Effects of Non-Steroid Anti-Inflammatory Drugs on the Lower Gastrointestinal Tract.

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Abstract:

BACKGROUND & AIMS: Adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDS) on the upper gastrointestinal (GI) tract and small intestine are well described. Evidence is also accumulating that NSAIDS can induce and/or exacerbate the underlying pathology in the distal GI tract. The aim of this study was to estimate the effect NSAIDs on distal GIT

METHODS: In 79 consecutive patients with chronic user of NSAIDs and 50 matched controls were included in this study which is done in Aldewanyia city. A detailed clinical history and physical examination were taking. Sigmoidoscopy; with or without colonoscopy were done were done to all patients and volunteer candidates, with histopathological study of rectal and colonic biopsies

RESULTS: Of the 79 cases of patients, 38 (48%) were had lower clinical manifestation and 31(39%) of patients had histopathological which is mainly non-specific colitis vs. 9 (22%), 4(8%) of controls; $P < 0.0001$). NSAID use was aspirin (alone or combined) in 34.2% of cases, and 70.25% were using other NSAIDs alone or combined. Other independent risk factors were also assessed like smoking, diabetes, and body weight.

CONCLUSIONS: NSAID use is strongly associated with an increased risk of upper GIT. This review study point up that NSAIDs can cause significant morbidity in some patients ranging from changing of bowel motion, profuse diarrhea, exacerbating of underlying inflammatory bowel disease, to chronic blood loss with iron deficiency anemia. The pathogenesis is likely multifactorial and is thought to be related to inhibition of prostaglandin synthesis with direct effect of drugs or its metabolites.

The high prevalence of aspirin and other NSAIDs use suggests that adverse effects on GIT are increasing and should increasing the clinical awareness of these adverse effect throughout the GI tract may reduce morbidity. Concomitant NSAID use, smoking, and alcohol use is a widely association.

Introduction:

Non steroid anti inflammatory drugs (NSAIDs) are the most common worldwide using drugs, usually used as analgesic, antipyretic, anti-inflammatory or as anti platelet [1]. The most common members of this group of these drugs are aspirin, diclofenic naproxen, indomethacin and ibuprofen. Paracetamol is generally not considered as NSAIDs because it had little activity as anti-inflammatory and its action by blocking COX-2 mostly in the central nervous system. Most of these medications act as non selectively inhibitors of both cyclooxygenas(COX) enzymes; (COX-1) and (COX-2) isoenzymes. This inhibition generally is competitively reversible except the mechanism of aspirin in which their inhibitors is irreversible[2]. Both isoenzymes are critical for production of prostaglandins which are necessary for promote inflammation which is necessary for healing. Also it supports the clotting function of platelets and protection the gastric lining mucosa from damage. But these two enzymes also induce fever and pain. However, only COX-1 will support the stomach and platelet function [3]. NSAIDs will block the COX enzymes and reduce prostaglandins production in the body. As a consequence to this blockage the inflammation, pain, and fever are reduced. NSAIDs can cause gastric ulceration and promote bleeding as a consequence to reduction of prostaglandins protection. The COX enzymes catalyze the formation of prostaglandins and thromboxane from arachidonic acid which is itself derived from the cellular phospholipid bilayer by phospholipase A2 [3,4].

Although incidence of NSAID-induced gastrointestinal complication is relatively low, the vast number of patients exposed to NSAIDs amount to a considerable clinical problem. Effects of NSAIDs on upper gastrointestinal tract (UGIT) are well known and widely studied, most of these effects ranging from erythema to ulcers which have the impending to perforate and bleed[5,6].

On other hand, effect of NSAIDs on lower GIT will not enough studied, although this effect is less extended, the effect of NSAIDs on lower GIT ranging from exacerbated of chronic of inflammatory bowel diseases ,non specific colitis, diverticulitis, microscopic colitis to rectal and colonic ulceration[7].

The effect of prostaglandins inhibiters on lower GIT is still controversy, while the direct effect of NSAIDs and it`s metabolites was suspected to have a role in this effect. It is thought that the pathogenesis of intestinal injury to be due to direct effects of NSAIDs to uncoupled oxidative metabolism in enterocyte mitochondria, leading to both impaired cellular energy metabolism and oxyradical injury with subsequent loss of cellular integrity and increasing intestinal permeability and opening the paracellular pathway, thus allowing the luminal aggressive agents, such as bacteria and bile, to enter the lamina properia where they induce inflammation[8,9,10].

Microscopic colitis is one of possible effect of NSAIDs on the large bowel, which is an umbrella term to cover lymphocytic colitis, collagenous colitis and microscopic colitis that is neither collagenous nor lymphocytic. Microscopic colitis is an inflammation of large bowel with intraepithelial lymphocytes infiltration with or without subepithelial collagenous layer deposition may causing many GIT manifestation like chronic watery diarrhea with or without abdominal cramp[11,12].

However many studies revealed that fecal diversion with illiostomy in many patients with microscopic colitis will show improving with ameliorate the mucosal inflammation[12].

Although there are many conditions and systemic diseases like diabetes mellitus and amylodosis, drugs, smoking and aging processing have effect on lower GIT[13,14].

Although most patients who using NSAIDs complaining of osteoarthritis, rheumatic or connective tissue diseases or ischemic heart disease, so whether the colonic changes is related to the underlining disease processing or to the using of NSAIDs is still uncertain. Many studies were revealed that the effects of NSAIDs on upper and lower GIT were differ from type of drug to other, that is show that indomethacin and piroxicam usually at the head of toxicity list while ibuprofen and aspirin seem to be more safer (might be because of the lower doses used) [14,15].

This study was carried out with the objective of histological analysis of rectal mucosa in patients on chronic NSAIDs intake with or without lower GIT manifestation.

Patients and methods:

This randomized cross-section study was done at Al-Diwaniya teaching hospital in medical department and GI center conducted from April 2016 through June 2017. Patients were randomly selected from the medical and orthopedic consultant departments and invited to participation this study. Other randomly selected persons were asked to be a volunteer to invite to this study as a controller group. We aimed to recruit the patient and control groups matched for number, sex, age and socially distribution.

One hundred forty patients were selected age 25-83 years with current NSAIDs using for at least six months and more, because of different causes ranging from migraine, rheumatoid arthritis, osteoarthritis, backache and others (as a patient group). After physical assessment, laboratory and questionnaire assessment, some patients were excluded because are not met the inclusion criteria or their refusing to invited the study and it's procedures, only seventy nine (male =41, female=38) were met the inclusion criteria and they agree to invited the study. Another ninety eight seem to be healthy persons at age 20-78 year had not used NSAIDs during last six months were asked to invited this study, only fifty persons (male =32, female =18) were agree to included in this study (as control group).

Any patients with diabetes mellitus, amyloidosis, chronic liver diseases, asthmatic, solid and hematological malignancy, and acute inflammatory gastroenteritis, were excluded. Any subjects refuse colonoscopy or unfit for procedure was excluded too.

Full history was taking included detailed drug history ;dose, duration, route, concomitant drugs and the underlining cause for which drug was taken; and physical history were done for both patient and control groups.

In addition to that, questionnaire information paper applied for each one for detailed question about lifestyle habits, family history and previous history of GI diseases, current medications and sociodemography distribution. History of any changing of bowel habit, bleeding per rectum, abdominal cramp, tinismus and abdominal discomfort and distension were reported. Also information about underling cause for NSAIDs using was collected from all patients.

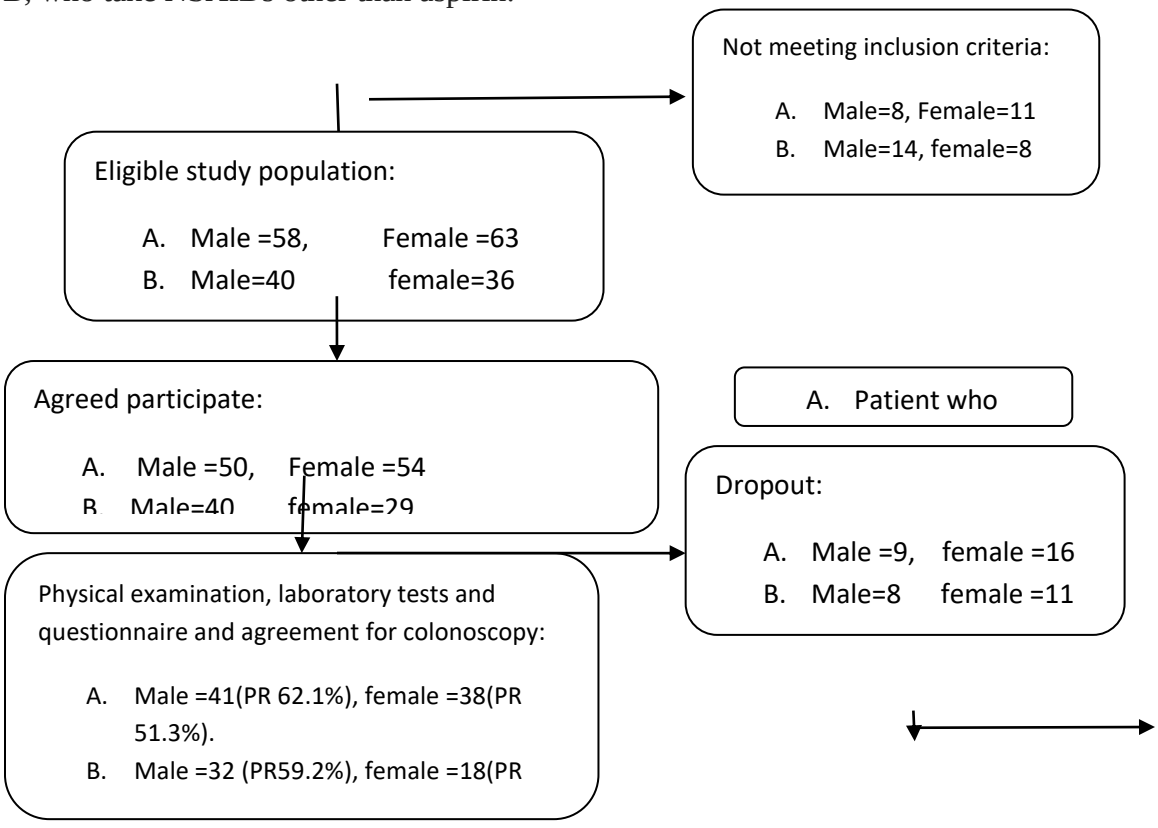
Laboratory tests including complete blood count, random blood sugar, blood urea and serum creatinine, liver function tests and anti Helicobacter pylori were done to all candidates of both patient and control groups. Thyroid function test was done to some patients to exclude hypothyroidism.

After taken the patient agreement, sigmoidoscopy with or without colonoscopy was done after good colonic preparation. Macrscopial finding during endoscopy insertion was reported for "any erythema, congested mucosa, polyp and ulceration" in addition to rectal and colonic biopsies were taken and sent to laboratory department of Al-Diwaniya hospital for histopathology, it is then processed and then stained the sections and examine by specialist histopathologist.

Safety was assessed on the basis measurement of vital signs, physical examination and laboratory tests before and after endoscopy done.

The patient group was subdivided into subgroups according to the type of NSAIDs use: group A, who taking aspirin only; group B, who take NSAIDs other than aspirin.

Statistical analysis was performed by Social Science Statistics and the Statistical Package For Social Sciences version 17 for Windows Software and Microsoft Excel 2013. Descriptive analysis was done by calculating frequencies and approximate percentages. The Pearson correlation (r) is used to measure the strength of a linear association between the variables, while the statistical significance of the relationships was examined by the Fisher Exact Probability Test or Chi-Square test (χ^2) that also used to measure the strength of association between two categorical variables. Odds ratios (OR) were standardized (SD OR) per 1SD unit variance for the independent variables. All these statistical tests considered that *P*- value less than the 0.05 level was statistically significant.



Flow program of the recruitment of the study population. Group A= patient group. Group B=control group. PR=participation rate.

Result:

Table (1): Case-control difference in the mean of age and gender

	Patient (n=79)	Control (n=50)	P value
Age /year			
Range	18-81	18-80	
Mean ± SD	52.45± 16.12	53.02±15.02	0.55 {Ns}
SE	1.87	2.15	
Gender	**N (%)**	**N (%)**	**P value**
Male	40(51)	32(64)	0.475 {Ns}
Female	39(49)	18(36)	0.466 {Ns}

❖ NS= No Significant (p > 0.05), SD= Standard Deviation, SE= Standard Error, N= Number

Table one revealed the distribution of patients and control cases according to their age and sex. The mean age of patient group was 52.45±16.12 year with a male / female ratio was 40/39 while the age of control group was 53.02±15.02 year with a male/female ratio was 32/ 18. In control group many volunteer females would refuse the procedure, so volunteer male will be more in control group. The middle age group was the main group included in the study; this will reflect the widely using of NSAIDs by those patients at this age might be because of their exertion work or because increasing the incidence of rheumatic diseases and this agree with other study.

Table(2): The case-control difference in the mean of BMI, HbAlc and duration of NSAIDs using.

	Patient (N=79)	Control (N=50)	P value
BMI			
Range	18-42	22-38	
Mean ± SD	30.72±5.26	29.04±3.14	0.75 {Ns}
SE	0.611	0.443	
HbAlc			
Range	4.5-10.1	4.2- 9.2	
Mean ± SD	6.8±1.19	5.44±2.12	0.66 {Ns}
SE	0.138	0.143	
Duration of NSAIDs			
Range (Month)	6-60	-	
Mean ± SD	14.42±4.1	-	-
SE	0.211	-	

❖ NS= No Significant (p > 0.05), SD= Standard Deviation, SE= Standard Error, N= Number

Table(3) : compared mean of BMI and HbAlc between male and females of patients and control.

BMI	Patient (n=79)		Control (n=50)		P value
	Male (n=40)	Female (n=39)	Male (n=32)	Female (n=18)	
Range	18-41	24-42	32-38	22-36	
Mean ± SD	28.3±5.39	31.94±2.71	29.22±3.57	29.28±3.10	0.332[NS]
SE	0.852	0.76	0.63	0.73	
HbAlc					
Range	4.5-10.1	4.5-9	4.2-9.2	5.1-7.5	
Mean ± SD	6.38±1.354	6.183±0.976	6.09±1.15	6.12±0.64	0.530[NS]
SE	0.214	0.167	0.203	0.152	

❖ NS= No Significant (p > 0.05), SD= Standard Deviation, SE= Standard Error, N= Number

Tables 2&3 would demonstrate the distribution of patients and control cases according to their body mass index and distribution of diabetes mellitus according to their HbA1c which is more in patients group. Also this table revealed the duration of using of NSAIDs in patient group which is ranging from 6 months to five years, most of them with daily intake.

Table(4) : Associated disease with NSAIDs among patient group

Associated disease	Patient (n=79)			X^2	P value
	Asp. (n=23)	Non.Asp (n=52)	Asp+non-Asp (n=4)		
	N (%)	N (%)	N (%)		
RH	0 (0)	14(27)	0(0)	8.83	0.012
IHD	21(91)	2(4)	1(25)	57.7	<0.0001
OA and other non RH	2(9)	36 (69)	3(75)	10.1	0.007

❖ RH= Rheumatic, Non RH =non Rheumatic, IHD= ischemic heart disease, OA= osteoarthritis

Table four revealed the distribution of NSAIDs into two subgroups; patients taking aspirin while the other group who taking other NSAIDs. The underlying disease in aspirin group was mainly IHD and the usual dose in those patient was 100 mg daily, while the other subgroup whose patients taking other NSAIDs mainly because of osteoarthritis and some rheumatic disease. Most of those patients are taking single drugs daily for long time.

Table (5): different types of NSAIDs use in patient group.

Type of NSAIDs	No. of patients	Duration (months)
Aspirin	27	36±2.7
Diclofenac	22	12±6.5
Celecoxib	7	9±1.7
Naproxen	9	18±2.76
piroxicam	7	9±1.4
ketoprofen	2	7±2.2
Others	5	8±1.2

Table five show the most widely NSAIDs which is taking by Iraqi patients. Diclofenac drug, which is the most popular drug and as over-counter medication, was the most drug taking by patients usually as analgesia and its anti inflammatory. Aspirin was taking by patients with IHD for life as secondary prevented measure as anti platelets rather than analgesia. The long duration of aspirin use reflect long duration of stable angina in those patients

Table (6): show relation of aspirin and other NSAIDs with mean of BMI and HbAlc in patient group.

BMI	Patient (n=79)			P value
	Asp. (N=23)	Non.Asp (N=52)	Asp+non-Asp (N=4)	
Range	18 - 41	18 - 42	18 - 28	
Mean ± SD	30.52 ±5.9	30.19±4.86	24.25±4.5	0.198[NS]
SE	1.26	0.71	2.25	
HbAlc				
Range	9.4 -10.1	4.5 - 9	4.5 – 6.4	
Mean ± SD	6.72±1.44	6.13±1.04	5.7±0.852	0.337[NS]
SE	0.299	0.151	0.426	

❖ NS= No Significant (p > 0.05), SD= Standard Deviation, SE= Standard Error, N= Number

This table usually demonstrates the body weight and diabetes mellitus which are well known risk factors for rheumatic and O.A. changes which making chronic use of NSAIDs. Also these factors are important for pathogenesis of IHD.

Table (7): The case-control difference in the symptoms, macro and microscopic finding

	Patient (N=79)	Control (N=50)	P value
Symptoms	**N (%)**	**N (%)**	**P value**
No symptoms	41(52)	39(78)	0.054 [NS]
Diarrhea	18(23)	2(4)	0.0012
Constipation	8(10)	2(4)	0.0055
Bleeding per rectum	4(5)	0(0)	>0.0001
Alteration of BM	8(10)	5(10)	0.041
MACRO	**N (%)**	**N (%)**	**P value**
normal	38(48)	43(86%)	0.0046
Congestion	31 (39%)	6(4)	<0.0001
Diverticulum	4(5%)	0(0)	0.0011
Polyp	3 (3.5%)	1(2)	0.044
Ulcer	3(3.5%)	0(0)	<0.0001
MICRO	**N (%)**	**N (%)**	**P value**
normal	48(61%)	46(92%)	
NSC	22(28)	3(6)	<0.0001
LYM.C	9(11)	1(2)	<0.0001

❖ NSC= non specific colitis. LYM C =lymphocytic colitis, N= Number

Table (7) shows the macroscopical and histopathologic finding of both groups. Patients of group A show significant microscopic changes than control group. In group A, non specific colitis was the predominant microscopic changes while nine cases had histologic finding of lymphocytic colitis.

Microscopic changes are most likely seen by patients on chronic NSAIDs with clinical manifestation mostly with diarrhea, this was agree to study done Riddle et al.

Table (8): Compared effect of smoking on lower GIT of case and control

MACRO	Patient (N=79)			Control (N=50)			X^2	P value
	Smoker (N = 21)	EX-smoker (N = 15)	Non-smoker (N= 43)	Smoker (N = 17)	EX-smoker (N = 15)	Non-smoker (N = 18)		
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)		
Congest	3(14)	4(27)	9(21)	1(6)	0(0)	1(5.6)	8.18	0.019
Diver	0 (0)	1(7)	2(5)	0(0)	0(0)	0(0)	3.7	0.11
Polyp	1(5)	1(7)	1(2.3)	0(0)	1(7)	0(0)	2.67	0.440
Ulcer	1(5)	0(0)	2(5)	0(0)	0(0)	0(0)	3.12	0.681
MICRO	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**		
NSC	4(19)	4(27)	16(37)	1(6)	0(0)	2(11)	14.6	0.012
LUM.C	2(10)	1(7)	6(14)	0(0)	1(7)	0(0)	5.40	0.370
Symptoms	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**		
No symptom	14(67)	9(6)	24(56)	11(65)	13(87)	15(83)	7.56	0.047
Diarrhea	4(19)	2(13)	13(30)	1(6)	1(7)	2(11)	8.23	0.144
Constipation	1(5)	3(2)	4(9)	1(6)	1(7)	0(0)	5.17	0.390
Bleeding PR	2(10)	1(7)	2(5)	0(0)	0(0)	0(0)	4.20	0.521
Alteration of bowel motion	0(0)	0(0)	0(0)	4(23.5)	0(0)	1(5.6)	21.6	0.001

Discussion:

Although injury to the proximal gastro-intestinal tract has received the greatest attention, NSAIDs may also have clinically important adverse effect on colon. A number of reports suggest an association between NSAIDs and lower GIT manifestation.

Riddel et al., found that 19 of 31 patients with collagenous colitis had taken NSAIDs for more than six monthsprior to colorectal biopsies demonstrating collagenous colitis. This was statistically significant ($P < 0.02$). In all these patients , NSAIDs use preceded the onset of diarrhea and the symptoms will improved in three patients when NSAIDs were withdrawn. Rechallenge in one was followed by a recurrence of diarrhea which improves after withdrawing the drug again[11].

In a study carried by Goff et al., to determine the natural clinical history of microscopic colitis, they found that 83% of the patients were female, with a mean age 66 years. Of 31 patients with microscopic colitis, 18 (56%) had some form of arthritis, and 22(71%) were using NSAIDs regularly at the time of diagnosis [16].

Our study shows that there is many lower GI manifestation in those patients who taking NSAIDs with no significant relation between the type or duration of NSAIDs intake and duration or severity of clinical manifestations. This finding is similar to a case-control study done by Riddell and Tanaka, where they postulate that

idiosyncratic hypersensitivity to NSAIDs may account for a proportion of cases [11].
There was a statistically significant different in histological finding in those patients who had clinical manifestation in chronic user of NSAIDs compared to those in control group (P<0.05). However there was no statistically significant different in histological finding of both subgroups (aspirin, non aspirin group), this support the involvement of other factors in the etiology of lower GI manifestation. However lymphocytic colitis was seen more frequent in non aspirin subgroup. The possible explanation of this finding could be related to the small dose of aspirin in aspirin-subgroup patients.
Lymphocytic colitis was statistically significant more frequent in patient group than control (P<0.001), explanation of this related to the chronic activation of mucosal immune system by the drugs as suggested by Beaugerie et al., when "they described three patients with lymphocytic colitis in whom the disease remitted on cessation of the drug. The authors examined marker of mucosal immune activation by immunocytochemistry and demonstrated the presence of CD25 expression by lamina properia mono nuclear cells and the appearance of diffuse HLA DR expression by epithelial cells. These changes will disappear on cessation of NSAIDs therapy. They concluded that lymphocytic colitis is likely to be secondary to chronic activation of the mucosal immune system by one or more components of drug". [17].

Conclusion and recommendation:

1. Patients on chronic use of NSAIDs with clinical manifestation are statistically significant different to those with no symptoms.
2. There is no relation between the clinical manifestation and its severity with the type and duration of the NSAIDs use.
3. The histological finding was much less in Aspirin-group patients than non aspirin- group patients.
4. It could recommended that patients with lower GI manifestation who were on chronic NSAIDs and they are in need of this drugs, may be advised to change their medications

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