

ADVERSE EVENTS OF NSAIDS AND RISK FACTORS FOR ADVERSE EFFECTSK. B. Sanal Kumar¹, K. T. Shenoy², K. Arun³, Leena K. B⁴, Nishakumari⁵**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: NSAIDs, which are nonselective inhibitors of COX enzymes, comprise the most frequently prescribed group of medicines. This widespread therapeutic benefit has been largely limited by association with an increased risk of serious upper gastrointestinal complications. Recently, this disadvantage has been overcome with the advent of COX-2 selective inhibitors. Though these were developed to improve the GI tolerability, COX-2 inhibitors also cause adverse reactions—some similar to traditional NSAIDs, while others are of a totally different spectrum. Hence cautious and rational use of NSAIDs are indicated to avoid a major catastrophe. We studied the pattern of adverse events and associated risk factors in a cohort.

KEYWORDS: NSAID, Adverse drug reactions-, Diclofenac-, Aspirin, Abdominal pain.

INTRODUCTION: Non-steroidal anti-inflammatory drugs (NSAIDs) are the largest groups of pharmaceutical agents used worldwide. Earlier, NSAIDs were used by 20% or more of the population. They are non-selective COX inhibitors.¹ NSAIDs are one of the most common causes of adverse drug reactions (ADRs) reported to drug regulatory agencies as well as in many clinical and epidemiological studies. The most common ADRs are related to gastrointestinal (GI) system, notably dyspepsia and bleeding.² This disadvantage has been, to a limit, been overcome by the use of COX-2 selective inhibitors.³ But the side effects of these are totally different from that of the traditional nonselective inhibitors.⁴ Clinical and experimental data as well as reviews suggest that use of selective COX-2 inhibitors is associated with increase in systolic blood pressure, cardiovascular morbidity and mortality due to myocardial infarction.⁵ The risk of GI complications varies widely among individual NSAIDs. Since there are no important differences among these drugs with regard to efficacy, the choice of first line treatment should be based on their relative toxicity.

MATERIALS AND METHODS:

OBJECTIVES: To study Adverse Events of NSAIDs and Risk Factors for Adverse Effects

STUDY DESIGN: Cross Sectional

STUDY SETTING: Secondary Health care facilities at District Hospital, Trivandrum and Taluk Hospital Chirayankeezhu and Tertiary Health Centre at Medical College, Trivandrum.

STUDY POPULATION: All patients, 18 years and above, attending the Orthopaedic Departments of General Hospital, Trivandrum and Trivandrum Medical College Hospital and Taluk Hospital Chirayinkeezhu.

The study was carried out from June to September 2006 after approval from the Institutional Ethics Committee. Sample size was calculated using software designed and developed by Biostatistics Resources and training center, Christian Medical College, Vellore-2, India. Based on proportion of expected NSAID use as 80%, with a precision of 5% and confidence level (1-alpha) of 95%.

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The sample size needed was 246. However, 769 patients were recruited; 262 patients from Medical College Hospital, Thiruvananthapuram; 250 cases from General Hospital, Thiruvananthapuram and 257 cases from Taluk Hospital, Chirayinkeezhu. Of these, only 752 received NSAIDs. All NSAIDs which were prescribed to the patients were included in the study irrespective of any criteria.

Using a structured pilot tested questionnaire, prescriptions from out patients in the Department of Orthopaedics were evaluated. Data was analysed using Epi info 2005 and SPSS software version 10. Descriptive statistics was used to describe the study variables. Degree of association of the study variables with the outcome, adverse events were analyzed by univariate as Odds ratio and multivariate analysis by logistic regression using the clinically and statistically significant variable.

RESULTS:

Baseline Character of Study Population: 769 patients were studied from three health facilities in Thiruvananthapuram District. Of these, 262 patients were from Medical College Hospital, Thiruvananthapuram; 250 cases from General Hospital, Thiruvananthapuram and 257 cases from Taluk Hospital, Chirayinkeezhu. Data was collected and analysed both separately and after pooling data of three centers; later they were grouped depending on whether they developed adverse reaction or not. In General Hospital, Thiruvananthapuram and Taluk Hospital, Chirayinkeezhu, more female patients sought health care. Age and sex distribution is depicted in Table 1 and Figure 1.

Age in years	Male	Female	Total
<25	44	36	80
26-40	113	148	261
41-50	79	137	216
51-60	51	82	133
>60	21	58	79
Total	308	461	769
Range	18-85	18-89	

Table 1: Age and Sex distribution in all facilities

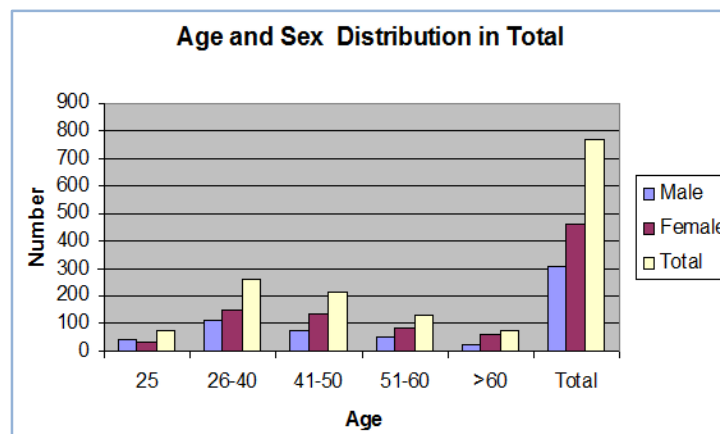


Fig. 1: Age and Sex Distribution in Total

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Out of 769 patients, 308 were males and 461 were females; age ranged from 18 to 85 in males and 18 to 89 in females. Majority were aged 26-40 years. Among females, 1st quartile of age was 34 and second quartile of age was 43 and 3rd quartile was 52 years of age.

Adverse drug reactions and its association with age, sex and other variables

Table 2-8 and figure 2-8 show the features.

Age Groups (Years)	ADR		OR	95% C.I.
	Yes	No		
<25	3	77	1	Reference
26-40	38	223	4.37	(1.25-18.30)
41-50	43	173	6.38	(1.83-26.62)
51-60	28	105	6.84	(1.89-29.39)
>60	14	65	5.53	(1.40-25.43)

Table 2: ADR and its Association with Age

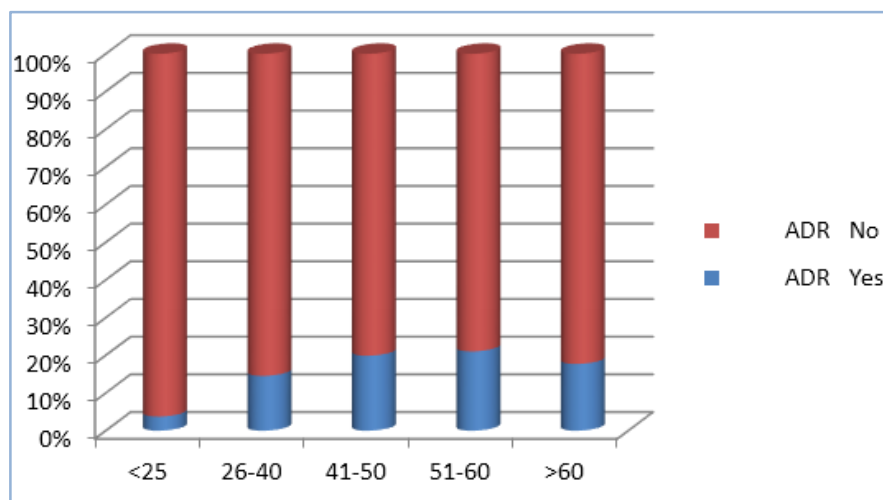


Fig. 2: ADR and its Association with Age

As age increases, the chance of developing ADR also increases. Most ADRs presented in the age group of 41-50 years. Minimal ADRs were seen below 25 years of age.

Analgesic use	Adverse reaction		Total
	Yes	No	
Aceclofenac	57	5	62
Diclofenac	126	17	143
Ibuprofen	38	3	41
Paracetamol	14	1	15
Indomethacin	3	2	5
Serratiopeptiase	2	0	2

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Etoricoxib	7	2	9
Meloxicam	1	1	2
Piroxicam	4	0	4
Nimesulide	9	1	10
Aspirin	3	0	3
No drug	0	12	12
TOTAL	264	44	308

Table 3: Adverse reaction and use of NSAID in males

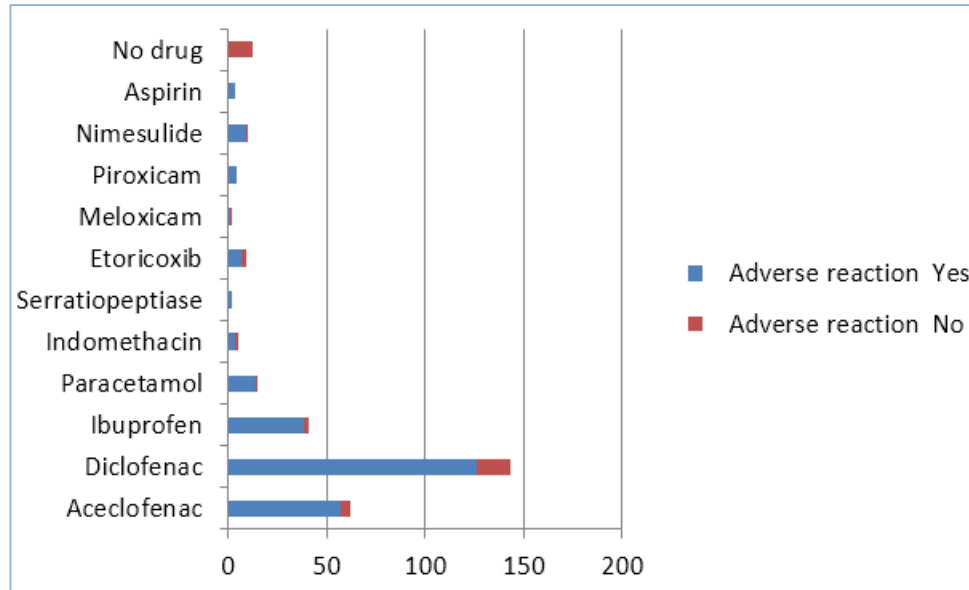


Fig. 3: Adverse reaction and use of NSAID in males

In males, both with ADR and No ADR groups, diclofenac was the commonly used drug; Diclofenac caused 11.8% ADR in males, followed by Aceclofenac (8%) and Ibuprofen(7.3%).

Analgesic Use	Adverse reaction		TOTAL
	Yes	No	
Aceclofenac	56	15	71
Diclofenac	140	33	173
Ibuprofen	74	23	97
Paracetamol	21	6	27
Indomethacin	23	1	24
Serratiopeptidase	7	0	7
Tramadol	1	0	1
Mefenamic acid	1	0	1
Etoricoxib	5	3	8

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Meloxicam	4	0	4
Piroxicam	4	3	7
Nimesulide	19	8	27
Aspirin	7	2	9
Nil	0	5	5
TOTAL	362	99	461

Table 4: Adverse reactions and Use of NSAID in females

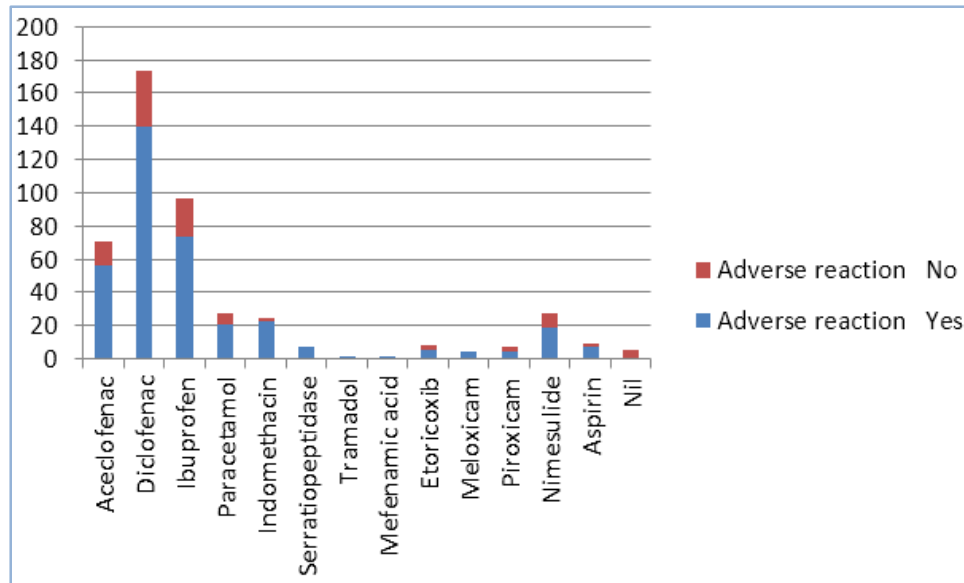


Fig. 4: Adverse reactions and Use of NSAID in females

In female patients also, diclofenac was the most commonly used NSAID in both ADR and no ADR groups. Ibuprofen caused 23% ADR, followed by Aceclofenac (21.1%) and Diclofenac (19%).

Age group (Years)	Adverse reaction		Total
	Yes	No	
Less than 25	44	0	44
26-40 Yrs.	101	12	113
41-50	70	9	79
51-60	42	9	51
>60	19	2	21
TOTAL	276	32	308

Fig 5: ADR and its Association with age in Male

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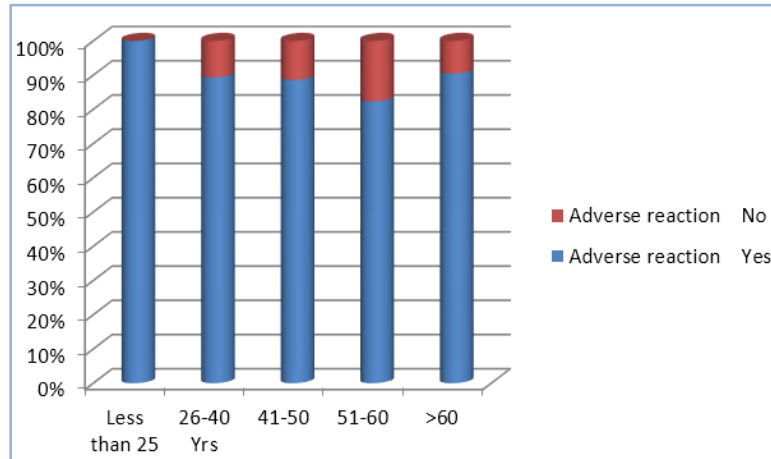


Fig. 5: ADR and its Association with age in Male

ADR increased with increase in age, with maximum ADR seen in the age group of 51-60 years (17.6%).

Age Group (Years)	Adverse reaction		TOTAL
	Yes	No	
Less than 25	33	3	36
26-40 Yrs.	122	26	148
41-50	103	34	137
51-60	63	19	82
>60	46	12	58
TOTAL	367	94	461

Table 6: ADR and its Association with age in Female

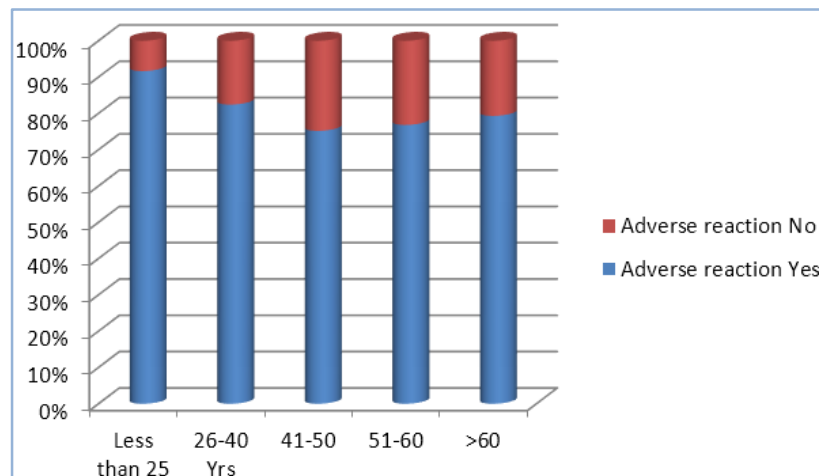


Fig. 6: ADR and its Association with age in Female

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In females, 24.8% ADR was seen in the age group of 41-50 years.

ADR Reported	Facility Wise			Total N=769
	GH N=250	MCH N=262	Taluk N=257	
Both Abdominal Pain and Heart Burn	45	19	55	119
Itching and skin rash	4	0	0	4
Ab.Pain and diarrhoea	1	0	0	1
Oedema	0	1	0	1
Ulcer Lower Lip	0	0	1	1
Total	50	20	56	126

Table 7: Pattern of Adverse drug reaction in health care settings

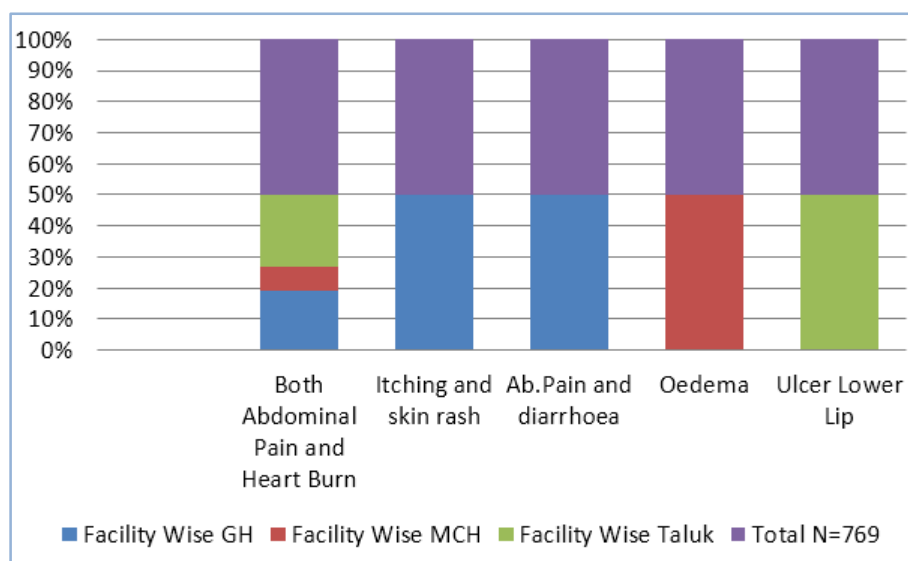


Fig. 7: Pattern of Adverse drug Reaction in health care settings

Of the 247 subjects who received NSAIDs in the General Hospital, 50 reported having any adverse event (20%); of 249 cases in MCH, Tvm, 20 had adverse reactions (8%). Of 256 cases who received NSAIDs in the Taluk Hospital, 56 had adverse reactions, 21.8%; this is the highest among the three centers, even though this center received highest percentage of gastro protective agent (96.6%).

Drugs	No ADR	Abdominal pain/Heart Burn	Generalised Oedema	Itching +and Skin rash	Ulcer on lower lip	Ab. Pain And Diarrhoea	Total
Aceclofenac	113	19	0	0	1	0	133
Diclofenac	266	47	1	1	0	1	316

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Ibuprofe	112	26	0	0	0	0	138
Paracetamol	35	6	0	1	0	0	42
Indomethacin	26	2	0	1	0	0	29
Serratiopeptidase	9	0	0	0	0	0	9
Tramadol	1	0	0	0	0	0	1
Mefenamic acid	1	0	0	0	0	0	1
Etoricoxib	12	5	0	0	0	0	17
Meloxicam	5	1	0	0	0	0	6
Piroxicam	8	2	0	1	0	0	11
Nimesulide	28	9	0	0	0	0	37
Aspirin	10	2	0	0	0	0	12
No Drug	17	0	0	0	0	0	17
Total	643	119	1	4	1	1	769

Table 8: Pattern of Analgesic Use and ADR in facilities

Fig:8: Pattern of Analgesic Use and ADR in facilities

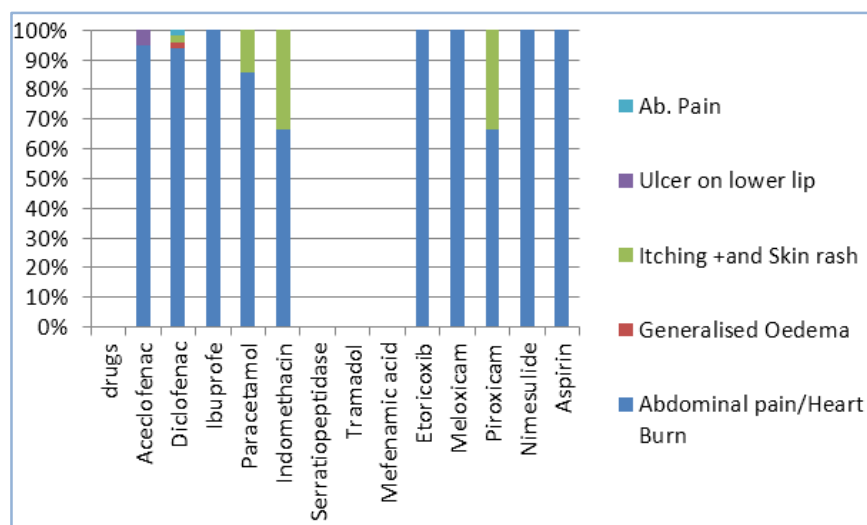


Fig. 8: Pattern of An Analgesic Use and ADR in facilities

Of the 752 case receiving NSAIDs in the health settings, 126 cases reported having any adverse event (16.7%); 119 cases with abdominal pain and 4 cases with itching and skin rash, one case with both abdominal pain and diarrhea and one with generalised oedema

DISCUSSION: 769 patients were studied from three health facilities in Thiruvananthapuram District. Of these, 262 patients were from Medical College Hospital, Thiruvananthapuram; 250 cases from General Hospital, Thiruvananthapuram and 257 cases from Taluk Hospital, Chirayinkeezhu. 40% were males and 60% were females. Thus it was found that females had more NSAID use than males. Dale et al, showed that females used more analgesics compared to males.⁶

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Most of the patients who presented were in the age group of 26-40 years of age. Karolina et al, also showed age group to be between 18-44 years of age.⁷ Mean ages were comparable in three different health care settings, but significantly different in those with adverse reaction and those without adverse reactions. As age increases, the chance of developing ADR also increases. In our study, it was seen that most ADRs presented in the age group of 41-50 years of age. Minimal ADRs were seen below 25 years of age. In General Hospital, percentage of ADR was 20%, whereas in MCH, Tvm and taluk hospital, it was 8% and 21.8%. Of these, most cases presented with dyspepsia.

In their journal, Wolfe and Lichtenstein found that 10 to 20 percent of patients have dyspepsia while taking an NSAID, although the prevalence may range from 5 to 50 percent. Among older nonselective drugs, Diclofenac, had the highest risk, appearing harmful at commonly used doses, which the authors say provides grounds for reviewing its regulatory status. McGettigan and Henry included 17 case-control and 6 cohort studies in their review-13 studies focusing on COX-2 inhibitors, 23 on NSAIDs, and 13 on both groups of drugs. Among older nonselective drugs, Diclofenac, had the highest risk, appearing harmful at commonly used doses, which the authors say provides grounds for reviewing its regulatory status.⁸

Of the 752 case receiving NSAIDs in the health settings, 16.7% presented with adverse effects. 119 cases with abdominal pain and 4 cases with itching and skin rash and one case with both abdominal pain and diarrhea and one with generalized oedema. Diclofenac caused 11.8% ADR in males, followed by Aceclofenac which caused 8% and Ibuprofen with 7.3%.⁹ while in females, Ibuprofen caused 23% ADR, followed by Aceclofenac with 21.1% ADR and Diclofenac caused 19% ADR. In this study it was seen that Diclofenac was maximum being prescribed in the age group of 26-40 years, comprising about 35%.⁷ For males, it was seen that maximum ADR seen in the age group of 51-60 years with about 17.6%, whereas for females, it was seen maximum in the age group of 41-50 years with about 24.8%.¹⁰

CONCLUSION: Use of NSAID was more among females compared to males. Adverse drug reactions were also found to be more among females. As age increases, the chance of developing adverse drug reaction of NSAIDs increases. The most common NSAID prescribed was Diclofenac followed by Aceclofenac. Only in Taluk hospital the commonly prescribed drug was Ibuprofen. The adverse drug reaction reported was 16.2% considering the three facilities together. Dyspepsia was the commonly observed adverse effect presenting with abdominal pain. Newer COX-2 selective inhibitors had lesser side effects.

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