ORIGINAL ARTICLE

A cohort study to evaluate cardiovascular risk of selective and nonselective cyclooxygenase inhibitors (COX-Is) in arthritic patients attending orthopedic department of a tertiary care hospital

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ABSTRACT

Background: Cyclooxygenase-2 inhibitors (COX-2-Is) have recently been concerned in the occurrence of adverse cardiovascular (CV) events. Rofecoxib and valdecoxib has been withdrawn from the market, but celecoxib, etoricoxib and parecoxib continues to be used. Other nonsteroidal anti-inflammatory drugs (NSAIDs) may also increase the risk of CV events. However, clinical trial databases for COX-2-Is had created lots of controversies regarding cardiovascular safety of selective and nonselective cyclooxygenase inhibitors (COX-Is). This study was, conducted to assess and compare the CV risk of COX-Is in arthritic patients over a period of time. **Materials and Methods:** In this prospective cohort study adult arthritics of either sex those were freshly diagnosed or taking COX-Is for < 3 months; were included. Patients were grouped into nonselective and selective COX-2-I groups with reference to treatment they received. The CV risk factors like blood pressure (BP), blood sugar level (BSL), lipid profile, body mass index (BMI) were assessed and compared; demography of CV risk factors was also studied. Data obtained was analysed using Student's 't'-test of OpenEpi statistical software. **Results:** Study clearly revealed that all NSAIDs exhibit variable CV risk; however, selective COX-2-Is found to exhibit more CV risk. BMI, BP and lipid profile; the potential CV risk factors, showed significant impairment in selective COX-2-Is group; $P < 0.01$, $P < 0.001$ and $P < 0.05$, respectively, compared to baseline and $P < 0.05$ vs. nonselective COX-Is for BMI. **Conclusions:** This study portrays the potential CV risk of selective COX-2-Is; confirms and re-evaluate the results of earlier studies in this regard.

Key words: Body mass index, cardio-vascular risk, cyclooxygenase inhibitors, lipid profile

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed group of therapeutic drugs worldwide, and include many common analgesics and anti-inflammatory agents.[1] Selective COX-2-Is have demonstrated improved gastrointestinal tract (GI) safety over nonselective NSAIDs.[2,3] The clinical trials have evidenced that, compared to nonselective COX -Is, COX-2-Is associated with a reduced rate of serious GI events as well as a reduced requirement for concomitant gastro-protective therapies.[4] This relative benefit may be due to a lack of COX-1-mediated inhibition of gastric mucous production and a lack of effect on platelet thromboxane production. However, the differential effects of COX-2-Is on platelet aggregation, prostacyclin/thromboxane balance, and inflammatory mediators involved in the development of atherosclerosis have also led to concerns that COX-2-Is increase the CV events.[5,6]

Evidence from large prospective clinical trials on CV risks has been largely limited as those trials were designed to evaluate primarily GI events. The VIOXX Gastrointestinal Outcomes Research Study (VIGOR) revealed an increased rate of thrombotic events in patients receiving COX-2 inhibitor (rofecoxib).[2] Mukherjee and colleagues have compared rate of CV events in rofecoxib and celecoxib

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in VIGOR and Celecoxib Long-term Arthritis Safety Study (CLASS) trials with four aspirin studies viz., the US Physicians Health Study, the UK Doctors Study, the Thrombosis Prevention Trial, and the Hypertension Optimal Treatment Trial and revealed significantly higher CV event rate in COX-2-Is treatment groups.[3,7]

In contrast to this, Konstam and colleagues[8] have analysed the results of multiple clinical studies involving rofecoxib and have not demonstrated any increased risk for CV events comparing COX-2 inhibitors and nonselective NSAIDs. Observational studies also have found mixed results when comparing select COX-2 Is and nonselective NSAIDs.[9,10] Hence, we chose to research this question with an observational prospective cohort study of CV risk of selective and nonselective COX-Is in adult arthritic patients. Many of the observational studies rely on case-control designs. In our cohort study, we evaluated the risk of cardiovascular events with COX-2 Is versus nonselective NSAIDs.

MATERIALS AND METHODS

In this observational prospective cohort study adult arthritic patients of either sex those were freshly diagnosed or taking COX-Is for < 3 months; were included. Patients those with history of any other disease (e.g., diabetes, hypertension, stroke, IHD, etc.) and medical treatment for the same were excluded. Initial ECG screening of every patient was done to rule out the cardiovascular disease. After getting the protocol approved by institutional ethics committee (Ref: SKNMC NO/Ethics/Corr/2011/103) patients were grouped into nonselective and selective COX-2-Is groups with reference to treatment they received (n = 34). Their CV risk factors i.e. BMI, BP, BSL, lipid profile, etc., were assessed at enrollment and recorded as baseline. All arthritic patients were followed up and CV risk factors were assessed at 6th and 12th month of treatment [see Figure 1]. Parameters were compared with their baseline records and among the groups. Demographics of CV risk factors (i.e., age, sex, smoking, alcohol, heredity) were also studied. BMI calculated by online BMI calculator while, 10-year CV risk was calculated using Framingham's calculator. Statistical test used was Student's 't'-test using OpenEpi statistical software package version 2.

RESULTS

In this prospective cohort study we have assessed the effects of NSAIDs on CV risk factors in arthritic patients over a period of time (1 yr). The demographic profiles of these arthritic patients were also studied and are presented in Table 1. There were 22 males and 46 females with mean age 50.7 yrs enrolled in this study. Subset arthritic patients with history of smoking were 10, alcohol consumption 6 and familial CVD 22. Arthritic patients with family history of CVD were maximum (15 out of 22) in selective COX-2-Is group. Arthritics in nonselective and selective COX-2-Is group received eight different NSAIDs [see Figure 2]. Among nonselective NSAIDs, diclofenac sodium was received by majority of the patients (23%) followed by aceclofenac (10%) and only 2% were treated by indomethacin. In selective COX-2-Is 47% arthritics received etoricoxib and 3% received celecoxib.

From the results of this study it becomes evident that all NSAIDs reason potential CV risk when taken over a period of time as in arthritic patients. However, selective COX-2-Is found to impart higher CV risk in this regard. BMI, BP, and lipid profile; the potential CV risk factors, showed statistically significant impairment in selective COX-2-Is-treated arthritic patients; $P < 0.01$, $P < 0.001$ (SBP) and $P < 0.05$, respectively, compared to baseline and $P < 0.05$ for BMI compared to nonselective COX-Is group at the end of 1yr treatment. Triglycerides (TGs) and cholesterol were apparently increased with apparent fall in HDL levels in COX-2-Is group after 6 month of treatment but this increase was statistically insignificant. No significant effect was observed on diastolic blood pressure and random BSL [see Tables 2, 3 and Figure 3].

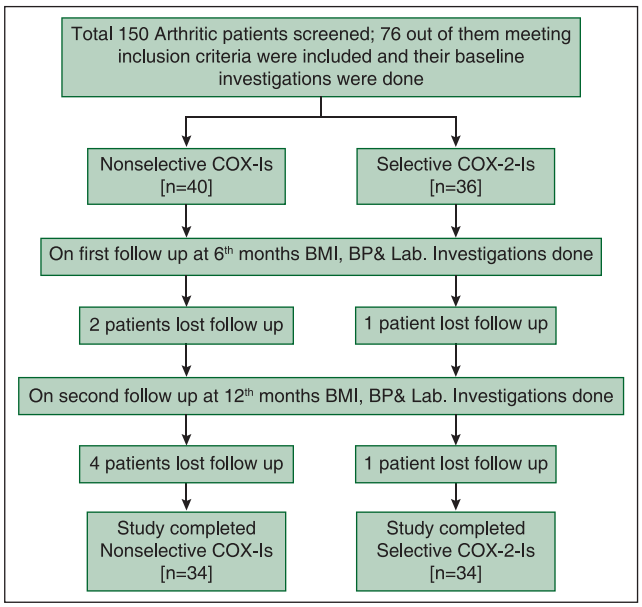

Figure 1: Study flow chart

Table 1: Demographic profile of the arthritic patients

Characteristics (n = 34)	Nonselective COX-Is	Selective COX-2-Is
Age (Mean±SD)	50.6±9.8	50.7±12.7
Sex: Male (Female)	12 (22)	10 (24)
Smokers	5	5
Alcoholic	2	4
Family history of CVD	7	15

n = 34; *P < 0.05; **P < 0.01; ***P < 0.001 compared to baseline and $^{\dagger}P$ < 0.05 compared to Nonselective COX-I group

When 10 year comparative CV Risk was assessed using Framingham's calculator; maximum over all CV risk percentage was reflected in selective COX-2-Is treated arthritics [see Table 4]. While significantly higher risk of getting CHD and MI ($P < 0.05$) and apparently high risk of stroke, CVD, CHD death and CVD death ($P > 0.05$) over 10 years was also observed in arthritic patients treated with selective COX-2-Is and same was observed in subset arthritic patients [see Table 5].

DISCUSSION

Arthritis is one of a 100 musculoskeletal conditions of varying etiologies and most prevalent disease involving middle age and elderly i.e., 50-65yrs and go on increasing in prevalence with age i.e. >65 yrs, the incident rate of arthritis is three times higher in females compared to males.[11,12] In this study also there were 22 men with 46 women with mean age 50.7 yrs, suggestive of high incidence rate in middle age women.

In present study arthritic patients received eight different NSAIDs; among nonselective COX-Is group 66% patients received diclofenac sodium and aceclofenac (i.e., phenylacetic acid derivatives) remaining patients were treated with other nonselective NSAIDs. In selective COX-2-Is group 94% patients received etoricoxib while only 6% treated with celecoxib.

Older age (≥ 45 years of age for men and ≥ 55 years for women), smoking, hypertension, low HDL concentration, hyperlipidaemia, hyperglycaemia and a family history of heart disease are major CV risk factors.[13] In present study we have evaluated CV risk of NSAIDs with reference to these risk factors. And the results have revealed that COX-2-Is cause significant increase in BMI, SBP and also significant impairment in lipid profile; the potential CV risk factors in arthritic patients. Nonselective COX-Is also showed impairment in lipid profile of the arthritics but except HDL this impairment was statistically insignificant. The effect of selective COX-2-Is on these CV risk factors could be attributed to etoricoxib as 94% of patients received etoricoxib while in nonselective COX-Is, these effects should be attributed to phenylacetic acid derivative with similar properties.

Presently rofecoxib, valdecoxib and lumiracoxib have been withdrawn from the market worldwide on the basis of results of various trials viz. VIGOR, APPROVe and

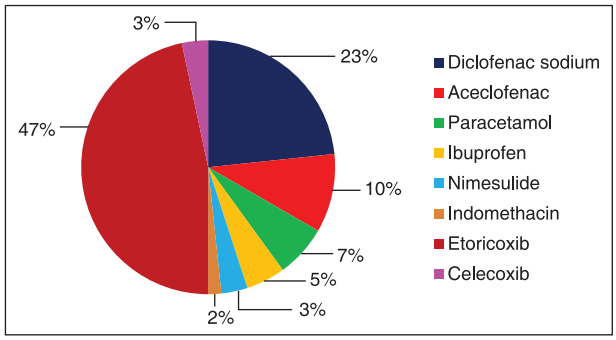

Figure 2: Distribution of cyclooxygenase inhibitors use in arthritic patients ($n = 68$)

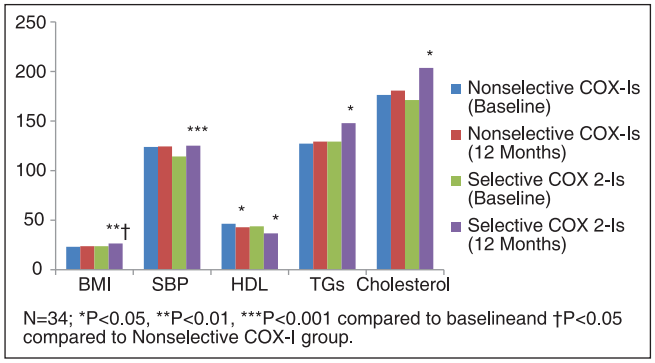

Figure 3: Cardiovascular risk of cyclooxygenase inhibitors

Table 2: Effects of cyclooxygenase inhibitors on physical cardiovascular risk factors

Parameters	Nonselective COX-Is			Selective COX-2-Is		
	Baseline	6 Months	12 Months	Baseline	6 Months	12 Months
BMI	23.2±5.1	23.3±5.3	23.8±3.2	23.8±2.7	24.2±2.3	26.5±4.8**†
SBP	123.9±11.3	124.2±10.8	124.4±14.3	114.3±4.5	116.3±5.2	125.2±10.6***
DBP	80.1±9	80.4±9.1	81±9.2	76.8±6.4	76.2±5.6	81.4±6.9

$n = 34$; values are Mean ± SD; *$P < 0.05$; **$P < 0.01$ compared to baseline and †$P < 0.05$ compared to Nonselective COX-I group; COX-I – Cyclooxygenase inhibitor; BMI – Body mass index; SBP – Systolic blood pressure; DBP – Diastolic blood pressure

Table 3: Effects of cyclooxygenase inhibitors on biochemical cardiovascular risk factors

Parameters	Nonselective COX-Is			Selective COX-2-Is		
	Baseline	6 Months	12 Months	Baseline	6 Months	12Months
Random BSL	111.9±40.3	114±32.6	113±38.9	117.8±10.6	117.2±12.2	118.2±14.6
HDL	46.4±7.6	43.3±8.6	42.9±11.3*	43.8±12.1	39.7±16.2	36.7±17.8*
TGs	127.2±38.8	127.8±32.5	129.3±45.7	129.3±34	138.1±36	147.9±46.9*
Cholesterol	176.3±42.8	176.8±38.2	180.7±42.6	171.2±22.1	186.2±25.3	203.6±35.5*

$n = 34$; values are Mean ± SD; *$P < 0.05$; **$P < 0.01$ compared to baseline and †$P < 0.05$ compared to Nonselective COX-I group; COX-I – Cyclooxygenase inhibitor; BSL – Blood sugar level; HDL – High density lipoprotein; TGs – Triglycerides

Table 4: Comparative percentage 10-year risk of CHD, MI, stroke, CVD, CHD Death and CVD Death in arthritic patients

Parameters	Nonselective COX-Is	Selective COX-2-Is
CHD	7.1±2.8	12±5.6*
MI	3.5±2.0	6.5±4.1*
Stroke	1.4±0.6	1.9±1.1
CVD	10.1±4.1	14.8±6.9
CHD Death	1.4±1.0	3.6±3.0
CVD Death	1.7±1.1	4.6±3.9

n = 34; values are Mean ± SD; **P* < 0.05 compared to nonselective COX-Is;
CHD – Coronary heart disease; MI – Myocardial infarction; CVD – Cardiovascular disease

Table 5: Comparative 10-year CV risk in subset arthritic patients

Drug Groups	Smokers (*n*) (%)	Alcoholic (*n*) (%)	Family history of CVD (*n*) (%)
Nonselective COX-Is	9.3 (5)	10 (2)	2.5 (7)
Selective COX-2-Is	23 (5)	20 (4)	9.6 (15)

n – number of patients; Values are mean percentage risk

TARGET.[2,14-16] Conflicting results of several clinical trials about CV safety of celecoxib created controversies.[3,17] Comparatively cardiovascular safety data about etoricoxib is scare although few clinical trials stated that etoricoxib exhibit less or comparable CV risk to nonselective NSAIDs and did not appear to significantly increase the risk for MI and stroke.[3,18,19] But in our study it has reasoned significant risk for CHD and MI ($P < 0.05$) whereas reflected apparent increase in risk of stroke, CVD and death due to CHD and CVD which was statistically insignificant compared to nonselective COX-Is. Hence though the results of our study confirm that selective COX-2-Is exhibit comparable CV risk to nonselective NSAIDs; our study results are in disagreement with the earlier studies that states selective COX-2-Is exhibit less CV risk and did not significantly increase the risk for MI and stroke.

Increased CV risk of selective COX-2-Is is said to be due inhibition of formation of the vasodilator PGI2, and leaving TXA2 unopposed, which facilitates vasoconstriction, platelet activation and smooth muscle cell proliferation but, their exact role on lipid profile, atherosclerosis and plaque formation is still unclear.[20] Recently molecular studies have identified cytochrome p-450 (CYP) pathway in arachidonic acid (AA) metabolism along with COX and lipooxygenase pathway (LOX). CYP epoxygenases are known to metabolise AA to four regioisomeric epoxyeicosatrienoic acids (5, 6-, 8, 9-, 11, 12-, and 14, 15-EET) and by CYP w -hydroxylases to 20-hydroxyeicosatetraenoic acid (20-HETE).[21] It is potent vasoconstrictor and induces oxidative stress. In clinical studies, it is associated with increased BMI and the metabolic syndrome.[22] COX pathway offer cardioprotection due to production of PGI2 by inducible COX 2 and blockade of this pathway may ultimately result into unopposed production of 20-HETE.[21] This could be the reason for increased BMI and impaired lipid profile in selective COX2-Is treated arthritic patients.

COX1 and COX2 exert opposite effects on systemic blood pressure and renal function. COX2 inhibitors reduce renal medullary blood flow, decrease urine flow, and enhance the pressor effect of Angiotensin II. In contrast, the pressor effect of Angiotensin II is blunted by COX1 inhibition.[23] Nonselective NSAIDs are said to increase blood pressure by nonselective blocking of COX1and 2 while selective NSAIDs by blocking of COX 2; hence nonselective NSAIDs are considered more renal toxic. But in our study significant increase was observed in COX-2-Is group and these findings are in agreement with various epidemiological studies that state hypertensive complications occur more commonly in patients treated with COX-2-Is.[24] LOX pathway has predominant role in insulin release and COX inhibition does not affect this release.[25] Our study also revealed no significant difference in BSL in both COX-Is groups compared to baseline.

In this study we have also explored the CV risk in subset arthritic patients i.e. with history of smoking, alcohol consumption and familial CVD which otherwise remained unexplored in majority of the earlier studies. History of familial CVD has positive correlation with CV risk as stated in earlier few studies;[2,26] our study results reflected higher CV risk in selective COX-2-Is group (9.6%). This high CV risk could be due to maximum number of arthritics (15 out of 22) with familial CVD were there in COX-2-Is group, which confirms this positive correlation.

Smoking is one of the most important CV risk factors for the development and progression of atherosclerosis. COX-derived prostanoids mediate the pathogenic effects of cigarette smoking on vascular health. Higher CV risk in smokers (23%) observed in arthritics treated with COX2-Is group could be explained on the basis of that all of these agents invariably cause an imbalance between PGI2 and TXA2; as they block COX2-derived prostacyclin (PGI2) keeping TXA2 biosynthesis unopposed by COX 1 in smokers.[27] Several epidemiological investigations have shown that a low to moderate level (i.e., 20 g-70/day) of alcohol intake has definitive protective role against CHD and stroke. Mechanisms for cardioprotective effects include increased HDL, decreased LDL, prevention of clot formation, reduction in platelet aggregation, and lowering of plasma apolipoprotein (a). In contrast to this heavy intake (i.e., <89 g-70/day) increase the CV risk due to increased homocysteine levels.[28] In this study CV risk was found to be high (20%) in COX2-Is group and alcohol consumption appears to compliment this.

CONCLUSIONS

Several earlier studies have affirmed CV risk of Selective COX-2-Is like rofecoxib, valdecoxib, lumiracoxib and celecoxib. Our study mainly emphasizes the potential CV risk of etoricoxib; CV safety data of which is scare and continued to be used in therapeutics. The results of this study encourage the proclamation that CV risk of COX-2-Is could be expressed as a class effect, derived from earlier studies in this regard. Although COX-2-Is preferred over nonselective COX-Is due to cardiovascular, GI and renal toxicity of these agents and are said to be safe, the use of selective COX-2-Is must be constrained to the arthritic patients with absolute contraindications (i.e., peptic ulcer, asthma and renal disease) for nonselective NSAIDs as arthritics need to take them over a long period of time and they impart substantial CV risk over a period of time. Thus this study could be a rewarding accumulation in CV safety data of selective COX-2-Is.

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