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Original Article

Effects of low-dose aspirin administration on cirrhosis-related thrombocytopenia: report of 26 cases

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Abstract: Background & Aims: Cirrhosis-related thrombocytopenia is explained mainly by hypersplenism and decreased thrombopoietin production. Alternatively, cirrhosis-related thrombophilia has also been suggested to contribute to thrombocytopenia via platelet overconsumption. Hence, anti-thrombotic therapy may increase circulating platelets in cirrhosis patients. To elucidate effects of aspirin administration, we performed the following retrospective study. Methods: Twenty-six patients (17 men and 9 women; 73±9 yr) with cirrhosis-related thrombocytopenia (platelets <130×10^9/L), who had received low-dose aspirin (LDA) as a therapy for thrombotic disorders, were selected. They were divided into three groups according to the presence or absence of splenomegaly and hypoalbuminemia. Outcomes were assessed at the end of administration in cases with 0.5-6 months administration and at the nearest point from 6 months of administration in cases with >6 months administration, as either "improved" (platelets ≥130×10^9/L or ≥10% greater than initial count) or "unimproved". Results: LDA improved the platelet count in 9 patients (34.6%) and did not improve the platelet count in 17 patients (65.4%). The pre-administration platelet count did not differ between the improved and unimproved patients. Recovery of platelet count was closely associated with the absence of splenomegaly (P=0.046). In contrast to the 100% efficacy in patients without splenomegaly and hypoalbuminemia (4/4 improved; P=0.0055), all patients with both splenomegaly and hypoalbuminemia had an unimproved platelet count (0/5 improved) and patients with either splenomegaly or hypoalbuminemia showed intermediate outcomes (5/17 improved). Conclusions: Aspirin administration may be a therapeutic option for cirrhosis-related thrombocytopenia, especially in patients without hypersplenism and hypoalbuminemia.

Keywords: Cirrhosis-related thrombocytopenia, aspirin, hypersplenism, thrombopoietin, platelet consumption

Introduction

Thrombocytopenia has been recognized as an important complication of cirrhosis for more than half a century [1-3]. Combined with decreased levels of coagulation factors, it induces hemorrhagic diathesis and serious hemorrhagic complications in patients with cirrhosis. Hence the circulating platelet count is not only a convenient index of disease severity of cirrhosis but also an important therapeutic target from the viewpoint of optimization of abnormal hemostatic condition in cirrhosis patients [4, 5].

Cirrhosis-related thrombocytopenia has been attributed to enhanced platelet pooling/sequestration and destruction in an enlarged spleen due to portal hypertension, and decreased synthesis of thrombopoietin (TPO), a key factor in platelet production-differentiation, in a cirrhotic liver [2, 3, 5-7]. In addition, we have suggested that platelet consumption due to thrombophilic complications of cirrhosis and platelet aggregation in diseased livers is the crucial third factor in cirrhosis-related thrombocytopenia [8, 9]. In cirrhosis patients, the circulating platelet count is determined by the triangular balance of platelet production, sequestration-destruction, and consumption. Correction of only one of the 3 factors is not sufficient as a treatment and cannot recover the platelet count as expected in some cases.

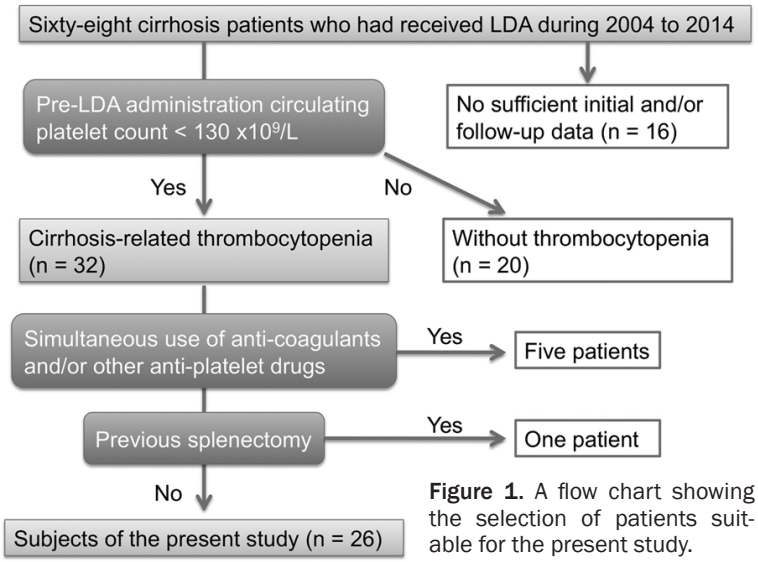

Figure 1. A flow chart showing the selection of patients suitable for the present study.

To date, however, platelet transfusion, splenectomy and TPO have been the sole methods used to control cirrhosis-related thrombocytopenia [5, 10]. In other words, no therapeutic strategy has been considered from the viewpoint of platelet consumption. Administration of anti-platelet drugs has been adopted to avoid excess platelet aggregation [11]. Thus it can potentially prevent platelet overconsumption, but has been recognized as a contraindication (relative or absolute) in cirrhosis patients with hemorrhagic diathesis [12-16]. Nevertheless, a number of cirrhosis patients receive anti-platelet drugs to treat cardiovascular disorders including coronary artery disease and arrhythmia. However, its effect on the circulating platelet count has never been a subject of scientific interest.

We conducted the present retrospective study to clarify the changes in the circulating platelet count in cirrhosis patients who received low-dose aspirin (LDA) administration.

Subjects and methods

Patients

A total of 68 cirrhosis patients received LDA (100 mg/day) administration during 2004 to 2014 at Takatsuki General Hospital, Chibune General Hospital, Akashi Medical Center and Kobe Asahi Hospital. Exclusion criteria were lack of sufficient initial and/or follow-up data, absence of thrombocytopenia (platelet count ≥130×10^9/L), simultaneous use of anti-coagulants and /or other anti-platelet drugs, and having undergone previous splenectomy (**Figure 1**). Twenty-six patients (17 men and 9 women; average age, 73±9 y.o.) with cirrhosis-related thrombocytopenia met the study criteria. The duration of LDA administration ranged from 0.5 to 120 months (median duration, 8 months).

The patients were divided into three groups on the basis of the presence or absence of splenomegaly (the long axis >10 cm) and hypoalbuminemia (serum albumin value <3.5 g/dL) before LDA administration as shown below.

Group 1: Patients without splenomegaly and hypoalbuminemia.

Group 2: Patients with either splenomegaly or hypoalbuminemia.

Group 3: Patients with both splenomegaly and hypoalbuminemia.

The clinical backgrounds of the patients in each group are shown in **Table 1**. As was expected, severity of cirrhosis estimated by platelet count and Child-Pugh classification intensified in order of Group 1, Group 2 and Group 3. All clinical and laboratory data were collected from hospital charts. Informed consent to research use of the data was obtained from every patient, and this study was approved by the ethical committee of Takatsuki General Hospital.

Definition of efficacy

Outcomes of LDA administration were assessed by the platelet count at the end of the therapy in patients with administration for 0.5-6 months, and by the platelet count at the nearest point to 6 months of administration in patients with administration of >6 months. The efficacy of LDA administration on the platelet count was defined as “improved” (platelet count recovered to ≥130×10^9/L, or increased by ≥10% of the initial count) or “unimproved” (not fulfilling the requirements for “improved”).

Table 1. Patients' clinical backgrounds

	Group 1 Splenomegaly (-) and Albumin ≥3.5 g/dL	Group 2 Splenomegaly (+) or Albumin <3.5 g/dL	Group 3 Splenomegaly (+) and Albumin <3.5 g/dL	*P*-value
No. of patients	4	17	5	
Sex (M/F)	4/0	9/8	4/1	0.153†
Age*	72±8	73±10	74±5	0.872‡
Platelet counts (×10^9/L)*	109±23	85±23	56±12	0.007‡
Child-Pugh classification				0.016†
Grade A	3	8	0	
Grade B	1	9	3	
Grade C	0	0	2	
Cause of cirrhosis				0.095†
HBV	0	1	0	
HCV	0	7	4	
Alcoholic	3	7	0	
NAFLD	0	2	1	
Others	1	0	0	
Reasons for LDA				0.541†
Cerebral infarction	0	6	3	
Coronary artery disease	1	5	1	
Retinopathy	1	3	0	
Portal vein thrombosis	0	1	1	
Arteriosclerotic obliteration	1	1	0	
Others	1	1	0	

*Data shown as mean ± standard deviation; †Chi-square test; ‡Kruskal-Wallis test.

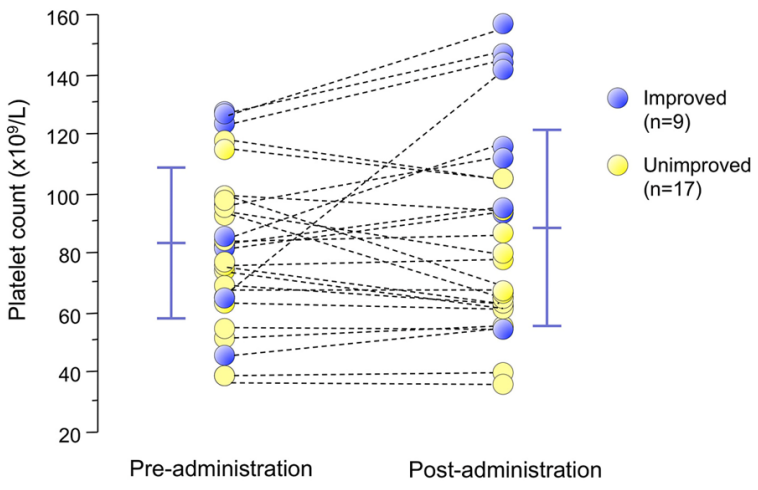

Figure 2. Transition of platelet counts by LDA administration. The horizontal bars indicate averages and standard deviations. The post-administration platelet counts (87±34 ×10^9/L) was greater than the pre-administration counts (83±26 ×10^9/L), but the difference was statistically not significant (Student's *t*-test).

Liver histology & immunohistochemistry

From two of 26 patients (one each of Group 2 and Group 3 patients; serum albumin was 3.9 g/dL and 2.7 g/dL, respectively, and both had splenomegaly), liver biopsies were obtained before LDA administration. The formalin-fixed paraffin-embedded liver tissues were examined histologically by hematoxylin-eosin stain and Azan-Mallory stain, and also immunohistochemically by using anti-CD41, a representative platelet marker.

Statistical analyses

We adopted the chi-square test for contingency table analysis. Concerning continuous variables, Kruskal-Wallis test was used for three groups (Groups 1, 2 and 3) comparison, and Student's t-test was used for comparison between "improved" and "unimproved" patients. A *P*-value of <0.05 was considered to indicate statistical significance. These statistical analyses were performed with

Table 2. Efficacy of LDA administration in individual patient groups

	Group 1 Splenomegaly (-) and Albumin ≥3.5 g/dL	Group 2 Splenomegaly (+) or Albumin <3.5 g/dL	Group 3 Splenomegaly (+) and Albumin <3.5 g/dL
Improved	4 (100%)	5 (29.4%)	0 (0%)
Unimproved	0 (0%)	12 (70.6%)	5 (100%)

P=0.0055 (Chi-square test).

Table 3. Differences in pre-administration conditions between improved and unimproved patients

	Improved (n=9)	Unimproved (n=17)	*P*-value
Platelet count ($\times 10^9$/L)	94±29	77±24	0.153*
Splenomegaly (-/+)	6/3	4/13	0.046†
Albumin (g/dL)	3.9±0.6	3.4±0.7	0.059*
Child-Pugh class (Grade A/B/C)	4/5/0	7/8/2	0.560†

*Student's *t*-test; †Chi-square test.

StatView version 4.0 (Abacus Concepts, Berkeley, CA).

Results

Efficacy of LDA administration

The platelet count of the 26 patients with cirrhosis-related thrombocytopenia tended to increase at post-administration (87±34 $\times 10^9$/L) compared to pre-administration (83±26 $\times 10^9$/L) of LDA although the difference was not statistically significant (**Figure 2**). The platelet count "improved" in 9 patients (34.6%) and was "unimproved" in 17 patients (65.4%) (**Table 2**). In contrast to the 100% efficacy in Group 1, all patients in Group 3 had an "unimproved" platelet count, while Group 2 showed an intermediate outcome (5/17 improved).

Irrespective of the efficacy, new thrombotic events did not occur during LDA administration in any patient.

*Relationship between efficacy and pre-administration conditions (**Table 3**)*

The pre-administration platelet count did not differ between the improved and unimproved patients. Recovery of platelet count was closely associated with the absence of splenomegaly (P=0.046). The serum albumin level tended to be higher in the improved patients than in the unimproved patients (P=0.059). Child-Pugh grade was not related to the efficacy of LDA administration.

Platelet aggregation in liver tissues

The liver biopsy specimens definitely showed histological features of cirrhosis (**Figure 3**). In addition, CD41 immunohistochemistry revealed presence of platelet aggregates in the hepatic sinusoids (**Figure 3C**). Platelet counts of the two patients before LDA administration were 39×10^9/L and 52×10^9/L, and their platelet counts were "unimproved" after LDA administration (40×10^9/L and 56×10^9/L, respectively).

Adverse effects of LDA administration

During LDA administration, no patient suffered from hemorrhagic complications of cirrhosis. Also, no patient complained of symptoms related to aspirin-induced gastrointestinal mucosal injury [17].

Discussion

Hemorrhagic complications of cirrhosis including esophageal varices and other types of gastrointestinal bleedings are associated with thrombocytopenia and determine the prognoses in some patients. Hepatologists had tried to overcome these life-threatening complications for a long time. Attention has been paid to the circulating platelet count, which is indeed one of the important prognostic factors in cirrhosis patients [4, 18].

Some patients with cirrhosis-related thrombocytopenia require an increase in the platelet count before receiving treatments such as invasive procedures and administration of drugs being known with a thrombocytopenic side effect [5, 19, 20]. Splenectomy is performed in many such cases, but sometimes the platelet count does not increase as expected [5, 21, 22]. Alternatively, TPO agonists, which promote platelet production from bone marrow, have been sought to treat cirrhosis-related thrombocytopenia. However, these trials revealed an increased risk of thrombotic events during TPO agonist administration [23-25]. A common mistake in the therapy failures was lack of insight

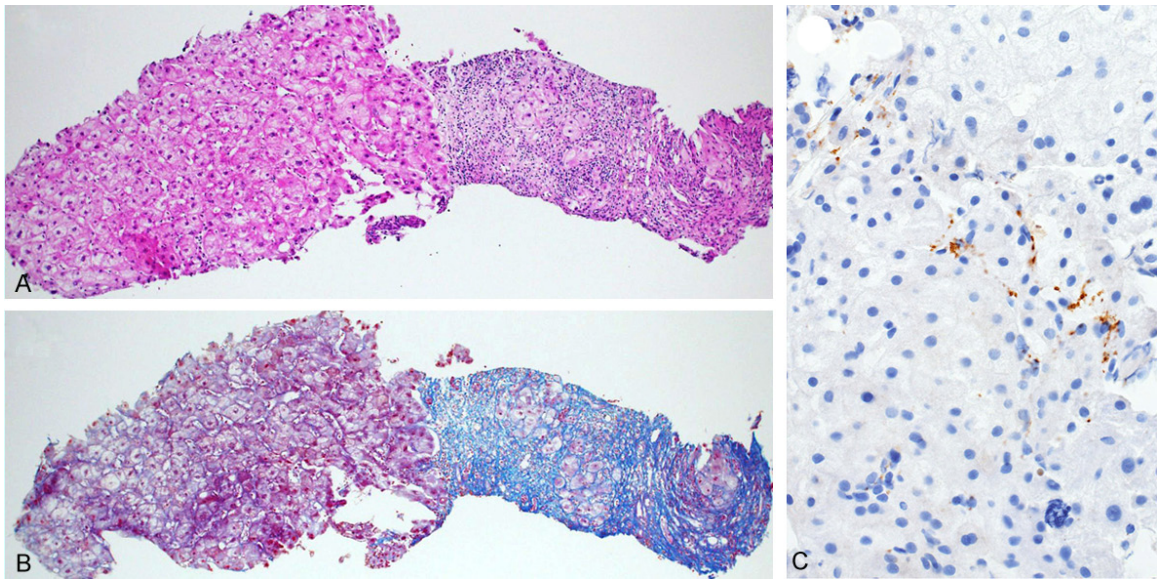

Figure 3. Histological and immunohistochemical findings of a liver biopsy obtained from a patient of Group 3 before LDA administration. A low-power view of (A) Hematoxylin-eosin stain and (B) Azan-Mallory stain. Histologically, the liver tissue shows severe fibrosis with destructed hepatic acinus structure, which can be diagnosed as being cirrhosis. (C) Immunoperoxidase staining with anti-CD41 (high-power view). Aggregated platelets (brown granules) are seen along hepatic sinusoids.

concerning augmented platelet consumption in cirrhosis patients [8, 9]. Favorable outcomes cannot be obtained with uniform methods lacking sufficient consideration of the triangular balance among decreased thrombopoiesis, exacerbated platelet sequestration/destruction and enhanced platelet consumption. Each patient has a thoroughly unique balance.

The results of the present study validated this concept. Although not statistically significant, the platelet count tended to recover with only administration of LDA, a classical anti-platelet drug. Moreover, LDA administration led to the best result on recovery of the platelet count in patients without both splenomegaly and hypoalbuminemia. The outcome could not be predicted by severity of cirrhosis simply estimated by Child-Pugh classification, suggesting theoretical linkages among splenomegaly, hypoalbuminemia and the efficacy of LDA on recovery of platelet count. Hypoalbuminemia can be used as a surrogate marker of decreased TPO production in cirrhosis patients [26]. Thus, platelet overconsumption, but neither hypersplenism nor TPO production deficiency, was a primary pathway of thrombocytopenia in such patients. Conversely, the platelet count of patients with both splenomegaly and hypoalbuminemia did not respond to LDA administration, suggesting that splenectomy or TPO agonists should be chosen to recover their platelet counts. A combination of the three treatment methods, i.e., splenectomy, TPO agonists and LDA administration, with a custom-made arrangement for each patient may lead to the best outcome. For example, simultaneous administration of LDA to a patient receiving TPO agonists may prevent thrombotic events, which are an adverse effect of TPO agonists, and gain a maximum efficacy in recovery of the platelet count.

Administration of anti-platelet drugs including LDA is expected to be an effective method not only for prevention of thrombotic complications of cirrhosis but also for therapies of cirrhosis-related thrombocytopenia. Because no patient showed hemorrhagic complications and gastrointestinal mucosal injury, which were predicted as adverse effects of LDA [12, 17], the safety of LDA was recognized to be at a sufficient level. Recently accumulating evidence suggests pleiotropic effects of LDA in cirrhosis patients. To date, many animal experiments and cohort studies have shown the efficacy of aspirin administration in prevention of fibrogenic process in chronic liver diseases and cirrhosis [27-30]. Suppression of platelet accumulation in diseased livers is suggested to be a possible

mechanism [21, 31-33]. This hypothesis is concordant with our previous pathologic observations and with the classical 'parenchymal extinction' theory proposed by Wanless et al [8, 9, 34-36]. Moreover, the suppressive effect of long-term aspirin administration on hepatocarcinogenesis has been reported [28]. Preventive LDA administration to patients with cirrhosis (or precirrhosis) before suffering from thrombocytopenia, thrombotic complications or hepatocellular carcinoma, may improve their prognosis.

Of 26 cases, two received liver biopsy before LDA administration and were examined histologically and immunohistochemically. Although both patients were categorized to "unimproved", platelet aggregation in hepatic sinusoids was seen in both of the liver tissue specimens. This indicated that platelet aggregation occurred in various degrees in every cirrhotic liver irrespective of patient's background conditions, including the circulating platelet count and presence or absence of splenomegaly and hypoalbuminemia. Unfortunately, no liver biopsy was obtained from the post-LDA patients, and there was no means to confirm reduction of intrahepatic platelet aggregation after LDA administration. However, the finding suggests that considering potential suppression of intrahepatic platelet aggregation by LDA all patients with cirrhosis become subjects of LDA administration. In addition, patients who were simultaneously administered anti-coagulants and/or anti-platelet drugs other than LDA were excluded from this study (**Figure 1**). It is possible that the combined use of LDA and other anti-coagulants would enhance recovery of the platelet count. In any case, a large-scale prospective study for clarifying the diverse effects of LDA on cirrhosis patients in greater detail is needed.

Conclusions

The results of this retrospective study indicate that LDA may be a therapeutic option for cirrhosis-related thrombocytopenia, especially in patients without hypersplenism and hypoalbuminemia. Combination usage of LDA with TPO agonists and/or splenectomy is a promising method to maximize recovery of platelet count in patients with cirrhosis-related thrombocytopenia.

Disclosure of conflict of interest

None.

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