ORIGINAL ARTICLE

Reduced Frequency of Bone Pain Crises in Patients with Sickle Cell Disease Given an Angiotensin-converting Enzyme Inhibitor

OJ Egesie[1], CS Raphael[2], SU Uguru[2], BN Okeahialam[2]

ABSTRACT

Objective: *To determine if sickle cell disease (SCD) bone pain crisis is mitigated by use of an angiotensin-converting enzyme inhibitor (ACEI), following a case report of ACEIs preventing bone pain crisis.*

Methods: *Patients with SCD who attended the Haematology Clinic at Jos University Teaching Hospital, Nigeria, were assessed with a questionnaire, given 2.5 mg of ramipril and followed up monthly for three months. Frequencies of bone pain crises in the month preceding enrolment and three months following treatment as well as the cardiovascular status were evaluated.*

Results: *Thirty-five patients with complete data were reported. Blood pressure remained stable, and cumulative frequency of bone pain crises fell. The relative risk reduction for bone pain was 56.2% at one month, 63.0% at two months and 13.0% at three months.*

Conclusion: *Vaso-occlussion-induced hypoxia, triggering bone pain crises, produces angiotensin II from angiotensin and worsens vasoconstriction. Angiotensin-converting enzyme inhibitors block this process, reducing severity or preventing bone pain crises. With these observations and a stable blood pressure profile, we recommend wider use of ACEIs in patients with SCD to cut down on the need of opioid use with attendant addiction risk, as a way of improving their quality of life.*

Keywords: Angiotensin-converting enzyme inhibitors, bone pain crisis, prevention, sickle cell disease

Reducción de la frecuencia de la crisis de dolor óseo en pacientes con la enfermedad de células falciformes mediante los inhibidores de la enzima convertidora de angiotensina

OJ Egesie[1], CS Raphael[2], SU Uguru[2], BN Okeahialam[2]

RESUMEN

Objetivo: *Determinar si la crisis de dolor por la enfermedad de células falciformes (ECF) es mitigada con el uso de los inhibidores de la enzima convertidora de angiotensina (IECA), luego de un informe que reporta que IECA previene la crisis del dolor óseo.*

Métodos: *A pacientes con ECF que asistían a la Cínica de Hematología del Hospital Docente de la Universidad de Jos, Nigeria, se les evaluó con un cuestionario, se les suministró 2.5 mg de ramipril, y se les hizo un seguimiento mensual por tres meses. Se evaluaron las frecuencias de las crisis de dolor óseo en el mes anterior al alistamiento y tres meses después del tratamiento, así como el estado cardiovascular.*

From: [1]Department of Haematology, Jos University Teaching Hospital, Jos, Nigeria and [2]Department of Medicine, Jos University Teaching Hospital, Jos, Nigeria.

Correspondence: Professor BN Okeahialam, Department of Medicine, Jos University Teaching Hospital, Jos Plateau State, Nigeria. Email: basokeam@yahoo.com

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Resultados: *Se reportaron treinta y cinco pacientes con datos completos. La presión sanguínea se mantuvo estable, en tanto que se produjo un descenso de la frecuencia cumulativa de las crisis de dolor óseo. La reducción del riesgo relativo del dolor óseo fue de 56.2% en un mes, 63.0% en dos meses, y 13.0% en tres meses.*

Conclusión: *La hipoxia inducida por vaso-oclusión, que desencadena la crisis de dolor óseo, produce angiotensina II a partir de la angiotensina y empeora la vasoconstricción. Los inhibidores de la enzima convertidora de angiotensina bloquean este proceso, reduciendo la severidad o previniendo las crisis del dolor óseo. Con estas observaciones y un perfil de presión arterial estable, recomendamos hacer un amplio uso de IECA en pacientes con ECF para reducir la necesidad del consumo de opioides y el consiguiente riesgo de adicción, como una manera de mejorar su calidad de vida.*

Palabras clave: Inhibidores de la enzima convertidora de angiotensina, crisis de dolor óseo, prevención, enfermedad de células falciformes

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INTRODUCTION

In medical practice, drugs primarily meant to treat an ailment could find secondary use in other clinical conditions. This is called 'off label use'. Sildenafil, a phosphodiesterase inhibitor meant for erectile dysfunction, found use secondarily in fetal growth restriction (1), pulmonary hypertension (2) and benign prostatic hyperplasia (3). Metformin, primarily used in the oral treatment of type II diabetes, found secondary use in polycystic ovary syndrome (4) and sickle cell anaemia (5). Angiotensin-converting enzyme inhibitors (ACEIs) cover cardiovascular, reproductive, endocrine and renal indications (6). However, another use was discovered about a decade ago when Williams and Moskowitz reported its benefit in preventing bone pain crisis in a patient with sickle cell disease (SCD) (7). They asked rhetorically why no one else had recorded such a dramatic observation with ACEIs among patients with SCD, despite their use in sickle cell-related proteinuria.

Although Africans have the highest prevalence, SCD is recognized as a global public health problem given current population mobility and migration of people from high to low frequency areas (8). Pain is the most common reason prompting patients with SCD to seek treatment (9), and effective analgesia is needed (10). It is responsible for frequent school absences (11) with attendant emotional morbidity. Its frequency is roughly 0.8 episode per patient year, and patients with higher rates tend to die earlier (12). Opioids are recommended for use in bone pain and other vaso-occlussive crises (13), but are fraught with tendency to develop tolerance in some patients (14). Adverse effects in the short term (such as respiratory depression, constipation, nausea and vomiting as well as cutaneous manifestations) are also causes for worry (13). Effective treatment for the chronic pain has been sub-optimal, especially in our local environment (15). Ibidapo and Akinyanju (16) reported that 23.5% of their SCD cohort presented with pain crises, and another 10% in combination with anaemia. This makes it desirable to continue studies on pharmacotherapy to reduce occurrence of bone pain and other vaso-occlussive syndromes. To avoid all these and the risk of dependence on opioids for severe painful crises (17), any method to reduce severity of bone pain crises becomes necessary. Therefore, we explored the effect of ACEIs on the frequency of bone pain crises in our SCD population, with a view to adding it as a standard of care. That way, the financial burden on sufferers and their families can be reduced (18). To the best of our knowledge, no record of the use of ACEIs in patients with SCD for bone pain crises had been undertaken locally.

SUBJECTS AND METHODS

Adult patients with SCD who accessed care in the Haematology Clinic of Jos University Teaching Hospital, Nigeria, and who were part of a study on Echocardiographic Assessment of Right Ventricular Systolic Function were invited to participate in a side study where they were given an ACEI, ramipril. This side study was interventional with a before and after design. Ethical clearance was granted by the hospital's Research Ethics Committee (JUTH/DCS/ADM/127/XIX/6033), and informed consent was obtained from

all patients. To avoid recruitment bias, the patients were recruited as they came to the clinic on appointments previously given by the haematologist without reference to the study.

Measurements

On enrolment, patients were administered a questionnaire which requested, among others, information on bone pain crises in the preceding one month. This was pain requiring self-use of analgesics and/or presentation to a hospital. Pulse rate was counted, and blood pressure was measured by standard mercury sphygmomanometry in the supine position. They were then given 2.5 mg of ramipril and were followed up monthly for three months when the study ended. At each visit, any side-effect of the drug was enquired about and blood pressure checked in sitting and standing positions. The number of bone pain crises in the intervening period was documented.

Statistical analyses

The number of bone pain crises before initiation of the ACEI, ramipril, was compared with that after drug initiation at one, two and three months, using Relative Risk Reduction (RRR = control event rate – treatment event rate/control event rate), Absolute Risk Reduction (ARR = control event rate – treated event rate) and Number Needed to Treat (NNT = 1/control event rate – treated event rate), given that the outcome being measured was clinical and subjective (19). Where outcome variables are subjective as in pain or nausea, assessment could be complicated, and RRR, ARR and NNT are recommended (19). Frequency and severity of pain vary widely within and between individuals, as pain threshold and socio-cultural conditions differ (8).

Relative risk reductions which are at least 50% and 30% over the baseline are considered substantial and moderate, respectively (20); and there are studies indicating that clinical efficacy of drugs with NNT values below 10 is acceptable as significant (21).

RESULTS

Fifty patients were enrolled, but 35 are reported here. They were the ones who had complete sets of data by the time a protracted industrial dispute disrupted our hospital services for several months which started in January 2016. The patients' ages ranged from 18 to 50 years, with a mean of 28.91 years (standard deviation: 8.31 years). Twenty-six were females, and nine were males. Table 1 shows the demographic variables of the patients.

Table 1: Demographic variables of the respondents

Variables	Frequency	Percentage
Gender		
Male	9	25.7
Female	26	74.3
Age group		
< 20 years	6	17.1
21–25 years	9	25.7
26–30 years	6	17.1
31–35 years	7	20.0
> 35 years	7	20.0

On enrolment in October 2015, the cumulative frequency of bone pain crises among the patients in the preceding one month (the control event rate) was 16, averaging 0.46/patient month. After one month of 2.5 mg of ramipril, it dropped to 7 (0.2/patient month), then to 6 (0.17/patient month) after two months, and rose to 14 (0.40/patient month) at three months. However, this coincided with a harsh cold dusty harmattan spell. The RRR, ARR and NNT were derived using appropriate formulae (19). The RRR was 56.2% in November 2015 after one month of treatment. In December 2015, after two months on the same treatment, it increased to 63.0%. However, by January 2016, it was 13.0%. The ARR for the first month was 0.26; after the second month, 0.29; and after the third month, 0.06. From these, NNT was derived as follows: 1/0.26 (3.8), 1/0.29 (3.5) and 1/0.06 (16.7) for the first, second and third months of treatment, respectively. None of the patients reported features suggestive of hypotension, and blood pressures remained stable (Table 2).

Table 2: Blood pressure profile of the respondents

Parameter	Baseline visit Mean (standard deviation)	One month of ACEI (ramipril) administration Mean (standard deviation)	Two months of ACEI (ramipril) administration Mean (standard deviation)	Three months of ACEI (ramipril) administration Mean (standard deviation)	F-test	*p*
Systolic blood pressure (mmHg)	113.60 (12.72)	107.31 (11.24)	108.00 (9.95)	111.03 (10.75)	2.34	0.076
Diastolic blood pressure (mmHg)	71.66 (10.88)	67.14 (10.17)	67.14 (7.89)	70.11 (9.64)	1.882	0.136

DISCUSSION

The cumulative frequency of bone pain crises that these patients experienced on enrolment before the drug was introduced fell sequentially in the first two months but went up in the third month when the temperature dropped during harmattan. However, the rise did not get to the pre-treatment level. Sickle cell disease bone pain, a cause of morbidity and analgesic abuse, is a consequence of tissue hypoxia due to vaso-occlussion. Hypoxia causes more red cell sickling. In the process of hypoxia, angiotensin-converting enzyme is activated, and angiotensin II is produced in excess. Angiotensin II results in local vasoconstriction and thrombosis (22). A vicious cycle is thus established that furthers tissue hypoxia and sustains pain. Angiotensin-converting enzyme inhibitors block this cascade resulting in amelioration of pain. This was borne out by this small-scale study confirming the experience of Williams and Moskowitz (7).

The RRR was over 50% in the first two months and thus considered substantial and clinically significant. This is supported by their NNTs that were below 10. The relative risk of pain reduction which consistently increased with the use of ramipril in the first two months fell in the third month, though not reaching the pre-treatment level. It is either that the benefit waned with time or the harsh cold dusty harmattan of the third month was responsible. During harmattan, the temperatures are lower, and the atmospheric dust count is high (23). The cold temperature and the particulate dust pollution of the harmattan season have been documented among environmental determinants of SCD (24), prompting the authors to posit that the knowledge of environmental factors was necessary for pharmacological intervention, especially with SCD, as therapeutic effect may be affected by confounding meteorological conditions. In our study, the steady reduction of cumulative frequency of bone pain crises dipped during the harmattan. Data from the weather station at the University of Jos, Nigeria, showed that the minimum temperature for January 2016 was 15.7ºC, having dropped from 16.1ºC in December 2015. This aligns with a finding in Jamaica that the number of admissions of sicklers with bone pain was inversely related with monthly minimum temperatures (25). The low dose of 2.5 mg of ramipril was well tolerated. We opted for this low dose since with all pharmacotherapies, the risk of adverse events is minimal with the lowest dose possible (8). Though used to treat albuminuria and cardiac disease, ACEIs have been well tolerated in patients with SCD (26–29), hardly affecting blood pressures adversely (30). Although the study was limited by a small sample size and restricted to one tertiary health facility, we recommend a wider use of tailored doses of ACEIs in patients with SCD to establish this phenomenon firmly and avail the benefit to patients with SCD disabled by recurrent bone pain crises.

CONCLUSION

This study showed that the use of a low dose of ACEIs in patients with SCD could reduce the frequency of bone pain crises. This will save them from the risk of opioid addiction and ameliorate their physical and emotional morbidity, while not adversely lowering blood pressures, ultimately improving their quality of life which is the goal of treatment.

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AUTHOR CONTRIBUTIONS

JO Egesie provided patients for the study from the cohort who attended the Haematology Clinic of Jos University Teaching Hospital, Nigeria. CS Raphael enrolled the patients, saw them at monthly intervals, examined them and took the necessary measurements. SU Uguru took part in the monthly evaluation. BN Okeahialam conceptualized and supervised the study, analysed data and wrote the manuscript.

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