Systematic review of the beneficial effects of thrombin and vitamin K inhibitors on migraine treatment

Revisão sistemática dos efeitos benéficos dos inibidores de trombina e de vitamina K no tratamento da enxaqueca

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ABSTRACT

Background: Prophylactic migraine therapy includes beta-blockers, anticonvulsants, tricyclic antidepressants and calcium channel modulators. These drugs have been serendipitously identified as agents capable of migraine control. In order to reduce drug intake, interactions and potential adverse events, patients who have high blood pressure and migraine are often prescribed beta-blockers or calcium channel antagonists. Patients with epilepsy and migraine can use anticonvulsants, those with depression and migraine can be treat with antidepressants, and those with heart arrhythmia or recurrent vertigo and concomitant migraine can benefit from use of calcium channel antagonists. The beneficial effects of vitamin K or thrombin inhibitors on migraine attacks were first described decades ago, and there may be a place for these drugs in migraine prophylaxis. **Objective:** To investigate the potential beneficial effects of this class of anticoagulants regarding prevention of migraine attacks. **Method:** Systematic review of the literature including papers with patients' results. **Results:** A search of the literature yielded 16 papers with data on patients using inhibitors of vitamin K or thrombin for thromboembolic conditions. Articles typically reported on single cases or small case series. In all but one of these reports, the effect of the drug was remarkable in decreasing migraine severity. **Conclusion:** Although the level of recommendation is low due to the lack of proper clinical trials, vitamin K or thrombin inhibitors may be useful for migraine management in patients who also require anticoagulation. For these individuals, use of this class of anticoagulants could avoid adding extra drugs for migraine management.

Keywords: Vitamin K, Migraine, Treatment

RESUMO

Introdução: O tratamento profilático da enxaqueca inclui betabloqueadores, anticonvulsivantes, antidepressivos tricíclicos e modulares dos canais de cálcio. Estas drogas foram identificadas de forma casual como agentes capazes de controlar enxaqueca. Os efeitos benéficos dos inibidores da vitamina K ou da trombina na prevenção de crises de enxaqueca foi inicialmente descrito há muitas décadas, podendo haver lugar para estas medicações na profilaxia. O objetivo desta revisão foi a investigação dos potenciais efeitos benéficos desta classe de anticoagulantes como preventivos de crises de enxaqueca. **Método:** Revisão sistemática da literatura usando como termos de busca "heparin" OR "warfarin" OR "coumarol" OR "thrombin" AND "migraine" nas seguintes bases de dados: Medline, PubMed, LILACS, SciELO e Google Scholar. **Resultados:** A busca sistemática resultou em 16 artigos com dados sobre pacientes que usavam inibidores da vitamina K ou da trombina para condições tromboembólicas. Os artigos relataram casos isolados ou pequenas séries de casos. Em todos, exceto um artigo, o efeito destas drogas foi ótimo na redução da gravidade da enxaqueca. **Conclusão:** Embora o nível de recomendação seja baixo pela falta de estudos clínicos apropriados, inibidores da vitamina K ou da trombina podem ser úteis no controle da enxaqueca de pacientes que necessitam anticoagulação. Para estas pessoas, o uso desta classe de anticoagulantes poderia evitar a adição de drogas extras para o controle da enxaqueca.

Descritores: Enxaqueca; Migrânea; Warfarina; Acenocoumarol; Vitamina K; Trombina

INTRODUCTION

Migraine is a common neurological disorder characterized by episodic attacks and by a chronic phase, both of which can be disabling.[1] In addition to cortical, thalamic and hypothalamic dysfunction, the cascade of reactions led by the trigeminovascular system requires adequate management and therapeutic interventions.[1] In subjects who do not tolerate or do not respond well to acute treatments, continuous use of a prophylactic drug is the best option. Interestingly, these prophylactic agents have mostly been identified by chance: while undergoing treatment for another disease with a certain drug, patients reported reduced numbers and lower intensity of migraine attacks. Beta-blockers, anticonvulsants, tricyclic antidepressants and calcium channel modulators have all been identified as potential prophylactic therapies for migraine. These are now approved and recommended for migraine prevention, with evidence supporting their use.[2]

It is only logical that patients who can benefit from the same drug to treat two diseases should receive this drug when they have no contraindication for this minimalistic approach. Therefore, patients who have high blood pressure and migraine can benefit from beta-blockers or calcium channel antagonists, and those with epilepsy and migraine can use anticonvulsants. Likewise, individuals with depression and migraine can be treat with antidepressants, while subjects with heart arrhythmia or recurrent vertigo and concomitant migraine can benefit from use of calcium channel antagonists. Following the same line of thought, migraineurs requiring anticoagulation can benefit from vitamin K or thrombin inhibitors, according to the theory and results presented in papers published over the last 55 years. Following an initial investigation on the potential role of basophil granulocytes in migraine.[3] heparin became a matter of interest in the physiopathology of migraine attacks. Thonnard-Neumann published a series of papers discussing the potential role of heparin in migraine[4, 5] after an initial case-control open trial.[6] Other papers followed but the subject is yet far from clear. The objective of the present review was to assess the potential beneficial effects of this class of anticoagulants on prevention of migraine attacks.

METHOD

This study was a systematic review and did not require approval from an Ethics Committee, since the authors only accessed published data. The present review followed the guidelines of the *Preferred Reporting Items for Systematic Review and Meta-Analysis* (PRISMA) protocol.[7]

The search terms were "heparin" OR "warfarin" OR "coumarol" OR "thrombin" AND "migraine" in the following databases: Medline, PubMed, LILACS, SciELO and Google Scholar. The term "headache" as an alternative to "migraine" generated thousands of unrelated papers and was, therefore, not used in the search. The search was not limited by date and only papers presenting data on patients were selected. Only articles that used the English language in title, key words and abstract were included. Abstracts from conferences and journal editorials were not included in this review. References from selected articles were further used in the search for other potential papers.

The authors individually searched for papers following the set criteria for inclusion and exclusion and, after two meetings, decided which articles should be included. The results from this systematic review are presented essentially in descriptive form with no meta-analyses or statistical assessment of the results.

RESULTS

The initial search generated 163 papers. After reading the titles of these papers and their abstracts, 16 articles were selected for this review. One article, published in 1974[8] had no authors listed and no abstract. It could not be retrieved and was, therefore, excluded, despite its potential interesting title. One case report from Sweden[9] was also excluded, although it had been identified as a reference to other authors. This paper is in Swedish and the search in the original journal rendered no results for that particular article.

There were 11 case reports from eight different countries (UK,[10], Holland,[11, 12] Brazil,[13] South Africa,[14] Italy,[15-17] Taiwan,[18] Canada,[19] USA[20]), one retrospective cohort from Holland,[21] one prospective cohort (from USA),[22] one open crossover trial from Holland,[23] two case control studies (USA,[4] Spain,[24]). Data were typically obtained from isolated cases or small series of patients. The results from 15 studies suggested that heparin, warfarin and coumarin derivatives can be very effective in reducing the intensity and/or frequency of migraine attacks. One of the studies did not obtain the same good result when comparing acenocoumarol to propranolol in migraine prophylaxis.[23] An International Normalized Ratio (INR) of around 2.5 was sufficient to induce improvement in migraine, thus indicating that full anticoagulation is not necessary to alleviate the headache. A summary of the papers with data on patients is presented in Table 1.

DISCUSSION

Serendipitous discoveries have been a characteristic of many drugs used in migraine prophylaxis. The present review showed that potent anticoagulants that are vitamin K inhibitors have shown remarkable beneficial effects in migraineurs. All studies have the same conclusion and it would be of great interest to prospectively study large cohorts of patients (who happen to have migraine) and need to be treated with vitamin K inhibitors.

Thrombin is a serine protease involved in a cascade of coagulation and inflammation via the proteinase-activated receptors (PARs).[25] Pro-inflammatory mediators are released through activation of PAR1, while the activation of PAR2 induces the release of substance P and calcitonin-gene-related peptide (CGRP).[26-28] The aberrant activity of serine proteases, including thrombin, can be identified in many neurological conditions,

Table 1. Summarized results from articles reported on migraine patients using vitamin K or thrombin inhibitors.

Author	Year	Ref	Country	Method	Result
Thonnard-Neumann	1973	4	USA	Case-control (n=20 migraine; 21 control)	5,000 U of heparin intravenously leading to a substantial reduction in severity and frequency of migraine attacks in 16 out of 20 migraine patients.
Suresh et al	1994	10	UK	Case report (n=1)	6mg/day warfarin prescribed to a 71 year-old woman (DVT) led to migraine control. Withdrawal resulted in migraine returning to basaline pattern. Patient was treated blindly with warfarin-placebo and only warfarin improved her headache attacks
van Puijenbroek	1996	11	Holland	Case report (n=1)	3-4mg/day acenocoumarol led to a dramatic reduction of migraine attacks in a 68 year-old woman. Migraines returned after drug was withdrawn and was well controlled again after re-starting acenocoumarol
Fragoso	1997	13	Brazil	Case report (n=2)	Two patients with remarkable improvement on the intensity and frequency of their migraine attacks after taking 5mg/day of warfarin (INR kept at 2.5).
Morales-Asin et al	2000	24	Spain	Case-control (66 migraine; 100 non-migraine headache)	Remarkable improvement on migraine during the use of acenocoumarol. More severe migraine had better response to this treatment
Rahimtoola et al	2001	21	Holland	Retrospective analyses (n=32 warfarin; n=60 aspirin)	Coumarin treatment was clearly associated with a reduction of migraine attacks and severity in comparison with low-dose aspirin treatment
Wammes-van der Heijden et al	2004	12	Holland	Case report (n=4)	Patients with migraine and thromboembolic predisposition improved of their headache during acenocoumarol therapy
Wammes-van der Heijden et al	2005	23	Holland	Open crossover study using propranolol or acenocoumarol (n=12)	No beneficial effect of propranolol or acenocoumarol could be established after 12 weeks
Asherson et al	2007	14	South Africa	Case report (n=1)	Patient with anti-phospholipid syndrome undergoing therapy with warfarin had dramatic improvement in migraine
Maggioni et al	2012	15	Italy	Case report (n=1)	Complete remission of migraine in a woman undergoing warfarin therapy. Migraines returned after drug was withdrawn and was well controlled again after re-starting warfarin
Russo et al	2013	16	Italy	Case report (n=1)	Patient undergoing therapy with warfarin had total remission of migraine pain but remained with aura
Mohanty et al	2015	22	USA	Prospective (n=40 migraine; n=85 control)	Migraine symptoms substantially decreased in 38 patients using warfarin
Kung et al	2015	18	Taiwan	Case report (n=1)	Dabigratan 110mg twice a day controlled migraine-like visual aura without headache
Maggioni et al	2015	17	Italy	Case report (n=1)	Complete remission of migraine with aura on warfarin. Return of symptoms within 3 weeks of switching to apixaban. Resolution of symptoms once again when warfarin was reintroduced
Nilsson et al	2017	19	Canada	Case report (n=1)	Complete remission of migraine with aura on warfarin. Return of symptoms within 3 weeks of switching to apixaban. Resolution of symptoms once again when warfarin was reintroduced
Beh	2018	20	USA	Case report (n=1)	Patient with vestibular migraine who improved when warfarin was associated to his previous topiramate therapy

including hemorrhagic, hypoxic, oncogenic, traumatic and infectious injuries.[29] Expressed in astrocytes, microglia and neurons, PAR1 has been described as a well-positioned receptor to play a central role mediating the complex inflammatory cascades within the central nervous system,[29,30] It is, therefore, perfectly plausible that thrombin might be involved in the inflammatory trigeminovascular cascade of events in migraine.

This review is not without limitations. The results are essentially based on case reports with the bias of publication of positive results. There may be migraineurs with no benefit at all from these drugs whose cases are never going to be reported. Even the larger series of patients and the prospective cohort identified by the reviewers typically reported on insufficient numbers of cases assessed in open studies. At present, it is only possible to give a low (Code C) or very low (Code D) recommendation for this therapy as a migraine prophylactic alternative. As a reminder, Code C means that there are only a few studies with severe limitations, while Code D, in essence, denotes a recommendation from experts.[31]

In order to improve the personal and societal impact of migraine, patients need to receive appropriate treatments and continuity of care.[32] Adherence to therapy is of essence and the fewer the numbers of drugs and daily doses a patient has to use, the higher the chances are that he/she will follow medical recommendations.[33,34] Patients who suffer from migraine and require anticoagulant therapy for any other reason might achieve improvement of their migraine through use of vitamin K and thrombin inhibitors, even when the target INR is relatively low. However, this recommendation is limited by the low level of evidence presented by the data in the medical literature. Prospective observational cohorts among patients who suffer from migraine and receive anticoagulant therapy for any other disease could be the next step in this investigation.

CONCLUSION

The present systematic review showed that vitamin K or thrombin inhibitors have a potential beneficial effect regarding prevention of migraine attacks. Careful interpretation of the results is recommended since most published data come from small series or single cases.

Role of authors:

Eduardo de Almeida Guimaraes Nogueira – recently graduated medical doctor, coordinated the study and prepared the final table of results.

Angela dos Anjos Couto - medical student in training for systematic reviews, had an active participation in the literature search and selection of papers

Beatriz Moraes Grossi - medical student in training for systematic reviews, had an active participation in the literature search and selection of papers

Gabriela Dias Nunes - medical student in training for systematic reviews, had an active participation in the literature search and selection of papers

Taliê Zanchetta B. Hanada - medical student in training for systematic reviews, had an active participation in the literature search and selection of papers

Yara Dadalti Fragoso - designed and supervised the study, wrote the final paper and is ultimately responsible for data collection and analyses.

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