Propofol for the Abortive Treatment of Adult Migraine Headache in the Emergency Department

Amber Kuklinski
Pacific University
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Abstract

Background: Migraine headache is a debilitating disorder that is difficult to manage and is often treated in the emergency department (ED). Many standard abortive therapies used in the ED have mixed efficacy and lead to unsatisfactory results. Propofol is a proposed treatment for acute migraine with the potential to have better efficacy than standard ED abortive medications. This review evaluates propofol's effectiveness at reducing pain severity and headache recurrence in adult patients with migraine headache when compared to typical abortive therapies.

Methods: An exhaustive search of medical literature was completed using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science. Key words used included: propofol, migraine, and headache. Relevant articles were assessed for quality using GRADE.

Results: Twenty-two articles were reviewed for relevancy. Two randomized, double blind studies met inclusion criteria and were included in this systematic review. The first randomized, double blind trial was conducted in an ED and demonstrated a significant decrease in pain severity, nausea and vomiting, and headache relapse within 24 hours when compared to sumatriptan. The second randomized, double blind trial was conducted in an ED and demonstrated a significant decrease in pain severity when compared to dexamethasone. Both studies revealed a significantly faster rate of pain severity reduction when compared to sumatriptan and dexamethasone.

Conclusion: Propofol can be an ideal abortive therapy for acute migraine in the ED. It has been shown to be more effective than sumatriptan and dexamethasone at treating migraine headache. More research is needed to compare propofol's efficacy to these and other accepted abortive therapies.

Keywords: Propofol, migraine, headache, emergency department

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Propofol for the Abortive Treatment of Adult Migraine Headache in the Emergency Department

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Faculty Advisor: Mark Pedemonte, MD
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Biography
Amber Kuklinski is a native of Wisconsin and graduated from the University of Wisconsin Stevens Point in 2011 with a double major in Biology and Biochemistry. While at UWSP, she worked as a genetic research assistant and as a certified nursing assistant. After completion of her Bachelor of Science degree, she moved to Minnesota where she worked as an Emergency Medicine Technician for two years prior to starting PA school.
Abstract

**Background:** Migraine headache is a debilitating disorder that is difficult to manage and is often treated in the emergency department (ED). Many standard abortive therapies used in the ED have mixed efficacy and lead to unsatisfactory results. Propofol is a proposed treatment for acute migraine with the potential to have better efficacy than standard ED abortive medications. This review evaluates propofol’s effectiveness at reducing pain severity and headache recurrence in adult patients with migraine headache when compared to typical abortive therapies.

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**Keywords:** Propofol, migraine, headache, emergency department
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List of Abbreviations

CER  Comparative Effectiveness Review
ED   Emergency Department
GABA_A Gamma aminobutyric acid A
GRADE Grading of Recommendations, Assessment, Development, and Evaluations
IHS  International Headache Society
IV   Intravenous
LOS  Length of stay
NS   Normal Saline
RCT  Randomized Control Trial
VAS  Visual Analogue Scale
WHO  World Health Organization
Propofol for the Abortive Treatment of Adult Migraine Headache in the Emergency Department

BACKGROUND

Migraine headaches are a common neurological disorder that can result in debilitating symptoms. It affects 18% of females and 7% of males in the United States with the highest prevalence between the ages of 35-45 years. The majority of migraine sufferers report functional and cognitive impairment due to their headaches and on average lose 20 days of work and productivity each year. Migraine headaches have become the 19th most disabling disorder worldwide according to the World Health Organization (WHO). Many persons with migraine will visit the emergency department (ED) for relief of their symptoms not abated by standard outpatient therapies. Migraine cases represent 2.2% of all ED visits. Current recommended ED abortive therapies include medications in the triptan class, antiemetics such as prochlorperazine and metoclopramide, dexamethasone, and more. Unfortunately, these current treatments have unwanted side effects, mixed efficacy, and up to 49% recurrence rate after treatment which is problematic for already congested EDs and for patients who have sought out effective treatment.

Current abortive treatments are not always effective for migraine sufferers because the mechanism of a migraine headache is not fully understood. Research has proven that multiple components including the central and peripheral nervous systems, the trigeminovascular system, the cerebral cortex, and vasculature of the meningeal and extra-cranial arteries all play a role in the initiation and continuation of a migraine. This evidence compels researchers to continue to search for more effective treatments for those patients who do not adequately respond to current abortive therapies.
Triptans are a family of tryptamine based medications that function by targeting and agonizing 5HT 1b/1d receptors which inhibit release of vasoactive neuropeptides, inhibit pain pathways within the trigeminocervical complex, and decrease nociceptive neurotransmission.\textsuperscript{9,10} Clinical success rate has been reported between 70-80%.\textsuperscript{11} A comparative effectiveness review (CER)\textsuperscript{12} found triptans to have a mean difference of pain intensity reduction versus placebo on a visual analog scale (VAS) of 15%. Triptan use in the ED is limited. It is estimated that 25% of patients will be non-responders and that up to 40% will have recurrence of their headache within 24 hours.\textsuperscript{13} Triptans also have unwanted side effects such as nausea and vomiting, paresthesias, and injection site reactions. Treatment with this drug class is also contraindicated in persons with cardiovascular disease, ischemic stroke, and pregnancy.\textsuperscript{6}

Prochlorperazine and metoclopramide are useful in migraine headaches because of their antiemetic properties. They decrease nausea and vomiting by antagonizing dopamine receptors and inhibiting stimulation of chemoreceptor triggerzones.\textsuperscript{11} Prochlorperazine and metoclopramide have also been found to reduce pain perception through their neuroleptic actions and central dopamine agonistic effects respectively.\textsuperscript{11,14} Prochlorperazine and metoclopramide have shown a clinical success rate of 67%-92% and 67% respectively.\textsuperscript{11} The CER\textsuperscript{12} found prochlorperazine and metoclopramide to have a mean difference of pain intensity reduction versus placebo on a VAS of 47% and 22% respectively. They also found that there was no significant difference in headache relapse when compared to placebo.\textsuperscript{12} These antiemetics have been proven to be useful in the ED but they also have unwanted side effects including sedation, postural hypotension, dystonia, and akathisia.\textsuperscript{6,11} It is highly recommended that diphenhydramine be administered simultaneously with both antiemetics to reduce possibility of akathisia.\textsuperscript{6}
Dexamethasone is a corticosteroid thought to be effective for migraine headache by its anti-inflammatory effects.\textsuperscript{15} It is believed to decrease perivascular neurogenic inflammation and central and peripheral sensitization.\textsuperscript{15} Oral steroids are commonly prescribed when the use of other abortive therapies have failed but studies suggest little benefit in initial pain reduction.\textsuperscript{15,16} Although, dexamethasone has proven beneficial in stopping recurrence of headache within 24-72 hours after initial treatment and should be administered before discharge from the ED.\textsuperscript{16} Dexamethasone has few serious side effects when administered in a one-time bolus form. These include hyperglycemia, mood disturbance, and insomnia.\textsuperscript{15} Patients were also found to be more likely to experience dizziness when compared to placebo.\textsuperscript{12}

A new proposed abortive treatment for acute migraine is the anesthetic agent, propofol. Propofol’s mechanism of action is through its agonist activity at gamma aminobutyric acid A (GABA\textsubscript{A}) beta 1 subunits, leading to hyperpolarization and inhibition of neuronal firing.\textsuperscript{17} It also has shown to enhance anti-nociceptive dorsal root potential by mediating depolarization of primary afferent nerve terminals and vasodilates vascular smooth muscle by modifying calcium dependent pathways.\textsuperscript{18,19}

Krusz et al\textsuperscript{17} published the first study of propofol use for migraine headache in 2000. The authors hypothesized that the GABAergic system may be in a low functional state during an intractable headache and that it may be overcome by stimulating the GABA\textsubscript{A} receptors.\textsuperscript{17} This study found that propofol, on average, reduced migraine headache pain severity on a VAS by 95.4\%.\textsuperscript{17} All cases of nausea and vomiting were completely resolved and only 4\% of patients had headache relapse within 24 hours.\textsuperscript{17} No significant adverse events except for transiently slurred speech or drowsiness were reported.\textsuperscript{17} Additional case studies\textsuperscript{20-23} have also proven propofol to be safe and effective at treating migraine headaches. Can propofol be more effective at reducing
pain intensity and headache relapse in adult patients with migraine headache when compared to current recommended abortive therapies in the emergency department?

**METHODS**

An exhaustive search of medical literature was completed using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science using the key words: propofol, migraine, and headache. These sources were then narrowed to only include articles which evaluated the treatment of migraine headache with propofol in adult patients. The bibliographies of these articles were further evaluated for relevant sources. Applicable articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)\textsuperscript{24}

**RESULTS**

The initial search yielded 22 articles for review. After screening the articles for relevant data two articles met inclusion criteria. Both of these articles were randomized controlled trials\textsuperscript{25,26} and can be seen in Table I.

**Moshtaghion et al**

This randomized, double blind study\textsuperscript{26} investigated the effectiveness of propofol versus sumatriptan in treating acute migraine headache pain intensity, nausea and vomiting, and the resulting adverse side effects. Minimum necessary calculated sample size was 45 participants in each group. There were 91 patients, between the ages of 18-45, who presented to the emergency department, met the International Headache Society (IHS) criteria for migraine, and were enrolled in this study. Exclusion criteria included pregnancy, coronary or vascular disease, allergy to the medication or its components, opium dependence, diastolic blood pressure > 105mm Hg, and the use of ergotamine or 5HT agonists within the past 24 hours.\textsuperscript{26}
Participants were randomly allocated into either Group 1: sumatriptan, or Group 2: propofol, using a random number table. The two treatment groups were prognostically balanced in demographic and baseline characteristics. The patients were assessed by an ED physician for headache severity using an 11-point VAS, as well for symptoms including nausea, vomiting, photophobia, and phonophobia before receiving treatment. The ED physicians were blinded to the patients’ assigned groups. All patients had an intravenous (IV) line established and were given a 500ml infusion of normal saline (NS). All syringes were wrapped so that the contents were indistinguishable by patients. All syringe contents were administered by an anesthesiology resident. Group 1 received 6mg of sumatriptan injected subcutaneously with an accompanying 3.5mL IV infusion of NS. An additional 1.5mL bolus of NS was administered every 4 minutes following the initial infusion up to a final dose of 7.5mL. Group 2 received 0.5mL of NS injected subcutaneously with an accompanying 30-40mg IV infusion of propofol. An additional 10-20mg bolus of propofol was administered every 3-5 minutes following the initial infusion up to a maximum dose of 120mg. Patients in group 2 were sedated to a Ramsey score of 3 to 4. If patients had persistent nausea or vomiting after treatment with either therapy, they were given a 1mg infusion of IV granisetron.²⁶

Each patient was reassessed for headache severity, improvement in accompanying symptoms, and adverse effects at 30 minutes, 60 minutes and 2 hours post treatment by the original ED physician who assessed them upon admission. Of the 91 patients enrolled in this study, one patient, in Group 1, could not complete the study due to severe chest tightness after administration of therapy. The remaining 90 patients were reassessed by phone call 24 hours later for headache recurrence.²⁶
Pain intensity in the propofol group was significantly lower at 30 minutes when compared to the sumatriptan group (P= 0.034). As well, the rate of pain intensity reduction in the propofol group was significantly faster (P= 0.002). However, pain intensity at 1 and 2 hours post therapy and response to therapy was similar in both groups (P= 0.53, 0.53, 0.78 respectively). Need for antiemetic therapy and the rate of headache recurrence was significantly lower in the propofol group (P= 0.045, 0.001). However, symptom improvement of photophobia and phonophobia at the time of discharge was not significantly different when compared to the sumatriptan group (P= 0.65, 0.29). Adverse effects including chest tightness and rash at injection site were also significantly lower in the propofol group (P= 0.001). No significant difference in hypotension and drowsiness was found when comparing the two groups. See Table II.

The main limitation mentioned in this study was the lack of a standard questionnaire used when assessing the patient for recurrence of their headache within 24 hours. In this study follow up was conducted by calling the patient and simply inquiring for headache recurrence.

Soleimanpour et al

This randomized, double blind clinical trial investigated the effectiveness of propofol versus dexamethasone in treating migraine headache pain intensity. Again, calculated sample size was 45 patients for each group. There were 90 patients, aged ≥ 18 years, who presented to the emergency department, met the IHS criteria for migraine, and were enrolled in this study. Exclusion criteria included a history of receiving prior abortive medications before presentation to the ED, allergy to the medications and its components, diabetes mellitus, active peptic ulcers, myocardial infarction within the last week, and familial hypokalemic periodic paralysis.

Participants were randomly allocated to either Group 1: propofol, or Group 2: dexamethasone, by picking a ballot. The two treatment groups were prognostically balanced in
demographics and baseline characteristics. The patients were assessed by a specialist for headache severity using a 10-point VAS, as well for symptoms of nausea and vomiting, photophobia, and phonophobia before receiving treatment. This specialist was blinded to the patient’s assigned group. All patients had an IV line established in their left hand. All injections were performed by the same specialist who assessed the patients’ headache severity. The injection performer was blinded to the type of injection the patient received by a curtain. All patients were blinded to the type of treatment they received as well. Group 1 received a 10mg IV infusion of propofol at a rate of 1mL per 10 seconds. An additional 10mg infusion of propofol was administered every 5-10 minutes following the initial bolus, up to a maximum dose of 80mg, until pain was reported as ≤ 2 on the VAS. To reduce possibility of pain at the injection site 1mL of 2% lidocaine was added to every 10mL of propofol. The authors of this study reported that prior studies showed that this dose would not have effect on headache severity. Group 2 received a 4mg/mL IV infusion of dexamethasone dosed at 0.15mg/kg, up to a maximum dose of 16mg. The infusion rate was set at 1mL per 10 seconds.25

Each patient was reassessed for headache severity at 5, 10, 20, 30, and 45 minutes after initiation of their treatment. Pain intensity was significantly lower in the propofol group at all times when compared to the dexamethasone group (P= 0.001). As well, the rate of pain intensity reduction in the propofol group was faster at all times when compared to the dexamethasone group (P= <0.05). See Table III. No significant difference in the two groups’ mean blood pressure, heart rate, and O2 saturation was noted. It was observed that 44.4% of the participants in the propofol group experienced mild sedation as a complication.25

The authors found that the administration protocol for the treatments in this study was a limitation. Propofol was administered in titrated doses whereas dexamethasone was administered
as a bolus. They were limited to this method due to the lack of a known effective titrated protocol for dexamethasone in the treatment of migraine headache. Another mentioned limitation in this study was the lack of patient follow-up for assessment of headache recurrence after discharge.25

DISCUSSION

Many of the accepted abortive therapies for migraine headaches used in the ED have questionable efficacy, leading to poor pain control, unwanted side effects, and possibility of readmission to the ED due to headache recurrence.7 Propofol is an anesthetic agent that has been proposed as a novel treatment for migraine headache. Many case studies have shown propofol to be an effective treatment for reducing migraine headache pain severity and recurrence of headache within 24 hours.17,20-23

This systematic review investigated two randomized control trials25,26 that compared propofols’ effectiveness to other standard abortive therapies including sumatriptan and dexamethasone in the treatment of migraine headache. Soleimanpour et al25 revealed that propofol overall was more effective at reducing pain severity in migraine headache when compared to dexamethasone. Moshtaghion et al26 revealed that propofol was more effective at reducing pain severity in migraine headache within 30 minutes after treatment when compared to sumatriptan. Both studies showed that the rate at which pain severity was reduced with propofol treatment was significantly faster than the other therapies,25,26 results can be seen in Tables II & III. These concepts are important when considering length of patient suffering and length of stay (LOS) in the ED. A shorter LOS is not only beneficial to the patient but also to overcrowded EDs. In one study,27 LOS of pediatric patients with migraine who were treated with propofol was
decreased when compared to the control. It is necessary that further studies should include LOS in the ED from admission to discharge as one of their assessed outcomes.

Moshtaghion et al\textsuperscript{26} also found propofol to be more effective at reducing nausea, vomiting, and headache recurrence within 24 hours when compared to sumatriptan. Again, this is important when considering patient suffering but also re-admittance rates to the ED and the costs associated. It is important that further studies not only include headache recurrence rates between treatment groups but as well as re-admittance rates to the ED for headache and symptom relapse.

While the studies\textsuperscript{25,26} demonstrated that propofol is more effective, they both have limitations. The Moshtaghion et al study\textsuperscript{26} lacked a standard questionnaire when assessing patients for headache recurrence. It is possible that individual interviewer styles of inquiring about headache recurrence could have affected the patients’ response.

The Soleimanpour et al study\textsuperscript{25} was limited by its medication administration protocol. Propofol was administered in titrated doses based on the patients VAS pain reduction score with a set maximum dose. Dexamethasone was administered in one bolus dependent on the patient’s weight with a set maximum dose as well. It is possible that patients in the dexamethasone group, that did not have good response to treatment, still had the ability to receive additional dexamethasone without exceeding the maximum dose. It is possible that additional administration of dexamethasone, to these patients, could have had an effect in their overall VAS pain reduction score.

An additional limitation noted between the two studies\textsuperscript{25,26} was the different dosing regimens of propofol. It is possible that treatment response at different time intervals within the propofol groups could be dose dependent and prove to have various results when compared to
other treatment groups. In future studies a standardized dosing protocol should be observed in the propofol treatment groups to minimize confounding variables.

CONCLUSION

Propofol can be an ideal abortive treatment for acute migraine in the ED. It is rapid acting, has few side effects when used at analgesic doses, and may be more effective at reducing pain severity, headache recurrence, and accompanying symptoms than sumatriptan and dexamethasone. Further studies to assess propofol’s effectiveness as compared to these and other standard abortive therapies used in the ED is warranted. These studies should include important factors like reduction of accompanying symptoms, adverse effects of the medications, patient’s average LOS in the ED, and headache recurrence and rate of re-admission. All of these points are important factors when choosing the most effective therapy for migraine headache.
References


Table I. Grade Evidence Profile, Characteristics of Reviewed Studies

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<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
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<tr>
<td>Reduction of pain intensity</td>
<td>2</td>
<td>2 RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No bias likely</td>
<td>Low</td>
</tr>
<tr>
<td>Rate of treatment response</td>
<td>2</td>
<td>2 RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Moderate</td>
</tr>
<tr>
<td>Recurrence of headache within 24 hours</td>
<td>1</td>
<td>1 RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Very Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Low</td>
</tr>
<tr>
<td>Unwanted side effects</td>
<td>1</td>
<td>1 RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Very Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Low</td>
</tr>
</tbody>
</table>

<sup>a</sup>Only two RCTs evaluated this outcome  
<sup>b</sup>The Moshtaghion et al study<sup>26</sup> demonstrated increased improvement only at 30 minutes while the Soleimanpour et al study<sup>25</sup> demonstrated increased improvement at all time frames  
<sup>c</sup>Only one RCT evaluated this outcome
Summary of Findings

### TABLE II. Moshtaghion et al\textsuperscript{26}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>P Value\textsuperscript{a}</th>
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<tr>
<td>Pain intensity before treatment</td>
<td>Propofol</td>
<td>Sumatriptan</td>
</tr>
<tr>
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<td>9.09 +/- 1.02</td>
<td>8.71 +/- 1.20</td>
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<tr>
<td>Pain intensity 30 minutes after treatment</td>
<td>2.62 +/- 2.12</td>
<td>3.69 +/- 2.55</td>
</tr>
<tr>
<td>Pain intensity 1 hour after treatment</td>
<td>2.69 +/- 2.63</td>
<td>2.36 +/- 2.31</td>
</tr>
<tr>
<td>Pain intensity 2 hours after treatment</td>
<td>1.62 +/- 2.04</td>
<td>1.36 +/- 1.96</td>
</tr>
<tr>
<td>Recurrence of headache within 24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for anti-emetic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest tightness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash at injection site</td>
<td>0.0%</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}P Values of <0.05 were considered significantly different

### TABLE III. Soleimanpour et al\textsuperscript{25}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>P Value\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity before treatment</td>
<td>Propofol</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>8 +/- 1.52</td>
<td>8.11 +/- 1.31</td>
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<tr>
<td>Pain intensity 5 minutes after treatment</td>
<td>5.46 +/- 1.56</td>
<td>6.57 +/- 1.57</td>
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<td>Pain intensity 10 minutes after treatment</td>
<td>3.08 +/- 1.7</td>
<td>5.13 +/- 1.47</td>
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<tr>
<td>Pain intensity 20 minutes after treatment</td>
<td>1.87 +/- 1.28</td>
<td>3.73 +/- 1.81</td>
</tr>
<tr>
<td>Pain intensity 30 minutes after treatment</td>
<td>1.44 +/- 1.63</td>
<td>3.06 +/- 2</td>
</tr>
<tr>
<td>Pain intensity 45 minutes after treatment</td>
<td>1.16 +/- 1.55</td>
<td>2.87 +/- 1.81</td>
</tr>
</tbody>
</table>

\textsuperscript{a}P Values of <0.05 were considered significantly different