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Are NSAIDS Really Responsible For Increasing Incidence Of Duodenal Perforation – Our Experience.

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ABSTRACT

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs for pain and inflammation all over the world by medical practitioners. Long-term overuse of these drugs leads to severe gastrointestinal complications such as peptic ulcers and erosions. Aim of study is to evaluate the incidence of NSAIDS related peptic ulcer perforation in our region and to know the role of NSAIDS in the causation of duodenal perforation. **Methods:** This was retrospective study conducted in the Department of General Surgery Rohilkhand Medical College and Hospital on 51 patients of duodenal perforations to know its causation with NSAIDS. The results obtained were compiled in a tabulated form. Mean ± Standard Deviation (SD) were analyzed using with Statistical Package for Social Sciences (SPSS 23.0). The level $P < 0.05$ was considered as the cutoff value for significance. **Results:** The Mean age of all patients was 43.86±11.05 years. In majority of 28 (54.90%) patients NSAIDS was responsible either alone or concomitantly associated with excessive smoking and alcohol in 20(71.42%) patients and NSAIDS alone in 8(28.57%) patients. **Conclusion:** Excessive high dose intake of these drugs and intake of the combination of two NSAIDS instead of single NSAIDS therapy has resulted in increased chances of peptic ulcer perforation. So indiscriminate use of NSAIDS should be avoided.

Keywords: Non-steroidal anti-inflammatory drugs (NSAIDs), duodenal perforation, and laprotomy.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs for pain and inflammation all over the world by medical practitioners. Long-term overuse of these drugs leads to severe gastrointestinal complications such as peptic ulcers and erosions.[1] In the duodenum, this peptic ulcer may perforate and thus lead to severe life-threatening complications even death if the perforation is not treated timely. In the earlier time, the Helicobacter pylori infection was the leading cause of peptic ulcer-related duodenal ulcer perforation but in recent years there is a paradigm shift in the epidemiology of peptic ulcer disease. A review of the medical literature suggests that the proportion of H. pylori negative peptic ulcer disease has been increasing in recent years.[2] Out of H.Pylori negative causes, the incidence of NSAIDS related duodenal perforation is an increasing trend.[3] Other causes of spontaneous perforation in the duodenum include peptic ulcer disease due to chronic alcohol intake, cigarette smoking and stress.[4]

The pathophysiology of NSAID's in the causation of peptic ulcer disease is by the various mechanisms of NSAID induced gastric injury which include a) damage of the gastric epithelium by intracellular accumulation of these drugs in an ionized state b) reducing the hydrophobicity of the mucous gel layer by changing the action of surface-active phospholipids c) suppression of the prostaglandin synthesis d) injury due to neutrophils adherence to the endothelium of gastric microcirculation.[5] Of these activities on the cyclooxygenase (COX) inhibition and the subsequent prostaglandin (PG) deficiency is one of the most acceptable mechanisms for peptic ulcer perforation. Prostaglandins are important for mucosal integrity. There are two distinct isoforms of COX. COX-1 is present in the majority of cells including endothelial cells, gastrointestinal epithelium and platelets and functions continuously. In contrast, COX-2 is present in only a few tissues and is induced by inflammation. NSAIDs exert their therapeutic anti-inflammatory and analgesic effects by inhibiting COX-2. The gastric and renal toxicities of the drugs are related to inhibition of the COX-1 isoform.[6,7] Peptic ulcer disease is a well-recognized

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complication of NSAID use. Inhibition of COX-1 in the gastrointestinal tract leads to a reduction of prostaglandin secretion and its cytoprotective effects in gastric mucosa. This, therefore, increases the susceptibility to mucosal injury.[8] The inhibition of COX leading to decreased mucosal PGs is considered as the most important in the pathogenesis of NSAID-induced gastric damage. Aspirin inhibits COX irreversibly, while other NSAIDs inhibit COX in a reversible, concentration-dependent manner Cyclo-oxygenase (COX 1 and COX 2) inhibition which is supposed to cause a gastric ulcer. Neutrophil adherence is known to cause damage to mucosa by liberating oxygen free radicals, protease release and reducing capillary blood flow. The role of nitric oxide (NO) and hydrogen sulfide (H2S), in maintaining the integrity of gastric mucosa is well-known. NO, and H2S increase blood flow to the mucosa, stimulate mucus secretion, and inhibit neutrophil adherence. NSAIDs inhibit also NO and H2S.[9]

Aim

To evaluate the incidence of NSAIDS related peptic ulcer perforation in our region and to know the role of NSAIDS in the causation of duodenal perforation.

MATERIALS AND METHODS

This was retrospective study conducted in the Department of General Surgery Rohilkhand Medical College and Hospital on 51 patients of duodenal perforations admitted from the casualty and outpatient departments in all surgical units from November 2015 to December 2016. All patients above 16 years were included in the study. Ethical permission was taken from the hospital ethical committee to carry out this study.

Methodology

All patients with a history suggestive of duodenal perforation were evaluated with symptoms and signs of perforation peritonitis. History with regards to long-term use of medicines like conventional NSAIDS, personal history regarding excessive smoking and consumption of alcohol was asked. Also, the time duration and quantity of intake of either of these were specifically asked. Conventional NSAIDs were defined as those lacking selective Cox-2 inhibition activity, i.e. those capable of inhibiting both Cox-1 and Cox-2 enzymes, such as diclofenac, ibuprofen, indomethacin, and naproxen. Confirmation of diagnosis was done by the radiological investigations like erect plain x-ray chest PA view and x-ray abdomen erect AP view showing free gas under the right side of the diaphragm and abdominal ultrasonography to look for the collection of free fluid in the peritoneum and intraperitoneal gas. Routine blood investigations were done in all patients. Special laboratory test wherever required were performed. These included H.pylori SD bioline immunochromatographic test for detection of H.pylori infection. The confirmation of duodenal perforation was done on basis of operative findings. Exploratory laparotomy was done for all cases and all perforations were closed by Modified graham's patch repair. The results obtained were compiled in a tabulated form. Mean ± Standard Deviation (SD) were analyzed using with Statistical Package for Social Sciences (SPSS 23.0). The level $P < 0.05$ was considered as the cutoff value for significance.

RESULTS

Table 1: Age and sex distribution of patients with duodenal perforation (N=51).

AGE Distribution (year)	DUODENUM		Total (N =51)	Percentage (%)
	Male (n = 47)	Female (n = 4)		
>16-20	1	0	1	1.96%
21-30	5	1	6	11.8%
31-40	18	0	18	35.3%
41-50	14	1	15	29.4%
51-60	6	2	8	15.7%
61-70	3	0	3	5.9%
Total	47	4	51	100%
Mean Age of patients was 43.86±11.05 years P value between both sexes =0.036				

Out of a total of 51 patients with duodenal perforation, 47 (92.15%) were males and 4(7.8%) were females. Maximum patients 18(35.3%) were in the age group of 31-40 year. Mean age of all patient was 43.86±11.05 years. Maximum males 18(38.29%) were in the 31-40 year age and maximum females 2(50%) were in the age group of 51-60 year. The p-value between both sexes was 0.036 which was significant as $p<0.05$.

Table 2: Etiologies of perforation in the duodenum.

Etiologies	Total no of patients (n)	Percentage (%)
1.NSAIDS	8	15.68%
2.NSAIDS+SMOKING or ALCOHOL	20	39.21%
2.H.PYLORI	10	19.60%
3.SMOKING	7	13.72%
4.ALCOHOL	6	11.76%

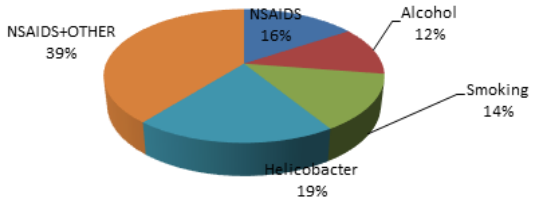

Chart 1: Pie chart showing etiologies of perforation in the duodenum.

All 51(100%) were due to peptic ulcer disease. In majority of 28 (54.90%) patients NSAIDS was responsible which was either concomitantly

associated with excessive smoking and alcohol in 20(71.42%) patients and NSAIDS alone in 8(28.57%) patients. This was followed by H.Pylori in 10 (19.60%), smoking 7(13.72%) patients and alcohol in 6 (11.76%) patients.

Table 3: Relationship of NSAIDS with peptic ulcer perforation in terms of quantity, dose, and duration (n = 28).

1.Quantity	No of patients (n)	Percentage (%)
Single NSAIDS	8	28.57%
Combination of two NSAIDS	20	71.42%
2.Dose of NSAIDS		
Low standard dose	6	21.42%
High standard dose	22	78.57%
3.Duration Of Consumption		
Up to 1 month	14	50%
1- 3 month	10	35.71%
> 3 months	4	14.28%

Peptic ulcer perforation was most commonly presented in those patients taking a combination of two NSAIDS 20 (71.42%) as compare to those taking single NSAIDS 8 (28.57%), most commonly associated in patients taking high dose NSAIDS therapy in 22 (78.57%) as compare to those taking a low standard dose 6 (21.42%) patients and those patients consuming NSAIDS up to one month 14(50%)patients as compare to those consuming NSAIDS for 1-3 months 10 (35.71%) and more than 3 months 4 (14.28%) patients.

DISCUSSION

Perforation peritonitis is the 2nd most common surgical emergency in our hospital reporting 120 out of 400 patients and duodenal perforation is one of the most common causes of perforation peritonitis accounted for 51 (42.5%) patients in one year. In duodenal ulcer perforation, peptic ulcer disease was the only cause of perforation in all 51 (100%) cases reported in our series.

The sex incidence in our study had a male predominance of 47 (92.15%) as compared to females 4 (7.8%) which was statistically significant (p = 0.036). Ullah A and Ullah S in their study also reported a male preponderance of 95.59 % as compared to females 9.41 %.[10]

Most of the patients with duodenal perforation 18(35.3%) presented in the 31-40 year age group and is close to 34% reported by Hannan et al in the same age group.[12] Mean age of all patient was 43.86±11.05 years. In young adults, life-style patterns like increased stress, smoking habits, alcohol consumption, irregular meals associated with increased NSAIDS intake prescribed by local practitioner add to the risk.[11]

In the majority of 28(54.90%) patients NSAIDS were found to be the cause of perforation. Out of 28 patients, in 20 (71.42%) patients NSAIDS overuse was associated with excessive bidi smoking or excessive consumption of alcohol while in remaining 8 (28.57%) patients NSAIDS alone was responsible. This was followed by H.pylori in 10 (27.45%), smoking 7 (15.68%) patients and alcohol in 6 (11.76%) patients.

Musumba CO, Van Eker D and Jorgensen A in their study also reported a higher incidence of increasing NSAIDS related peptic ulcer perforation in 57% patients as compare to H.Pylori in 41% patients same as reported by us.[13] However, additional risk factors like smoking and alcohol increases the risk of peptic ulcer as reported in our study was also reported by C Svanes et al and Andersen IB et al.[20,21]

The increased prevalence of NSAIDS perforation in our region is due to its indiscriminate prescription by local practitioners in rural areas. This sharply contrasts to the west where NSAIDS/Steroids perforations are actually decreasing −29.9 %.[14]

The type, dose, and duration of NSAID therapy appear to independently determine the risk for development of gastro duodenal ulcers and their complications. The ulcer risk is present throughout the duration of therapy, but appears to be greatest during the first month.[15-18]

Gabriel et al identified a risk that varied with duration of NSAID use from an 8.0-fold increased risk for <1 month of exposure to 3.3-fold for 1-3 months of exposure to 1.9-fold for >3 months of exposure.[18] In our study, we have also observed increased peptic ulcer perforation as a complication of peptic ulcer in those patients consuming NSAIDS up to one month 14 (50%)patients as compared to those consuming NSAIDS for 1-3 months 10 (35.71%) and more than 3 months 4 (14.28%) patients. The decreased risk of peptic ulcer complication in long-term use of NSAIDS therapy may be due to the development of mucosal adaptation allowing the gastro-duodenal mucosa to withstand injury during long-term use of NSAIDS. Unfortunately, the mechanisms responsible for mucosal adaptation and the reasons for its failure in those who develop ulcers remain unknown.[19]

As with acute mucosal injury, a direct relationship has been found between NSAID dose and the risk of GI complications.[15,16] Griffin et a1 found a relative risk that increased from 2.8 during therapy with standard doses to a relative risk of 8.0 for the highest-dose category. In our study,[16] we have also observed that 22(78.57%) patients taking high dose NSAIDS had increased complication of peptic ulcer as perforation as compared to those taking a low standard dose in 6(21.42%) patients.

Henry D, Dobson A, Turner C found an additive risk when NSAIDs are used in combination with aspirin or second non-aspirin NSAID.[15] In our study, we have also observed that when NSAIDS are used in combination with aspirin or second non-aspirin

NSAID the peptic ulcer perforation was observed in the higher group of patients 20(71.42%) as compared to those who were taking the single NSAIDS 8 (28.57%) patients.

CONCLUSION

In our region indiscriminate use NSAIDS prescribed by the local practitioner in addition to bidi smoking and alcohol consumed by a large number of rural people attributed to the high incidence of peptic ulcer-related duodenal ulcer perforation. Excessive high dose intake of these drugs and intake of the combination of two NSAIDS instead of single NSAIDS therapy has resulted in increased chances of peptic ulcer perforation. However the judicious use of these drugs in the appropriate dose and adding the H,-receptor antagonists like ranitidine or omeprazole along with NSAIDS appears to accelerate the healing process and can prevent the peptic ulcer-related complications.

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