Aspirin prophylaxis and the prevalence of anaemia

ROBERT HAMMERMAN-ROZENBERG, JEREMY M. JACOBS, DANIEL AZOULAY, JOCHANAN STESSMAN

Department of Geriatrics and Rehabilitation, Hadassah Hebrew University Medical Center, Mount Scopus, Jerusalem, Israel

Address correspondence to: J. M. Jacobs. Tel: (+) 972 2 5844473. Fax: (+) 972 2 5810918. Email: jeremyj@clalit.org.il

Abstract

Background: anaemia and vascular disease are both common amongst the elderly and frequently co-exist. Whilst a consensus exists concerning the benefits of low-dose aspirin in reducing risk from atheromatous disease, nonetheless concerns arise in view of its harmful effect on gastric mucosa and its influence upon haemostasis, with the possibility of subsequent gastrointestinal bleeding. This study examined the relationship between chronic low-dose aspirin therapy and the presence of anaemia.

Setting: a cross-sectional study of a representative cohort of 464 community-dwelling subjects aged 77 years.

Methods: Subjects underwent comprehensive assessment of psychosocial, functional, medical and laboratory variables. In accordance with the World Health Organization criteria, anaemia was defined as less than 13 g/dl for men and 12 g/dl for women.

Results: chronic low-dose aspirin use was found amongst 29% of the 227 women and 38% of the 237 males (P = 0.026). Aspirin use was significantly associated with hypertension, ischaemic heart disease and diabetes mellitus. Anaemia was 42% less common among aspirin users, a statistically robust finding (OR 2.44, 95%CI 1.28–4.66) according to logistic regression analysis which included the confounding variables of gender, education, diabetes, hypertension, heart disease, peptic diseases, antipeptic therapy and smoking. Similarly, no association was observed between aspirin use and reduced serum iron or iron saturation, reduced mean corpuscular haemoglobin or mean corpuscular volume.

Conclusions: chronic low-dose aspirin use amongst an elderly cohort was associated with increased likelihood of normal haemoglobin.

Keywords: anaemia, aspirin, cohort, elderly

Introduction

The presence of anaemia amongst the elderly significantly diminishes longevity [1] and function [2, 3]. Furthermore, the impact of anaemia is heightened by the co-existence of vascular disease, whether acute [4] or chronic [5–7]. The interaction of anaemia and vascular disease invites special evaluation of the role of aspirin, a staple in the therapy of arterial disease. On the one hand, aspirin has proven benefit in treating all types of atheromatous disease, including coronary artery, cerebrovascular and peripheral arterial disease. Yet on the other hand, it is known to damage the gastrointestinal mucosa and impede haemostasis, threatening an increased danger of bleeding and subsequent anaemia.

The possible correlation between aspirin and anaemia was investigated using cross-sectional data analysis amongst an age homogenous, thoroughly delineated cohort of older subjects, taken from the ongoing Jerusalem Longitudinal Study.

Materials and methods

The Jerusalem Longitudinal Study follows Jerusalem residents born in 1920–1 and has characterised subjects comprehensively through interview and physical and laboratory examination at both age 70 and 77 years. At both ages, subjects were studied in two sessions. In the first visit, occupational therapist collected information regarding personal history, socioeconomic status, functional level, activities and health habits and services including medication use. In the second stage, a physician took a detailed medical history, including review of systems, and physical examination was performed including neurological, cognitive and affective testing. At this visit, blood was also sent for standard clinical, laboratory testing. The present study utilises cross-sectional data collected at age of 77 years from the study cohort.

Aspirin use was defined as regular, daily use of the drug. Anaemia was defined according to the World Health
Organization Criteria as haemoglobin of less than 13 g/dl for men and 12 g/dl for women. Subjects were determined to suffer from a specific diagnosis when listed in the medical history or when conclusive evidence was uncovered in the study examination. Cigarette smokers were defined as subjects who had smoked regularly at any time. In the Jerusalem cohort, this definition correlated with increased mortality [8].

Cross-sectional analysis was performed on data from 464 subjects aged 77 years. Differences between categorical variables were determined by chi-square analysis. Logistic regression analysis was used to measure the significance of associations in the presence of multiple variables, and the regression model included those variables identified by univariate analysis with \( P < 0.1 \).

**Results**

At age of 77 years, low-dose regular aspirin was in use by 65 (29%) of 227 women and 91 (38%) of 237 men, with a significant gender difference \( (P = 0.026) \). The overwhelming majority of subjects chronically using aspirin took 100 mg daily. The average haemoglobin concentration among aspirin versus non-aspirin users was 13.99 versus 13.60 g/dl \( (P = 0.0037) \) for men and women together, 14.42 versus 14.07 g/dl \( (P = 0.068) \) for men alone and 13.30 versus 13.18 g/dl \( (P = 0.404) \) for women. The average MCH for aspirin versus non-aspirin users was 29.48 versus 29.52 \( (P = 0.82) \) for men and women together, 29.45 versus 29.58 \( (P = 0.844) \) among men and 29.63 versus 29.57 \( (s = 0.822) \) among women. Similarly, no significant differences were found for MCV between aspirin versus non-aspirin users (88.95 versus 88.70, \( P = 0.682) \).

The relative prevalence of important study findings among subjects according to their use of aspirin is presented in Table 1. For the most part, these findings confirm the indications for which primary or secondary aspirin prophylaxis is warranted. Peptic disease was expectedly less prevalent among subjects taking aspirin. Surprisingly, there was a 42% diminution in the prevalence of anaemia among aspirin users.

A logistic regression was used to test the confounding effects of co-morbid disease on the relation between aspirin use and anaemia. The dependent variable was a normal haemoglobin level as defined by World Health Organization, and the independent variables included in the model were gender, completion of 12 years of education, aspirin use, diabetes, hypertension, coronary artery disease, peptic disease, use of agents to treat peptic disease (H2 antagonists, proton pump inhibitors or sucralfate) and cigarette smoking. In this analysis, aspirin use significantly correlated with normal haemoglobin levels (OR 2.44, 95% CI 1.28, 4.66).

The correlation of aspirin to decreased iron concentration, <60 mg/dl, was also examined to further delineate the relation between aspirin use and bleeding. The prevalence of diminished serum iron levels was nearly identical among aspirin users and non-users, 19 versus 18%. Analysing this relationship in a logistic regression, accounting for gender and the presence of peptic disease, coronary disease, hypertension and diabetes also revealed no association between aspirin use and diminished serum iron. Similarly, there was no correlation between aspirin use and decreased serum iron saturation.

**Discussion**

The target population for aspirin prophylaxis is growing in size [9], in keeping with the evidence that the regular use of aspirin prevents or reduces cardiovascular events in individuals at risk [10, 11]. As might be expected, the controversy over such intervention has grown accordingly [12, 13]. Even well-established consensus recommendations for aspirin prophylaxis of cardiovascular disease would dictate almost universal treatment at age 70 [14]. However, the suggested advantages of this step have been mitigated by concern over treatment side-effects, primary among them bleeding [6, 14–16].

Whereas the direct effects of aspirin on the gastrointestinal mucosa and the direct danger of bleeding have been analysed thoroughly [15, 16], less attention has been paid to the effect on hematological balance of long-term, regular aspirin use in a setting of careful supervision. In a randomised, double blind study which was performed on 400 subjects over 70 [17], the study group received 100 mg daily of aspirin for a year while controls received a placebo. Not only were there six clinically evident bleeding episodes among aspirin users as opposed to none among controls but also

**Table 1. Prevalence of characteristics among aspirin users and non-users at age of 77 years**

<table>
<thead>
<tr>
<th>Finding</th>
<th>% of ASA users</th>
<th>% of non-users</th>
<th>( P )</th>
<th>% of ASA users</th>
<th>% of non-users</th>
<th>( P )</th>
<th>% of ASA users</th>
<th>% of non-users</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twelve years of education</td>
<td>59</td>
<td>53.2</td>
<td>0.241</td>
<td>53.8</td>
<td>51.8</td>
<td>0.786</td>
<td>62.6</td>
<td>54.8</td>
<td>0.234</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>53.2</td>
<td>25.3</td>
<td>&lt;0.0001</td>
<td>50.8</td>
<td>24.7</td>
<td>0.001</td>
<td>55</td>
<td>26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59.6</td>
<td>52.3</td>
<td>0.133</td>
<td>64.6</td>
<td>67.3</td>
<td>0.700</td>
<td>56</td>
<td>35.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30.8</td>
<td>14.3</td>
<td>&lt;0.0001</td>
<td>26.2</td>
<td>14.8</td>
<td>0.045</td>
<td>34.1</td>
<td>13.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>51.7</td>
<td>36</td>
<td>0.002</td>
<td>37.8</td>
<td>24</td>
<td>0.044</td>
<td>61.4</td>
<td>49</td>
<td>0.066</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>25</td>
<td>23.7</td>
<td>0.757</td>
<td>29.2</td>
<td>24.7</td>
<td>0.481</td>
<td>22</td>
<td>22.6</td>
<td>0.911</td>
</tr>
<tr>
<td>Renal disease</td>
<td>9</td>
<td>3.6</td>
<td>0.015</td>
<td>3.1</td>
<td>1.8</td>
<td>0.570</td>
<td>13.2</td>
<td>5.5</td>
<td>0.038</td>
</tr>
<tr>
<td>Peptic disease</td>
<td>18.6</td>
<td>24.4</td>
<td>0.160</td>
<td>15.4</td>
<td>25.3</td>
<td>0.105</td>
<td>20.9</td>
<td>23.3</td>
<td>0.665</td>
</tr>
<tr>
<td>Anaemia</td>
<td>11.5</td>
<td>19.8</td>
<td>0.025</td>
<td>7.7</td>
<td>18.5</td>
<td>0.041</td>
<td>14.3</td>
<td>21.2</td>
<td>0.181</td>
</tr>
</tbody>
</table>

ASA, aspirin.
haemoglobin decreased significantly more with aspirin use, 0.33 versus 0.11 g/dl. However, the strength of this study is also its weakness; as a randomised, controlled trial, no special interventions to accommodate aspirin therapy were permitted. These findings, however, are echoed in a follow-up study of 3044 patients enrolled in trials treating congestive heart failure [7]. In this setting, the use of the target drug, losartan, was randomised, but aspirin use was revealed to physicians, and still, mean haemoglobin concentrations were 0.2 g/dl lower among aspirin users, 13.9 versus 14.1 g/dl. This difference was statistically significant and is identical to that found in the controlled study. The authors add that it is unlikely that such a small difference would be clinically relevant. Other studies have also found aspirin use to be associated with decreased ferritin levels, indicating depleted iron stores [18, 19].

The finding in our cohort of lower prevalence of anaemia among aspirin users defies all expectations and contravenes prevailing wisdom. The statistical significance of this difference, however, is sufficiently large to warrant serious consideration. Aspirin users in this study were less likely to have peptic disease, reflecting the caution of their physicians. However, in a regression including peptic disease as an independent variable, the association between aspirin use and normal haemoglobin levels remained highly significant. It is possible that physicians withheld aspirin from anaemic subjects even without peptic disease, but it is unlikely that this practice, which finds no support in clinical guidelines [13, 14], was common enough to influence the overall prevalence of anaemia. The possibility that subjects using aspirin are those who seek regular medical attention and thereby are more likely to receive therapy for anaemia must be addressed. Israeli citizens enjoy government-funded, universal access to medical care, so availability of care is not an issue. Also, aspirin users were only negligibly more likely to have attended 12 years of education so that this measure of awareness of health concerns is not likely to have a significant impact on the prevalence of anaemia. Furthermore, education was an independent variable in the logistic regression.

Of interest are the findings of a recent study, which showed chronic use of aspirin to be associated with a significantly lower risk of gastrointestinal bleeding [20]. The tendency of aspirin users to suffer gastrointestinal bleeding may also be partially offset in this cohort by the use of gastroprotective agents. Although H2 antagonists do not prevent significant gastrointestinal bleeding in users of non-steroidal anti-inflammatory agents [21], they have been shown to prevent some NSAID-induced ulcers [22] and may be more effective in countering the milder gastrointestinal damage of low-dose aspirin [23]. Furthermore, as revealed in a recent exhaustive epidemiologic review of anaemia among the elderly in the United States [24], iron deficiency is not the most common form of anaemia. Both anaemia of chronic inflammation and unexplained anaemia are twice as prevalent as iron deficiency anaemia. In fact, low-dose aspirin has been postulated to diminish cytokine release and its inflammatory consequences [19] and may on balance prevent anaemia even while promoting bleeding to a small degree. Indeed, the absence of diminished iron levels and saturation, as well as the normal range of MCH and MCV, would certainly support a dampening in the suppression of erythropoietic haemoglobin synthesis due to chronic disease.

In light of their surprising and somewhat counterintuitive nature, the findings in this study must be interpreted very cautiously. Limitations to the study include the absence of ferritin levels, which would have provided a better indication of iron stores than iron levels or iron saturation. However, ferritin levels also rise in the presence of inflammation and must be understood in context of reduced haemoglobin concentration [19]. Because of the postulated impact of low-dose aspirin on inflammation, the absence of a direct measure of inflammatory response is a further handicap in interpreting our results. Finally, longitudinal data comparing the changes in haemoglobin during aspirin administration would provide a more direct measure of the influence of low-dose aspirin on the prevalence of anaemia. These findings suggest that the fear of anaemia need not pre-empt the use of aspirin to prevent vascular incidents. In the future, the increasing use of proton pump inhibitors may even permit wider utilisation of aspirin therapy [25]. Now, however, these results already add an important consideration to the risk-benefit calculus of aspirin prophylaxis. In a clinical setting where physicians select which patients will receive aspirin and initiate treatment to avert bleeding complications, there may actually be haematological advantages for aspirin therapy.

Key points
- Anaemia and vascular disease commonly co-exist among the elderly.
- The role of chronic low-dose aspirin therapy in the pathogenesis of anaemia is unclear.
- Among an elderly cohort, chronic low-dose aspirin treatment was independently associated with significantly increased likelihood of normal haemoglobin.
- Possible reasons are discussed, including the potential dampening of chronic inflammation.

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Conflict of interest
There were no conflicts of interest involved in the undertaking of this study for any of the authors.

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