NSAIDs are ineffective or contraindicated.
            - Closely monitor use with headache diary and prescription monitoring.
            - Avoid combination analgesics with barbiturates due to risks of sedation, cognitive adverse events, and medication overuse headache.
- Evidence is limited for nonpharmacologic therapies; some that may reduce symptoms include acupuncture, oxygen therapy, transcranial magnetic stimulation, electrical stimulation, and cold neck wrap.
- For treatment of acute menstrual migraine:
    - triptans are recommended as first-line treatment. (Strong recommendation)
    - acute treatment of menstrual migraine is similar to acute treatment of attacks during other times of menstrual cycle.

B. Migraine- Treatment of Acute Attacks in Adults. Kriegler JS. In: DynaMed [database online]. Available at: www.dynamed.com. Access date: August 2, 2021. Last Updated: June 29, 2021.

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
No mention of timolol.

D. UpToDate excerpts
SUMMARY AND RECOMMENDATIONS

●Approach to treatment – Abortive treatments are usually more effective if they are given early in the course of the headache; a large single dose tends to work better than repetitive small doses. For patients who present with significant nausea or vomiting, a nonoral (eg, intravenous, intramuscular, or subcutaneous) agent may be preferred. (See 'Approach to treatment' above.)

●Patients with mild to moderate migraine attacks – For patients with mild to moderate migraine attacks not associated with vomiting or severe nausea, we suggest initial treatment with simple analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, rather than migraine-specific agents (Grade 2C). (See 'Mild to moderate attacks' above and 'Simple analgesics' above.)

For patients unresponsive to analgesics, the combined use of an NSAID with a triptan may be effective. When attacks are associated with severe nausea or vomiting, an antiemetic drug can be used along with analgesics. (See 'Triptans with NSAIDs' above and 'Antiemetics' above and 'Simple analgesics' above.)

●Patients with moderate to severe migraine attacks – For patients with moderate to severe migraine attacks, we suggest treatment with a triptan or the combination of sumatriptan-naproxen, rather than other migraine-specific agents (Grade 2C). Patients who do not respond well to one triptan may respond to a different triptan. (See 'Moderate to severe attacks' above and 'Triptans' above and 'Triptans with NSAIDs' above.)

Alternative options include calcitonin gene-related peptide (CGRP) antagonists, lasmiditan, antiemetic drug, and dihydroergotamine. (See 'CGRP antagonists' above and 'Lasmiditan' above and 'Antiemetics' above and 'Ergots' above.)

●Patients with severe migraine attacks in an emergency department – For patients with refractory migraine attacks who present to the hospital emergency department (ED), we suggest initial treatment with either subcutaneous sumatriptan or a parenteral antiemetic agent rather than other migraine-specific drugs (Grade 2C). When giving intravenous (IV) metoclopramide or prochlorperazine for migraine, we suggest adjunctive use of diphenhydramine to prevent akathisia and other dystonic reactions (Grade 2C). (See 'Emergency settings' above and 'Triptans' above and 'Antiemetics' above.)

In addition, we recommend adjunctive treatment with IV or intramuscular dexamethasone to reduce the risk of early headache recurrence (Grade 1B). (See 'Abortive therapy plus parenteral dexamethasone' above.)

For patients in the ED unresponsive or unable to tolerate triptans or antiemetics, IV dihydroergotamine (DHE 45) 1 mg combined with IV metoclopramide 10 mg is a reasonable alternative. DHE 45 is contraindicated in patients with ischemic vascular disease. (See 'Dihydroergotamine' above.)

●Status migrainosus – For patients with status migrainosus (ie, a debilitating attack lasting for more than 72 hours), we suggest a combination of intravenous fluids plus parenteral medications, including ketorolac and a dopamine receptor blocker (eg, prochlorperazine, metoclopramide, chlorpromazine) (Grade 2C). Other options include valproate and/or dihydroergotamine; some patients may require admission for persistent disabling symptoms. (See 'Status migrainosus' above.)

●Prophylactic treatment – Prophylactic headache treatment is indicated if the headaches are frequent, long lasting, or account for a significant amount of total disability. This topic is discussed separately. (See "Preventive treatment of episodic migraine in adults".)

E. UpToDate citation. Schwedt T, et al. Acute treatment of migraine in adults. In Basow DS, 2021; UpToDate [database online]. Available at www.uptodate.com. Last updated: July 2021. Accessed: August 2, 2021.

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

No comments about opt timolol use.

G. Other excerpts (USPSTF; other guidelines; etc.)

H. Citations for other excerpts

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

A. **Validity**: Are the findings scientifically valid? Yes

B. If **A** was coded "Other, explain or No", please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

C. **Relevance**: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?
Yes

D. If **C** was coded "Other, explain or No", please provide an explanation.

E. **Practice changing potential**: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?
Yes

F. If **E** was coded as "Yes", please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.
Timolol eye drops taken orally are a cheap, safe, easy way to treat acute migraine attacks.

G. **Applicability to a Family Medical Care Setting**:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? Yes

H. Please explain your answer to **G**.
Family medicine providers see a fair amount of patients with acute migraines in the primary care setting and some abortive treatments are ineffective for patients.

I. **Immediacy of Implementation**:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? Yes

J. If **I** was coded "Other, explain or No", please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes**:
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?
Yes

L. If **K** was coded "Other, explain or No", please explain why.

M. In your opinion, is this a pending PURL? Yes

1. Valid: Strong internal scientific validity; the findings appear to be true.

2. Relevant: Relevant to the practice of family medicine.

3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.

4. Applicability in medical setting.

5. Immediacy of implementation

N. Comments on your response for question M.
Our group feels that the accessibility, cost, and ease of use of timolol eye drops elevates this information to a PURL.