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# Evaluation of clopidogrel use on gastric precancerous lesions: does it have chemopreventive effect?

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## ABSTRACT

**Aims**: Gastric malignancies are the third most common cause of cancer-related deaths. Although aspirin and clopidogrel have been reported to reduce the risk of colorectal cancer, their effects on gastric cancer are still under investigation. In this study, we aimed to determine whether clopidogrel has an effect on the development of gastric precancerous lesions.

**Methods**: The study was designed as a retrospective case-control study. The study was conducted between January 2021 and April 2023 in the Gastroenterology Clinic of Samsun Training and Research Hospital. Patients who underwent upper GIS endoscopy and biopsy examination due to dyspeptic complaints were scanned from the electronic data system of the hospital and their data were recorded by forming 4 groups as clopidogrel (89 patients), low-dose aspirin (ASA) (172 patients), non-aspirin non-steroidal anti-inflammatory drug (NA-NSAID) users (110 patients) and control group without antiplatelet use (110 patients).

**Results**: Mean duration of drug use was 2 years for clopidogrel, 1.47 years for ASA and 0.35 years for NA-NSAID. The incidence of peptic ulcer was 7.2% in the control group, 38%, 15.1%, 49% in clopidogrel, ASA, NA-NSAID users, respectively ($p<0.001$). The frequencies of *H. pylori* infection in the groups were 61%, 53.5%, 40.1%, 46.1%, respectively. There was a significant difference between ASA and control group ($p<0.001$). Intestinal metaplasia was observed in 23.1%, 29.5%, 31.2%, 23.1%, respectively ($p=0.291$). Atrophic gastritis was seen in 16.6%, 35.2%, 19.2%, 29.3%, respectively ($p=0.003$). No difference was observed between the groups in terms of dysplasia, gastric cancer and esophageal cancer.

**Conclusion**: According to our results, no preventive effects of clopidogrel, ASA and NA-NSAID use on precancerous lesions or gastric cancer development were observed. However, the use of these drugs was associated with severe gastroduodenal lesions.

**Keywords**: Aspirin, clopidogrel, gastric cancer, gastric precancerous lesions

## INTRODUCTION

Gastric cancer (GC) is the fifth most common type of cancer in the world and is the third leading cause of cancer-related deaths worldwide.[1,2] Most of the patients miss the chance of curative surgical treatment when diagnosed.

The most important risk factor for the development of GC is *Helicobacter pylori* (HP) infection.[3] HP infection causes chronic gastritis of the gastric mucosa and thus initiates the Correa cascade, progressing to atrophic gastritis (AG), gastric intestinal metaplasia (GIM), dysplasia and finally gastric cancer.[4]

Although HP eradication reduces the risk of GC and may regress precancerous gastric mucosal changes, the risk of GC development persists even after eradication.[5] The persistence of GC development after HP treatment suggests that there are different pathogenesis and therefore other methods to prevent GC development should be investigated.

Meta-analyses and some studies have reported that aspirin and NA-NSAIDs reduce the risk of both colorectal cancer (CRC) and GC through cyclooxygenase (COX-2) inhibition.[6,7] Although aspirin and NA-NSAID use may have beneficial effects in the prevention of gastric cancer, their clinical significance remains unclear. To reduce the risk of GC after HP eradication, new preventive agents such as anti-inflammatory (COX-2 inhibitors), statins and metformin continue to be investigated.[8]

Clopidogrel, an alternative antiplatelet to aspirin, acts by irreversibly inhibiting the platelet adenosine diphosphate (ADP) receptor and prevents ischemic events. A case-control study reported that the use of clopidogrel alone or in combination with low-dose aspirin reduced the risk of CRC by 20% to 30%, and it is considered that this anti-cancer effect is probably due to its antiplatelet property.[9]

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Aspirin, NA-NSAIDs and clopidogrel cause gastroduodenal lesions. In many studies, clopidogrel has been reported to cause less gastroduodenal lesions than aspirin.[10] However, not all patients receiving antiplatelet agents are at the same risk. The presence of HP infection in patients receiving antiplatelet agent therapy is one of the high-risk factors for gastroduodenal complications.[11] In subgroup comparisons of one study, it was noteworthy that the frequency of HP infection was significantly lower in patients receiving clopidogrel than in those receiving aspirin (17% and 35%, respectively. p= 0.007).[10] In addition to the mechanisms of action, the fact that HP infection, which is one of the major causes of gastroduodenal lesions, is less common in patients using clopidogrel may be one of the important reasons why clopidogrel causes gastroduodenal lesions less frequently and this issue has not been investigated in the literature before. In addition, the low incidence of HP, which is known to be associated with gastric cancer, in clopidogrel users suggests that clopidogrel may have chemoprevention effects similar to aspirin and NA-NAID. As far as we searched, we could not find any study investigating the relationship between clopidogrel and gastric premalignant lesions and GC development. We tried to clarify these issues in our study.

Our aim was to determine whether clopidogrel, aspirin and non-aspirin non-steroidal anti-inflammatory drugs have beneficial effects on reducing gastric premalign lesions and the risk of gastric cancer development

## METHODS

The study was carried out with the permission of Samsun Training and Research Hospital Non-interventional Clinical Research Ethics Committee (Date: 30.10.2019, Decision No: 2019/1/9). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Study Design and Patient Selection

The study was designed as a retrospective case-control study. Patients who underwent upper GIS endoscopy and biopsy examination due to dyspeptic complaints in the Gastroenterology Clinic of Samsun Training and Research Hospital between January 2021 and April 2023 were scanned from the electronic data system of the hospital and their data were recorded by forming 4 groups as clopidogrel, low-dose aspirin and non-aspirin non-steroidal anti-inflammatory drug users and control group (those who did not use any antiplatelet or NSAID drugs).

After analyzing the data, patients who had been using clopidogrel or low-dose aspirin for at least 1 year before the procedure and patients who started to use at least 1 non-aspirin NSAID per day at least 3 months before the procedure were included in the study. Age, gender, endoscopic diagnosis, histopathological diagnosis and HP status were recorded. Cases with hepatic and renal insufficiency, malignancy, primary immunodeficiency, immunosuppressive therapy, gastric surgery, dual antithrombotic or NSAIDs and antithrombotic drugs were excluded from the study. Moreover, a control group was formed from patients without chronic disease and drug use and who underwent upper GIS endoscopy and biopsy examination due to dyspepsia.

Histopathological examination and grading of endoscopic biopsies were evaluated by two senior pathologists according to the current Sidney classification.[27]

### Statistical analysis

Statistical analysis was performed using SPSS software (Statistical Package for the Social Sciences, version 20.0, SPSS Inc., Chicago, USA). Categorical data were defined as percentage. Chi-squared test was used to evaluate statistical differences between clinical features according to treatments groups. $p<0.05$ was considered statistically significant.

## RESULTS

A total of 461 patients including 110 patients in the control group (group 1), 89 patients in the clopidogrel group (group 2), 172 patients in the ASA group (group 3) and 90 patients in the NA-NSAID group (group 4) were included in the study. There was no difference between the groups in terms of gender (p=0.064). In terms of age, clopidogrel and NA-NSAID group were older than the other groups (p<0.001). The mean drug use duration was 1.47 year for ASA, 2 year for clopidogrel and 0.35 year for NA-NSAID. Demographic characteristics, endoscopic and histological findings of the groups included in the study are shown in Table 1.

### Endoscopic findings

The incidence of erosive gastropathy was 10.9%, 21.3%, 18%, 22.2% in the control, clopidogrel, ASA, NA-NSAID groups, respectively. There was no significant difference between the drug groups. When compared with the control group, the incidence of erosion was significantly higher in the clopidogrel and NA-NSAID groups (p=0.043, p=0.030).

There was a significant difference between the groups in terms of peptic ulcer (7.2%, 38%, 15.1 %, 49%, respectively) (p<0.001). Peptic ulcer was observed more in all groups using drugs than in the control group and was statistically significant.

Ulcer frequency was higher in both clopidogrel and NA-NSAID groups than in ASA group and was statistically significant (p<0.001 for both). The frequency of HP infection in the groups was 61%, 53.5%, 40.1%, 46.1%, respectively. There was no statistically significant difference between the groups using drugs.

Compared with the control group, the frequency of HP infection was lower in all groups using drugs, but only the difference between the ASA group and the control group was statistically significant (p<0.001).

### Histological Findings

There was no significant difference between the groups in terms of intestinal metaplasia (23.1%, 29.5%, 31.2%, 23.1%, respectively) (p=0.291). The incidence of atrophic gastritis (16.6%, 35.2%, 19.2%, 29.3%, respectively) was significantly different between the groups (p=0.003). GA was observed more in clopidogrel and NA-NSAID groups than in control and ASA groups (clopidogrel p= 0.004, 0.009, NA-NSAID p= 0.009, 0.019). No difference was observed between the groups in terms of neutrophil activity, chronic inflammation, dysplasia, gastric cancer and esophageal cancer.

Statistical analyses of all findings between groups are given in Table 2.

**Table 1.** Demographic characteristics, endoscopic and histological findings of the groups included in the study

| | | Control group 1 | Clopidogrel group 2 | ASA group 3 | NA-NSAID group 4 | All groups p |
|---|---|---|---|---|---|---|
| Gender | Female<br>Male | 68<br>42 | 39<br>50 | 89<br>83 | 43<br>47 | 0.064 |
| Age | <65 years<br>>65 years | 67<br>43 | 30<br>59 | 84<br>86 | 26<br>64 | <0.001* |
| Esophagitis | No<br>Yes | 65<br>45 | 58<br>31 | 120<br>52 | 82<br>8 | <0.001* |
| Gastritis | No<br>Yes | 17<br>93 | 31<br>58 | 50<br>122 | 53<br>37 | <0.001* |
| Peptic ulcer | No<br>Yes | 102<br>8 | 55<br>34 | 146<br>26 | 44<br>46 | <0.001* |
| Erosive gastropathy | No<br>Yes | 98<br>12 | 70<br>19 | 141<br>31 | 70<br>20 | 0.136 |
| Duodenitis | No<br>Yes | 102<br>8 | 84<br>5 | 169<br>3 | 88<br>2 | 0.077 |
| *H. pylori* | No<br>Yes | 42<br>66 | 33<br>38 | 95<br>66 | 35<br>30 | 0.011* |
| Intestinal metaplasia | No<br>Yes | 83<br>25 | 50<br>21 | 108<br>52 | 50<br>15 | 0.291 |
| Atrophic gastritis | No<br>Yes | 90<br>18 | 46<br>25 | 130<br>31 | 43<br>22 | 0.003* |
| Neutrophil activity | No<br>Yes | 36<br>72 | 33<br>38 | 70<br>91 | 21<br>44 | 0.131 |
| Chronic inflammation | No<br>Yes | 6<br>102 | 5<br>66 | 6<br>155 | 1<br>64 | 0.403 |
| Dysplasia | No<br>Yes | 107<br>1 | 69<br>2 | 160<br>1 | 65<br>0 | 0.347 |
| Gastric cancer | No<br>Yes | 109<br>1 | 83<br>4 | 168<br>4 | 88<br>2 | 0.414 |
| Esophageal cancer | No<br>Yes | 110<br>0 | 86<br>1 | 170<br>2 | 90<br>0 | 0.506 |

*p<0.05 was considered statistically significant.

**Table 2.** Statistical analysis of findings between groups

| | Group 1-2<br>p | Group 1-3<br>p | Group 1-4<br>p | Group 2-3<br>p | Group 2-4<br>p | Group 3-4<br>p |
|---|---|---|---|---|---|---|
| Gender | 0.011* | 0.097 | 0.047* | 0.225 | 0.595 | 0.542 |
| Age | <0.001* | 0.059 | <0.001* | 0.016* | 0.487 | 0.001* |
| Esophagitis | 0.380 | 0.066 | <0.001* | 0.449 | <0.001* | <0.001* |
| Gastritis | 0.001* | 0.009* | <0.001* | 0.340 | 0.001* | <0.001* |
| Duodenal ulcer | | | | 0.001* | 0.015* | <0.001* |
| Gastric ulcer | | | | 0.003* | 0.055 | <0.001* |
| Peptic ulcer | <0.001* | 0.048 | <0.001* | <0.001* | 0.082 | <0.001* |
| Erosive gastropathy | 0.043 | 0.105 | 0.030* | 0.518 | 0.887 | 0.415 |
| Duodenitis | 0.639 | 0.019* | 0.103 | 0.085 | 0.241 | 0.788 |
| *H. pylori* | 0.314 | 0.001* | 0.055 | 0.077 | 0.391 | 0.477 |
| Intestinal metaplasia | 0.336 | 0.097 | 0.991 | 0.659 | 0.391 | 0.161 |
| Atrophic gastritis | 0.004* | 0.590 | 0.009* | 0.009* | 0.867 | 0.019* |
| Neutrophil activity | 0.077 | 0.095 | 0.889 | 0.672 | 0.092 | 0.121 |
| Chronic inflammation | 0.685 | 0.476 | 0.194 | 0.273 | 0.118 | 0.390 |
| Dysplasia | 0.335 | 0.775 | 0.437 | 0.172 | 0.173 | 0.524 |
| Gastric cancer | 0.102 | 0.379 | 0.447 | 0.318 | 0.383 | 0.958 |
| Esophageal cancer | 0.260 | 0.256 | | 0.992 | 0.308 | 0.304 |

*p<0.05 was considered statistically significant. **Group 1; Control, Group 2; Clopidogrel, Group 3; ASA, Group 4; NA-NSAID.

## DISCUSSION

To the best of our knowledge, whether clopidogrel has chemoprevention activity for GC was investigated for the first time in our study. We compared the endoscopic and histological findings of patients using clopidogrel for a mean of 2 years with those using low-dose aspirin and NA-NSAIDs, which have been suggested to be chemopreventive for GC, and with the control group not using any drug and tried to reveal the relationship with gastric lesions.

In our study, both gastric erosions and ulcers were more common in the drug users compared to the control group. While there was no difference between the drug groups in terms of erosions, more ulcers were observed in the clopidogrel and NA-NSAID groups than in the aspirin group, which was statistically significant. These results clearly show that clopidogrel, ASA and NA-NSAID drugs all cause gastric lesions. The group with the highest number of gastric lesions was symptomatic NA-NSAID users. Although ASA causes gastric damage essentially through the same mechanism as aspirin (COX-1 inhibition), gastrointestinal damage varies in a dose-dependent manner.[12]

Although clopidogrel is safer than aspirin in terms of the risk of gastrointestinal (GI) bleeding, the frequency of GI lesions in studies conducted with symptomatic patients in general was compatible with our results.[10,13] When compared with the control group, the frequency of HP infection was lower in all groups using drugs, but the difference between the ASA group (40.1%) and the control group (61%) was statistically significant ($p<0.001$). The fact that HP infection, which is the most important risk factor for the development of GC, is lower in aspirin users may be related with the lower incidence of gastric cancer in long-term low-dose aspirin users.

In this current study, the presence of HP was evaluated by histological examination, which is considered to be one of the gold standard methods.[14] Although the prevalence of HP infection in the clopidogrel group was lower than in the control group, it was not statistically significant, which can be clarified with larger studies.

Despite advances in endoscopy and HP eradication, gastric cancer remains the third leading cause of cancer-related death.[1] Preventive research is ongoing, including the search for GC preventive drugs such as NSAIDs, statins and metformin, and screening programs to identify patients at risk.

There have been various studies suggesting that aspirin and other NSAIDs may prevent gastric cancer and bowel cancers. Although NSAIDs cause gastrointestinal damage, their long-term use may be associated with a reduced risk of gastric cancer. This effect is thought to be due to COX-2 inhibition.[15,16] However, a meta-analysis has suggested that aspirin use has no evidence-based beneficial effect on gastric cancer.[8] Although general opinion and evidence suggest that NSAIDs have a beneficial effect, it has not been proven and the actual clinical effect is uncertain.[17]

Gastric intestinal metaplasia (GIM) is a premalignant lesion that progresses to dysplasia and intestinal-type gastric cancer.[18] The prevalence of GIM varies between 3.4% and 29.6% according to ethnicity.[19,20] In a study conducted by Ozdil et al.[21] among 3031 adult dyspeptic patients in Turkey, GIM and HP were found to be 17.8% and 71.3%, respectively. In that study, it was reported that the prevalence of intestinal metaplasia increased inversely proportionally while the intensity of HP infection decreased. In addition, it has been shown that HP colonization density may be important in the development of other diseases.[22] In our results, the prevalence of GIM (31.2%, 23.1%) was high in the group with low prevalence of HP (40%, 61%). The prevalence of GIM was 23.1% in the control group, 29.5% in the clopidogrel group, 31.2% in the aspirin group and 23.1% in the NA-NSAID group. No significant difference was found between the groups.

In the study by Nagata et al.[23] comparing the rate of gastric cancer, intestinal metaplasia and neutrophil infiltration in ASA, NA-NSAID users and non-users, no difference was observed between the groups in terms of GIM. However, it was suggested that long-term (>2 years) aspirin use had no preventive effect on the development of intestinal type gastric cancer developing through the Correa cascade, but was associated with a decrease in the development of diffuse type gastric cancer, suggesting that the chemopreventive effects of aspirin may be specific to this type of histological cancer.[23] In this current study, no difference was observed between ASA, NA-NSAID and control group. Moreover, although not statistically significant, the fact that GIM was higher in the aspirin group compared to the control group supported that it had no preventive effect on the Correa cascade. We did not encounter any other study on clopidogrel in this regard. The results of our study suggest that clopidogrel has no favorable effect on GIM in patients using clopidogrel for an average of 2 years.

In our study, the incidence of atrophic gastritis was 16.6%, 35.2%, 19.2%, 29.3% in the control, clopidogrel, aspirin and NA-NSAD groups, respectively. The incidence of AG was higher in the drug groups compared to the control group. The presence of AG was significantly different between the groups ($p=0.003$). AG was observed more in clopidogrel and NA-NSAID groups than in control and ASA groups (clopidogrel; $p=0.004$, $p=0.009$, NA-NSAID; $p=0.009$, $p=0.019$). AG is more common in the elderly and may occur as a long-term consequence of HP infection or as a result of autoimmune gastritis.

Since clopidogrel and NA-NSAID groups were older than the other groups in our study population, AG may have been observed more in these groups. Nevertheless, AG is associated with an increased risk of gastric cancer.[24] On the other hand, patients using clopidogrel and NA-NSAIDs may be selected for endoscopic follow-up according to the intragastric distribution of gastric atrophy and other risk factors.[25] No difference was observed between the groups in terms of neutrophil activity, chronic inflammation, dysplasia, gastric cancer and esophageal cancer.

The total incidence of gastric cancer was 0.9%, 5.7%, 3.5%, 2.2% in the control, clopidogrel, ASA, NA-NSAID groups, respectively, and there was no statistically significant difference between the groups. However, more cancer was observed in the drug group compared to the control group. Important point for this may be related to the discovery of anticoagulant-induced GI bleeding or anemia and pre-existing malignancies.[26]

There are some limitations in this current study. We could not standardize the groups in terms of other cancer related factors (Epstein-Barr virus infection, genetic susceptibility, dietary habits, alcohol and smoking) that increase the risk of GC other than HP. In addition, especially elderly patients may have used more NSAIDs outside the hospital records because they can easily access and use non-prescription NSAIDs. Moreover, relatively small study population, the retrospective design, low drug duration, being an single centered study and not to excluding patients with gastrointestinal bleeding are other limitations of the study.

## CONCLUSION

In our study, no preventive effects of clopidogrel, aspirin and other nonsteroidal anti-inflammatory drugs on gastric premalign lesions were observed. In addition, all these drugs were associated with severe gastric lesions. Considering these gastrointestinal side effects, new evidence is needed for the use of these drugs as gastric cancer preventive agents in well-standardized studies with larger numbers and longer duration of observation.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Samsun Training and Research Hospital Non-interventional Clinical Research Ethics Committee (Date: 30.10.2019, Decision No: 2019/1/9).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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