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Clinical use of low-dose aspirin for elders and sensitive subjects

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Abstract

The use of low-dose aspirin (LDA) has been a common preventive measure to reduce the risk of cardiovascular events. This is attributed to aspirin's ability to inhibit platelet activation. On the other hand, the use of LDA in human subjects has been associated with the development of gastrointestinal injuries like ulcer and bleeding, especially for those sensitive subjects such as elder human subjects. This opinion review will summarize the recent clinical reports regarding the use of LDA and the development of gastrointestinal conditions in China. Based on these reports, it seems that the use of LDA is commonly associated with gastrointestinal injuries, and stopping its use leads to recovery in elderly subjects. Therefore, we would like to suggest that gastroduodenal health and conditions should be seriously taken into consideration when LDA is recommended to the elderly, or other alternative means to reduce the risk of cardiovascular events such as nutritional interventions should be suggested.

Key words: Low-dose aspirin; Gastrointestinal damages; Upper gastrointestinal bleeding; Human subjects; Chinese elders

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Core tip: Low-dose aspirin (LDA) has been used widely for prevention of cardiovascular and cerebrovascular diseases. This is attributed to the role of aspirin in the inhibition of cyclooxygenases to prevent or reduce thrombosis. However, the use of LDA has been associated with gastrointestinal injuries such as ulcer and bleeding in sensitive human subjects. This opinion review summarized recent Chinese publications showing gastrointestinal damages in Chinese elders using LDA. We argue that cautions should be taken when LDA is recommended, and alternative means should be considered for those elderly and sensitive subjects in China.



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ASPIRIN STRUCTURE AND FUNCTIONAL MECHANISMS

Aspirin, acetylsalicylic acid, is one of the most commonly used medicines, and is a nonsteroidal anti-inflammatory drug (NSAID) with an estimated 40000 metric tons produced per year globally^[1]. NSAIDs, including aspirin, inhibit the activities of cyclooxygenases (COXs) to prevent the formation of prostanoids from arachidonic acid^[1]. The prostanoids prostaglandin (PG) E₂ and thromboxane A₂ (TXA₂) are responsible for the inhibition of gastric acid secretion and the increase in platelet aggregation, respectively^[2,3]. PGE₂ production is needed to inhibit histamine-induced hydrochloric acid secretion, which protects the stomach from the acid damage^[1]. The activated platelets synthesize TXA₂, which is a potent platelet aggregator and induces thrombosis^[4].

Aspirin covalently acetylates serine residues in the active site of COX-1 (Ser 530)^[5] and COX-2 (Ser 516)^[6], leading to the steric hindrance of the enzymatic reaction to proceed. The irreversible modification through acetylation of COX allows aspirin, with only a 20 min half-life, to be an effective antiplatelet drug throughout the life cycle of the platelets^[7]. Based on a meta-analysis containing 287 studies, low-dose aspirin (LDA) at 75-150 mg daily as an antiplatelet regimen reduces risk of myocardial infarction and stroke in high risk patients^[8]. Additional benefits can be seen when a second antiplatelet drug is combined with LDA^[8].

Since COX-2 is inducible, in addition to the production of PGE₂ and TXA₂, COX-1 plays a critical role in the production of other eicosanoids, which are thought to be involved in the cross-talks between the platelets and other cells in the body^[4]. Therefore, the use of aspirin for the reduction of thrombosis may have other effects in the body.

Different doses of aspirin have been used for primary and secondary prevention of cardiovascular and cerebrovascular diseases^[9-11]. A collaborative meta-analysis has shown that low (75-150 mg/d) and medium (160-325 mg/d) doses of aspirin have similar antithrombotic effects as high-doses (500-1500 mg/d) of aspirin^[8]. However, high-doses of aspirin are more gastro toxic^[8]. The effects of low (100 mg/d) and high (1000 mg/d) doses of aspirin in patients having received percutaneous transluminal angioplasty have been evaluated after the treatments for 24 mo^[12]. Fewer patients in the low-dose group withdraw from the study than that in the high-dose group. In them, the number of patients with gastrointestinal symptoms in the low group is also less than that in the high-dose group^[12]. In addition, compared with relatively high-dose of aspirin (287 mg/d), LDA (30 mg/d) produced less gastric discomfort and bleeding after the treatments for 2.6 years^[13].

ASSOCIATION OF UPPER GASTROINTESTINAL DISEASES WITH THE USE OF LDA

Parietal cells of the stomach produce and secrete hydrochloric acid after being stimulated by histamine, gastrin, and acetylcholine in response to neuronal and hormonal stimuli^[14]. Upon stimulation, the intracellular H⁺/K⁺-ATPase moves to the cell membrane of parietal cells, where it pumps out H⁺ in exchange for K⁺. The excessive production of acid leads to the development of gastroesophageal reflux disease and gastric and duodenal ulceration^[14]. Drugs that interfere with these pathways have been used to attenuate the acid-induced diseases^[14].

The use of aspirin to prevent the development of cardiovascular disease has been associated with the development of gastrointestinal ulcer in human subjects^[15]. On the other hand, if a proton pump inhibitor (PPI) is used to reduce the acid release in the presence of aspirin, the incidence of upper gastrointestinal ulcer development is significantly reduced^[15], demonstrating the role of excessive acid production during the use of aspirin. The score of gastric mucosal injury in patients who stopped the use of LDA (observed *via* endoscopy) was lower than those who did not stop^[16]. In 2002, guidelines from the American Heart Association indicated that LDA increases risk for gastrointestinal bleeding and did not recommend LDA in persons with this risk^[17].

Gastroduodenal ulcers associated with the use of aspirin or NSAID contribute to 30%-35% of hematemesis^[18], while doses of daily aspirin use between 75 mg to 300 mg may be protective against vascular diseases. They nevertheless cause gastric bleeding, indicating that these doses may not be safe^[19]. In a single center study of patients taking NSAIDs after hip and knee arthroplasty, 4.5% of patients developed upper gastrointestinal bleeding^[20]. A single maximal dose of NSAIDs that preferentially inhibit COX-1, but not COX-2, in pregnant rats and rabbits, caused septal defects in the fetus^[21]. It seems that the eradication of *helicobacter pylori* (*H. pylori*) is helpful in reducing aspirin-induced (300 mg/d) injury^[22]. The combined use of anticoagulant warfarin (an inhibitor of vitamin K epoxide reductase) and aspirin (325 mg/d) significantly increases upper gastrointestinal bleeding, suggesting that cautions should be taken when aspirin is used in combination with other anticoagulation therapies^[23].

In China, aspirin has been widely used in a variety of diseases, especially in the treatment and prevention of coronary artery disease. Recently, multiple publications report upper gastrointestinal injuries occurring with the use of aspirin, as shown in Tables 1 and 2.

Table 1 summarizes the factors associated with the development of gastrointestinal injuries. Accordingly, the use of LDA increases the risk of upper gastrointestinal injuries such as erosion, ulcer, and ulcer bleeding. Factors attributable to the increased risk of upper gastrointestinal complications during the use of LDA include advanced age (age > 70 years), history of ulcer or upper gastrointestinal bleeding, and *H. pylori* infection.

Table 2 shows the reduction of gastrointestinal events when LDA is not used and stopped. In addition, discontinuing LDA use effectively stopped the bleeding associated with the use of LDA. The data shown here indicate that the use of LDA in elderly Chinese should be considered seriously.

EFFECTS OF ASPIRIN USE ON THE ELDERLY

Elevation of gastric mucosal injury and reduction of the expression level of vascular endothelial growth factor in gastric mucosa biopsy samples of 136 subjects at age 60 to 80 years taking 100 mg/d of aspirin have been observed in comparison with that of 48 age-matched healthy subjects^[24]. The results suggest that the elderly are sensitive to aspirin-induced gastric injury. Based on the data collected in a prospective study containing 103 participants (40- to 86-years-old) taking LDA (enteric-coated 100 mg/d), the incidence of aspirin-induced gastric ulcers was calculated to be 0.97% for Japanese patients^[25]. Following transnasal endoscopy in patients taking LDA for the treatment of ischemic heart disease, 20.0% and 10.7% developed ulcer and hemorrhagic gastritis, respectively^[26].

Recently, it has been shown that daily aspirin use does not help survival in healthy elderly individuals (> 70-years-old), where the primary end points were death, dementia, or persistent physical disability^[27]. On the other hand, the aspirin group had a higher rate for major hemorrhage than the placebo control group^[27].

There are geographic differences on the prevalence of gastroduodenal ulcer following LDA use^[28], indicating that certain populations may be more sensitive to aspirin's side effects. Interestingly, in elderly Japanese, advanced age (~70-years-old) seems to be not linked to an increase of severity of the gastroduodenal ulcer with the use of only LDA^[29]. In addition, it was shown that the use of aspirin in white and black men is inversely associated with prostate cancer mortality^[30]. In addition, it is worth noting that the effect of aspirin on the prevention of cardiovascular events depends on body weight^[31]. LDA (75 to 100 mg/d) appears to be ineffective when the body weight of subjects is above 70 kg^[32].

USE OF ASPIRIN IN THE PRESENT OF OTHER DRUGS

The combination of aspirin and acetaminophen (also known as paracetamol), a common drug for the treatment of pain and fever, has been shown to increase gastric injury and ulcer development in a randomized and double-blind study, demonstrating a potential interaction between these two drugs^[33].

On the other hand, rabeprazole, a PPI at 20 mg/d only attenuated the heart-burn phenotype by 52%, but not others associated with the LDA use (80 mg/d) in a double-blind, placebo-controlled randomized trial including 150 subjects^[34]. A clinical trial involving 1045 patients with osteoarthritis indicated that the combination of LDA with celecoxib (a specific COX-2 inhibitor belonging to NSAID) or with naproxen (a

Table 1 Use of LDA and upper gastrointestinal damages (ulcer and bleeding) in Chinese elders

Study Type (dose)	Subject number (M/F)	Age in yr	Study duration	Inclusion/Exclusion criteria	Conclusion	Title
Observations (75-100 mg/d)	80 (58/22)	50-70	1 yr	Coronary artery disease with the use of LDA, and then follow-up for 1 yr	Gastric ulcer/duodenum ulcer (%) 37.5/28.8	Gastrointestinal mucosal injury of long-time aspirin use in patients with coronary artery disease ^[41]
Cross sectional comparison	39 (21/17)	54-80	01/2016-01/2017. NA	Ulcer	Aspirin use is associated with more bleeding	Clinical analysis of gastrointestinal bleeding with LDA in elderly patients ^[42]
The association of upper GI bleeding and aspirin use	(60/27)	> 55	05/2013-05/2015	Upper GI bleeding and whether used aspirin 1 wk before	Aspirin group has higher gastroduodenal ulcer rate	Study of upper gastrointestinal bleeding in elderly patients treated with aspirin ^[43]
The association of length of aspirin use and upper GI damages	120 (75/45)	< 65	01/2009-01/2014	LDS use. < 4 mo, 4-12 mo, and > 12 mo	More than 4 mo use of LDA is associated with upper gastrointestinal ulcer	Gastroscopy analysis of upper gastrointestinal damage in patients using aspirin with different periods ^[44]
Aspirin/Clopidogrel and upper GI bleeding in PCI patients in 1 yr	343 PCI (244/99)	31-79	06/2016-06/2018	PCI, and use of aspirin 100 mg/Clopidogrel 75 mg	7% bleeding rate in 1 yr	Risk evaluations of upper gastrointestinal bleeding from aspirin with clopidogrel in patients undergoing percutaneous coronary intervention after 1 yr ^[45]
The role of aspirin in upper GI bleeding	40 (29/11)	> 60	2012-2014	Upper GI bleeding with or without LDA use	LDA is associated with higher gastroduodenal ulcer	Clinical study of upper gastrointestinal bleeding in elderly people treated with aspirin ^[46]
The association of long-term LDA (> 2 mo) and upper GI bleeding.	84 (37/47)	47-69	Not specified	Cardiovascular patients using LDA for the treatment, not using PPI for the experimental group, no bleeding for the control group	More gastroduodenal ulcer in bleeding group (47.6%) than the control group (9.5%)	42 cases of upper gastrointestinal bleeding with the use of LDA ^[47]

LDA: Low-dose aspirin; M: Male; F: Female; PCI: Percutaneous coronary intervention; GI: Gastrointestinal.

NSAID) plus lansoprazole (a PPI) have similar rates of gastroduodenal ulceration^[35]. However, a meta-analysis including nine studies and 6382 subjects concluded that the clinical use of PPIs is effective in reducing symptoms of gastroduodenal ulceration^[36]. This seems to justify the use of both aspirin and PPIs at the same time to reduce the risk of gastric ulcer^[37].

CONCLUSION

If the use of LDA does not increase the survival of elder individuals^[27], extreme caution should be used when recommending its use in the elderly. How to balance the harm and benefit will always be a challenge for clinicians, particularly when recommending aspirin use for the elderly^[38]. The use of a selective COX-1 inhibitor, such as ASP6537, which is more potent than aspirin, may be a solution for gastric mucosa injury^[39]. Certainly, one should consider whether aspirin should be prescribed for elderly patients and patients with a history of gastric ulcers or *H. pylori* bacterial infection. The choice of drugs would be dependent upon both the individual's cardiovascular and GI risks. Alternatively, nutritional interventions such as the use of

Table 2 Non-use of aspirin and incidence of upper gastrointestinal bleeding

Study type (dose)	Subject number (M/F)	Age in yr	Study duration	Inclusion/Exclusion criteria	Conclusion	Title
Comparison of using or non-using LDA in bleeding in elders	76 (40/36)	> 65	10/2015-11/2017	Gastric ulcer	45% LDA users with upper gastrointestinal bleeding vs only 8% without the use	Clinical study of gastrointestinal bleeding in elderly patients with the use of LDA ^[48]
Interventional study of LDA in the upper GI bleeding	112 (71/41)	Mean 62.3	03/2010-05/2012	LDA use (100 mg) and upper GI bleeding	Stop the use of LDA, but use other drug lead stop of bleeding 69/112 in 3 d	Clinical analysis of upper gastrointestinal bleeding from aspirin use ^[49]

LDA: low-dose aspirin; M: Male; F: Female; GI: Gastrointestinal.

fish oils rich in eicosapentaenoic acid should be considered, which has been shown to benefit patients with high risk of cardiovascular events in a long-term study^[40]. At least, more studies should be done to assess the risk/benefit ratios, especially for elderly patients.

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