International Journal of Research in Medical Sciences
Gosavi RV et al. Int J Res Med Sci. 2017 Sep;5(9):3851-3855
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20173676

Original Research Article

Study of clinical effects of aspartame in sickle cell disease and sickle cell crisis

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Received: 29 July 2017
Accepted: 02 August 2017

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ABSTRACT

Background: Sickle cell disease is the commonest heritable hematologic abnormality affecting humans and is highly prevalent in central India. Aspartame is the only agent that can prevent sickling tested in-vitro and in-vivo so far. With the available data being relatively scarce, this study aims to study the efficacy of aspartame in sickle cell crisis and sickle cell disease.
Methods: Forty cases and controls each were selected as per predefined criteria. Controls were treated with standard therapy of analgesics, IV fluids, antibiotics and oxygen, if needed. Cases were treated with oral aspartame in addition to standard therapy. Clinical grading was done before respective treatment in both cases and controls and comparisons were drawn.
Results: 78.9% cases and 66% controls were pain free at the end of 72 hours; with p-value of 0.093, which is statistically insignificant. 78.7% cases (n=33) and 64.4% controls (n=33) with SS pattern had grade 0 pain at the end of 72 hours, results being statistically insignificant. 81% cases (n=7) and 75% controls (n=7) with AS pattern had grade 0 pain at the end of 72 hours, which was similar in both groups with statistically insignificant p-value of 0.753.
Conclusions: Oral Aspartame as an add-on therapy to standard therapy for vaso-occlusive crisis in sickle cell disease appears to have better response than standard therapy alone.

Keywords: Aspartame, Crisis, Sickle cell disease

INTRODUCTION

Sickle cell disease is the commonest heritable hematologic abnormality affecting humans.[1] The average incidence of sickle gene among Indians is approximately 4.3%.[2] The frequency is much higher (up to 45%) in many tribal population in India.[3] The prevalence of sickle cell disease is high in central India and certain localities of Maharashtra.[4]

The most troubling presentation of sickle cell disease is the crisis. Despite substantial increase in knowledge in sickling phenomenon, not much has been gained in terms of therapies for prevention of crisis. Currently accepted management of painful crisis includes prophylactic measures to reduce the incidence and therapy to relieve the crisis by appropriate treatment of precipitating factor, analgesics for pain, stabilization of red cell membrane and vasodilatation to improve microcirculation. Many drugs like Phenothiazine, Nitrates, Urea, Nicotinic acid, Dextran, Alkali, Androgen, Aspirin, Desmopressin acetate, 5-Azacytidine etc. have been tried with limited or no success. New compounds continue to be sought, that might interfere with sickling and be useful clinically. Aspartame is the only agent that can prevent sickling tested in-vitro and in-vivo so far.[5] The data regarding utility of aspartame in sickle cell disease is relatively scarce. This study aims to plug the gap with the objective

of studying the efficacy of aspartame in sickle cell crisis and sickle cell disease.

METHODS

Hospital based case control study, open-labelled study conducted in Medicine wards, tertiary care government institute, during the period of November 2011 to October 2013 (2 years).

Inclusion criteria

- Patients of sickle cell anemia (SS) and sickle cell trait (AS) presenting with vaso-occlusive crisis
- Age >12 years.

Exclusion criteria

- Hb electrophoresis pattern other than SS or AS
- Patients on hydroxyurea
- History of blood transfusion in last 4 months
- Critically ill patients: septicemia/ encephalopathies/ respiratory failure
- Pregnancy/lactation
- Known patients of phenylketonuria
- Refusal to give consent.

Operational definitions

Vaso-occlusive/painful crisis- Pain in back, extremities, abdomen or chest severe enough to require hospitalization; with other causes of pain being excluded. The crisis was considered to be terminated on the day pain subsided. Patients were considered to be in steady state where there was no painful crisis within preceding two weeks of study.[6]

Sickle cell disease

Replacement of at least one of the beta-globin subunits in hemoglobin by hemoglobin S and was diagnosed by electrophoresis.

Sickle cell anemia

Replacement of both beta-globin subunits in hemoglobin by hemoglobin S and was diagnosed by single band at hemoglobin S, on electrophoresis.

Sickle cell trait

Replacement of single globin unit by hemoglobin S and was diagnosed by two bands at hemoglobin S and at hemoglobin A on hemoglobin electrophoresis.

Cases

Patients of sickle cell disease in vaso-occlusive crisis receiving Aspartame in addition to standard therapy.

Controls

Age and gender matched patients of sickle cell disease in vaso-occlusive crisis of similar severity and same Hb electrophoresis pattern as the case, receiving standard therapy.

Forty cases and controls each were selected as per criteria mentioned above. Detailed relevant clinical history was elicited. Detailed general and systemic examination was conducted. Hematological and biochemical investigations including Complete blood count, peripheral smear, sickling test, hb electrophoresis and liver function test were performed on all the participants.

Clinical grading was done before respective treatment in both cases and controls and comparison was made. Severity of vaso-occlusive crisis was graded for pain, tenderness, mobility and functional capacity w.r.t. day to day's work. Pain was graded as per Visual Analogue Scale (Wong Baker Faces Pain Rating Scale).[7] Accordingly; Grade 0 means no pain, grade I- mild pain, grade II- moderate pain and grade III indicates severe/worst possible pain (Figure 1).

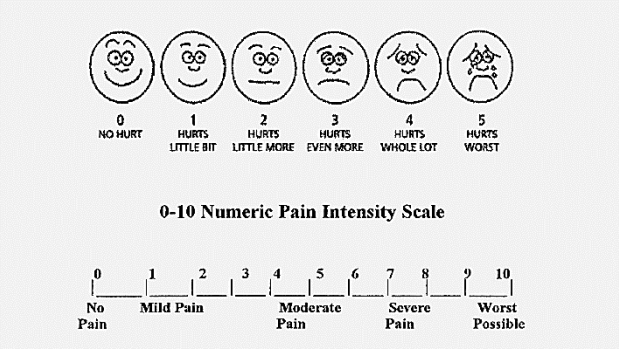

Figure 1: Wong-Baker faces pain rating scale.

The controls were treated with standard therapy of analgesics, IV fluids, antibiotics and oxygen, if needed. The cases were treated with oral Aspartame (6 mg/kg body weight, in 30ml, in 3 divided doses per day), in addition to standard therapy. The clinical response to treatment was recorded at 24, 48 and 72 hours and the clinical severity was graded each time as above.

The data was analysed using SPSS (version 20); by applying unpaired t-test and ANOVA wherever applicable. Approval from institutional ethics committee was obtained before start of the study. Informed written consent was obtained from each patient before participation in the study.

RESULTS

Study enrolled 80 patients (40 cases, 40 controls) of sickle cell disease as per mentioned selection criteria. Out of 40 cases, 33 (82.5%) were of SS pattern and 7 (17.5%)

of AS pattern as per Hb electrophoresis. Mean age of cases and controls were 19.27±5.91 and 20.35±6.22 years respectively. In both cases and control groups, 26 patients (65%) were male and 12 (30%) were females. Around 69% participants belonged to Mahar community, equally distributed in cases and controls.

Table 1: Progress of grade of pain in cases at 24, 48 and 72 hours after aspartame initiation.

Pre-therapy pain grade	Pattern	At 24 hours				At 48 hours				At 72 hours			
		Grade				Grade				Grade			
		III	II	I	0	III	II	I	0	III	II	I	0
III (n=17)	SS (15)	8	5	2	0	3	3	5	4	2	1	5	7
	AS (2)	1	1	0	0	0	1	1	0	0	0	1	1
II (n=21)	SS (16)	0	5	8	3	0	3	7	6	0	1	2	13
	AS (5)	0	2	2	1	0	1	2	2	0	0	2	3
I (n=2)	SS (2)	0	0	1	1	0	0	0	2	0	0	0	2
	AS (0)	0	0	0	0	0	0	0	0	0	0	0	0
Total (n=40)		9	13	14	5 (12.5%)	3	8	15	14 (35%)	2	2	10	26 (65%)

The mean number of crises in last one year was 1.87±1.96 for cases and 1.57±1.81 for controls. Maximum number of patients were having 1-3 crises.

Most of the patients (38, 95% in each group) were having grade II or grade III pain before treatment. Similar values in both the groups were recorded for tenderness, mobility and functional capacity w.r.t. day to day's work before start of respective group's treatment; as was designed to be; for the two groups to be comparable.

Table 1 shows the clinical response for pain after oral Aspartame at the end of 24, 48, 72 hours in cases. The results showed that 5 (12.5%) patients had excellent response (improved to grade 0) at the end of 24 hours. The number went up to 14 (35%) and 26 (65%) at the end of 48 and 72 hours respectively.

Table 2 shows the clinical response for pain amongst controls at the end of 24, 48 and 72 hours after standard therapy initiation. Only 2 (5%) patients had excellent response (improved to grade 0) at the end of 24 hours; while 12 (30%) and 19 (47.5%) patients had this response at the end of 48 and 72 hours respectively of initiation of standard therapy.

Table 2: Progress of grade of pain in controls at 24, 48 and 72 hours after standard therapy initiation.

Pre-therapy pain grade	Pattern	At 24 hours				At 48 hours				At 72 hours			
		Grade				Grade				Grade			
		III	II	I	0	III	II	I	0	III	II	I	0
III (n=16)	SS (14)	7	4	3	0	4	4	3	3	2	3	5	4
	AS (2)	1	1	0	0	0	1	1	0	0	0	1	1
II (n=22)	SS (17)	0	9	8	0	0	5	7	5	0	3	5	9
	AS (5)	0	2	2	1	0	1	2	2	0	1	1	3
I (n=2)	SS (2)	0	0	1	1	0	0	0	2	0	0	0	2
	AS (0)	0	0	0	0	0	0	0	0	0	0	0	0
Total (n=40)		8	16	14	2 (5%)	4	11	13	12 (30%)	2	7	12	19 (47.5%)

Table 3 shows summary of comparison of number of patients with grade 0 pain in cases and controls at the end of 24, 48 and 72 hours of respective treatment. The differences were not statistically significant.

The study of means of grade of pain at the time of admission and at the end of 24, 48, 72 hours in cases and controls (Table 4) shows it to be 2.37±0.58 and 2.35±0.58 respectively on admission. It comes down to 0.5±0.81 and 0.8±0.91 respectively at the end of 72 hours. ANOVA reveals benefit from both the modalities to be statistically significant over mentioned time period. But the difference between the two groups wasn't statistically significant at any point in time.

Table 3: Comparison of number of patients with grade 0 pain in cases and controls at the end of 24, 48 and 72 hours of treatment.

Time	Cases (n=40)	Controls (n=40)	P-value
24 hours	5 (12.5%)	2 (5%)	0.432
48 hours	14 (35%)	12 (30%)	0.633
72 hours	26 (65%)	19 (47.5%)	0.115

Table 4: Mean pain scores at different time points in cases and controls.

Time	Cases (n=40)	Controls (n=40)	P-value
Baseline	2.37±0.58	2.35±0.58	0.878
24 hours	1.65±0.97	1.75±0.84	0.222
48 hours	1.0±0.81	1.17±0.98	0.4
72 hours	0.5±0.81	0.8±0.91	0.1234
P-value	<0.0001	<0.0001	

DISCUSSION

The present study included eighty patients of sickle cell disease in vaso-occlusive crisis, which were divided into 40 cases and 40 controls. Cases received aspartame along with standard therapy. Controls received standard therapy only. The clinical response was analyzed in both groups at 24, 48 and 72 hours.

We studied clinical effects of aspartame in sickle cell disease as well as sickle cell anemia and sickle cell trait patients; which were not included in previous studies. The mean age and gender distribution in present study was largely comparable to previous similar studies.

As in study of Zawar et al, we also found that disease is more severe with more number of crises per year in patients with sickle cell anemia (SS) than sickle cell trait (AS).[8] More than 50% of patients with sickle cell anemia suffer from >2 crises per year as compared with sickle cell trait (<10%).

For pain, there were 95% patients with grade II and III in both groups. Only 5% of patients manifested with grade I pain. Painful crises were one of the most characteristic manifestation of SCD. Pain resulting from ischemia of the bone marrow is gnawing and progressive in severity, as reported by Serjeant and Chalmer.[9]

In present study, if we compare the pain relief in cases after oral aspartame; out of 17 patients with grade III pain, 8 patients improved to grade 0; out of 21 patients with grade II pain, 16 patients improved to grade 0 at the end of 72 hours. All patients from grade I showed excellent resolution at 48 hours. Therefore, it can be said that response to Aspartame, as observed in this study, was better in patients with mild and moderate pain than in patients with severe pain (who showed only marginal improvement in pain). Overall, 26 (65%) cases and 19 (47.5%) controls showed response to treatment at the end of 72 hours. So, it can be said that response to Aspartame plus standard therapy was better than standard therapy alone, as observed in this study

Comparison of the efficacy of treatment for pain relief in cases and controls by Mann-Whitney test showed that 78.9% cases and 66% controls were pain free at the end of 72 hours; with p-value of 0.093, which is statistically insignificant.

Similar study was performed in the state of Orissa (India) by Swain SK et al.[10] They observed that 8 (13.3%) showed excellent result to oral Aspartame in the case group (n=60) and no patient showed similar improvement in the standard therapy group (n=60) at 24 hours. Thirty-six (60%) showed good response within 24-48 hours in the case group and 18 (30%) in the control group. The comparative efficacy of Aspartame in case group in comparison group was reported to be statistically significant (p=0.001) by them.

For pain relief, comparing the efficacy of treatment in cases and controls according to Hb electrophoresis pattern by Mann-Whitney test showed that 78.7% cases (n=33) and 64.4% controls (n=33) with SS pattern had grade 0 pain at the end of 72 hours, results being statistically insignificant. 81% cases (n=7) and 75% controls (n=7) with AS pattern had grade 0 pain at the end of 72 hours, which was similar in both groups with statistically insignificant p-value of 0.753. The results sit well with the study done by Swain SK et al.[10] In the present study, it was observed that 65% cases who were on oral aspartame showed good response for decreasing the duration of vaso-occlusive crisis, though it wasn't statistically significant when compared to controls (47.5%) (p=0.093).

CONCLUSION

The present study showed that oral aspartame as an add-on therapy to standard therapy for vaso-occlusive crisis in sickle cell disease appears to have better response than standard therapy alone, but the results were not statistically significant. Being conducted as open-label and with relatively small sample size were major limitations of the study. Conduction of randomized, double blind, placebo controlled study with larger sample size may be recommended to substantiate the claim.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Gosavi RV, Aher MU. Study of clinical effects of aspartame in sickle cell disease and sickle cell crisis. Int J Res Med Sci 2017;5:3851-5.