Curr Pain Headache Rep (2014) 18:464
DOI 10.1007/s11916-014-0464-x

MIGRAINE (R COWAN, SECTION EDITOR)

What Is the Evidence for the Use of Corticosteroids in Migraine?

Y. W. Woldeamanuel · A. M. Rapoport · R. P. Cowan

Published online: 6 November 2014

Abstract Corticosteroids are widely prescribed for the management of migraine attacks. The earliest clinical studies examining the efficacy of corticosteroid monotherapy for managing migraine attacks date back to 1952. Since then, 26 heterogeneous clinical studies and four meta-analyses have been conducted to assess the efficacy of corticosteroids in either aborting acute migraine attacks, prolonged migraine attacks or recurrent headaches. Most of these (86 %) studies employed different comparator arms with corticosteroids monotherapy administration while some studies (14 %) evaluated adjunctive corticosteroid therapy. The majority of these clinical studies revealed the superior efficacy of corticosteroids as mono- or adjunctive-therapy both for recurrent and acute migraine attacks, while the remaining showed non-inferior efficacy. Different forms of oral and parenteral corticosteroids in either single-dose or short-tapering schedules are prescribed; there are clinical studies supporting the efficacy of both methods. Corticosteroids can be administered safely up to six times annually. Corticosteroids are also useful in managing patients who frequent emergency departments with "medication-seeking behavior." Migraine patients with refractory headaches, history of recurrent headaches, severe baseline disability, and status migrainosus were found to have the most beneficial response from corticosteroid therapy.

Keywords Corticosteroids · Critical appraisal · Migraine · Migraine attack management · Emergency room management of migraine · Neurogenic inflammation · Prolonged migraine · Recurrent migraine

This article is part of the Topical Collection on *Migraine*

Y. W. Woldeamanuel (✉) · R. P. Cowan
Stanford Headache Program, Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Room H3160, 300 Pasteur Drive, Stanford, CA 94305-5235, USA
e-mail: ywoldeam@stanford.edu

A. M. Rapoport
Department of Neurology, The David Geffen School of Medicine at UCLA in Los Angeles, Los Angeles, CA, USA

Background

The early years of synthetic production of corticosteroids dates to circa 1950. Corticosteroids early proven efficacy for different inflammatory musculoskeletal conditions (e.g., rheumatoid arthritis) were shortly followed by various clinical trials to study their efficacy to treat migraine attacks [1, 2]. Blumenthal (1952) [2] and Frohner (1953) [1] were the earliest to empirically test and demonstrate the clinical efficacy and utility of corticosteroids to manage migraine attacks among patients. Since those early days and to date, there have been 26 [3••, 4] heterogeneous clinical studies and four meta-analyses [5•, 6–8] examining the efficacy of corticosteroids in either aborting acute migraine attacks or recurrent headaches. Today, corticosteroids are known to be widely prescribed either as monotherapy or adjuvant therapy to other abortive medicines to treat for migraine attacks both within the outpatient and emergency clinical settings worldwide. In this article, we aim to provide careful examination and related updated discussions into the current evidence for corticosteroid administration, and offer type and dosage recommendations for treating in clinical practice to effectively abort migraine attacks.

Pain and Neurogenic Inflammation Interplay in Migraine Attacks

Present-day evidences indicate that migraine is a neurovascular inflammatory disorder, starting in the nervous system and secondarily affecting the vascular system [9–11]. Its head pain and accompanying sensory symptomatic phases are produced either

peripherally or centrally; the former is triggered by abnormal activation of trigeminocervical neurons as primary afferents [12], while the latter is generated centrally at second-order neurons due to abnormal transition and regulation of orthodromically travelling peripheral signals [13–15]. That the trigeminal nucleus forms an inferior or caudal extension subserving not only facial and head but also nuchal sensory modulation explains the head and neck pain accompanying migraine attacks. Meningeal inflammatory symptoms are common during migraine presentation—which reminds the significance of sterile neural and meningeal inflammation occurring during these attacks.

Based on animal studies, trigeminocervical triggers emanating from peptidergic nociceptive afferents result in the release of neuropeptides onto second-order neurons of the trigeminal nucleus caudalis [11, 16, 17]. The very same peptidergic primary afferents are known to convey dual sensory-efferent functions whereby peptidergic peripheral terminals surrounding dural arterioles similarly release neuropeptides [17]. Neuropeptides are important in the neural regulation of arteriolar vasodilation, inflammatory cascades, and smooth muscular changes [11, 18]. At collateral neuronal branches, axon reflexes convert orthodomical action potentials to antidromic signals—thereby supplementing prejunctional trigeminovascular neuropeptide neuroregulation [11]. Vasodilatory neuropeptides released into dural vasculature include calcitonin gene-related peptide (CGRP), tachykinin peptides such as substance P (SP), and neurokinin A [19–21]. SP is known to stimulate histamine degranulation of dural mast cells and release of other pro-inflammatory molecules, i.e., nitric oxide (NO), prostaglandins (PGs particularly PGE2), leukotrienes (LT), serotonin (5-HT), histamine, proteolytic enzymes, and phospholipases from inflamed dura [21]. PGs and LTs, produced as a result of arachidonic acid metabolism are known to have algogenic (pain-inducing) properties through nociceptive afferent sensitization by lowering firing threshold [22].

Feedback mechanisms orchestrate between dural mast cells and trigeminal nociceptor terminals [23], where released histamine further stimulates discharge of vasoactive peptides, i.e., CGRP and SP [24]. Most of these inflammatory mediators can activate platelet aggregation around dural inflammation site; when activated, platelets secrete 5-HT which is another known nociceptive via actions specific to 5-HT_3 receptor [19, 25, 26]. Neurally-induced inflammatory discharge of algogenic pro-inflammatory mediators, plasma protein extravasation, meningeal irritation, perivascular edema, and dural platelet aggregation are found to be important in animal models of trigeminal ganglion stimulation or animal dura mater inflammation [11, 27]. Neuronal changes are accompanied by pro-inflammatory and vascular changes [11, 27]. Among leaking proteins, bradykinin produces powerful algogenic responses on trigeminal nociceptor terminals [28]. This sequence of events related to complex inflammation-pain interplay is broadly termed sterile neurogenic inflammation (SNI) [11, 27]. In these animal models, SNI contributes to the development of hyperalgesia, pain prolongation, and peripheral sensitization of polymodal receptors [11, 13, 29]. SNI is theorized to be important in understanding perpetuated headache long after initial migraine triggers [11, 13]. However, SNI has not been translated to be relevant in the human condition of migraine [30, 31]. Among the vasoactive neuropeptides, CGRP has been inconsistently elevated in clinical studies [32]. Different clinical trials employing SNI inhibitors (e.g. SP or neurokinin receptor antagonists, neurosteroids such as ganaxolone) have been ineffective in both acute and preventive management of migraine [31, 33]. At this point, it would be interesting for future studies to explore for possible anti-nociceptive properties of corticosteroids.

Migraine Recurrence among Common Abortive Medications

Migraine patients receiving acute treatments measure the efficacy and outcome of the intervention as optimal when the headache is completely gone, does not recur and there are no adverse events. Headache recurrence is a common experience following discharge of migraine patients from both emergency and outpatient clinical settings. Here, we briefly describe migraine recurrence among the common acute care medications of triptans and discuss situations where corticosteroids can be helpful options.

Headache recurrence following oral triptan administration for migraine ascendingly averages 17 % for frovatriptan 2.5 mg [34], 20 % for naratriptan 2.5 mg [35], 26 % for eletriptan 40 mg [35], 28 % for zolmitriptan 5 mg [35], 31 % for sumatriptan 100 mg [35], 31 % for zolmitriptan 2.5 mg [35], 33 % for almotriptan 12.5 mg [35], and to 38 % for rizatriptan 10 mg [35] while 37 % for placebo [35]. When contraindications preclude the use of triptans or ergots (i.e., ergotamine tartrate or dihydroergotamine) or when such therapies fail, parenteral dexamethasone may provide another reasonable option for the office or ED treatment of resistant, severe, or prolonged episodic migraine [36]. Doctors often add a nonsteroidal anti-inflammatory to a triptan in patients with repeated bouts of recurrence following treatment. Another way to attempt to decrease recurrence is to ensure that the patient is taking the optimal dose and route of administration of the triptan they are using. Triptans come in a number of different forms and doses; the correct dose typically is the highest allowable dose. It is a common practice for physicians to decrease the dose only if patients have adverse effects, rather than increase the dose if they have recurrence. The goal is to treat with the highest dose initially; patients are much more likely to continue the medication than if there is no efficacy. When there are adverse effects, a patient can decrease the dose; if there is no effect, a patient would be much more

reluctant to try the drug again at a higher dosage. In those patients who continue to have recurrence, one option is to add an NSAID and another is, the use of a longer-acting triptan, e.g., frovatriptan, although there is no proof that it might prevent the recurrence. Another consideration in the ED is the use of IV, SC, or IM dihydroergotamine, but this is contraindicated within 24 h of triptan use. One author (AMR) will use DHE after 4-5 half lives of the triptan have past. For sumatriptan that is 8-10 hours and for zolmitriptan it is 12-15 hours. When patients come to the ED having failed their triptan in appropriate doses, many ER physicians repeat the triptan by injection, use pain medication or start an IV for hydration or give dopamine antagonists. The last option would seem to work the best, but giving corticosteroids in this setting would be safe, easy and probably produce the desired result.

Guidelines and Recommendations for Systemic Corticosteroids Administration in Migraine

A recently completed pooled analysis of a 65-year systematic review has shown that corticosteroid administration can be effective in controlling both recurrent and acute migraine headaches; a slightly higher efficacy (in 78.6 % of the studies) was shown for controlling recurrent headaches, compared to controlling acute migraine headache (in 61.2 % of the studies) [3••]. The numbers needed to treat (NNT) was found to be 3 for 24-h and 10 for 72-h effective headache recurrence management [3••]. The different forms and dosages used within the studies reviewed in this recent systematic review include the following: parenteral dexamethasone in 56 % (median 10 mg), parenteral methylprednisolone in 4 % (500 mg), oral dexamethasone in 8 % (4 mg), oral dexamethasone in 4 % (8 mg), oral prednisolone (100 mg) 5-day-taper dose in 4 %, oral prednisolone (60-40-20 mg) 6-day-taper dose in 12 %, oral prednisolone (150 mg) in 4 %, oral dexamethasone (12-8-4 mg) 3-day taper in 4 %, and oral cortisone (50 mg) in 4 %—all these methods have shown either observable superior or non-inferior efficacy as compared to other abortive medications [3••]. As there exists positive clinical scientific evidence for effective oral dosing of corticosteroids (36 % of the clinical studies in this 65-year systematic review used oral doses successfully) [3••], it makes sense to consider using lower dose, oral corticosteroids, as they work well. Recommendations for systemic corticosteroid administration in managing migraine in emergency situations vary greatly as they do in the outpatient setting [36]. One author (AMR) uses 4 mg of dexamethasone orally (which may be repeated in 3 h for non-efficacy) for prolonged headache, lasting greater than 48 hour, status migrainosus, non-responsive headache and to avoid recurrence. Patients appear to go into a refractory period and say they feel great for several days and do not have to worry about migraine for a while.

Some independent guidelines such as the Agency for Healthcare Research and Quality (AHRQ) recommend corticosteroids only as a last resort for status migranosus and to be included only in an effort to smoothen transfer of care to specialty referral centers [3••, 36], while others, e.g., Canadian guidelines [37], relegate dexamethasone to a fourth-line treatment for resistant migraines [37, 38]. We certainly do not agree that this safe, inexpensive medication, with strong clinical evidence for efficacy in the most difficult migraineurs, should be relegated to fourth line or last resort. The cohort of patients for whom the efficacy of corticosteroids was high includes those presenting with status migrainosus, severe and resistant or refractory migraines, higher baseline disability, and previous history of recurrent headaches [3••]. In lower- and middle-resource settings where migraine burden is currently on the rise [39], corticosteroids offer not only effective treatment option but also being relatively available and affordable as compared to triptans or other parenteral forms of migraine medications [3••].

Approach to the Repetitive Emergency Visitor and Difficult-to-Treat Patient

At this juncture, it is essential to recognize the challenge presented by the common phenotype of the frequent emergency department visitor with migraine. Such patients usually have compulsive preoccupation with symptoms and express decompensated emotions besides other psychological and medical comorbidity [37, 40]. Some of them are opiate seekers or are simply convinced that their severe headaches has to be treated with opiates. Therefore, it is important to identify these difficult-to-treat patients who have developed such preconceived notions and may have comorbidities which overshadow their migraine. Corticosteroids may be useful in breaking their recidivism or "medication-seeking behavior" cycles.When it does not work, these patients need to be referred to headache specialists and behavioral psychologists and occasionally addiction specialists.

So we all need to conduct a careful assessment of each new patient headache type, patient expectation management, consideration of opiate and barbiturate use and dependency, medical and psychological comorbidities, previous misdiagnosis, mistreatment and undertreatment, and overmedication leading to medication overuse headache. Corticosteroids have also been shown to be efficacious as a bridge therapy for managing medication overuse headache. Expert recommendations for intermittent corticosteroids therapy include short tapering doses of up to six times per year. The recent systematic review did not reveal major adverse events; the lowest number needed to harm was 30 patients among the studies included [3••]. Treatment

resistant and chronic migraineurs are often managed in a multimodal fashion where multiple disciplinary experts attend the patient's problems from different angles, both on an inpatient and outpatient basis; corticosteroids are one of the main options for effective management of these patients.

Conclusion

Corticosteroids are among the oldest medicines used to treat migraine attacks. The cohort of patients for whom the efficacy of corticosteroids was high in our review includes those presenting with status migrainosus, severe and resistant or refractory migraines, higher baseline disability, and previous history of recurrent headaches. Various types of steroids and dosing protocols have been used both as mono- and adjunctive-therapies. Both oral and parenteral dosing have shown to be efficacious in aborting migraines, preventing recurrence and when other acute care medications have failed. Corticosteroid administration can smoothen transfer of care to a specialist setting; they should not be administered more than six times within 1 year. Adverse effects of short-tapers or single doses are mild and tolerable. Corticosteroids can be especially useful in the management of migraineurs who frequent the emergency room, and any patient in the outpatient setting whose migraine attack will not break or has not responded to appropriate migraine specific medications like triptans.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Yohannes W. Woldeamanuel declares no potential conflicts of interest.

Dr. Alan M. Rapoport is a consultant for Merck and received honoraria from Allergan.

Dr. Robert P. Cowan is a section editor for *Current Pain and Headache Reports*.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Frohner RN. Cortisone in migraine and histamine headaches. Rocky Mt Med J. 1953;50(11):882.
2. Blumenthal JS. Cortisone in allergic migraine. Minn Med. 1952;35(3):209–12.
3.•• Woldeamanuel YW, Rapoport AM, Cowan RP. The place of corticosteroids in migraine attack management: a 65-year systematic review with pooled analysis and critical appraisal. Cephalalgia. Forthcoming 2014. *This recently completed study is the most up-to-date and thorough paper providing a 65-year systematic review with pooled analysis and critical appraisal on the place of corticosteroids for the management of migraine attacks. The study is unique in the fact that it provides a comprehensive methodical analysis of all clinical trials ever since the mass production of corticosteroids which evaluated the efficacy of corticosteroid administration in migraine management.*
4. Shahrami A, Assarzadegan F, Hatamabadi HR, Asgarzadeh M, Sarehbandi B, Asgarzadeh S. Comparison of Therapeutic Effects of Magnesium Sulfate vs. Dexamethasone/Metoclopramide on Alleviating Acute Migraine Headache. J Emerg Med. 2014 Sep 30. pii: S0736-4679(14)00757-4.
5.• Huang Y, Cai X, Song X, Tang H, Xie S, Hu Y. Steroids for preventing recurrence of acute severe migraine headaches: a meta-analysis. Eur J Neurol: Off J Eur Fed Neurol Soc. 2013;20(8):1184–90. *This study provides useful and powerful statistical meta-data containing weighted meta-analysis of the effect size for corticosteroid adminstration in preventing recurrence of acute severe migraine headaches.*
6. Neill A, Brannigan D. Towards evidence-based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 2: Dexamethasone for reduction of migraine recurrence. Emergency Medicine Journal : EMJ. 2013;30(2):165–6.
7. Colman I, Friedman BW, Brown MD, Innes GD, Grafstein E, Roberts TE, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. BMJ. 2008;336(7657):1359–61.
8. Singh A, Alter HJ, Zaia B. Does the addition of dexamethasone to standard therapy for acute migraine headache decrease the incidence of recurrent headache for patients treated in the emergency department? A meta-analysis and systematic review of the literature. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2008;15(12):1223–33.
9. Moskowitz MA. Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. Trends Pharmacol Sci. 1992;13(8):307–11.
10. Hargreaves RJ, Shepheard SL. Pathophysiology of migraine—new insights. Can J Neurol Sci Le J Can Des Sci Neurol. 1999;26 Suppl 3:S12–9.
11. Waeber C, Moskowitz MA. Migraine as an inflammatory disorder. Neurology. 2005;64(10 Suppl 2):S9–15.
12. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral sensitisation. Lancet Neurol. 2009;8(7):679–90.
13. Fusco M, D'Andrea G, Micciche F, Stecca A, Bernardini D, Cananzi AL. Neurogenic inflammation in primary headaches. Neurol Sci: Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2003;24 Suppl 2:S61–4.
14. Kaube H, Hoskin KL, Goadsby PJ. Activation of the trigeminovascular system by mechanical distension of the superior sagittal sinus in the cat. Cephalalgia: Int J Headache. 1992;12(3):133–6.
15. Nixdorf DR, Velly AM, Alonso AA. Neurovascular pains: implications of migraine for the oral and maxillofacial surgeon. Oral Maxillofac Surg Clin North Am. 2008;20(2):221–35. *vi-vii*.
16. Hardebo J, Suzuki N. Evidence for neurogenic inflammation upon activation of trigeminal fibers in the internal carotid artery and dural vessels, but not to pial arteries and their cortical branches. In: CR F, editor. New advances in headache research. London: Smith-Gordon; 1991. p. 173–6.
17. Markowitz S, Saito K, Moskowitz MA. Neurogenically mediated leakage of plasma protein occurs from blood vessels in dura mater but not brain. J Neurosci: Off J Soc Neurosci. 1987;7(12):4129–36.

18. Geppetti P, Rossi E, Chiarugi A, Benemei S. Antidromic vasodilatation and the migraine mechanism. J Headache Pain. 2012;13(2):103–11.
19. Buzzi MG, Carter WB, Shimizu T, Heath 3rd H, Moskowitz MA. Dihydroergotamine and sumatriptan attenuate levels of CGRP in plasma in rat superior sagittal sinus during electrical stimulation of the trigeminal ganglion. Neuropharmacology. 1991;30(11):1193–200.
20. Knyihar-Csillik E, Tajti J, Samsam M, Sary G, Buzas P, Vecsei L. Depletion of calcitonin gene-related peptide from the caudal trigeminal nucleus of the rat after electrical stimulation of the Gasserian ganglion. Exp Brain Res. 1998;118(1):111–4.
21. Messlinger K, Fischer MJ, Lennerz JK. Neuropeptide effects in the trigeminal system: pathophysiology and clinical relevance in migraine. Keio J Med. 2011;60(3):82–9.
22. Bley KR, Hunter JC, Eglen RM, Smith JA. The role of IP prostanoid receptors in inflammatory pain. Trends Pharmacol Sci. 1998;19(4):141–7.
23. Alstadhaug KB. Histamine in migraine and brain. Headache. 2014;54(2):246–59.
24. Ottosson A, Edvinsson L. Release of histamine from dural mast cells by substance P and calcitonin gene-related peptide. Cephalalgia: Int J Headache. 1997;17(3):166–74.
25. Dimitriadou V, Buzzi MG, Moskowitz MA, Theoharides TC. Trigeminal sensory fiber stimulation induces morphological changes reflecting secretion in rat dura mater mast cells. Neuroscience. 1991;44(1):97–112.
26. Dimitriadou V, Buzzi MG, Theoharides TC, Moskowitz MA. Ultrastructural evidence for neurogenically mediated changes in blood vessels of the rat dura mater and tongue following antidromic trigeminal stimulation. Neuroscience. 1992;48(1):187–203.
27. Edvinsson L. Sensory nerves in man and their role in primary headaches. Cephalalgia: Int J Headache. 2001;21(7):761–4.
28. Davis KD, Dostrovsky JO. Activation of trigeminal brain-stem nociceptive neurons by dural artery stimulation. Pain. 1986;25(3):395–401.
29. Moskowitz MA. Neurogenic inflammation in the pathophysiology and treatment of migraine. Neurology. 1993;43(6 Suppl 3):S16–20.
30. Diener HC. RPR100893, a substance-P antagonist, is not effective in the treatment of migraine attacks. Cephalalgia: an international journal of headache. 2003;23(3):183–5.
31. Ramadan NM. Acute treatments: some blind alleys. Current medical research and opinion. 2001;17(Suppl 1):s71–80.
32. Hansen JM, Ashina M. Calcitonin gene-related peptide and migraine with aura: A systematic review. Cephalalgia: an international journal of headache. 2014;34(9):695–707.
33. Data J, Britch K, Westergaard N, Eihnuller F, Harris S, Swarz H, et al. A double-blind study of ganaxolone in the acute treatment of migraine headaches with or without an aura in premenopausal females (abstract). Headache. 1998;38(380).
34. Geraud G, Keywood C, Senard JM. Migraine headache recurrence: relationship to clinical, pharmacological, and pharmacokinetic properties of triptans. Headache. 2003;43(4):376–88.
35. Asseburg C, Peura P, Oksanen T, Turunen J, Purmonen T, Martikainen J. Cost-effectiveness of oral triptans for acute migraine: mixed treatment comparison. Int J Technol Assess Health Care. 2012;28(4):382–9.
36. Schellenberg ES, Dryden D, Pasichnyk D, Ha C, Vandermeer B, Friedman B, et al. Acute Migraine Treatment in Emergency Settings. Comparative Effectiveness Review (Prepared by the University of Alberta Evidence based Practice Center under Contract No 290-2007-10021-I) AHRQ Publication No 12(13)-EHC142-EF Rockville, MD: Agency for Healthcare Research and Quality November 2012 www.effectivehealthcare.gov/reports/final.cfm. 2012; 84.
37. Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, et al. Guidelines for the diagnosis and management of migraine in clinical practice. Can Headache Soc CMAJ. 1997;156(9):1273–87.
38. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000;55(6):754–62.
39. Woldeamanuel YW, Andreou AP, Cowan RP. Prevalence of migraine headache and its weight on neurological burden in Africa: a 43-year systematic review and meta-analysis of community-based studies. Journal of the Neurological Sciences. 2014;342(1–2):1–15.
40. Edmeads J. Emergency management of headache. Headache. 1988;28(10):675–9.