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Dexamethasone Hastens Migraine Resolution

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Abstract

Purpose: If corticosteroids are an effective abortive migraine treatment in the non-pregnant adult population, corticosteroids could be trialed for acute, severe migraine treatment in pregnancy. The purpose of this evidence-based practice review was to determine the efficacy of DXM at achieving acute severe migraine resolution in non-pregnant adult migraineurs.

Methods: PubMed and Academic Search Complete searches for randomized controlled trials (RCT) of steroids for migraine treatment yielded two RCT and two pooled analyses for inclusion.

Results: The pooled analyses showed that at 24- to 72-hour follow-up, 12– 24 mg parenteral DXM added to standard abortive migraine therapy reduces moderate or severe migraine recurrence by 29%. DXM 16 mg intravenous treats acute migraine without aura, as well as, does 400 mg intravenous sodium valproate. For migraine resolution comparable to that achieved by intravenous magnesium sulfate 1 gram, intravenous low dose DXM 8 mg may best be administered without intravenous metoclopramide 10 mg.

Conclusion: Given dose-dependent efficacy of DXM for treatment of acute severe migraine, migraine resolution needs higher initial DXM doses than used for FLM. To benefit pregnant migraineurs, RCT of intramuscular DXM 12-24 mg, with or with anti-emetics such as dimenhydrinate, doxylamine/pyridoxine, ondansetron, or promethazine, in comparison to 1-2 mg intravenous magnesium sulfate are needed.

Keywords: Betamethasone; Corticosteroids; Dexamethasone; Migraine; Pregnancy; Migraine recurrence; Migraine resolution

Introduction

Globally, migraine affects about 14.7% of all individuals, 12% of adults, 17% of women, and 6% of men [1-4]. Migraine, a primary headache disorder, is ranked as the third most common illness and the seventh most disabling illness [4]. In the United Kingdom, migraine related absenteeism accounts for 25 million lost work days [5]. Migraine treatment costs Europe USD 21.2 billion annually [3]. Over 30 million Americans have migraines, leading to USD 29 billion direct and indirect migraine costs in the United States [6,7]. Randomized controlled trials (RCTs) have shown that 76% of migraineurs seeking emergency department treatment have recurrent migraines [7].

Pregnancy-associated migraines

As female migraine prevalence rises from menarche to menopause, most female migraneurs are affected during their reproductive years [8]. The hormonal milieu of pregnancy varies with estimated gestational age (EGA), affecting migraine incidence and severity. From about 13 weeks EGA estrogen rises to a peak in the late third trimester, preceding delivery. In the third trimester, progesterone also rises, increasing venous distensibility. These hormonal changes may be linked to pregnancy-associated migraine, cardiovascular disease, and stroke [9]. The literature indicates that while 50% to 75% of pregnant migraineurs experience diminished migraine-related disability in pregnancy, more than 26% of pregnant migraineurs experience moderate or severe migraine-related disability in pregnancy [8]. Migraine with aura worsens with pregnancy-related hormonal changes [10]. Some women may have their first migraines in pregnancy [10].

Therapeutic options for migraines

Several classes of medications and supplements used to treat migraine disorder are contraindicated or relatively contraindicated in pregnancy: Anti-epileptics, barbituates, beta blockers, caffeine, ergot alkaloids, fever few, nonsteroidal anti-inflammatories (NSAIDs), onabotulinumtoxin A, opioids, petasites, serotonin antagonists, and triptans [11]. Anti-emetics, magnesium sulfate, and the corticosteroids betamethasone (BTM) and dexamethamsone (DXM) all have pregnancy-

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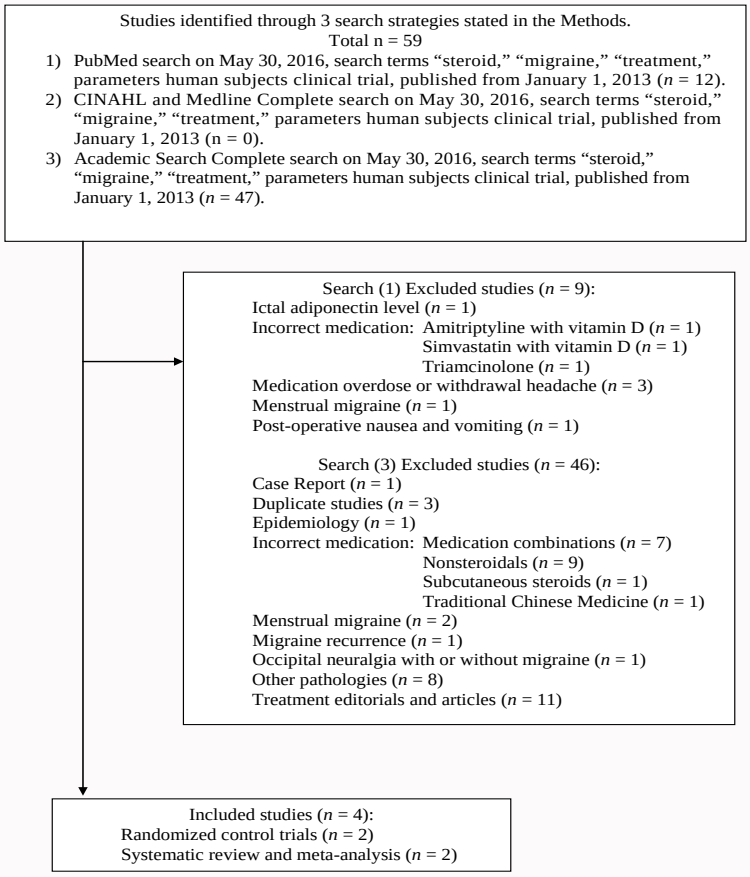

Figure 1: Article inclusion process.

specific indications unrelated to migraine treatment, in addition to non-pregnancy indications for migraine treatment. Parenteral DXM may be the most used corticosteroid, due to less fluid retention and other mineralocorticoid effects [7]. Relevant contraindications to corticosteroid use are active fungal infections, active peptic ulcer disease, and immediate NSAID use [7].

The efficacy of magnesium sulfate is limited to magnesium deficient persons and migraine with aura [12]. Opioids have been used for severe migraine treatment in pregnancy [1]. However, opioids exacerbate pregnancy-associated gastroparesis and constipation, are under scrutiny due to addictive potential and neonatal withdrawal, and are discouraged in the third trimester [1,11].

Considerations of approved corticosteroid use in pregnancy

While only one course of antenatal steroids for fetal lung maturity (FLM) is recommended, fewer than five courses of antenatal steroids have not been shown to result in significant neonatal morbidity [13]. When five courses of FLM steroids are given, median fetal birth weight has been reduced, p =.01 [13]. There may be an association between receipt of five or more courses of FLM steroids and cerebral palsy [13]. Of note, children whose mothers received more than four courses of FLM steroids are less likely to have asthma than children whose mothers received four or fewer courses of FLM steroids [13]

Randomized controlled trials on FLM steroids do not focus on maternal outcomes, but temporary, spontaneously resolving maternal glucose intolerance is a known adverse effect of FLM steroids [14-16]. While it is biologically plausible that FLM steroids may contribute to maternal infections, including chorioamnionitis [15], FLM steroids do not increase chorioamnionitis, maternal death, or puerperal sepsis [17]. FLM steroids are associated with a 44% reduction in systemic neonatal infections within 48 hours of birth [17]. Systematic review actually supports the use of FLM steroids in maternal chorioamnionitis, due to reduced neonatal mortality (odds ratio [OR] .49, 95% confidence interval [CI] .34 to .73), respiratory distress syndrome (OR .58, 95% CI .44 to .76) intraventicular hemorrhage (OR: .41, 95% CI .24 to .69), and severe intraventricular hemorrhage (OR .40, 95% CI .24 to .69) [18].

Previously, the FLM steroid window was for impending deliveries at 23 weeks to 34 weeks estimated gestational age (EGA; 13). Currently, the recommended FLM steroid window in the United States is now impending deliveries between 23 weeks and 37 weeks EGA [13,19]. The corticosteroids BTM and DXM could provide acute severe migraine treatment in pregnant women from 23 to 37 weeks EGA who have not received a course of FLM steroids. Seeking treatments to ameliorate the quality of life of potentially over one-quarter of pregnant women is consistent with the global "Lifting the Burden" campaign to improve health care received by persons with headache [8]. For acute migraine treatment, parenteral DXM is more studied than parenteral BTM. Therefore, this evidence-based practice review seeks to elucidate the effectiveness of parenteral DXM for acute migraine treatment in adults, evaluated 20 to 120 minutes after administration, in comparison to other accepted acute migraine treatments.

Methods

A PubMed search using the terms steroid, migraine, and

treatment, with search parameters clinical trial, publication date from January 1, 2013 onwards, and human subjects yielded 12 articles of which two RCTs and one meta-analysis predating the RCT were included. The three included articles focus on DXM, not BTM. Addition of pregnancy to the search terms did not yield any clinical trials irrespective of date range. Nine articles were excluded due to content mismatch: Adiponectin, amitriptyline, medication overuse headache, migraine prophylaxis, nausea and vomiting, menstrual migraine, prednisolone or triamcinolone, and vitamin D. Figure 1 illustrates the article inclusion process. Searching the CINAHL and Medline Complete databases did not yield additional relevant clinical trials or meta-analysis. Academic Search Complete yielded 47 articles of which one was the meta-analysis found via PubMed, and one other systematic review with pooled analysis covering 1950 through August 30, 2014 was included (Figure 1).

Results

Dexamethasone with metoclopramide versus magnesium sulfate

In a Level 1b, unregistered, double-blind, RCT in Iranian adults [3,20], 1 gram intravenous magnesium sulfate was compared to intravenous DXM/metoclopramide 8 mg/10mg. Patients had numeric migraine severity pain scale scores greater than 4 on an 11-point numeric rating scale of 0 representing no pain to 10 representing the worst possible pain. Patients did not have other chronic diseases and were not taking anti migraine medication before presentation to the academic medical center emergency department (ED) in 2011. Excluded patients had fewer than five lifetime migraines, were pregnant or breastfeeding, had renal failure, were allergic to any of the study medications, or had been pretreated prior to ED presentation [3]. For ethical reasons, there was not a placebo control.

Of 120 potential participants, 27 did not have migraine, 12 met exclusion criteria, and 11 were not randomized. Automated online permutated blocks of five random number generation selected two demographically similar groups of 35 participants each with equivalent pain severity scores of 8-8.2/10, at baseline [3]. Metoclopramide with DXM achieved pain scores of 7.4 ± 1.4, 6 ± 2.4, and 2.5 ± 2.9 at 20 minutes, 60 minutes, and 120 minutes respectively, indicating that therapeutic effect onset takes 60 minutes. Magnesium sulfate more rapidly and more effectively decreased migraine severity with pain scores 5.2 ± 1.7, 2.3 ± 1.9, and 1.3 ± .66 at 20 minutes, 60 minutes, and 120 minutes respectively, $p < .0001$ at each time point. Nausea was equally frequent in each group, with lethargy, vertigo, and emesis, also occurring in the DXM with metoclopramide group [3].

In adult Iranians with migraine rated as 8-8.2/10, 1 gram intravenous magnesium sulfate had a more rapid onset of action and more effectively reduced migraine pain than intravenous DXM/metoclopramide 8 mg/10mg, with fewer side effects. When co-administered, metoclopramide may reduce the efficacy of magnesium sulfate [3]. It is postulated that metoclopramide reduces the efficacy of DXM when co-administered, and/or that a higher dose of DXM is required. The anti-inflammatory benefits of DXM may become significant with increased time from administration [3].

Despite presentation according to the Consolidated Standards of Reporting Trials, unregistered RCT risk the perception of lacking a registered RCT's validity. Awareness that metoclopramide may reduce the efficacy of magnesium sulfate in migraine treatment could have prompted trial redesign [3]. Addition of a DXM only arm and addition of an arm combining DXM and an antiemetic with a different pharmacological mechanism of action than metoclopramide could have led to more clinically useful outcomes.

Dexamethasone versus sodium valproate

From April 2012 to June 2014, adult patients at two Iranian EDs participated in a Level 1b, registered, double blind, RCT of 400 mg intravenous sodium valproate or 16 mg intravenous DXM [20,21]. A visual analog scale (VAS), from 0 for no pain to 10 representing severe pain was used. Included patients had VAS scores greater than 5, and at least a 1-year migraine history. Exclusion criteria were having other chronic diseases, including uncontrolled hypertension, acute infection or inflammatory disease, hypotension, allergy to any trial medications, tension headache, or pretreatment of migraine prior to ED presentation [21].

Of the 104 eligible patients, six patients declined study participation, 18 patients were excluded, and 14 randomized participants were lost to follow-up. Manual balance block pooled randomization was performed. The sodium valproate group, mean age 37.29 years, was younger than the DXM group, mean age 32.05 years, $p = .036$. Otherwise the groups were similar with mean VAS pain scores of 8.2 and 8.46 respectively [21].

Sodium valproate achieved pain scores of 5.31 ± .58 and 3.66 ± .67 at 30 minutes and 120 minutes respectively post infusion. DXM achieved pain scores of 5.46 ± .65 and 3.59 ± .76. Compared to initial pain scores, each treatment produced significant improvement at each time point, $p = .001$ [21]. Compared to each other, the treatment effects of sodium valproate 400 mg and DXM 16 mg, both intravenous, were similar for migraine without aura. Sodium valproate was more efficacious than DXM for the 11 patients who had migraine with aura, $p = .001$ at 30 minutes and 120 minutes [21].

Manual randomization, a protocol change from 8 mg to 16 mg dexamethasone, small sample size for migraine with aura, and failure to perform intention to treat analysis, limited this RCT [21]. In clinical practice for treatment of acute migraine, intravenous sodium valproate may be dosed up to 1200 mg [22]. Therefore, this RCT could have used a higher sodium valproate dose, which may have affected the trial outcome. Nonetheless, intravenous sodium valproate 400mg and DXM 16 grams showed comparable efficacy in the treatment of acute migraine without aura [21].

The 65-year systematic review with pooled analysis and critical appraisal

This Level 1a, systematic review and pooled analysis of 3,989 participants, median age 37.5 years, 1:4.23 median male: female ratio, from 25 studies, included 14 RCTs with Jadad scores of 5, which is the highest score possible for an RCT and reporting quality [7,20]. Four systematic reviews were also included. Emergency department-based studies achieved good outcomes with parenteral DXM average dose 12.8 mg, range 4-24 mg [7]. Only three migraineurs needed corticosteroid treatment to reduce recurrence in 24-hours, but 10 migraineurs needed corticosteroid treatment to reduce recurrence in 72-hours. Corticosteroid use is supported by 78.6% of studies evaluating migraine recurrence and 61.2% of studies measuring acute migraine resolution. Overall, corticosteroid treatment reduced recurrent migraine intensity and increased recurrent migraine response to NSAIDs [7].

The major limitation is the diversity of corticosteroid protocols studied [7]. With eight protocols, in addition to an array of parenteral

DXM at a median dose of 10 mg, it is difficult to know which protocol will work best for any given patient. The recommended outpatient oral DXM 4 mg repeated up to five times in three days protocol actually has not undergone rigorous trials [7]. Parenteral DXM protocols have withstood more scrutiny than oral protocols and can be performed outpatient, but did not receive the same recommendation as oral protocols.

The 12-year review with meta-analysis

A Level 1a, systematic review and pooled meta-analysis included 905 participants from eight RCTs with 24 – 72 hour surveillance, reported 1999 – 2011 [20,23]. The PubMed, Embase, and Cochrane Library were searched for placebo controlled RCTs of additive steroids to standard abortive therapy for treatment of acute migraine from 1950 through 2012 [23]. Five RCTs used 10-24 mg intravenous DXM, one RCT used 10 mg parenteral DXM, one RCT used 10 mg oral DXM, and one RCT used 10 mg intravenous DXM or 40 mg oral prednisone. Seven of the RCTs received a Jadad Quality Scale of 5. The remaining RCTs had Jadad scores of 4 [23].

Addition of steroids to standard abortive therapy was found to improve response, (risk ratio [RR] .71, 95% CI .59 to .86, p = .0004), with a number needed to treat (NNT) of 10 prevent one moderate or severe recurrent migraine in 72-hours [23]. For two RCTs of oral steroids, neither route of steroid administration, nor the type of steroid administered affected outcomes, p = .37. Subgroup analysis found that intravenous or intramuscular steroid administration was significantly more effective than standard abortive therapy, (RR .68, 95% CI .55 - .84, p = .0003), with a NNT of eight to prevent one severe recurrent migraine [23]. However, when compared to standard abortive migraine therapy, overall steroids did not significantly improve complete migraine resolution, (RR 1.11, 95% CI .94 - 1.32, p = .22). A non-significant dose-dependent effect was seen at 15 mg DXM, (X^2 = 2.52, p = .11). Dizziness following steroid administration was the most common adverse effect, (RR 2.78, 95% CI 1.02 – 7.61).

Based on the statistically nonsignificant trend of improved clinical efficacy with DEX 15 mg or more (p = .11), doses of 15 – 24 mg intravenous or intramuscular DXM added to standard abortive migraine therapies may be more effective than unaided standard abortive migraine therapies in completely resolving a migraine [23]. As only half of the RCTs studied, with 379 of 905 participants (41.9%), dosed intramuscular or intravenous DXM at 15 – 24 mg, a few additional RCT of at least 200 participants each might provide definite data.

In comparison to the 65-year systematic review, the 12-year review may have been overly selective in RCT inclusion criteria [7,23]. As a result, the RCT included in the 12-year review had limited use of oral steroids, and a small total study population that limited subgroup analysis [23]. When seeking parenteral corticosteroid recommendations, the lack of oral corticosteroid recommendations is not a limitation. However, the lack of subgroup analysis defining patient populations that would benefit most from each treatment modality is a limitation.

Conclusion

The clinical question asked in this review was: In adults, what is the effectiveness of parenteral BTM or DXM for acute migraine treatment in comparison to other accepted acute migraine treatments? In response, the 12-year review suggested that 15 – 24 mg intravenous or intramuscular DXM might be more effective than standard abortive therapies in completely resolving a migraine [23]. However, a 65-year systematic review found parenteral DXM 12.8 mg should be sufficient to achieve a response [7]. For treatment of acute migraine without aura, 16 mg intravenous DXM has comparable efficacy to 400 mg intravenous sodium valproate 400mg [23]. To achieve better migraine resolution than magnesium sulfate 1 gram, low dose DXM, 8 mg intravenous, should not be administered with metoclopramide 10 mg intravenous [3].

The future

To facilitate comparison with the literature, future RCTs should be conducted to evaluate the effectiveness of steroids for migraine treatment with outcomes at 20-30 minutes, 2 hours, and 24 – 72 hours from administration. Outcome measures should consistently include complete migraine resolution. Selection of uniform pain measures would also improve comparison with the existing literature. Intravenous DXM 8 mg may be under dosed, and 12 – 24 mg necessary for therapeutic response [7,23]. Anti-emetics other than metoclopramide should be trialed with steroids, as anti-emetic reduction of steroid efficacy may be limited to metoclopramide [3]. Distinctions need to be made as to the migraine classification treated: Planned subgroup analysis may be necessary as treatment outcomes can vary for migraine with or without aura.

Clinical bottom line

Steroid use in pregnancy is rarely an initial treatment option. However, with moderate to severe migraines, resistant to acetaminophen, anti-emetics, and intravenous magnesium, steroids may play a role in reducing opioid prescribing, and reducing migraine-related disability. As a penultimate treatment for moderate to severe pregnancy-associated migraines, steroids have a role consistent with the global "Lifting the Burden" campaign, which also reduces the potential for maternal opioid use and abuse, as well as, reducing the need for neonatal opioid withdrawal [1,8,11].

Steroids for FLM protocols are based on split dosing: In the United States, intramuscular BTM 12 mg given twice, 24 hours apart, or intramuscular DXM 6 mg, given 4 times, 12 hours apart are recommended [24]. Given that 12.8 mg is the average trialed DXM dose, and dose-dependent therapeutic effects occur at 12 – 24 mg, migraine resolution needs higher initial DXM doses than those used for FLM [7,23]. To benefit pregnant women with severe migraines, consideration should be given to RCT of intramuscular DXM 12-24 mg, with, or with anti-emetics such as dimenhydrinate, doxylamine/pyridoxine, ondansetron, or promethazine, in comparison to 1-2 mg intravenous magnesium sulfate. Of note, ante partum trials of DXM include protocols for two doses of 14-24 mg 24 hours apart [16]. Therefore, the basis for the maternal and fetal safety evaluation of DXM 12-24 mg as single doses with possible additional DXM 8 mg 12 or 24 hours later for FLM already exists.

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References

1. Aubé M. Migraine in pregnancy. Neurology. 1999; 53: S26-S28.

2. Nikkhah K, Ghandehari K, Jouybari AG, Mirzaei MM, Ghandehari K.

Clinical trial of subcutaneous steroid injection in patients with migraine disorder. Iranian Journal of Medical Sciences. 2016; 41: 9–12.

3. 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. The Journal of Emergency Medicine. 2015; 48: 69-76.
4. Steiner TJ, Stovner LJ, Birbeck GL. Migraine: The seventh disabler. The Journal of Headache and Pain. 2013; 14: 1
5. The Migraine Trust. Facts and figures. Key facts and figures about migraine. 2016.
6. American Migraine Foundation. 36 million migraine campaign. n.d. [cited 2016 April 30].
7. 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. 2015; 35: 996-1024.
8. Ihunnaya O. Frederick, Chunfang Qiu, Daniel A. Enquobahrie, Sheena K. Aurora, B. Lee Peter, Bizu Gelaye, et al. Lifetime Prevalence and Correlates of Migraine among Women in a Pacific Northwest Pregnancy Cohort Study.Headache. 2014; 54: 675-685.
9. Wabnitz A, Bushnell C. Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature. Cephalalgia. 2015; 35: 132-129.
10. Pakalnis A. Migraine and Hormones. Seminars in Pediatric Neurology 2016; 23: 92-94.
11. Wells RE, Turner DP, Lee M, Bishop L, Strauss L. Managing migraine during pregnancy and lactation. Current Neurology and Neuroscience Reports. 2016; 16: 1-24.
12. Kabbouche MA, Khoury CK. Management of primary headache in the emergency department and inpatient headache unit. Seminars in Pediatric Neurology. 2015; 23: 40-43.
13. Wapner RJ, Gyamfi-Bannerman C, Thom EA. What we have learned about antenatal corticosteroid regimens. Seminars in Perinatology. 2016.
14. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. The Cochrane Library. 2013.
15. Mariotti V, Marconi AM, Pardi G. Undesired effects of steroids during pregnancy. The Journal of Maternal-Fetal and Neonatal Medicine. 2004; 16: 5-7.
16. McGoldrick E, Brown J, Middleton P, McKinlay CJ, Haas DM, Crowther CA. Antenatal corticosteroids for fetal lung maturation: an overview of Cochrane reviews. The Cochrane Library. 2016.
17. Vogel JP, Souza JP, Gülmezoglu AM, Mori R, Lumbiganon P, Qureshi Z, et al. Use of antenatal corticosteroids and tocolytic drugs in preterm births in 29 countries: an analysis of the WHO Multicountry Survey on Maternal and Newborn Health. The Lancet. 2014; 38: 1869-1877.
18. Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R. Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis. PloS one. 2016; 11: e0147604.
19. American Congress of Obstetricians and Gynecologists. Practice advisory: Antenatal corticosteroid administration in the late preterm period.
20. Oxford Centre for Evidence-Based Medicine. Levels of evidence. 2009.
21. Mazaheri S, Poorolajal J, Hosseinzadeh A, Fazlian MM. Effect of intravenous sodium valproate vs dexamethasone on acute migraine headache: A double blind randomized clinical trial. PLoS ONE. 2015; 10: e0120229.
22. Marmura, MJ, Silberstein, SD, Schwedt TJ. The acute treatment of migraine in adults: The American headache society evidence assessment of migraine pharmacotherapies. Headache. 2015; 55: 3-20.
23. Huang Y, Cai X, Song X, Tang H, Huang Y, Xie S, et al. Steroids for preventing recurrence of acute severe migraine headaches: A meta-analysis. European Journal of Neurology. 2013; 20: 118490.
24. Hofmeyr GJ. Antenatal corticosteroids for women at risk of preterm birth: RHL commentary. The WHO Reproductive Health Library. 2009.