Original Article

Improve cognitive impairment using mefenamic acid non-steroidal anti-inflammatory therapy: additional beneficial effect found in a controlled clinical trial for prostate cancer therapy

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Abstract: Inflammation is an essential component of prostate cancer (PCa), and mefenamic acid has been reported to decrease its biochemical progression. The current standard therapy for PCa is androgen deprivation therapy (ADT), which has side effects such as cognitive dysfunction, risk of Alzheimer's disease, and dementia. Published results of in vitro tests and animal models studies have shown that mefenamic acid could be used as a neuroprotector. Objective: Examine the therapeutic potential of mefenamic acid in cognitive impairment used in a controlled clinical trial. Clinical trial phase II was conducted on patients undergoing ADT for PCa. Two groups of 14 patients were included. One was treated with a placebo, while the other received mefenamic acid 500 mg PO every 12hrs for six months. The outcome was evaluated through the Mini-Mental State Examination (MMSE) score at six months. At the beginning of the study, both groups had similar MMSE scores (mefenamic acid vs. placebo: 26.0±2.5 vs. 27.0±2.6, P=0.282). The mefenamic acid group improved its MMSE score after six months compared with the placebo group (27.7±1.8 vs. 25.5±4.2, P=0.037). Treatment with mefenamic acid significantly increases the probability of maintained or raised cognitive function compared to placebo (92% vs. 42.9%, RR=2.2, 95% CI: 1.16-4.03, NNT=2.0, 95% CI: 1.26-4.81, P=0.014). Furthermore, 42.9% of the placebo group patients had relevant cognitive decline (a 2-point decrease in the MMSE score), while in patients treated with mefenamic acid, cognitive impairment was not present. This study is the first conducted on humans that suggests that mefenamic acid protects against cognitive decline.

Keywords: Alzheimer's disease, mefenamic acid, cognitive impairment, non-steroidal anti-inflammatory drugs

Introduction

Cancer is becoming a leading cause of mortality, and prostate cancer (PCa) is the most prevalent non-dermatologic cancer and the second cause of cancer death in males [1]. Its incidence continues to rise due to the progressive increase in life expectancy in the population [2]. Almost half of those patients will receive androgen deprivation therapy (ADT) to reduce androgens to castration levels which delays tumor growth while improves survival [2]. ADT has been used in metastatic disease because it improves or prevents symptomatology while achieving control for 18-24 months before transitioning into a castration-resistant disease [2]. Nevertheless, ADT’s side effects, including
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deterioration of musculoskeletal health, increased cardiometabolic risk, cognitive dysfunction, dementia, and even Alzheimer’s disease, have been reported [3-5].

Patients with PCa undergoing treatment with ADT present an accelerated cognitive deterioration concerning that expected with aging [3]. Cognitive impairment is a determinant independently associated with functional decline (the limitation of daily living activities) in older persons with cancer [6]. Its control is relevant to maintaining an adequate quality of life. Therefore, it is crucial to search for new therapies that aid in detaining said cognitive deterioration.

Publish literature has linked testosterone levels with cognitive functions such as working, talking, and focus, leading to the hypothesis that ADT affects cognitive function [7]. A Korean study with PCa patients (n=236,391) has confirmed the association between ADT and accelerated cognitive dysfunction, while the use of statins or antiplatelets (such as aspirin) decreased the risk for cognitive dysfunction [7]. However, information against the relationship between anticoagulants, antiplatelets, and statins with dementia or Alzheimer’s disease in patients with PCa has also been published [7, 8].

Given the conflicting results, the subject remains a controversial one. Preclinical studies have reported decreased inflammation and oxidative stress with aspirin treatment in the central nervous system [9]. However, once again, the controversy persists since there is also evidence that low-dose aspirin does not improve in any manner cognitive test scores or prevent cognitive dysfunction [10]. The different doses of non-steroidal anti-inflammatory drugs (NSAIDs) utilized in the preclinical or clinical trials could cause the variability of the effects reported.

Observational study results have mainly shown that statin or NSAIDs use was associated with a lower risk for dementia. A review of clinical trials revealed the low-to-insufficient quality of evidence that antihypertensive treatment, NSAIDs, and statins do not alter the risk for dementia. There is no evidence on aspirin, diabetes, or dementia medications on incident dementia or mild cognitive impairment (MCI) [11]. Specifically, in patients with PCa treated with ADT, an observational study has estimated that the use of statins or aspirin generates a lower risk of cognitive dysfunction [7].

Neurodegenerative diseases such as Alzheimer’s disease or Parkinson’s disease have an inflammatory component, which can be observed in the latter’s amyloid plaques. Such a finding led to the assumption that anti-inflammatory treatment with NSAIDs delays disease progression [12]. Even more so, NSAIDs have been found to protect against the cognitive decline that happens naturally with aging [11, 13] while they have also been presumed to decrease the incidence of Alzheimer’s disease [14, 15], but that is still a subject of debate [16].

Studies in animals with Alzheimer’s disease have shown that mefenamic acid, an NSAID, has improved cognitive impairment and even reverse memory loss and brain inflammation [12, 17]. It has even protected against alcohol-induced cognitive impairment [18].

Distinct mechanisms of neuroprotection and cognitive function improvement have been proposed for mefenamic acid. It targets the NL-RP3 inflammasome pathway [17], decreasing the free radical production, nitric oxide (NO), and decreases the release of cytochrome C [18]. Besides, mefenamic acid has been shown to up-regulate the anti-apoptotic protein expression, Bcl-XL [18], and scavenge radical nitric oxide in a dose-dependent manner in vitro and reduce NO donor-induced death in the B 65 neuroblastoma cells [19].

Preclinical trials have shown that mefenamic acid can be used as a neuroprotector that attenuates cognitive impairment [12, 18]. However, those findings have not been analyzed in humans. One study reported that mefenamic acid therapy decreased biochemical progression in PCa [20]. In the present study, we examine the therapeutic potential of mefenamic acid in cognitive impairment in PCa patients with ADT receiving this anti-inflammatory drug as part of a clinical trial against cancer.

Patients and methods

Study design

We conducted a prospective, double-blind phase II clinical trial with 2-arms in parallel with randomized groups. The study was conducted
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according to the “CONSORT statement” guidelines for clinical trials. The main objective of the project was to evaluate the efficacy of mefenamic acid in preventing cancer progression. However, in this report, we only analyzed the effects on cognitive impairment.

The National Scientific Commission (Mexican Social Security Institute; Chairperson Name: Dr. Fabio Salamanca-Gomez) approved the present study (protocol number R-2018-785-058; June 12, 2018). All patients signed the informed consent form, and their anonymity was guaranteed. All procedures performed were under the Declaration of Helsinki. The clinical trial was registered as MEFEPROST: RPCEC00000248 in the “Cuban Public Registry of Clinical Trials (RPCEC) Database”. The RPCEC trial registration data set is part of the International Platform Registry data set established by the World Health Organization (WHO).

Patients

Inclusion criteria: histologic diagnosis of PCa, metastatic cancer, ADT carried out for six months or longer before recruitment, ADT considered by the treating oncologist to be feasible and appropriate in the patient during the 6-month follow-up period, an ECOG functional status of 0 to 2, and patients with no history of liver or kidney disease (creatinine clearance had to be greater than 60 milliliters/minute). The following exclusion criteria were used: the presence of another primary cancer, uncontrolled arterial hypertension or diabetes, leucocyte count of less than 3,000 per microliter or platelet count of less than 100,000 per microliter, or showing data of systemic infection, blood hemoglobin level below 9 g/deciliter, alcohol or drug addiction, acid peptic diseases, ulcerative colitis or Crohn’s disease, chronic heart failure, diagnosis of ischemic heart disease, autoimmune or neurodegenerative diseases, depression, and other pathologies decided upon at the discretion of the investigator. Elimination criteria: patients in whom the treating physician suspended the mefenamic acid, regardless of the cause, for more than two weeks, patients with severe toxicity (grade 3 or higher) according to the “common terminology criteria for adverse events (CTCAE) version 4.0” (US Department of Health and Human Services), that was attributable to the administration of the mefenamic acid, or patients who voluntarily decided to leave the study. The participants were recruited from the “General Hospital in Zone No1 of the Mexican Social Security Institute (IMSS)” and the “Cancerology State Institute of the health services of the State of Colima” (Mexico).

Intervention

The 6-month intervention was performed in patients with ADT divided into two arms. One arm with mefenamic acid, and the other arm with placebo. Androgen deprivation therapy included administering oral antiandrogens (flutamide and bicalutamide), gonadotropin-releasing hormone agonists (leuprolide and goserelin), or bilateral orchiectomy. The treatment group took mefenamic acid (500 mg) every 12 h for six months. The other group took a placebo every 12 h for the same amount of time. The pills were recommended to be taken with milk or with meals to reduce gastrointestinal adverse events. All patients took one omeprazole 20 mg tablet daily during the study. The treating physician was blinded to the treatment groups and could add any treatment they considered necessary (usual medical care), including taxane chemotherapy [22] or palliative radiotherapy [21].

Outcome measures and follow-up

The project’s primary endpoint was to determine the variations in the patients’ serum PSA levels at six months. This result was previously published [20]. This report analyzes the Mini-Mental State Examination (MMSE) change score at month six as the primary endpoint. The total score is calculated by adding the points for each item together (the total score ranging from 0 to 30 points), with a higher score indicating better cognitive status. In the present study, the previously validated Spanish version of the MMSE was employed [23]. Studies have reported an annual cognitive decline at a mean of 1.5 points on the MMSE in the first year and 2.5 points after the second year in patients with Alzheimer’s disease [24]. Our patients were classified as having “relevant cognitive decline” based on MMSE score changes, with a decrease of two or more points after six
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months. Adverse events related to NSAIDs’ chronic ingestion were evaluated monthly in all patients through a complete blood count, biochemical kidney and liver function tests, and a clinical interview by the physicians conducting the research.

**Blinding**

The researchers who evaluated the effectiveness of treatment through the MMSE and performed the statistical analyses were blinded, as were the patients.

**Sample size**

The calculation was based on the incidence of patients who did not decrease their MMSE score at six months, resulting in 40% for the placebo group and 90% for the mefenamic acid group. Thirteen patients from each group were needed to reach the required power (0.8) when the statistical analysis was performed at the two-tailed alpha level (0.05). Statistical power was determined at the end of the study to detect a difference between two different groups (alpha =0.05), and its result was 85%.

**Statistical analysis**

Data were presented as mean ± standard error or standard deviation or percentages. For inferential statistics, the equality of variances was confirmed by the Levene test, and the Kolmogorov-Smirnov test first determined the normal distribution of the data. Categorical values were compared using Fisher’s exact test or the Chi-square test of the likelihood ratio. The Student’s t-test was used to compare the numerical variables (with normal distribution) of the two groups (mefenamic acid and placebo). The number needed to treat (NNT), the relative risk (RR), and 95% confidence interval were calculated to determine the probability of not having relevant cognitive decline (a decrease of 2 or more points on the MMSE), comparing the mefenamic group vs. the placebo group. The statistical analysis was performed using the SPSS software, version 20 (IBM Corp., Armonk, NY, USA), except for the RR and NNT, which were calculated using the MedCalc v17.7.2 software (MedCalc Software bvba, Ostend, Belgium). Sample size and the posthoc power analysis were calculated using the ClinCalc.com online software (ClinCalc LLC, Indiana, USA). A one-sided P<0.05 was considered statistically significant.

**Results**

Forty-six patients were screened, and 31 were randomized into one of the two study groups. Fifteen patients were in the mefenamic group, while 16 patients were included in the placebo control group (Figure 1). For two patients, one from the placebo group and one from the experimental group, the treating physician suspended the experimental drug due to rapid cancer progression. With no serious adverse effects, another patient from the placebo group voluntarily abandoned the study after one month of treatment. A total of 14 patients in each group completed the study and were analyzed (Figure 1).

**Figure 1.** Consort 2010 flow diagram showing the number of patients screened, included, eliminated, and analyzed in the study.
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Table 1. Distribution of the main clinical characteristics of the study subjects. Values are presented numerically (%) or mean ± standard deviation

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Mefenamic</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>70.8±8.1</td>
<td>69.3±6.5</td>
<td>0.591*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50%</td>
<td>42.9%</td>
<td>0.576*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14.2%</td>
<td>14.2%</td>
<td>0.542*</td>
</tr>
<tr>
<td>PVD</td>
<td>28.5%</td>
<td>28.5%</td>
<td>0.617*</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>28.5%</td>
<td>28.5%</td>
<td>0.500*</td>
</tr>
<tr>
<td>Baseline Hemoglobin*</td>
<td>12.6±1.4</td>
<td>13.0±1.0</td>
<td>0.455*</td>
</tr>
<tr>
<td>Baseline Glucose**</td>
<td>114.4±35.7</td>
<td>100.7±19.9</td>
<td>0.223*</td>
</tr>
<tr>
<td>Final Hemoglobin*</td>
<td>11.4±2.1</td>
<td>12.1±1.6</td>
<td>0.436*</td>
</tr>
<tr>
<td>Final Glucose**</td>
<td>134.7±70.9</td>
<td>111.9±39.9</td>
<td>0.365*</td>
</tr>
<tr>
<td>Cancer clinical stage</td>
<td></td>
<td></td>
<td>0.437*</td>
</tr>
<tr>
<td>IIC</td>
<td>14.2%</td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>14.2%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>42.9%</td>
<td>42.9%</td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>0%</td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>28.5%</td>
<td>42.9%</td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td>6.2±2.0</td>
<td>6.6±0.8</td>
<td>0.513*</td>
</tr>
<tr>
<td>Treatments before and during the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>14.2%</td>
<td>14.2%</td>
<td>0.674*</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>50.0%</td>
<td>42.9%</td>
<td>0.576*</td>
</tr>
<tr>
<td>Antidiabetic drugs</td>
<td>14.2%</td>
<td>21.4%</td>
<td>0.383*</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>7.1%</td>
<td>7.1%</td>
<td>0.326*</td>
</tr>
<tr>
<td>Anticoagulant drugs</td>
<td>7.1%</td>
<td>7.1%</td>
<td>0.741*</td>
</tr>
<tr>
<td>Other NSAIDs</td>
<td></td>
<td></td>
<td>0.326*</td>
</tr>
<tr>
<td>Previous cancer treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>28.5%</td>
<td>28.5%</td>
<td>0.450*</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>14.2%</td>
<td>28.5%</td>
<td>0.542*</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7.1%</td>
<td>0.0%</td>
<td>0.483*</td>
</tr>
<tr>
<td>Other NSAIDs</td>
<td>7.1%</td>
<td>21.4%</td>
<td>0.326*</td>
</tr>
<tr>
<td>Days with ADT</td>
<td>446±375</td>
<td>499±832</td>
<td>0.832*</td>
</tr>
<tr>
<td>Cancer treatment during the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>0.0%</td>
<td>14.2%</td>
<td>0.527*</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>28.5%</td>
<td>7.1%</td>
<td>0.143*</td>
</tr>
</tbody>
</table>

PVD: Peripheral vascular disease; ADT: androgen deprivation therapy; *g/dL; **mg/dL; ¥Student’s t test; †Fisher’s exact test; #Likelihood ratio Chi-square test.

The clinical characteristics of the patients that completed the study are shown in Table 1.

Based on the MMSE score, there were no differences between the two groups at the beginning of the study (mefenamic acid vs. placebo group: 26.0±2.5 vs. 27.0±2.6, P=0.282), but at the end of the study, the mefenamic acid group had a significantly higher MMSE score than the placebo group (27.7±1.8 vs. 25.5±4.2, P=0.037). The patients treated with mefenamic acid raised their MMSE scores (before and after comparison: 26.0±2.5 vs. 27.7±1.8, P=0.002), whereas the patients that received placebo tended to lower their scores (27.0±2.6 vs. 25.5±4.2, P=0.079). Taking the initial MMSE value as 100% for each patient, the treatment with mefenamic acid produced a mean increase of 7.4±8.2% in the MMSE score, and the treatment with placebo produced a mean decrease of 5.4±15.7% (107.4 vs. 94.6, P=0.005). A total of 92.9% of the patients treated with mefenamic acid maintained or raised their MMSE score at six months, whereas only 42.9% of the placebo group did the same (P=0.014, see Table 2). It is essential to mention that eight patients (57.1%) treated with mefenamic acid raised their MMSE score by 2 points, compared with only two patients in the placebo group (14.3%) (P=0.045). In contrast, 42.9% of patients treated with placebo had relevant cognitive impairment (a 2-point decrease in MMSE score at six months), while in patients treated with mefenamic acid, cognitive impairment was not present (P=0.071). Also, the number needed to treat (NNT) with mefenamic acid to prevent a patient with PCa undergoing ADT from presenting with relevant cognitive decline was 2.5 (see Table 2).

Regarding the adverse effects possibly related to the experimental treatment (mefenamic acid), 3 (23.0%) patients presented grade 1 or 2 gastritis during the follow-up, but temporary suspension of the mefenamic acid (2 weeks)
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Table 2. Relevant changes in the MMSE at 6 months of follow-up and its association with mefenamic acid consumption

<table>
<thead>
<tr>
<th>Relevant changes</th>
<th>Mefenamic group</th>
<th>Placebo group</th>
<th>RR (CI 95%)</th>
<th>NNT (CI 95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who maintained or raised their MMSE score</td>
<td>13 (92.9%)</td>
<td>6 (42.9%)</td>
<td>2.2 (1.16-4.03)</td>
<td>2.0 (1.26-4.81)</td>
<td>0.014</td>
</tr>
<tr>
<td>Patients who raised their MMSE score by 2 points</td>
<td>8 (57.1%)</td>
<td>2 (14.2%)</td>
<td>4.0 (1.02-15.59)</td>
<td>2.3 (1.34-9.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>Patients who reduced their MMSE score by 2 points*</td>
<td>0 (0%)</td>
<td>6 (42.9%)</td>
<td>0.07 (0.00-1.24)</td>
<td>2.5 (1.50-7.50)</td>
<td>0.071</td>
</tr>
</tbody>
</table>

RR: relative risk; NNT: number needed to treat; CI 95%: 95% confidence interval; MMSE: Mini-Mental State Examination. *Patients who had a relevant cognitive decline.

was required in only one of those patients. Symptomatology ceased after insisting that the patients take the medication with meals. No pathologic alterations were found in the liver function and kidney tests or the complete blood count. No patient required definitive suspension of the experimental treatment due to adverse effects.

**Discussion**

Treatment with the anti-inflammatory drug mefenamic acid significantly increases the probability of maintained or raised cognitive function in patients with PCa undergoing ADT. After 6 months of treatment, the mefenamic acid group had a significantly higher MMSE absolute score than the placebo group. After 6 months, patients’ MMSE scores that received placebo decreased by 5.4%, whereas the patients treated with mefenamic acid increased by 7.4%. Even though that level of change appears to be minor, it is similar to the change in patients in the early stages of Alzheimer’s disease at one year, which is a decrease of a mean 1.5 to 2 points in the MMSE score [24]. The present study is the first conducted on humans that shows mefenamic acid’s effect on cognitive function.

Evidence suggests that fenamates can modulate neuronal functioning by modifying ion channel activity, depending on the subunits forming the GABA receptor complex [25]. Other fenamates (flufenamic acid and niflumic acid) also inhibit NMDA-activated currents recorded from spinal neurons [26]. Flufenamic acid has been shown to block non-selective calcium-activated cation channels in rat hippocampal CA1 neurons [27]. Those studies in vitro and animal models have led to the postulation that mefenamic acid is a neuroprotector or a potential therapeutic agent in Alzheimer’s disease.

However, no previous study on humans has evaluated its protective or therapeutic effect on the loss of cognitive functions. The present study demonstrated that mefenamic acid prevented cognitive decline in patients with PCa undergoing ADT and relevantly raised the cognitive function scores on the MMSE by 2 points in nearly half the patients, concurring with the results of preclinical trials on the same theme [12, 17]. Nevertheless, it should be pointed out that the subjects of our study did not present with dementia at the beginning of the analysis, albeit they did present with two factors that have significantly been associated with cognitive decline, which are a mean age close to 70 years and undergoing continuous treatment with antiandrogens [7].

Mefenamic acid is often used to treat dysmenorrhea and heavy menstrual bleeding, administering an oral dose of 1.5 g per day for 3 to 5 days [28]. The exact dose for prolonged periods was proposed decades ago [29]. Nevertheless, its chronic use is not customary. There are other medications with a similar analgesic or anti-inflammatory effect and fewer adverse effects. In particular, there is less risk for overdose [30]. A dose of mefenamic acid (1 g PO per day) lower than that recommended daily was used in the present study, but it was administered for a more extended time. There were no serious adverse events with that drug regimen, but there were signs clinically consistent with mild gastritis. Therefore, taking the medication with meals and receiving omeprazole throughout the study was a prime necessity. It was decided not to administer the drug for more than six months due to the risk of kidney damage [31], which did not occur during the study.

It is essential to point out that the administration of mefenamic acid for six months in a group of patients with prostate cancer did not have
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the sole objective of stopping the cognitive impairment because perhaps this sole reason does not ethically justify said prescription. The main objective of the clinical trial was to prevent the progression of cancer [20]. The effect reported here was a finding, which exemplifies the potential use of this NSAID against cognitive impairment and could serve as the basis for future research. A limitation of the present study was the small sample size and the duration of the follow-up period. Further study should include many patients and a more extended follow-up period that strictly evaluates adverse effects.

Conclusions

The present study is the first study carried out on humans, suggesting that mefenamic acid protects against cognitive decline. Even though this clinical trial was conducted on patients with prostate cancer undergoing androgen deprivation therapy, mefenamic acid’s therapeutic potential could include other diseases that present with cognitive decline. Future studies are needed to strengthen the results of the present analysis.

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Disclosure of conflict of interest

None.

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