

Study of Effect of Selective COX-2 Inhibitors on Bleeding Time, Clotting Time, Heart Rate, Blood Pressure and ECG In Comparison With Conventional NSAIDs

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Abstract

Introduction: Non-steroidal anti-inflammatory drugs presently are the most widely used over the counter drugs in medicine and the most frequent cause of adverse drug reactions, affecting even the cardiovascular system, which is a major & alarming public health concern. Previous studies report, that selective COX-2 inhibitors are safer when compared to non-selective cyclooxygenase inhibitors, regarding their cardiovascular toxicity. But, recent studies reveal, that the safety of these selective COX-2 inhibitors is not much better than that of conventional NSAIDs. In view of the wider usage of selective COX-2 inhibitors, the study has been taken up to report, whether selective COX-2 inhibitors have got any advantages over conventional NSAIDs or not, regarding their effect on the basic parameters of cardiovascular system – bleeding time, clotting time, heart rate, blood pressure & ECG.

Methods: Patients were divided into eight groups, fifteen patients of each. Each group was given one of the NSAIDs from the eight drugs those were selected for the study, for 15 days. In the selected group, both pre and post-treatment values of bleeding time, clotting time, heart rate & blood pressure are estimated, tabulated & subjected to statistical analysis. ECG readings were also taken both before & after treatment & analyzed.

Results: Non-selective NSAIDs like paracetamol & diclofenac have shown significant changes in their bleeding time. Preferential COX-2 inhibitors like nimesulide & meloxicam; selective COX-2 inhibitors like celecoxib & valdecoxib also have shown significant changes in their bleeding time. There is no significant change in clotting time, heart rate, systolic & diastolic blood pressure & also ECG.

Conclusion: Selective COX-2 inhibitors also have shown significant changes in bleeding time, like that of non-selective NSAIDs, when used for a short-term treatment.

Keywords: Adverse drug reactions, Conventional NSAIDs, COX-2 inhibitors, Cardiovascular Toxicity.

1. Introduction

NSAIDs are among the most widely used therapeutic agents, some of which are often taken without prescription for minor aches & musculoskeletal pains. Apart from this, the use of NSAIDs can also be expected to increase in the years ahead, either because of the increasing age of the population or of the developing indications, particularly in vascular disease and cancer prevention. So, there is always a need to assess the safety of these most commonly used drugs.

Effect of conventional NSAIDs on platelet TXA2 is more predominant. Therapeutic doses of most NSAIDs inhibit platelet aggregation & thus bleeding time is prolonged. But, COX-2 inhibitors at usual doses have been

shown to have no impact on platelet aggregation, which is mediated by thromboxane produced by the COX-1 isozyme. In contrast, they don't inhibit COX-2 mediated prostacyclin synthesis in the vascular endothelium. As a result, COX-2 inhibitors do not offer the cardioprotective effects of traditional non selective NSAIDs [1].

So, patients at high risk for cardiovascular events & patients prone to thrombosis should not be treated with COX-2 selective NSAIDs. But, in patients, who do not require platelet inhibition, COX-2 inhibitors seem to be a true advancement & an attractive alternative to classical NSAIDs because of their gastroprotective action. Placebo-controlled trials have revealed an increased incidence of

myocardial infarction and stroke in patients treated with rofecoxib, valdecoxib, and celecoxib consistent with a mechanism-based cardiovascular hazard for the class. Regulatory agencies in the United States, Europe, and Australia have reviewed these studies and other available evidence and have concluded that all three drugs increase the risk of heart attack and stroke and will be labeled accordingly and restricted with respect to marketing directly to consumers. Patients at increased risk of cardiovascular disease or thrombosis are particularly prone to cardiovascular adverse events on these agents [1].

This first arose during trials of the COX-2 inhibitor rofecoxib. Uncertainty about the cardiovascular risk posed by this drug during clinical trials led to the addition of a 'warning label' in 2002, but the results from a later long-term trial designed to assess the anticancer activity of rofecoxib showed that the risk of cardiovascular events increased significantly after 18 months of drug treatment. As a result of this, the drug was withdrawn in 2004 [1].

Clinical data have suggested a higher incidence of cardiovascular thrombotic events associated with COX-2 inhibitor valdecoxib also, resulting in its withdrawal from the market.

Conventional NSAIDs, such as meloxicam and diclofenac, which resemble celecoxib in terms of their selectivity also, have shown the risk of cardiovascular toxicity from observational studies, but controlled trials to address this hypothesis have not been performed. The cardiovascular hazard from both celecoxib and rofecoxib, the two selective COX-2 inhibitors for which data are available from placebo-controlled trials lasting more than one year, increased with chronicity of dosing. [1].

So, it has been recommended that all NSAID product labels be revised to include cardiovascular risks. If COX-2 inhibitors are selected, they should be used at the lowest possible dose for the shortest period of time, and patients at risk of cardiovascular disease or prone to thrombosis should not be treated with these drugs.

It is therefore important to assess the cardiovascular safety and side effects of newer selective COX-2 inhibitors. In view of the wider usage of this new group of drugs, the basic study has been taken up to report, whether selective COX-2 inhibitors have got any advantages over conventional NSAIDs or not, in regard to their effect on the basic parameters of cardiovascular system, i.e., on bleeding time, clotting time, heart rate, blood pressure & ECG, especially when used for a routine short-term treatment; by analyzing few non-selective and selective groups of NSAIDs [2].

1.2. Aims and objectives

To study the impact on bleeding time, clotting time, heart rate, blood pressure & ECG; of both non-

selective NSAIDs and selective COX-2 inhibitors.

2. Materials and methods

The present interventional & prospective study was taken up with the approval of institutional ethical committee. All patients included in our study gave informed consent for their participation and the study was done at Mahatma Gandhi Memorial Hospital, Warangal.

2.1. Subjects selected for the study:

2.1.1. Inclusion criteria:

Patients of above 30 years age; of either sex
Osteoarthritis patients
Rheumatoid arthritis patients
Patients with fractures and dislocations

2.1.2. Exclusion criteria:

History of acid peptic disease
History of bronchial asthma
History of bleeding disorders

2.2. Drugs used in the study and their doses:

Paracetamol	:650 mg tid (about 2 gm per day)
Ibuprofen	:400 mg tid (1200 mg per day)
Diclofenac	:50 mg bd (100 mg per day)
Nimesulide	:100 mg bd (200 mg per day)
Meloxicam	:7.5 mg bd (15 mg per day)
Rofecoxib	:25 mg bd (50 mg per day)
Celecoxib	:100 mg bd (200 mg per day)
Valdecoxib	:10 mg bd (20 mg per day)

2.3. Methodology

Patients were divided into eight groups, fifteen patients of each. Each group was given one of the NSAIDs from the eight drugs those were selected for the study. In the selected group, prior to the administration of drug, bleeding time, clotting time, heart rate & blood pressure readings were taken manually & tabulated. ECG readings were also taken prior to the treatment.

The patients were advised to take the concerned NSAID, for a period of fifteen days, and they were not put on any antacid or H₂- blocker or proton pump inhibitor. All the out patients were briefed, of the common toxicity of the concerned NSAID and they were advised to inform us soon after the onset of symptoms like nausea, vomiting, diarrhea, epigastric pain, heartburn, dyspepsia, facial and pedal edema, headache and tinnitus. Whenever the patient reported an adverse effect, it was taken as the primary end point of our study, for that particular patient & he or she was advised to stop the treatment. After the completion of treatment, all the parameters were noted down again, tabulated & both the pre & post treatment values were subjected to statistical analysis, with the help of paired 't' test & Anova test. ECG readings were taken once again after the treatment and were compared with that of readings before treatment.

3. Results

Table I: Bleeding time (in seconds)

Pre and Post - Treatment (Bleeding time values) (in seconds)															
Paracetamol		Ibuprofen		Diclofenac		Nimesulide		Meloxicam		Rofecoxib		Celecoxib		Valdecoxib	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
120	120	85	115	145	120	110	170	115	120	110	115	110	110	145	120
85	120	110	110	85	115	115	120	115	115	135	110	115	110	85	115
85	110	110	120	135	135	145	170	110	120	115	115	135	145	135	135
120	145	85	205	115	115	115	120	135	145	115	110	115	110	115	115
110	115	85	115	145	120	115	145	115	120	110	115	115	110	145	120
115	85	115	115	115	115	115	145	115	115	170	170	110	110	115	115
115	145	115	120	145	120	145	175	115	145	110	110	170	145	145	120
115	120	85	110	170	120	120	145	110	120	110	110	135	135	170	120
115	110	120	85	170	120	85	110	120	145	115	115	110	85	170	120
145	175	85	110	115	115	110	110	120	110	110	110	115	105	115	115
145	175	110	115	115	110	85	120	110	120	117	115	115	100	115	110
85	110	85	85	175	120	115	145	115	145	115	110	145	120	175	120
145	175	110	115	145	145	145	170	115	120	110	170	145	135	145	145
85	120	110	120	115	115	110	85	120	145	110	110	85	85	115	115
85	110	85	85	110	110	145	120	95	115	115	115	110	110	110	110

Table II: Clotting time (in seconds)

Pre and Post Treatment (Clotting Time Values) (in seconds)															
Paracetamol		Ibuprofen		Diclofenac		Nimesulide		Meloxicam		Rofecoxib		Celecoxib		Valdecoxib	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
205	230	210	230	290	205	205	290	180	180	265	230	290	205	205	230
230	230	230	230	240	240	230	225	265	290	235	180	225	240	230	265
180	205	225	205	230	230	180	180	240	240	230	230	180	205	275	275
245	245	230	290	180	230	180	290	105	180	180	290	240	265	180	290
230	180	180	230	180	265	240	230	265	265	265	230	180	230	290	290
230	170	180	290	225	225	225	180	290	290	230	180	220	230	240	240
180	350	230	240	180	225	180	225	240	290	240	290	230	235	230	240
180	180	285	230	295	225	195	180	240	265	240	225	180	205	235	240
145	180	210	230	265	265	290	290	110	165	265	230	240	265	180	205
230	225	265	240	265	265	240	240	105	165	235	180	230	230	265	240
350	350	180	180	290	290	230	265	240	290	230	180	225	235	265	240
230	180	225	205	180	205	230	180	240	240	230	180	180	205	290	290
180	205	285	230	230	225	230	230	205	215	240	290	180	180	180	230
240	240	290	220	240	265	195	180	180	230	230	230	215	235	240	265
180	180	225	180	220	225	225	265	105	165	240	225	180	205	235	230

Table III: Heart rate (per minute)

Pre and Post - Treatment (Heart Rate Values) (per minute)															
Paracetamol		Ibuprofen		Diclofenac		Nimesulide		Meloxicam		Rofecoxib		Celecoxib		Valdecoxib	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
62	66	80	80	70	70	70	70	72	72	80	80	72	72	82	80
72	72	72	74	82	82	72	72	70	70	72	72	72	72	84	84
78	76	74	72	82	82	72	72	86	86	76	74	74	72	86	86
74	74	74	74	84	84	76	74	86	84	76	76	76	78	88	88
80	80	76	76	82	82	78	80	90	90	82	84	90	90	80	80
76	76	78	78	72	74	78	78	92	90	84	84	72	70	76	74
82	84	80	82	74	76	80	82	60	64	86	86	74	74	76	72
84	84	80	80	76	76	82	80	74	72	72	70	86	86	74	74
90	86	82	82	76	76	74	72	76	78	74	74	86	86	60	64
72	74	84	86	80	84	74	74	82	82	86	84	86	86	72	72
76	76	86	86	72	72	76	76	82	82	86	86	84	84	74	74
78	78	72	72	76	76	60	62	84	84	72	74	82	80	76	76
78	78	72	72	74	72	84	82	86	86	74	70	84	82	82	80
78	72	72	70	78	76	86	86	88	88	72	72	86	86	82	80
72	70	76	74	78	80	86	86	82	80	72	72	82	80	84	80

Table IV: Systolic Blood Pressure (in mm Hg)

Pre and post treatment Systolic (Blood Pressure Values) (in mm Hg)															
Paracetamol		Ibuprofen		Diclofenac		Nimesulide		Meloxicam		Rofecoxib		Celecoxib		Valdecoxib	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
110	120	120	120	110	110	110	110	120	120	120	120	120	120	110	110
120	120	120	120	110	110	120	120	130	130	130	130	120	120	150	150
120	120	150	140	120	120	130	130	120	120	120	120	130	130	150	150
130	130	140	150	120	120	140	140	120	130	110	110	130	140	120	120
120	120	110	110	130	130	130	130	130	140	120	120	120	120	120	120
110	110	120	130	110	110	120	120	140	140	130	130	130	130	110	110
110	110	120	130	120	120	120	120	150	150	130	130	130	130	120	120
120	110	130	120	140	140	150	150	110	120	110	110	140	140	130	130
120	130	130	130	140	140	150	150	110	120	140	140	140	140	120	120
130	130	140	140	120	120	110	110	130	130	150	150	110	110	110	110
130	130	120	120	130	130	120	130	120	120	110	110	120	120	120	120
120	130	120	120	140	140	120	130	130	130	120	120	120	120	110	110
110	110	130	130	130	130	140	140	110	110	120	120	130	130	120	120
140	130	130	130	120	120	110	110	120	120	110	110	140	140	130	120
120	120	110	110	110	110	110	120	120	120	140	140	110	110	110	110

Table V: Diastolic Blood Pressure (in mm Hg)

Pre and post treatment Diastolic (Blood Pressure Values) (in mm Hg)															
Paracetamol		Ibuprofen		Diclofenac		Nimesulide		Meloxicam		Rofecoxib		Celecoxib		Valdecoxib	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
80	70	70	70	70	60	70	80	70	70	80	80	100	100	70	70
80	80	80	80	80	80	80	80	80	70	80	90	90	90	60	70
70	70	80	80	60	70	70	80	60	60	70	80	80	80	70	70
70	80	70	70	80	70	70	60	70	70	80	80	60	70	80	70
80	80	70	70	70	80	70	70	80	80	60	60	80	80	80	80
60	80	80	80	60	60	70	80	60	70	70	70	60	60	70	70
70	70	70	70	70	70	80	80	70	70	80	80	80	80	90	80
70	60	60	70	90	80	70	60	80	80	60	70	90	80	100	100
60	60	80	80	80	70	80	70	80	80	60	60	80	80	90	90
80	80	80	80	70	80	70	70	70	80	70	70	60	60	90	80
80	80	70	80	60	60	70	70	70	70	80	70	80	80	90	90
70	80	70	60	70	60	80	80	80	80	90	80	90	80	80	60
70	80	80	80	70	70	60	70	70	70	90	90	90	90	80	60
80	80	80	80	70	80	60	70	70	60	60	70	80	80	60	70
80	70	70	80	70	70	70	70	60	70	90	90	60	60	60	60

4. Discussion

4.1. Effect on cardiovascular system:

4.1.1. Effect on bleeding time and clotting time:

In the present study, bleeding time is prolonged with non-selective NSAIDs like paracetamol & diclofenac. This is due to the fact that platelets contain only COX-I and non-selective NSAIDs inhibit both COX-1 and COX-2, resulting in inhibition of TXA₂ synthesis and thus, prolongation of bleeding time [1, 3].

Nimesulide and meloxicam also showed prolongation of bleeding time, even though they are preferential COX-2 inhibitors. This may be due to the fact that preferential COX-2 inhibitors do have some COX-1 activity. Meloxicam had much prolongation of bleeding time compared to nimesulide. This may be due to its long half-life and long lasting effect on platelets [4].

But, highly selective COX-2 inhibitors, celecoxib and valdecoxib also showed significant change in bleeding time, even though they do not inhibit platelet COX-1 [5-8].

Non-selective NSAIDs are associated with prolonged bleeding time. So, in patients who do not require platelet inhibition, selective COX-2 inhibitors seem to be a true advance and an attractive alternative to conventional NSAIDs, combined with other gastro-protective strategies. But, in our short-term study, even the selective COX-2 inhibitors like celecoxib & valdecoxib showed a significant change in their bleeding time.

In our short-term study, there is no significant change in clotting time, with either non-selective NSAIDs or selective COX-2 inhibitors, except with meloxicam. This may be due to the fact that there is no significant hepatic effect in our short-term study.

4.1.2. Effect on heart rate and blood pressure

There is no significant change in heart rate and both systolic & diastolic blood pressure values in our short-term study, with either selective COX-2 inhibitors or non-selective NSAIDs, except for a mild change for diastolic blood pressure with meloxicam.

4.1.3. Effect on electrocardiographic readings

In our short- term study, there is no significant change in ECG readings; no risk of cardio vascular complications with either selective COX-2 inhibitors or non-selective NSAIDs.

5. Conclusion

In our short-term study, non-selective NSAIDs, and preferential COX-2 inhibitors like nimesulide and meloxicam & selective COX-2 inhibitors like celecoxib & valdecoxib are associated with prolonged bleeding time. But it is unlikely to be of major clinical significance, as the values are within normal range. But, they should be used with caution in patients suffering from haemopoietic disorders such as thrombocytopenia or hemophilia. Further long-term studies are required to assess the clinical cardiac safety of these selective COX-2 inhibitors, compared to the non-selective NSAIDs.

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