ACETYLSALICYLIC ACID IN THE PROPHYLAXIS OF MIGRAINE WITH AURA

Abstract

Migraine with aura (MA) has a prevalence of about 1-5% and an incidence of 14.1‰ person-years, and can strongly affect lifestyle and quality of life. Although many known and effective prophylaxis drugs are now available for migrainous headache, none of these showed a particular specificity on the management of MA. While the use of Acetylsalicylic acid (ASA) in the acute management of migraine is well documented, evidences on its employment in prophylaxis of headache are few and contrasting; continuous use of ASA seems to affect the frequency of migraine episodes and higher week dosages could be consistently associated with better results. None of these studies stratified patients according to the presence of aura. Since many years, we started treating specifically patients with MA with low doses of ASA. Aim of our retrospective study was to assess the efficacy and the tolerability of ASA in the management of migraine with aura, and to identify potential predictors of positive outcome in prophylaxis of MA. We observed a cohort of MA patients and evaluated the average number of attacks per month of migraine with aura according to the headache diary. After the start of a prevention therapy (T0), outcome was evaluated at 2, 4 and 6 months (T1, T2 and T3, respectively) as percentage of the average number of attacks with aura reported in the first three months of observation. Only attacks with aura were considered for the evaluation. To evaluate improvement, we considered successful a treatment that induced a reduction of at least 50% in the number of attacks with aura at follow-up timelines compared to the baseline (T0). Report of side effects and treatment switch were recorded. In the end, 43 patients completed the 6 months of observation

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necessary for the evaluation of outcome of ASA therapy, and we tracked 33 that were treated with other therapies. Positive response to treatment was reported by 86.1% of patients in the ASA series and 41.9% in the other one ($p< 0.001$). Discontinuation of therapy at the end of the follow-up period was markedly higher in the group of patients treated with more classical courses of medication (18.6% vs 56.7%). We found that ASA is very effective in reducing the frequency of attacks with aura ($p<0.001$) and is well tolerated by patients ($p<0.001$). Moreover, our results show a better response to treatment with ASA compared with other therapies in the reduction of frequency of attacks with aura, with a probability of success that is difficult to evaluate seeing that we just observed two cases series, but apparently many times greater in the ASA group. Ideally the study should be replicated as a case-control study on a larger sample and a homogenous control group. In the end, we think that ASA can be safely used as an effective treatment in patients suffering from MA, or from a combination of MA and migraine without aura (MoA) if the attacks with aura are the most frequent migraine feature. Even though the number of patients with these characteristics is not very great, treatment with low-dose daily ASA could be interesting in this smaller group because of its being an extremely wieldy and inexpensive drug.

Keywords: Migraine with aura, acetylsalicylic acid, migraine prophylaxis

I. INTRODUCTION

Headaches are extremely common pathologies that can strongly affect lifestyle and quality of life; migraine, in particular, is associated with many medical comorbidities, as cardiovascular diseases, sleep disturbances, psychiatric issues, and is the second most disabling condition worldwide.

Migraine with aura (MA) has a prevalence of about 1-5% and an incidence of 14.1‰ person-years, being thus definitely less frequent than migraine without aura (MoA), which is observed in more than 14% of the general population [1,2,3].

First known descriptions of MA go back to Hippocrates, who wrote about a shiny light obscuring the visual field of the patient, followed by a sharp lateralized pain of the temples, extending to all head and neck ; Hildegarde of Binden, badess in a Middle Age convent, described her own aura in a very poetic manner, speaking of 'a very beautiful, wonderful star, surrounded by thousands of other falling sparks, that fell downside… and suddenly all was muted to black charcoal, and precipitated in the abyss'.

MA is defined as follow: recurrent attacks, lasting minutes, of unilateral, fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms. Often patients complain much more about aura than they do about the headache phase; the experience of the transient deficit is associated with acute anxiety, while the subsequent pain, often shorter in MA than in MoA, is often perceived just as a dull post-attack phase [4]. Pathogenesis of MA has still unclear aspects, but many authors suggested an association between endothelial dysfunction, platelets disease and migraine [5]. Evidence of abnormal platelet activation in migraineurs is well-known and patients affected by platelet disease have an increased risk of developing MA [6,7]. Moreover, signs of endothelial dysfunction are evident in subjects with migraine of recent onset [8]. It has been shown that vasoconstrictors as Endothelin-1 can induce cortical spreading depression in *in vivo* rat model, underlining a connection between endothelial dysfunction and Leao's cortical spreading depression [9]. Moreover, altered reactivity of cerebral endothelium seems to be more pronounced in the occipital regions of brain [10]. Migraineurs with aura present an excessive arterial response to hyperemia, likely as an effect of endothelium dysfunction, compared to controls with MoA [11].

Although many known and effective prophylaxis drugs are now available for migrainous headache, none of these showed a particular specificity on the management of MA. For more than a century, AcetylSalicylic Acid (ASA) has been used to treat acute pain, even in migraine. It acts peripherally inhibiting the inflammatory process by blocking the cyclo-oxygenases, stopping vasoactive neuropeptides release from the C-fibers and reducing NO synthesis. It shows a central effect, too, binding to nociceptive structures of the trigeminal nuclei and reducing the serotonin-mediated firing of neurons in the hypothalamus and brainstem [12-14]. ASA is commonly used for primary and secondary prevention of many diseases linked to endothelium dysfunctions. While the use of ASA in the acute management of migraine is well documented, evidences on its employment in prophylaxis of headache are few and contrasting. Since the 1970s, small open studies suggested a possible role for it, but the reduction of attacks was mild to moderate [15- 18]. Masel et al. described

the overall effectiveness of ASA coupled with dipyridamole in migraineurs: some patients showed hyperaggregability only at some determinations, suggesting that migraineurs may present fluctuations in platelet activity [19]. Few trials comparing ASA with other drugs exist. Grotenmeyer et al. evaluated a small sample of 28 patients in a double-blind crossover study, where ASA at the dose of 1500 mg/day was compared with metoprolol [20]: they showed a significant efficacy of ASA, in the presence, though, of a more pronounced activity of metoprolol. When a similar experience was repeated on a larger scale and with lower doses of ASA, results were unclear [21]. ASA efficacy was tested at low doses of 100 mg every other day in women with high frequency migraine, but the outcome was even more uncertain [22]; prophylactic activity of ASA was never denied, but it didn't prove outstanding, and showed possibly a dose-related effect. ASA could therefore be recommended as a treatment in patients intolerant to other treatments [23]. When a metanalysis was finally produced, based on the main published articles on the subject up to 2016, Pellegrino Baena et al. found that continuous use of ASA affects the frequency of migraine episodes. Additionally, they found that higher week dosages were consistently associated with better results [24]

None of these studies stratified patients according to the presence of aura. To the best of our knowledge, there is one report of a case series where only patients with aura were observed, after treatment with ASA, and they found a remarkable suppression of aura frequency by aspirin prophylaxis in migraine wit aura patients [25].

Since many years, after diffusion of reports of platelet alterations in migraineurs and some episodic positive responses to ASA, we started treating some patients with MA with low doses of ASA. Aim of our retrospective study was to assess the efficacy and the tolerability of ASA in the management of MA, and to identify potential predictors of positive outcome in prophylaxis of MA.

II. MATERIALS AND METHODS

1. **Study Design and Data Collection:** For this retrospective study we screened all the medical records of patients seen for the first time at our Headache Centre between the 1st January 2013 and 30th June 2015. This period of time was chosen according to the beginning of the Third International Classification of Headache (ICHD-III). During the first visit a diagnosis is made, and therapy for the attacks is prescribed. The patient starts a three-month period of observation without prevention therapy, during which she/he fill in a headache diary. At the second visit, the headache diary is evaluated, the diagnosis confirmed and a prevention therapy is prescribed, if needed. For the purpose of our study, the main inclusion criterion was a diagnosis of MA (1.2.1) according to the latest International Classification of Headaches (ICHD III) [26]. Here is a reminder of MA is currently defined: «A. At least two attacks fulfilling criteria B and C. B: One or more of the following fully reversible aura symptoms: 1.visual ; 2.sensory ; 3.speech and/or language ; 4. Motor ; 5. Brainstem ; 6.retinal. C : At least three of the following six characteristics: 1.at least one aura symptom spreads gradually over ≥5 minutes ; 2. two or more aura symptoms occur in succession ; 3.each individual aura symptom lasts 5-60 minutes ; 4. at least one aura symptom is unilateral ; 5. at least one aura symptom is positive ; 6. the aura is accompanied, or followed within 60 minutes, by headache. D. Not better accounted for by another ICHD-3 diagnosis».

Exclusion criteria were age younger than 18 years old or older than 65, chronic assumption of ASA for reasons other than migraine and a very low migraine frequency (less than 2 attacks in three month). We evaluated the average number of attacks per month of migraine with aura according to the headache diary, and thus excluded from the study all the patients who did not fill the diary correctly. After the start of a prevention therapy (T0), outcome was evaluated at 2, 4 and 6 months (T1, T2 and T3, respectively) as percentage of the average number of attacks with aura reported in the first three months of observation. Only attacks with aura were considered for the evaluation. Patients who did not continue follow up for at least 6 months were discarded from the study.

On the other hand, we grouped the data from all patients diagnosed with MA but treated with other drugs (propranolol, flunarizine, topiramate, duloxetine, pizotifen, biofeedback and amitriptyline). Efficacy of these prophylactic treatments are known and commonly considered equivalent [27-29]. Since the study is retrospective and backed by the guarantee of anonymity of the data extracted from medical records during the analysis, the involvement of the ethics committee was unnecessary. To evaluate improvement, we considered successful a treatment that induced a reduction of at least 50% in the number of attacks with aura at follow-up timelines compared to the baseline (T0). Report of side effects and treatment switch were recorded.

2. **Statistical analysis:** Descriptive analyses were performed using frequencies, percentages, frequency tables for categorical variables. For the bivariate analysis chi-square tests were performed to evaluate differences for categorical variables. Primary outcome was to assess the potential relationship between the improvement in MA patients' clinical condition (measured as a reduction of at least 50% of attacks with aura) and the treatment taken. A binary logistic regression model was used to identify possible factors associated with the positive response to treatment. According to the Hosmer-Lemeshow procedure, only covariates having a p-value<0.25 at univariate analysis were introduced into the models [30]. Results are expressed as Crude OR (univariate analysis) and Adjusted OR with 95% CI (multivariate), and the goodness of fit of the model was assessed by the Hosmer-Lemeshow test. A two-tailed p-value of 0.05 was considered significant for all analyses, which were carried out using Stata, version 10.1 (Stata Corp., College Station, TX, USA, 2007).

III. RESULTS

Between the 1st January 2013 and 30th June 2015, a total of 3535 patients were seen for the first time at our Centre.

After excluding all patients diagnosed with MoA, tension-type headache, cluster headache and other less frequent primary headaches or secondary headaches, our sample consisted of 375 patients with MA. 89 patients never returned for the second visit, to have evaluation of headache diary and receive a possible prevention therapy. A large number, 114 patients, suffered from such infrequent attacks that never started prevention therapy. Forty-nine patients were excluded because they were under age. Three patients were discarded from the study as they presented major psychiatric diagnosis, and another one because of an intracerebral aneurism of the 119 who received a therapy, 43 did not complete the 6-month observation (36,13%). No patients switched therapy until the end of the study. In the end, 43

patients completed the 6 months of observation necessary for the evaluation of outcome of ASA therapy, and we tracked 33 more that were treated with other therapies.

In both series, female gender was more represented, a mean age of 37.49 was found in patients treated with ASA and 36.99 in the control group. Description of the sample is displayed in Table 1; no significant differences were found between the demographics of the two series, with the possible exception of migraine attacks frequency, slightly higher in the group treated with ASA.

Positive response to treatment was reported by 86.1% of patients in the ASA series and 41.9% in the other one ($p< 0.001$). The improvement of clinical condition was rated as "none" (when the reduction was under 50% of episodes), "good" (reduction between the 51 and 75% of attacks) or "excellent" (reduction of more than 75% of episodes). A significant difference was assessed between the two series at T1, T2 and T3 (2,4 and 6 months after the start of the therapy).

Discontinuation of therapy at the end of the follow-up period was markedly higher in the group of patients treated with more classical courses of medication (18.6% vs 56.7%, $p< 0.001$), as shown in Table 2.

Side effects occurred in 9 patients of the ASA-treated series (20%),of whom 6 complained about mild gastralgia, 2 of nose bleedings and 1 of skin pruritus. In the other group, 12 patients lamented side effects (28.33%). This difference did not show a statistical relevance ($p >0.05$). It has to be said, though, that ASA-induced gastralgia was easily managed with antacids or Protonic Pump Inhibitors; on the other hand, the side effects caused by the others drugs used in Group B were less easily dealt with. We registered in particular remarkable weight gain (flunarizine, amitriptyline), drowsiness (flunarizine, amitriptyline, topiramate) and bradycardia (propranolol). Constipation was seldom reported from patients using amitriptyline and flunarizine. One patient for each group discontinued therapy before completion of the six-month observation: in the ASA group because of important nose bleeding, in the second group, a single case of leucopenia occurred in a patient treated with topiramate.

Table 3 shows the results of the univariate (Crude OR) and multivariate (Adjusted OR) analysis aimed to identify the potential predictors of positive response to treatment. At the univariate analysis only the belonging to the group treated with ASA was significantly related with a greater probability of a positive response to treatment (Crude OR 8.53, $p< 0.001$). When main confounders factors were controlled for, only therapy and higher frequency of migraine attacks were significantly related with a positive response to treatment (Adjusted OR 6.26, $p<0.001$ and Adjusted OR 0.12, $p=0.021$ respectively), while relationships between response and gender, age class or diagnosis subtype were not individuated.

Table 1: Description of the sample according to group of treatment.

	ASA-treated series (n=43) % (N)	Other treatments (n=31) % (N)	P
Gender			
Male	37.2 (16)	22.6 (7)	0.180
Female	62.8 (27)	77.4 ((24)	
Age class			0.439
18 – 35 y	48.8 (21)	45.2 (14)	
36 – 50 y	39.5 (17)	32.3 (10)	
51 – 65 y	11.6 (5)	22.6 (7)	
Aura			<0.001
Visual	56.7	83.8	
Dysphasic	4.4	4.8	
Sensorial	28.9	10.5	
Complex**	10.0	0.9	
Mean age	37.49 (±12.90)	36.99±12.39)	

- Propanolol 80 mg/day or Flunarizine 5 mg/day or Amitryptiline 20 mg/day or Topiramate 100 mg/day or Biofeedback (ten sessions of 60 minutes, two or three times per week, followed by home practice of 15 minutes every day).
- Complex aura is defined as the kind of aura consisting of the totality of symptoms (visual, sensorial and dysphasic).

Table 2: Outcome of therapy with mild doses of ASA

	ASA series (n=43) %(N)	**Other (%)*(n=31) %(N)**	**p**
Response to treatment			<0.001
Yes	86.1 (37)	41.9 (13)	
No	13.9 (6)	58.1 (18)	
Improvement after 4 weeks (T1)**			0.024
Excellent	53.5 (23)	25.8 (8)	
Good	16.3 (7)	12.9 (4)	
None	30.2 (13)	61.3 (19)	
Improvement after 8 weeks (T2)**			<0.001
Excellent	60.5 (26)	9.3 (6)	
Good	27.9 (12)	22.6 (7)	
None	11.6 (5)	58.1 (18)	
Improvement after 12 weeks (T3)**			0.006
Excellent	64.3 (27)	29.0 (9)	
Good	16.7 (7)	19.4 (6)	
None	19.0 (8)	51.6 (16)	
Discontinuation of the therapy at the end* **			0.001
Yes	18.6 (8)	56.7 (17)	
No	81.4 (35)	43.3 (13)	

- Propanolol 80 mg/day or Flunarizine 5 mg/day or Amitryptiline 20 mg/day or Topiramate 100 mg/day or Biofeedback (ten sessions of 60 minutes, two or three times per week, followed by home practice of 15 minutes every day).

- The improvement was rated as “none” (when the reduction was under 50% of episodes), “good” (reduction between the 51 and 75% of crisis) or “excellent” (reduction of more than 75% of episodes).
  After 3 months of follow-up

Table 3: Potential predictors of positive response to treatment

	Crude OR	95% CI	p	Adjusted OR	95% CI	p
Group						
Other*	Ref	--	--	Ref	--	--
ASA	8.53	(2.79 – 26.16)	<0.001	15.88	(3.63 – 69.39)	<0.001
Gender						
Male	Ref	--	--	Ref	--	--
Female	2.14	(0.68 – 6.70)	0.194	1.49	(0.34 – 6.47)	0.593
Age class						
18-35 y	Ref	--	--	Ref	--	--
36-50 y	0.69	(0.23 – 2.08)	0.513	0.52	(0.13 – 2.05)	0.348
51-65 y	0.35	(0.09 – 1.35)	0.127	0.37	(0.06 – 1.57)	0.153
Aura						
Visual	Ref	--	--	Ref	--	--
Dysphasic	4.64	(0.56 – 38.1)	0.15	4.74	(0.46 – 48.8)	0.2
Sensorial	1.80	(0.79 – 4.12)	0.16	0.44	(0.11 – 1.74)	0.24
Complex	2.32	(0.47 – 11.34)	0.3	-	-	-

- Propanolol 80 mg/day or Flunarizine 5 mg/day or Amitryptiline 20 mg/day or Topiramate 100 mg/day or Biofeedback (ten sessions of 60 minutes, two or three times per week, followed by home practice of 15 minutes every day).

- Complex aura is defined as the kind of aura consisting of the totality of symptoms (visual, sensorial and dysphasic).

IV. DISCUSSION

Aim of our study was to assess the efficacy and tolerability of ASA in the management of migraine with aura. At the best of our knowledge, this is the second study targeting the effectiveness and tolerability of prophylaxis with ASA in the subgroup of patients with MA, strictly diagnosed according to ICHD-III criteria, and it strictly replicates the results of the first case series [25]. Other studies compared the effectiveness of ASA in migraine versus other prophylactic therapies, considering MA and MoA together in small samples. In those setting, ASA appeared to be mildly effective, but less than other drugs, as metoprolol; in other series, some patients developed moderate side effects, due to the high doses employed [18-21].

We found that ASA is very effective in reducing the frequency of attacks with aura ($p<0.001$) and is well tolerated by patients ($p<0.001$). Moreover, our results show a better response to treatment with Acetylsalicylic acid compared with other therapies in the reduction of frequency of attacks with aura, with a probability of success that is difficult to evaluate seeing that we just observed two cases series, but apparently many times greater in

the ASA group. Ideally the study should be replicated as a case-control study on a larger sample and a homogenous control group. [26-28].

The results of our study could be consistent with the evidences of platelet dysfunction in migraineurs, though its role in the pathogenesis of the disease is still debated [6,7]. Finally, it must be mentioned that epidemiological studies have established an increased risk for ischemic vascular events among patients with migraine, especially MA [31]. In particular it is likely that migrainous women with aura displaying a TT genotype for the MTHFR gene are exposed to even a greater risk for ischemic stroke [32]. The role of ASA in primary prevention is not impaired in the presence of MA, making it even more suitable and recommended the use of ASA as prophylaxis in MA [31].

The most frequent registered side effect, mild to moderate gastralgia, was easily dealt with using low doses of antacids or PPI. In many cases appropriate instructions to take ASA after a meal were enough to avoid the occurrence of pyrosis. No major bleeding was reported, nor thrombocytopenia. On the other hand, the treatments used in the control group often induced side effects that led to discontinuation of the prophylaxis. Biofeedback was often interrupted because of scarce compliance.

V. CONCLUSIONS

MA is a relatively common disturb that causes major discomfort, as the aura is frequently perceived as something very disturbing from the patients.

We think that ASA can be safely used as an effective treatment in patients suffering from MA, or from a combination of MA and MoA if the attacks with aura are the most frequent migraine feature. Even though the number of patients with these characteristics is not very great, treatment with ASA could be interesting in this smaller group because of its being an extremely wieldy and inexpensive drug. In the absence of contraindications, treatment with ASA at the doses of 300 mg/day seems a very good option for MA, considering its efficacy, safety and the primary prevention offered from vascular events.
Other trials, ideally double blind, case-control ones with a larger sample, are needed to confirm with more certainty our results.

VI. CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

REFERENCES

[1] Smitherman TA, Burch R, Sheikh H, Loder E, The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies, Headache, 2013, 53(3), pp.427-36.
[2] R.B.Lipton and M.E. Bigal, Migraine: Epidemiology, Impact, and Risk Factors for Progression of Headache, 2005, 45(1), pp.3-13.
[3] Burch RC, Buse DC, Lipton RB, Migraine: Epidemiology, Burden and Comorbidity, 2019, Neurol Clin, 37(4), pp.631-649.
[4] Manzoni GC and Torelli P, Migraine with and without aura: a single entity? Neurol Sci, 2008, 29(1), pp.40–3.

[5] Tietjen GE, Migraine as a systemic Vasculopathy. Cephalalgia, 2009, 29(9), pp.987-96.
[6] D'Andrea G, Toldo M, Cortelazzo S, Milone FF, Platelet activity in migraine. Headache, 1982, 22(5), pp.207-12.
[7] Tozzi-Ciancarelli MG, De Matteis G, Di Massimo C, Marini C, Ciancarelli I, Carolei A, (1997) Oxidative stress and platelet responsiveness in migraine, Cephalalgia, 1997, 17(5), pp.580-4.
[8] Vanmolkot FH, van Bortel LM, de Hoon JN, Altered arterial function in migraine of recent onset, Neurology, 2007, 68, pp.1563–70.
[9] Dreier JP, Kleeberg J, Petzold G, Priller J, Windmuller O, Orzechowski HD et al., Endothelin-1 potently induces Leao's cortical spreading depression in vivo in the rat: a model for an endothelial trigger of migrainous aura? Brain, 2002, 125, pp.102–12.
[10] Perko D, Pretnar-Oblak J, Sabovič M, Zvan B, Zaletel M, Cerebrovascular reactivity to l-arginine in the anterior and posterior cerebral circulation in migraine patients, Acta Neurol Scand, 2011, 124(4), pp.269-74.
[11] Vernieri F, Moro L, Altamura C, Palazzo P, Antonelli Incalzi R, Rossini PM, Pedone C, Patients with migraine with aura have increased flow mediated dilation, BMC Neurol, 2010, 10(10), pp.18.
[12] Goèbel H, Acetylsalicylic acid affects 5-HT mechanisms in the central nervous system, In: Olesen J, Saxena PR, editors. 5-Hydroxytryptamine Mechanisms in Primary Headaches. New York: Raven Press, 1992, pp. 338-42.
[13] Olesen J, Thomsen LL, Iversen H, Nitric oxide is a key molecule in migraine and other vascular headaches, TIPS, 1994, 15, pp.149-53.
[14] Goadsby PJ, HoskinKL, Kaube H, Autoradiographic evaluation of acetylsalicylic acid distribution in the brain-stem of the cat, In: Rose FC, editor. New advances in headache research: 4. London: Smith-Gordon, 1994, pp. 151-3.
[15] Limmroth V, Katsarava Z, Diener HC, Acetylsalicylic acid in the treatment of headache, Cephalalgia,1999, 19, pp.545-51.
[16] O'Neill BP, Mann JD, Aspirin prophylaxis in migraine, Lancet, 1978, 2, pp.1179-81.
[17] Peto R, Gray R, CoBins R, WheatIy K, Hennekens C, Jamrozik K, Randomized trial of prophylactic daily aspirin in British male doctors, Br Med J, 1988, 296, pp.313-6.
[18] Buring JE, Peto R, Hennekens CH, Low-dose aspirin for migraine prophylaxis, J Am Med Assoc, 1990, 264, pp.1711-3.
[19] Masel BE, Chesson AL, Peters BH, Levin HS, Alperin JB, Platelet antagonist in migraine prophylaxis, A clinical trial using Aspirin and Dipyridamole, Headache, 1980, 20, pp.13-18.
[20] Grotemeyer KH, Scharafinski HW, Schlake HP, Husstedt IW, Acetylsalicylic acid vs. metoprolol in migraine prophylaxis--a double-blind cross-over study, Headache, 1990, 30(10), pp.639-41.
[21] Diener HC, Hartung E, Chrubasik J, Evers S, Schoenen J, Eikermann A, Latta G, Hauke W; Study Group, A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study, Cephalalgia, 2001, 21(2), pp.120-8.
[22] Bensenor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE (2001) Low-dose aspirin for migraine prophylaxis in women, Cephalalgia, 2001, 21, pp.175-83.
[23] HC Diener, Editorial Commentary, Cephalalgia, 2001, 21, pp.167-68.
[24] C Pellegrino Baena, RC D'Amico, H Slongo, AR Brunoni, AC Goulart, I Bensenor, The effectiveness of aspirin for migraine prophylaxis: a systematic review, Sao Paulo Med J, 2017, 135(1), pp.42-49
[25] WE Turk, A Uiterwijk, R Pasmans, V Meys, C Ayata, PJ Koehler, Aspirin prophylaxis for migraine with aura: an observational case series, European Neurology, 2017, 78, pp.287-289
[26] Headache Classification Subcommittee of the International Headache Society, The International Classification of Headache Disorders, 3rd Edition (ICHD- III), Cephalalgia, 2018, 38(1), pp.1-211.
[27] Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sándor PS, European Federation of Neurological Societies, EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force, Eur J Neurol, 2009, 16(9), pp.968-81.
[28] Dodick DW, Silberstein SD, Migraine prevention, Pract Neurol, 2007, 7(6), pp.383-93.
[29] Nestoriuc Y, Martin A, Rief W, Andrasik F (2008) Biofeedback treatment for headache disorders: a comprehensive efficacy review, Appl Psychophysiol Biofeedback, 2008, 33, pp.125-140.
[30] Hosmer DW, Lemeshow S, Applied Logistic Regression, New York: John Wiley & Sons, Inc, 1989.
[31] Kurth T, Schürks M, Logroscino G, Buring JE, Migraine frequency and risk of cardiovascular disease in women, Neurology, 2009, 73(8), pp.581-88.
[32] Schürks M, Zee RY, Buring JE, Kurth T (2008) Interrelationships among the MTHFR 677C>T polymorphism, migraine, and cardiovascular disease, Neurology, 2008, 71(7), pp.505-13.

