International Journal of Basic & Clinical Pharmacology
Chaudhary PS et al. Int J Basic Clin Pharmacol. 2020 Mar;9(3):480-486
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20200726

Original Research Article

Comparative effectiveness of S-adenosylmethionine and etoricoxib in newly diagnosed patients of knee osteoarthritis

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Received: 27 December 2019
Revised: 05 February 2020
Accepted: 06 February 2020

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ABSTRACT

Background: Knee osteoarthritis is an important cause for morbidity in elderly people. Therapy is largely symptomatic with nonsteroidal anti-inflammatory drugs which pose risk in the elderly. Methionine is natural body constituent with novel property of blunting S-adenosylmethionine (SAMe) inflammatory process and cartilage degradation. The aim of this study was to compare effectiveness of SAMe, with standard etoricoxib therapy in newly diagnosed knee osteoarthritis cases.
Methods: 127 newly diagnosed knee osteoarthritis patients were randomized into two groups. 55 participants received treatment of etoricoxib 600 mg extended release once daily for 90 days (group 1) and 72 received etoricoxib 600 mg extended release once daily and SAMe 400 mg twice daily for initial 15 days followed by SAMe once daily 400 mg as maintenance dose for next 75 days (group 2). The outcomes were measured by knee injury and osteoarthritis outcome score (KOOS). Pre and post treatment KOOS scores of all cases were separately pooled to define the median for whole as well as components of KOOS parameters. Relative frequencies of cases with values around respective medians were compared by MOODS median test. Patient characteristics, disease characteristics were also examined for bearing on outcomes besides the treatment.
Results: SAMe treatment was associated with significantly greater improvement in symptoms, activities of daily life, spontaneous recreational activities and the quality of life compared to etoricoxib therapy. The therapy was well-tolerated.
Conclusions: The study confirms SAMe as superior therapeutic option in osteoarthritis. SAMe indeed has been reported to have specific anti-arthritic effects and promotive to general well-being.

Keywords: Knee injury and osteoarthritis outcome score, Nitric oxide, Nonsteroidal anti-inflammatory drug, Osteoarthritis, S-adenosylmethionine

INTRODUCTION

Deoxyribonucleic acid (DNA) methylation defect is best characterized epigenetic hallmark for variety of immune, degenerative and neoplastic pathologies. It is crucial to gene expression, cellular differentiation and functional vitality.[1] Analysis of genome wide aberration in DNA methylation has increasingly led to define phenotypes

predisposed to occurrence of diverse disease types.[2] Genetic aberrations in osteoarthritic chondrocytes is established.[3,4] Current view of pathogenesis of osteoarthritis as an imbalance of overactive inflammatory mediators in face of debility of protective and reparative mediators bears accord with possibility of hypomethylation state which deserves due investigation.[5]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drug, but their use is limited because of their propensity to cause gastrointestinal (GI) injury.[6] Many patients with OA are elderly and have comorbid disease. They are often at highest risk of NSAID associated side effects (GI, renal, cardiovascular) and drug interactions.[7]

S-adenosylmethionine (SAMe) is a natural substrate for physiological methylation and sulfuration reactions which bears default with advance of age and obesity. The latter states also have increased prevalence of osteoarthritis.[8,9] SAMe is shown to directly stimulate the metabolism and proteoglycan synthesis by chondrocytes.[10] After the initial promise in clinical trials in osteoarthritis.[11] SAMe however came to be better recognized for antidepressant profile. Neuro-serotonergic dysfunction in depression is relevant to neuro-endocrine disturbance afflicting immune and inflammatory responses as well.[11]

Predominant orthopaedic care of osteoarthritic patients remains oriented to palliative and surgical interventions. The logic of rational therapy and need of majority of cases for long time conservative treatment makes enough sense to elaborate the adequate evidence base and clinical status of disease modifying agent SAMe in osteoarthritis. In this study we aimed to compare the effectiveness of SAMe and etoricoxib in newly diagnosed patients of knee osteoarthritis.

METHODS

Newly diagnosed patients of knee osteoarthritis (n=127) reporting at orthopaedic outpatients were included in the study. Clinically diagnosed cases of knee osteoarthritis were also radiologically investigated for osteoarthritis grading. The present study was conducted in Sir Sundarlal Hospital, Institute of Medical Sciences Banaras Hindu University, Varanasi and the duration of the study was from 3rd January 2010 to 3rd July 2011.

Inclusion criteria of patients within 40-70 years age range of either sex, bearing radiologic disease up to grade III (Kellgren and Lawrence) and free from co-morbidities except therapeutically well controlled mild to moderate diabetes or hypertension without secondary complications were acceptable for inclusion.[12]

The exclusion criteria were presence of uncontrolled or severe grades of diabetes/hypertension or other significant co-morbidities, history of knee injury, surgery or pregnancy in last 3 years, recent hospitalization for 3 or more days within 1 year, history of medication for osteoarthritis more than once a week in preceding 4 weeks. Patients non-compliant to treatment at more than 2 recalled instances during any fortnight through course of study were excluded as well. Informed consent of patients for participating in study was obtained with assurance to keep identity undisclosed and with an approval of institutional ethics committee.

A prospective comparative study with intent to treat analysis, effectiveness of palliative nonsteroidal anti-inflammatory drug, etoricoxib therapy against therapy with SAMe was carried out. 55 were enrolled in etoricoxib group (group 1) and 72 in etoricoxib plus SAMe group (group 2). At the end of the three months therapy, 14 and 28 cases lost follow-up. Group 1 received oral etoricoxib 600 mg extended release preparation once daily for 90 days and group 2 received oral etoricoxib 600 mg ER once daily and oral SAMe 400 mg twice daily for initial 15 days followed by oral SAMe alone once daily 400 mg as maintenance dose for next 75 days (Figure 1). Medicines were recruited from central medical store of Institute of Medical Sciences, Banaras Hindu University, Varanasi.

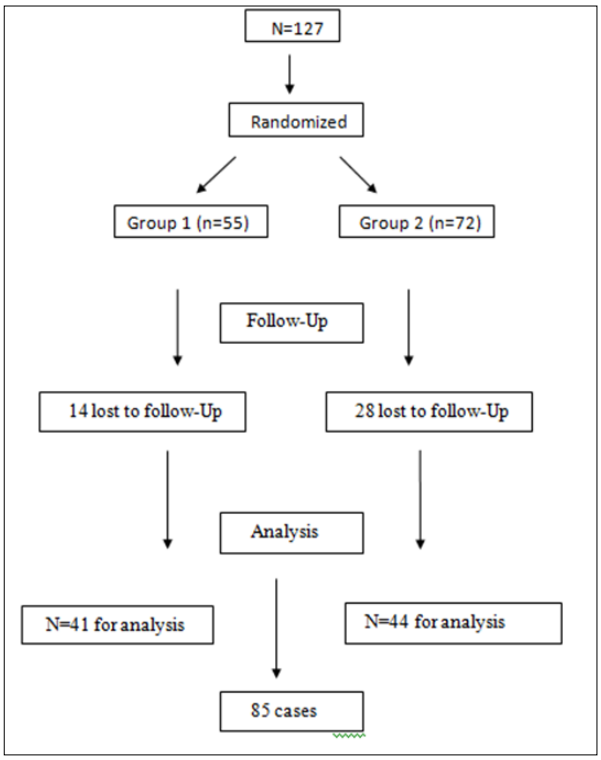

Figure 1: Flow chart of the study.

Osteoarthritis morbidity profile of knee was then graded by symptom-sign-quality of life enquiry in patients adopting the knee injury and osteoarthritis outcomes assessment score (KOOS) and scores recorded.[13,14] The KOOS assesses the patient's self-report of pain, other symptoms, activities of daily living, sports and recreation

function, and knee related quality of life, in 42 questions which take about 10 minutes to complete. The KOOS is scored from 0 to 100, separately for each subscale, 0 indicating extreme problems and 100 indicating no problems. The questionnaire and scoring manual can be found at http://www.koos.nu. The Western Ontario and McMaster Osteoarthritis Index (WOMAC) is also included in KOOS. Through monthly follow-up visits, enquiries were made on compliance to the prescribed treatment and any accidental illness meriting consideration for exclusion from study. After three months uninterrupted therapy period repeat KOOS scoring was performed and the differences of final to initial scores form basis for outcome analyses. Radiological evaluation was done at only at baseline for grading of OA using Kellgren and Lawrence classification.[12]

The statistical analysis was done using Mood's median test. KOOS scale was administered at baseline and at the end of 3 months of therapy. Pre and post treatment KOOS scores of all cases were separately pooled to define the median for whole as well as components of KOOS parameters. Relative frequencies of cases with values around respective medians were compared by MOODS median test. Patient characteristics, disease characteristics were also examined for bearing on outcomes besides the treatment.

RESULTS

The patients included under SAMe treatment group significantly exceeded the etoricoxib treatment group in regard to diseases severity based on KOOS score. However net improvement in KOOS score (reduction) was significantly greater in SAMe treatment group compared to etoricoxib treatment group after 3 months of therapy (Table 1). Selective effects on components of KOOS are summarized in (Table 2a and 2b).

SAMe treatment was associated with significantly greater improvement in symptoms, activities of daily life, spontaneous recreational activities and the quality of life. The NSAID therapy did not differ with SAMe therapy in regard to improvements in pain and stiffness. (Table 3a and 3b) examines the independent variables among two treatment groups which may be confounding elements of the outcome. However, no significant difference in subjects composing the two studied groups were found with regard to sex, age, radiologic grade, duration of complaints, body mass index, family history, alcohol, smoking or tobacco habits. Improvement was seen in stiffness in patients above or below 53 years of age bearing radiologic grade I+II and grade III OA (Table 4a). Improvement in pain was shown in (Table 4b), recreational activities improvement in (Table 4c), improvement in symptom in (Table 4d), improvement in quality of life was mentioned in (Table 5).

Table 1: KOOS score profiles studied in the two therapy groups.

Group	Pre-treatment KOOS profiles around median 57			Post-treatment KOOS profiles around median 68			Net improvement KOOS profiles around median 11		
	>median	Median and below	P value	>median	Median and below	P value	>median	Median and below	P value
Etoricoxib	17	24	0.041*	4	37	0.0001***	5	36	0.0001***
SAMe	28	16		37	7		29	15	

(* significant (p<0.05), ** highly significant(p<0.001), *** very highly significant (p<0.0001).

Table 2a: Profile of percent improvement (around median 25%) in component scores under KOOS.

Group	% improvement in pain score around median 25%			% improvement in stiffness score around median 0.00%			% improvement in symptom score around median 16.67%		
	>median	Median and below	P value	>median	Median and below	P value	>median	Median and below	P value
Etoricoxib	18	23	0.886	16	25	0.549	11	30	0.029*
SAMe	20	24		20	24		22	22	

(* significant (p<0.05), ** highly significant(p<0.001), *** very highly significant(p<0.0001).

Table 2b: Profile of percent improvement (around median 10%) in component scores under KOOS.

Group	% improvement in activities of daily life score around median 10%			% improvement in recreational activity score around median 16.67%			% improvement in quality of life score around median 40%		
	>median	Median and below	P value	>median	Median and below	P value	>median	Median and below	P value
Etoricoxib	12	29	0.000***	14	27	0.021*	11	30	0.029*
SAMe	34	10		26	18		22	22	

(* significant (p<0.05), ** highly significant(p<0.001), *** very highly significant(p<0.0001)

Table 3a: Distribution of patients as per sex, age, radiological, duration of complaints, BMI.

Group	Sex			Age (median-53 yrs)			Radiological grade			Duration of complaints (median-2 yrs)			Body mass index (median -26)		
	M	F	P value	>median	Median and below	P value	I+II	III	P value	>median	Median and below	P value	>median	Median and below	P value
Etoricoxib	18	23	0.440	19	22	0.473	21	20	0.466	19	22	0.473	16	25	0.221
SAMe	23	21		17	27		25	18		17	27		23	21	

(* significant (p<0.05), ** highly significant(p<0.001), *** very highly significant(p<0.0001).

Table 3b: Distribution of patients as per family history of osteoarthritis, alcohol use, smoking habit, tobacco use.

Group	Family history of osteoarthritis			Alcohol use			Smoking habit			Tobacco use		
	Positive	Negative	P value	Present	Absent	P value	Present	Absent	P value	Present	Absent	P value
Etoricoxib	24	17	0873	4	37	0.398	9	32	0.664	12	29	0.658
SAMe	25	19		7	37		8	36		11	33	

(* significant (p<0.05), ** highly significant(p<0.001), *** very highly significant(p<0.0001).

Table 4a: Percent improvement in stiffness component of KOOS score in different grades.

Percent improvement in STIFFNESS (median 0.00%)					
Age strata	Radiological Grade I+II		Radiological Grade III		P value (within group)
	>Median	Median and less	>Median	Median and less	
>53 years	9	2	2	7	0.008
53 years and below	4	11	5	4	0.757
Intergroup p value	0.005		0.147		

(* significant (p<0.05), ** highly significant(p<0.001), *** very highly significant(p<0.0001).

Table 4b: Percent improvement in pain component of KOOS score score in different grades.

Percent improvement in pain (median 40%)					
Age strata	Radiological grade I+II		Radiological grade III		P value (within group)
	>Median	Median and less	>Median	Median and less	
>53 years	7	4	2	7	0.064
53 years and below	9	6	4	5	0.459
Intergroup p value	0.851		0.317		

(* significant (p<0.05), ** highly significant(p<0.001), *** very highly significant(p<0.0001)

Table 4c: Percent improvement in recreational activities component of KOOS score in different grades.

Percent improvement in Recreational Activities (median 16.67%)					
Age strata	Radiological Grade I+II		Radiological Grade III		P value (within group)
	>Median	Median and less	>Median	Median and less	
>53 years	8	3	3	6	0.078
53 years and below	10	5	5	4	0.586
Intergroup p value	0.741		0.343		

(* significant (p<0.05), ** highly significant(p<0.001), *** very highly significant(p<0.0001).

Table 4d: Percent improvement in symptoms component of KOOS score in different grades.

Percent improvement in symptoms (median 16.67%)					
Age strata	Radiological Grade I+II		Radiological Grade III		P value (within group)
	>Median	Median and less	>Median	Median and less	
>53 years	4	7	2	7	0.492
53 years and below	12	3	4	5	0.074
Intergroup p value	0.024*		0.317		

(* significant (p<0.05), ** highly significant(p<0.001), *** very highly significant(p<0.0001).

Table 5: Percent improvement in quality of life component of KOOS score in different grades.

Percent improvement in quality of life (median 40%)					
BMI strata	Radiological Grade I+II		Radiological Grade III		P value (within group)
	>Median	Median and less	>Median	Median and less	
Above 26	3	2	1	8	0.052
26 and below	13	8	5	4	0.745
Intergroup p value	0.937		0.046		

(*significant (p<0.05), **highly significant(p<0.001), *** very highly significant(p<0.0001)

Benefits of SAMe treatment in terms of improvement in KOOS score are considered for influence of some host factors. KOOS score improvements by SAMe treatment did not significantly differ in patient subsets of different sex, BMI, and age on higher or lower side of the median values, in either early or advanced radiologic grade of osteoarthritis. Sex, age and BMI strata were also examined for any selective benefits either in early or in more advanced radiological stages of osteoarthritis on various components of KOOS score. Sex differences did not significantly influence relative benefits of SAMe therapy on any of the components.

Analysis of SAMe treatment effects in patients sub stratified by age above median 53 years or under indicated that older patients bearing radiologically early stages of osteoarthritis were significantly more relieved of stiffness feeling in the joint (Table 4a). Superior benefits also manifested in quality of life and recreational activities (Table 4b and 4c). Younger patients with early radiologic osteoarthritis gained significantly more relief of symptoms (Table 4 D).

When SAMe treatment related benefits were analyzed in patient subsets with BMI above median 26 or on lower side, significant lack of benefit in quality of life manifested among the higher BMI cases (Table 5).

DISCUSSION

The patients included under standard NSAID group had advantage that majority cases had BMI lower than general median 26 and there was no tobacco use among them. Majority of the SAMe treated group of patients were under 60 years and with radiologically early stages of osteoarthritis.

Etoricoxib is relatively safe in causing little gastrointestinal adverse effects and constitutes primarily palliative treatment of pain and inflammation. SAMe treatment has shown to reduce key inflammatory mediators TNF-alpha and generation of NO injurious to the chondrocytes. SAMe also boosts glutathione synthesis within joint tissues improving defense against oxidative damage and impairment of capacity to produce proteoglycans. SAMe effects on membrane fluidity of chondrocytes and facilitates chondrocyte receptors better binding to growth factors, thus supporting vitality as well as functions. Although SAMe is protective to chondrocytes and counters inflammatory process, the consequence would be relief of symptoms and improved functions. Analgesic and anti-inflammatory effects of SAMe are duly reported.[15]

Significant improvement of KOOS scores by SAMe treatment superior to standard etoricoxib treatment confirms and supports the claimed pharmacological effects of the drug mentioned above. SAMe treatment resulted in no different benefits on relief of pain and symptoms as that produced by etoricoxib treatment. Superiority of SAMe treatment significantly shows on functional parameters and improved quality of life. The drug also has welcome effect on mood since it supports synthesis of neurotransmitters like serotonin and dopamine. The therapy raises feelings of wellbeing and at the same time may rectify any deficit in neurohumoral response to stress that the patient of osteoarthritis certainly suffers.[11]

SAMe treatment therefore constitutes a rational therapy with the pharmacodynamics correlating and rectifying pathomechanisms of osteoarthritis. Analgesic, anti-inflammatory and antidepressant effects16 on one hand, and virtually nontoxic profile, being natural body constituent, renders much appeal to SAMe in osteoarthritis therapy. Roos et al showed that KOOS is a valid, reliable and responsive self-administered instrument that can be used for short-term and long-term follow-up of several types of knee injury including osteoarthritis.[13] In a study conducted by CD Padova, based on the findings, SAMe is proposed as a new class of safe drugs for the treatment of osteoarthritis and well tolerated for long periods.[8]

Certain apparent differences in the composition of groups have been stated at the outset. It may be seen that several such independent factors likely to confound the observed outcomes did not significantly differ in compared groups of the study (Table 3 A and B). Hence the observations may be taken as valid consequences of the treatment.

The effects of SAMe were further examined by subtracting the patients with higher or relatively lower load of known and suspected independent risk factors of osteoarthritis. Age and excess weight are established risk factors while sex was also included for associating different weight patterns and body mechanics. SAMe treatment benefited similarly in either of the sexes which suggest the drug effect overriding any differences relevant to pathogenesis of osteoarthritis among two sexes.

The patients of older age and early stages of osteoarthritis got the best benefit. This is in agreement with the reported decline of endogenous SAMe with advancing.[5] The benefit in earlier grades may point to need for early institution of SAMe therapy before the diseases progresses to structural disorder, not convertible with drug therapy. Observations that younger patients with early osteoarthritis get better relief in knee symptoms and particular improvement in older patients in knee related quality of life, indicate positive drug effects on psyche and morale as well.

Overweight patients with higher radiologic grade of osteoarthritis particularly failed to gain from SAMe treatment in regard to quality of life. Higher radiologic grade represents more advanced structural changes particularly worse in overweight patients with added burden of greater stress. The employed SAMe regimen may not have been adequate to meet their dose requirements.

Alternatively, obesity, degenerative diseases of ageing and sub-clinical inflammatory state constitutes phenotype that commonly suffers derangement of folic acid metabolism and hypomethylation state.[8] Although not evaluated, occurrence of hyperhomocysteinemia, erosion of glutathione reserves as well as decline of polyamine formation necessary to cell renewal process accompany hypomethylation phenotypes which would obviously be detrimental for condition like osteoarthritis. SAMe may be tailor made remedy in such cases.

CONCLUSION

The present study showed SAMe as superior therapeutic option in osteoarthritis. SAMe indeed has been reported to have specific anti-arthritic effects and promotive to general well-being.

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: Chaudhary PS, Deshmukh SV, Jaybhaye DL, Johar SK, Pandey BL, Sharma GA. Comparative effectiveness of S-adenosylmethionine and etoricoxib in newly diagnosed patients of knee osteoarthritis. Int J Basic Clin Pharmacol 2020;9:480-6.