EMA Emergency Medicine Australasia

Emergency Medicine Australasia (2020) **32**, 542–547 doi: 10.1111/1742-6723.13542

ORIGINAL RESEARCH

Propofol for migraine in the emergency department: A pilot randomised controlled trial

Biswadev MITRA [1,2] Cristina ROMAN [1,3] Eric MERCIER,[4,5,6] John MOLONEY [7,8] Gary YIP,[9] Keshav KHULLAR,[1] Kieran WALSH,[1] De Villiers SMIT[1,2] and Peter A CAMERON [1,2]

[1]Emergency and Trauma Centre, The Alfred Hospital, Melbourne, Victoria, Australia, [2]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, [3]Department of Pharmacy, The Alfred Hospital, Melbourne, Victoria, Australia, [4]CHU de Québec-Université Laval Research Center, Population Health and Optimal Health Practices Axis, Université Laval, Quebec, Quebec, Canada, [5]Département de Médecine Familiale et Médecine d'Urgence, Faculté de Médecine, Université Laval, Quebec, Quebec, Canada, [6]Centre de recherche sur les soins et les services de première ligne de l'Université Laval, Quebec, Quebec, Canada, [7]Department of Anaesthesiology and Perioperative Medicine, The Alfred Hospital, Melbourne, Victoria, Australia, [8]Department of Community Emergency Health and Paramedic Practice, Monash University, Melbourne, Victoria, Australia, and [9]Department of Neurology, The Alfred Hospital, Melbourne, Victoria, Australia

Abstract

Objective: To test the administration of intravenous (i.v.) propofol at a procedural sedation dose compared to standard therapy for initial management of migraine in the ED.

Methods: This was an open label, randomised controlled pilot trial. Eligible patients were adults with a diagnosis of migraine and planned for treatment with i.v. medications. Patients were randomised to propofol or standard therapy groups. The primary outcome variable was time to discharge (TTD) defined as time from intervention to discharge from the ED. Secondary outcomes were safety of propofol administration and change in pain scores. A reduction of pain by ≥50% or discharge from the ED was defined as favourable. All analyses were performed on an intention-to-treat basis.

Results: Data from 29 patients were analysed, with 15 patients in the propofol group and 14 patients in the standard therapy group. TTD was significantly lower in the propofol group with median of 290 (interquartile range 162–500) min compared to 554.5 (interquartile range 534–639) min in the standard therapy group (P = 0.021). The hazard ratio for the defined favourable outcome of reduction of pain scores or discharge from the ED was 1.54 (95% CI 0.69–3.41).

Conclusions: Initial management of migraine with i.v. propofol at procedural sedation doses significantly reduced TTD compared to standard therapy. We did not detect any significant safety concerns although the study was not adequately powered to detect safety of the intervention and requires validation.

Key words: *analgesia, headache, migraine disorder, pain, propofol.*

Key findings

- Randomisation of patients with migraine to propofol or standard therapy required availability of resuscitation cubicles, greatly limiting enrolment.
- There were 30 patients randomised over a period of 28 months.
- Initial intravenous therapy with propofol, using a procedural sedation dose, resulted in shorter times to discharge from the ED for patients presenting with migraine.

Introduction

Migraine affects 1 in 10 people worldwide and is twice as common in females as males.[1] The majority of the patients with migraine successfully manage their symptoms and exacerbations at home, but a proportion of patients with moderate to severe migraines present to the ED for treatment. Up to 3% of ED visits have headache as their presenting complaint.[2]

The treatment of migraine in patients presenting to the ED is more challenging than a typical attack at home. This is because such patients are usually the non-responders to oral medications, with many having already tried at least one rescue medication without adequate relief.[3,4] The severity of the headache and its associated symptoms tends to increase over time, making it more difficult to treat.[5–7] The typical duration of headaches following ED presentations ranges from 24 to 72 h.[3,8] On presentation to the ED, management is often diverse, associated with long lengths

Correspondence: Professor Biswadev Mitra, Emergency and Trauma Centre, The Alfred Hospital, 55 Commercial Road, Melbourne, VIC 3004, Australia. Email: biswadev.mitra@monash.edu

Biswadev Mitra, MBBS, MHSM, PhD, FACEM, Director of Emergency Medicine Research; Cristina Roman, BPharm (Hons), MPP, Lead Pharmacist; Eric Mercier, MD, MSc, FRCPC, Emergency Physician; John Moloney, MBBS, FANZCA, Consultant Anaesthetist; Gary Yip, MBBS, FRACP, Consultant Neurologist; Keshav Khullar, MBBS, FACEM, Emergency Physician; Kieran Walsh, BMedSc (Hons), Medical Student; De Villiers Smit, MBChB, FACEM, Director of Emergency Medicine; Peter A Cameron, MBBS, MD, FACEM, Academic Director, Professor.

Accepted 29 April 2020

of stay and patients are frequently discharged with ongoing pain.[9] Furthermore, the recurrent headaches can predispose patients to the misuse of analgesic medications contributing to rebound headaches.

A number of small trials and observational studies have shown rapid relief of both chronic and acute migraine headache using propofol, a lipid soluble short-acting intravenous (i.v.) anaesthetic.[10] It seems that the therapeutic effects of propofol are because of its agonist effects on the chloride channels in the β1 subunit of GABA receptors, in addition to its inhibition of afferent sympathetic action and cardiac baroreceptor reflexes.[11–13] As a result, propofol's anaesthetic effects on the central nervous system may diminish the central sensitisation causing allodynia and hyperalgesia. This may be the mechanism of pain relief in migraine patients.[14]

However, current evidence is limited by the small number of studies, heterogeneity in intervention doses and outcome measures and study settings. The aim of this pilot clinical trial was to determine whether the administration of i.v. propofol at a procedural sedative dose (1 mg/kg) results in a shorter time to discharge (TTD) in the ED. Secondary aims were to collect data on safety and effectiveness on pain scores compared to standard therapy.

Methods

This was a single-centre, open label, randomised controlled pilot trial conducted at an adult tertiary referral hospital in Melbourne, Australia. The Alfred Hospital Emergency and Trauma Centre is a major metropolitan centre that receives over 65 000 patients per year. The Alfred Hospital is also the state-wide referral centre for a variety of medical services.

Eligible patients were adult (age 18–65 years), had a diagnosis of migraine after initial assessment by the treating emergency medicine clinician (emergency physician or registrar) and a decision was made to commence i.v. therapy to manage the migraine. No objective diagnostic criteria for migraine were mandated. Excluded were patients with fever, altered mental status or impairment of conscious state, allergy to any of the study drugs, eggs or soy products, presence of abnormal neurological signs or suspicion of alternate diagnosis, history of head trauma, failure to provide informed consent, inability to mark a visual analogue pain scale (VAS), nursing home residents and pregnant patients. In addition, prior to randomisation, a resuscitation cubicle had to be available with staff present for safe delivery of the intervention. If patients had received i.v. therapy in the pre-hospital phase of care or in the ED prior to consideration for the trial, they were not eligible to be enrolled. A pharmacist and an emergency physician had to be present and hence enrolment was only possible during their working hours.

Using a pseudo-random number generator and a 1:1 allocation ratio, eligible patients were randomised to either propofol or standard therapy groups. Randomisation was performed by the clinical pharmacist, in conjunction with the treating clinician and/or member of the research team. After obtaining informed consent, the pharmacist and emergency physician opened an opaque envelope that determined allocation. Patients indicated the level of their pain on a 10 cm non-hatched VAS, marked from '0' at one end to '10' at the other. Patients were verbally instructed that '0' meant 'no pain' and '10' meant the worst pain ever.

For patients randomised to the propofol arm, clinicians followed the hospital protocol for procedural sedation. Patients were transferred to the resuscitation bay, placed on a cardiac monitor, provided supplemental oxygen by nasal cannula, end-tidal CO_2 monitor, with 1:1 nursing care during the sedation. Propofol was administered at a dose of 1 mg/kg as a slow push over 1 min through a peripheral i.v. canula with a 20 mL syringe.[15] Patients were allowed to sleep until they woke up on their own. Patients in the standard therapy arm were managed as per clinician preference, with the ED's migraine protocol available as a reference (Appendix S1).

The first post-treatment VAS pain score was collected from patients at 30 min following the completion of initial therapy. The VAS pain scores were repeated successively every half hour until discharge of the patient from the ED. Rescue therapy was allowed at any time-point for ongoing pain.

The primary outcome variable was TTD from the ED. This was calculated as time of first i.v. medication after randomisation to discharge time. For patients admitted to the Emergency Short Stay Unit (ESSU), the discharge time was time of discharge from ESSU. Overall length of stay in the ED that included pre-intervention, that is triage, waiting and assessment times were also reported.

Secondary outcome measures were safety of propofol administration and change in pain scores. Variables to assess safety were the lowest Richmond-Agitation-Sedation Scale Score, the lowest systolic blood pressure (SBP), the lowest oxygen saturation and a qualitative (free text) recording of any manoeuvres to maintain an open airway. A favourable outcome was defined as ≥50% reduction in VAS score or discharge from the ED.

All outcome measures were assessed on an intention-to-treat basis. TTD was summarised using median (interquartile ranges [IQRs]) and differences assessed using the Wilcoxon rank sum test. Differences in proportion of patients achieving clinically significant reduction in pain were assessed using Fisher's exact test. The association between two continuous variables was assessed using univariable linear regression. Differences between time to favourable outcomes were presented using Kaplan–Meier curves and differences were assessed using hazard ratio and 95% confidence intervals.

Being a pilot trial, a pre-determined sample size was not calculated and enrolment of 40 patients was planned. We determined this number through consensus among the investigators, to be enough to inform effect size for planning of a definitive trial. A *P*-value of <0.05 was defined to be statistically significant. All analyses were conducted using Stata V 15.1 (College Station, TX, USA). The trial was

approved by The Alfred Hospital Ethics Committee (Project number 328/16). The protocol for this pilot is registered at The Australian New Zealand Clinical Trials Registry (ACTRN12619001595101).

Results

There were 30 patients randomised in the trial over a period of 28 months. Data from one patient were missing, leaving 29 patients for analysis (Fig. 1). Most exclusions (n = 39; 54.2%) were secondary to a resuscitation cubicle not being available. There were 7 (9.7%) patients who declined consent to be randomised. Demographics, time of presentation, initial pain scores and vital signs are listed in Table 1 and were similar except for sex distribution. All patients were admitted to the ESSU as part of their care.

Among patients in the propofol arm, median TTD was 290 (IQR 162–500) min compared to 554.5 (IQR 534–639) min in the standard therapy arm (Fig. 2; P = 0.021). There was no association between TTD and time of presentation to the ED (P = 0.47). There was no association between TTD and initial pain scores (P = 0.63). Overall ED length of stay was also significantly shorter in the propofol arm of 335 (207–545) min compared to 595 (572–705) min for standard therapy (P = 0.01). There was no difference in TTD between males and females (P = 0.34).

Among patients managed in the standard therapy arm, nine patients received chlorpromazine at doses of 12.5–25 mg with crystalloids (range 700 mL to 2.2 L). Two patients were managed with i.v. metoclopramide (10 mg), ondansetron (8 mg) and fluids only. One patient received

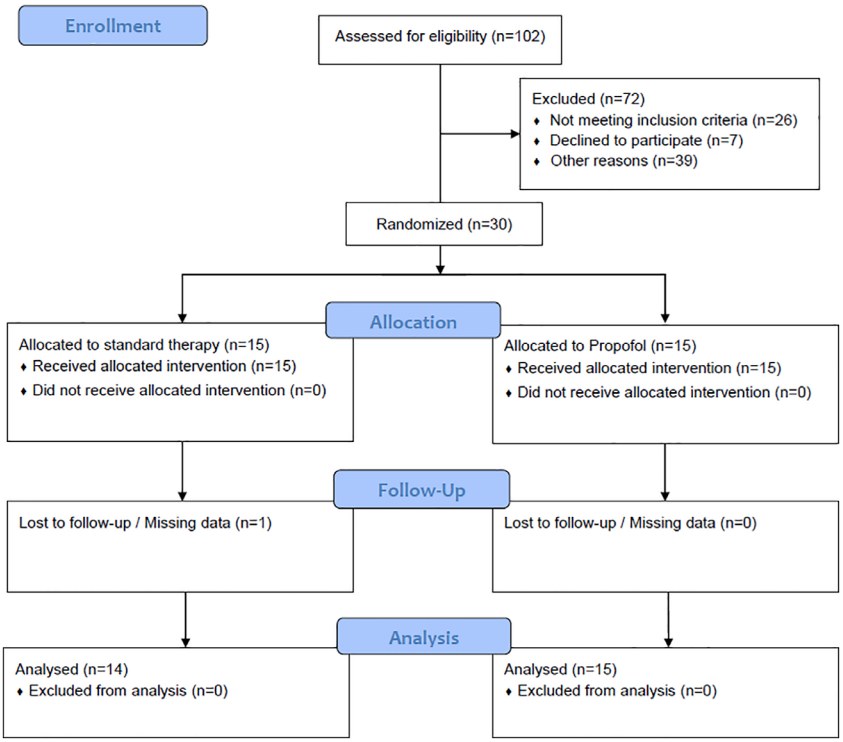

Figure 1. *Patient enrolment and randomisation.*

TABLE 1. *Baseline characteristics*

	Standard therapy arm (n = 14)	Propofol arm (n = 15)
Age	37.9 (SD 9.4)	32.9 (SD 10.3)
Male sex	1 (11.1%)	8 (53.3%)
Presentation time		
08.00–16.59 hours	4	5
17.00–21.59 hours	7	8
22.00–07.59 hours	3	2
Initial pain score	7.5 (7–9)	8 (7–9)
Initial heart rate (/min)	71.1 (SD 8.6)	74.1 (SD 15.4)
Initial systolic BP (mmHg)	123.1 (SD 14.1)	124.3 (SD 13.8)
Initial resp. rate (/min)	15.4 (SD 2.7)	14.5 (SD 3.3)
Initial temperature (°C)	36.5 (SD 0.3)	36.3 (SD 0.3)
Initial oxygen saturations (%)	98.5 (SD 1.8)	99.4 (SD 1.2)

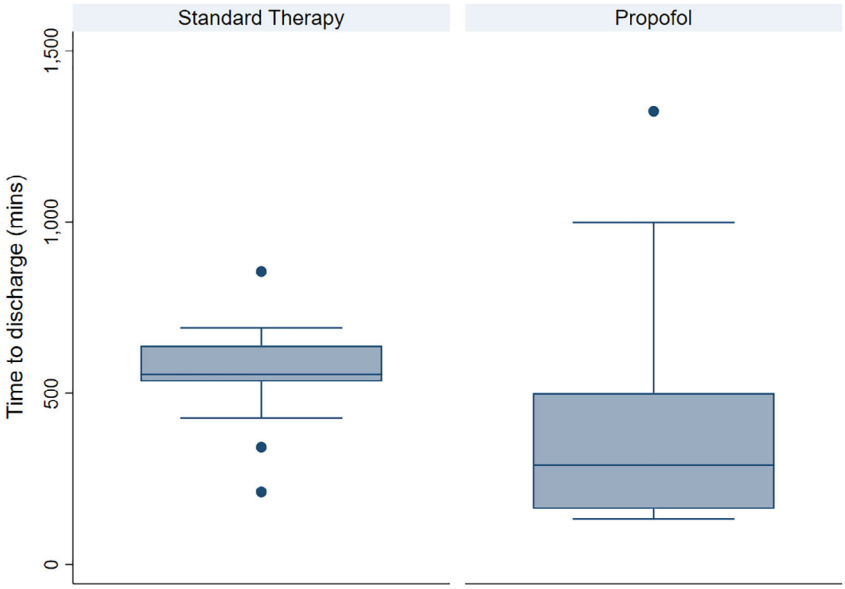

Figure 2. *Difference in time to discharge (primary outcome).*

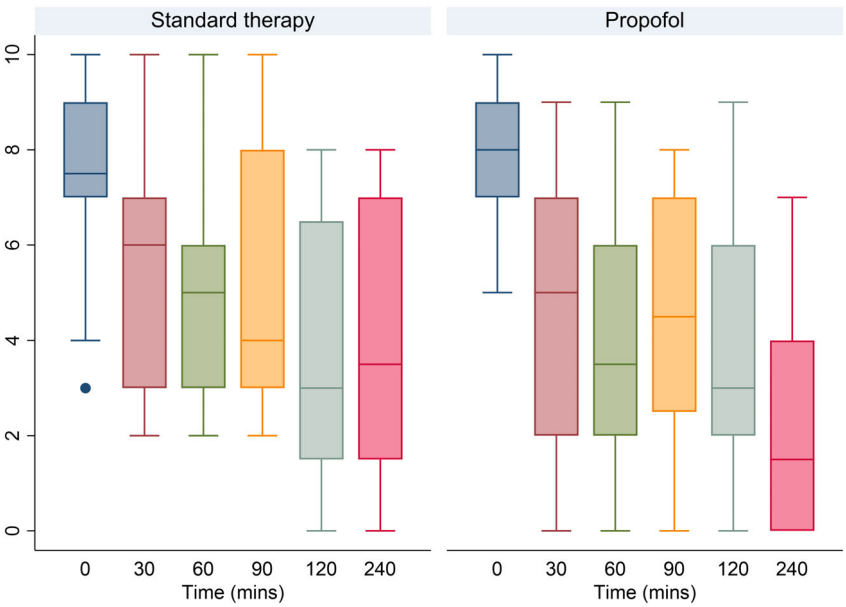

Figure 3. *Pain scores among patients remaining in the ED.*

i.v. lignocaine (4.8 g) with crystalloids (2 L), one received magnesium sulphate (10 mmol) with crystalloids (1 L) whereas the remaining patient was treated with i.v. morphine and i.v. ondansetron.

Among the 15 patients who received propofol, there were six patients who required additional analgesia. Of these, two patients were managed with oral analgesia only, whereas four patients were managed with i.v. chlorpromazine (12.5–25.0 mg). Among patients who received propofol, the median lowest sedation score achieved was −4 (IQR −3 to −5). There were no patients who recorded SBP <100 mmHg during procedural sedation. There was one episode (6.7%; 95% CI 1.7–32.0) of desaturation recorded with lowest oxygen saturation of 88%. This patient required assisted manual ventilation for less than 1 min prior to improvement in oxygen saturations. There was one additional patient who required temporary jaw thrust to maintain oxygenation, but no episodes of hypoxia were recorded. There were no patients who were diagnosed with an alternative diagnosis during the index presentation.

Change in VAS scores of patients remaining in the ED at the listed time points are illustrated in Figure 3. All patients had recovered to normal conscious state following administration of propofol and pain scores were available for all patients at 30 min. Time to favourable outcome, that is pain reduction of ≥50% or discharge from the ED is illustrated in Figure 4. The hazard ratio for the defined favourable outcome was 1.54 (95% CI 0.69–3.41).

Discussion

Initial i.v. therapy with propofol, using a procedural sedation dose resulted in shorter times to discharge from the ED for patients presenting with migraine. There appeared to be favourable improvements in pain scores and shorter times to favourable outcomes. Management of patients with i.v. propofol is feasible but requires incorporation into clinical practice to facilitate availability of a safe environment. Further validation of these results and ongoing surveillance regarding safety are indicated.

This pilot randomised study required 28 months to enrol 30 patients and was stopped early because of the slow enrolment rate. However, at conclusion, the trial had 91% power to detect the observed difference of TTD of 264 min with SD of 190 min. A key barrier to enrolment was the availability of a resuscitation cubicle. In a busy tertiary referral hospital, resuscitation cubicles are often occupied. In standard clinical practice, when a critically unwell patient presents, a cubicle is made available after transferring a relatively more stable existing patient to the next safest location. However, in the setting of

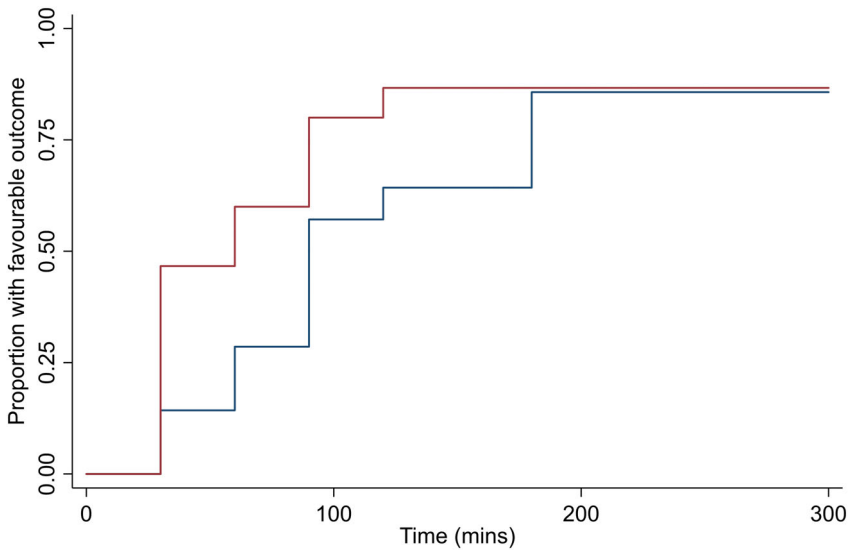

Figure 4. *Time to favourable outcome. (——) Standard therapy; (——) propofol.*

this clinical trial, it was not considered ethical to move a patient to facilitate procedural sedation. Additionally, if there was any doubt regarding the final diagnosis of migraine, such as consideration given to imaging of the brain, the patient was not eligible for the trial. Therefore, a large proportion of patients with provisional diagnoses of migraine were either not screened, or upon screening, considered ineligible because of lack of a suitable location to deliver procedural sedation dose propofol. The requirement of a clinical pharmacist and an emergency physician to be present prior to randomisation also limited the time during which a patient could be randomised. Results of this trial, therefore, are only applicable to situations where a resuscitation cubicle is available for safe administration of the intervention.

Procedural sedation with propofol has been proven to be a safe practice within EDs and requires strict adherence to clinical practice guidelines. Key recommendations are to pre-oxygenate and use supplemental oxygen during the procedure to minimise hypoxia during brief periods of potential apnoea. Additionally, one provider should be dedicated to administering the agent; monitoring vital signs (cardiac monitoring, pulse oximetry, capnography, and blood pressure and respiratory rate every 5 min); and performing any needed resuscitation, with a separate provider to perform any procedures.[16]

Strict adherence to procedural sedation guidelines was maintained during this trial but may have introduced confounders in the association between propofol and favourable outcomes. For example, treatment of patients with headache using inhaled high-flow oxygen has been suggested to be efficacious.[17] Additionally, it is well established that participation in clinical trials improves outcomes, and it is possible that the propofol group received a higher level of clinical care because of the ratio of caregivers to patient, at least in the initial phase of care.[18–20] This may have resulted in more prompt medication administration, earlier transfer to the ESSU and more efficient discharge planning.

A key issue in migraine management that was not adequately assessed was recurrence of headache. In the short term, there was some suggestion of worsening headache at 90 min after therapy with propofol (Fig. 3). However, on discharge, pain scores appeared lower than in the standard therapy group. The change in pain scores over time demonstrates that most patients after management with propofol were not pain free and a pain-free status is perhaps an unreasonable target outcome. Rather, including propofol in the management regime achieved a favourable outcome in a shorter time-period than standard therapy. In addition, migraine recurrence after discharge was also not assessed. Representations with migraine have been frequently reported and maintenance of favourable outcomes should be the aim of effective management.

Future studies can improve the methodology by more standardised management of the two groups being in similar management settings such as cubicle, clinical staff and delivery of oxygen. Dosing protocols have varied, with incremental small doses also associated with favourable outcomes.[21] The optimal dose and frequency therefore require further investigation.

In recognition of the chronic nature of migraine, varied levels of pain and that patients with migraine are often discharged with substantial pain, we chose the pragmatic primary outcome measure of TTD. This was determined to be a proxy variable for favourable outcome from both the patient and clinician perspective, without pre-empting a satisfactory level of pain for all patients with migraine. In future studies, outcome measures can be expanded to include longer term follow-up after discharge. Clinical practice guidelines for migraine vary across institutions. It is possible that the differences observed may not generalise when compared to other guidelines or when pre-hospital i.v. analgesia has been administered and ongoing external validation remains essential. Finally, we observed a significant imbalance in distribution of sex among the two arms. This was a random effect and we remain unsure if the results were biased by this imbalance. Stratification of randomisation by sex may be considered in future studies.

Conclusions

In this small pilot study of patients who were clinically diagnosed with a migraine on presentation to the ED, initial management with i.v. propofol at procedural sedation

doses significantly reduced TTD. The study was under-powered to assess safety and the intervention requires further evaluation. When considered as a therapeutic option for acute presentations with migraine, strict adherence to clinical practice guidelines for procedural sedation in the ED remains essential.

Competing interests

BM and PAC are section editors for *Emergency Medicine Australasia*.

Data availability statement

Data available subject to ethics committee approval.

References

1. Woldeamanuel Y, Cowan R. Worldwide migraine epidemiology: systematic review and meta-analysis of 302 community-based studies involving 6,216,995 participants (P6.100). *Neurology* 2016; **86**: P6.100.
2. Holdgate A, Kelly AM. *Emergency Care Evidence in Practice Series: Management of Acute Migraine*. Melbourne: Emergency Care Community of Practice, National Institute of Clinical Studies, 2006.
3. Ginder S, Oatman B, Pollack M. A prospective study of iv magnesium and iv prochlorperazine in the treatment of headaches. *J. Emerg. Med.* 2000; **18**: 311–5.
4. Miner JR, Fish SJ, Smith SW, Biros MH. Droperidol vs. prochlorperazine for benign headaches in the emergency department. *Acad. Emerg. Med.* 2001; **8**: 873–9.
5. Goadsby P. The 'Act when Mild' (AwM) study: a step forward in our understanding of early treatment in acute migraine. *Cephalalgia* 2008; **28**: 36–41.
6. Goadsby P, Zanchin G, Geraud G *et al*. Early vs. non-early intervention in acute migraine – 'Act when Mild (AwM)'. A double-blind, placebo-controlled trial of almotriptan. *Cephalalgia* 2008; **28**: 383–91.
7. Kelley NE, Tepper DE. Rescue therapy for acute migraine, part 1: triptans, dihydroergotamine, and magnesium. *Headache* 2012; **52**: 114–28.
8. Trottier ED, Bailey B, Lucas N, Lortie A. Prochlorperazine in children with migraine: a look at its effectiveness and rate of akathisia. *Am. J. Emerg. Med.* 2012; **30**: 456–63.
9. Cheng CT, Law GTWM, Roman C, Tan G, Mitra B. Evaluation of the assessment and management of acute migraines in two Australian metropolitan emergency departments. *J. Emerg. Med. Trauma Acute Care* 2016; **2016**: 10.
10. Piatka C, Beckett RD. Propofol for treatment of acute migraine in the emergency department: a systematic review. *Acad. Emerg. Med.* 2020; **27**: 148–60.
11. Ebert TJ, Muzi M, Berens R, Goff D, Kampine J. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. *Anesthesiology* 1992; **76**: 725–33.
12. Krusz JC, Scott V, Belanger J. Intravenous propofol: unique effectiveness in treating intractable migraine. *Headache* 2000; **40**: 224–30.
13. Sellgren J, Ejnell H, Elam M, Pontén J, Wallin B. Sympathetic muscle nerve activity, peripheral blood flows, and baroreceptor reflexes in humans during propofol anesthesia and surgery. *Anesthesiology* 1994; **80**: 534–44.
14. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J. Pain* 2009; **10**: 895–926.
15. Miner JR, Burton JH. Clinical practice advisory: emergency department procedural sedation with propofol. *Ann. Emerg. Med.* 2007; **50**: 182–7.e1.
16. Miller KA, Andolfatto G, Miner JR, Burton JH, Krauss BS. Clinical practice guideline for emergency department procedural sedation with propofol: 2018 update. *Ann. Emerg. Med.* 2019; **73**: 470–80.
17. Cohen AS, Burns B, Goadsby PJ. High-flow oxygen for treatment of cluster headache: a randomized trial. *JAMA* 2009; **302**: 2451–7.
18. Nijjar SK, D'Amico MI, Wimalaweera NA, Cooper N, Zamora J, Khan KS. Participation in clinical trials improves outcomes in women's health: a systematic review and meta-analysis. *BJOG* 2017; **124**: 863–71.
19. Majumdar SR, Roe MT, Peterson ED, Chen AY, Gibler WB, Armstrong PW. Better outcomes for patients treated at hospitals that participate in clinical trials. *Arch. Intern. Med.* 2008; **168**: 657–62.
20. Kandzari DE, Roe MT, Chen AY *et al*. Influence of clinical trial enrollment on the quality of care and outcomes for patients with non-ST-segment elevation acute coronary syndromes. *Am. Heart J.* 2005; **149**: 474–81.
21. Ward DI, Mulcahy R, Bailey P, Morgan D. Use of intravenous propofol in the treatment of migraine headache. *Emerg. Med. Australas.* 2013; **25**: 619.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Appendix S1. Standard treatment protocol – acute migraine management in the emergency department.