Postoperative Bleeding in Cardiac Surgery

The Role of Tranexamic Acid in Patients Homozygous for the 5G Polymorphism of the Plasminogen Activator Inhibitor-1 Gene

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Background: Plasminogen activator inhibitor 1 (PAI-1) attenuates the conversion of plasminogen to plasmin. Polymorphisms of the PAI-1 gene are associated with varying PAI-1 levels and risk of prothrombotic events in nonsurgical patients. The purpose of this study, a secondary analysis of a clinical trial, was to investigate whether PAI-1 genotype affects the efficacy of tranexamic acid (TA) in reducing postoperative chest tube blood loss of patients undergoing cardiopulmonary bypass.

Methods: Fifty patients were classified according to PAI-1 genotype (4G/4G, 4G/5G, or 5G/5G). Twenty-four received 2 g TA before and after cardiopulmonary bypass, whereas 26 received placebo. The authors recorded data related to coagulation, fibrinolysis, and bleeding before surgery, at admission to the intensive care unit (0 h), and 4 and 24 h later.

Results: In patients not receiving TA, those with the 5G/5G genotype had significantly higher chest tube blood loss and transfusion requirements compared with patients with the other genotypes at all time points. Patients with the 5G/5G genotype receiving TA showed significantly lower blood loss compared with the placebo group. There were no significant differences in blood loss or transfusion requirements between patients with the 4G/4G genotype when TA was used.

Conclusions: Plasminogen activator inhibitor-1 5G/5G homozygotes who did not receive TA showed significantly greater postoperative bleeding than patients with other PAI-1 genotypes. 5G/5G homozygotes who received TA showed the greatest blood-sparing benefit.

CARDIOPULMONARY bypass (CPB) is known to invoke a systemic inflammatory response and to impair hemostasis. Postoperative bleeding is a frequent complication of surgery with CPB that contributes to perioperative morbidity and mortality. Although excessive bleeding after cardiac surgery is multifactorial in etiology, fibrinolysis plays a determinant role in this process. Plasminogen activator inhibitor 1 (PAI-1) blocks the conversion of plasminogen to plasmin, thus inhibiting fibrinolysis (fig. 1). The PAI-1 gene has several variant forms that influence PAI-1 levels. The 4G PAI-1 allele is associated with higher levels of PAI-1 and risk of thrombotic events in nonsurgical patients. Polymorphisms of the PAI-1 gene, by influencing plasmin concentrations, may thus be useful to identify varying susceptibility to perioperative bleeding and, in theory, should be favorable for less bleeding, and vice versa for the 5G allele. Antifibrinolytic drugs are commonly given to patients undergoing cardiac surgery to inhibit plasminogen activation. The influence of patient PAI-1 genotype on blood loss after cardiac surgery and whether PAI-1 genotype affects the efficacy of antifibrinolytic drugs is unclear.

The objective of this study was to investigate whether the efficacy of tranexamic acid (TA) for reducing excessive bleeding after CPB surgery is influenced by patient PAI-1 genotype.

Materials and Methods

Study Design and Patient Population

This was a secondary analysis of a randomized, double-blind, placebo-controlled study to investigate the effect on blood loss of a single dose of TA (2 g) administered before and after elective CPB surgery. The main study was discontinued by the hospital ethics committee (University Hospital of the Canary Islands, Tenerife, Spain) before completion of enrollment due to a higher rate of excessive bleeding in the placebo group. The study population consisted of 50 patients classified according to PAI-1 genotype (4G/4G, 4G/5G, or 5G/5G). Twenty-four received 2 g TA before and after CPB, whereas 26 received placebo. In this report, we investigate the secondary endpoint of the influence of patient PAI-1 genotype on TA acid efficacy.

Inclusion criteria were consecutive white adult patients undergoing elective CPB surgery. Exclusion criteria included chronic coagulopathy (prothrombin time <50% or international normalized ratio >2, and platelets <50,000/mm³ or aggregation dysfunction), renal dysfunction (creatinine >2 mg/dl), hepatopathy (Child B or higher degree), or use of immunosuppressant drugs. Before CPB, participants had normal bleeding time, platelet collagen/epinephrine and collagen/adenosine diphosphate closure time, prothrombin time, activated partial thromboplastin time, and thrombin time. The patients did not receive antiinflammatory agents or...
anticoagulant therapy (acetyl salicylate acid, heparin, warfarin, antiplatelet therapy) for 5 days before surgery and for the first 24 h after surgery. The study was approved by the hospital ethics committee, and all patients gave written informed consent for genetic analysis and enrollment in the clinical trial.

**Perioperative Management**

Anesthetic procedures were standardized and consisted of an opioid-based anesthetic supplemented with volatile agents and muscle relaxants. The extracorporeal circuit consisted of a hard-shell membrane oxygenator (Optima XP; Cobe, Denver, CO, or Quantum Lifestream International, Inc., Woodlands, TX), a Tygon® extracorporeal circuit (Saint-Gobain, Charny, France), and a Medtronic Biopump® centrifugal pump (Tolochenaz, Switzerland). The patients received heparin to achieve an activated clotting time of greater than 480 s. Body temperature was decreased to 28°–30°C during CPB, and the pump flow was adjusted to maintain a mean arterial pressure of greater than 60 mmHg and a flow index of 2.2 l m⁻¹ min⁻¹ m⁻². St. Thomas 4:1 blood cardioplegia was used at 12°C. Heparin was reversed with protamine with a dose based on blood heparin levels measured by Hepcon® HMS (Medtronic, Minneapolis, MN). A blood salvage device was used in all patients. Based on our clinical practice, the patients received packed erythrocytes when hemoglobin was less than 8 g/dl. When postoperative blood loss was deemed clinically excessive, the patients received fresh frozen plasma when the prothrombin time was less than 50% (reference range, 70–100%) or the international normalized ratio was greater than 2, and a platelet transfusion (reference range, 70–100%) or the international normalized ratio was greater than 2, and a platelet transfusion (reference range, 70–100%) or the international normalized ratio was greater than 2, and a platelet transfusion (reference range, 70–100%) or the international normalized ratio was greater than 2, and a platelet transfusion (reference range, 70–100%) or the international normalized ratio was greater than 2, and a platelet transfusion (reference range, 70–100%) or the international normalized ratio was greater than 2, and a platelet transfusion (reference range, 70–100%) or the international normalized ratio was greater than 2, and a platelet transfusion (reference range, 70–100%) or the international normalized ratio was greater than 2, and a platelet transfusion.

**Data Collection**

Demographic information, comorbid conditions, and other clinical data were recorded. The patient surgical risk was calculated by Parsonnet and Acute Physiology and Chronic Health Evaluation II scores. Chest tube blood loss was measured at admission to intensive care unit (0 h) and at 4 and 24 h after surgery.

**Coagulation and Fibrinolysis Assessments**

Quantitative PAI-1 antigen (range, 2–47 ng/ml; intraassay variation, 5.7%) and tissue plasminogen activator antigen (tPA) (range, <9.0 ng/ml; intraassay variation, 4.2%) were measured using enzyme-linked immunosorbent assay (Imubind®; America Diagnostica Inc., Stanford, CT). An automated chromogenic method (Berichrom®; Dade Behring Inc., Newark, NJ) was used for the quantitative determination of the functional activity of antithrombin (reference range, 80–130%).

**PAI-1 Genotype Determination**

Blood was collected before surgery into EDTA-containing glass tubes. DNA purification was conducted using proteinase K, phenol-chloroform extraction, and ethanol precipitation. The DNA samples were stored at 4°C in Tris-EDTA buffer, and genotyping was performed in a double-blinded manner. Analysis of PAI-1 gene polymorphism was performed using primers and restriction endonuclease digestion as previously described. This polymorphism is due to the insertion of an extra G in the 5G allele, which also generates a restriction site. Thus, while the 4G allele is only 99 bp long, the 5G allele is indeed 100 bp long in the initial amplification, but it becomes 77 + 23 as a result of restriction enzyme treatment. Briefly, primers PAI-F: CACAGAGAGAGTCTGGCCACGTT and PAI-R: CCAACAGAGACTCTTTGCTT were used to amplify a 99-bp fragment, which was subject to digestion with restriction enzyme BstI. The 5G PAI-1 allele, which contains the BstI recognition sequence (CCN7GG), yields 77- and 23-bp fragments, whereas the 4G allele (resistant to BstI) remains as a 99-bp fragment. Restriction fragments were resolved by 5% acrylamide gel electrophoresis. Because spurious genetic associations can result from the existence of genetic substructure in the population sampled, we also genotyped 22 neutral genetic markers (polymorphic sites in the genome that are considered to be functionally neutral) as a genomic control strategy. If the associations were due to population substructure, some of the unrelated, neutral markers would be expected to yield significant association with the phenotype studied also. The neutral markers chosen were Alu repeats and short tandem repeats distributed throughout the genome.

**Statistical Analysis**

Quantitative variables are reported as median and interquartile range. Nominal variables are reported as frequency and percentage. Assumption of normality of the TA and placebo groups was tested with the Kolmogorov-Smirnov test, and homoscedasticity was tested with the Levene test. First, comparisons between placebo and TA groups were conducted. The Pearson chi-square or Fisher exact test was used to compare sex, type of surgery, erythrocyte and plasma requirements, and Parsonnet score using the Kruskal-Wallis test for single-factor analysis. Nominal variables were compared using the Fisher exact test.

References:


2. Smirnov test, and homoscedasticity was tested with the Levene test. First, comparisons between placebo and TA groups were conducted. The Pearson chi-square or Fisher exact test was used to compare sex, type of surgery, erythrocyte and plasma requirements, and Parsonnet score using the Kruskal-Wallis test for single-order categories. Comparison between these groups on age, platelets, hemoglobin, international normalized ratio.
bleeding),12 and body mass index (significant distribution in order to perform an analysis of covariance test of 5G/5G
4G carriers together. Twenty-four–hour chest tube blood loss was analyzed after pooling potential confounding variables, the effect of the PAI-1 polymorphism on bleeding was analyzed after pooling each genotype. Given the small sample size, to adjust for logistic regression analysis using as independent variables the neutral markers and as the dependent variable the treatment group, as suggested by Setakis et al.13 Only one marker was included in each logistic regression analysis. Genotypes were tested for Hardy–Weinberg equilibrium by using Online Encyclopedia for Genetic Epidemiology software.11 Hypotheses were two-tailed. Statistical significance was defined as a P value less than 0.05 for comparisons between placebo and TA groups. An uncorrected P value was established as 0.05. The Bonferroni correction with a corrected P value was applied for a posteriori comparisons between genotypes and independent variables as follows: demographic variables, P < 0.0125; hematocrit, P < 0.025; PAI-1 and tPA levels, P < 0.0125; coagulation parameters such as prothrombin time, fibrinogen, and antithrombin, P < 0.0125; chest tube blood loss, P < 0.017; and transfusion requirements during intensive care unit stay (erythrocyte, plasma, and platelets units), P < 0.017. We used SPSS version 12 (SPSS Inc., Chicago, IL) and StatXact 5.0.3 (Cytel Software, Cambridge, MA).

Results
Of the 70 patients initially enrolled, only 50 were randomly assigned to receive either TA (n = 24) or placebo (n = 26). Exclusion reasons were “off-pump” surgery (n = 5), coagulopathy (n = 2), emergency surgery (n = 5), endocarditis (n = 4), Jehovah’s Witness faith (n = 1), hemodialysis (n = 1), or protocol violation (n = 2).

Baseline demographic and other patient data were similar between TA and placebo groups. Bivariate analysis showed that the TA group had significantly lower chest tube blood loss at all postoperative time points as compared with the placebo group. In addition, the TA group showed significantly lower transfusion requirements of erythrocytes and plasma during their intensive care unit stay (table 1).

PAI-1 Polymorphism
There were no differences between the TA and placebo groups with respect to neutral markers (data not shown). The 4G/4G genotype was found in 10 patients (20%), the 4G/5G was found in 26 (52%), and the 5G/5G was found in 14 (28%) of the 50 patients studied. The distribution of PAI-1 polymorphism was similar to that observed in 100 consecutive blood donors from our institution, in Hardy–Weinberg equilibrium.

PAI-1 Polymorphism Effect without TA
The perioperative data grouped according to PAI-1 polymorphism are shown in table 2. There were differences in serum levels of PAI-1 between the three PAI-1 genotypes, before surgery (4G/G: 49 [33–56] ng/ml, 4G/5G: 54 [25–48] ng/ml, and 5G/5G: 28 [17–35] ng/ml; P = 0.046; corrected P nonsignificant) and to intensive care unit admission (4G/G: 67 [46–97] ng/ml, 4G/5G: 61 [36–82] ng/ml, and 5G/5G: 54 [29–42] ng/ml; P = 0.018; corrected P nonsignificant). Significant differences were found between PAI-1 genotype groups (4G/4G, 4G/5G, and 5G/5G) in chest tube blood loss at 0 h (30 [28–45], 114 [88–215], 160 [98–250] ml, respectively; P = 0.05; corrected P nonsignificant), at 4 h (160 [98–210], 255 [185–574], 661 [505–1,045] ml, respectively; P = 0.001;
corrected $P$ significant), and at 24 h (428 [313–548], 715 [475–1,175], 1,220 [1,045–1,855] ml, respectively; $P$ 0.009; corrected $P$ significant) after surgery.

The 5G/5G genotype was associated with 24-h chest tube blood loss, controlling for reoperation ($F_{1,26}$ 9.48, $P$ 0.005), combined surgical procedures ($F_{1,26}$ 11.29, $P$ 0.003), and body mass index ($F_{1,26}$ 6.36, $P$ 0.02).

Fresh frozen plasma was required during the intensive care unit stay in 50% of 5G/5G, 25% of 4G/5G, and none of 4G/4G carriers ($P$ 0.021; corrected $P$ nonsignificant). There were no differences in other transfusion requirements (erythrocyte units and platelets).

Efficacy of TA versus Placebo According to PAI-1 Genotype

Tranexamic acid decreased chest tube blood loss in 5G carriers. 4G/4G patients did not show significant differences in blood loss between TA and placebo groups. 4G/5G patients receiving TA had lower blood loss than placebo group at 0 h (60 [40–93] vs. 114 [88–215] ml, respectively; $P$ 0.012; corrected $P$ significant) and at 24 h after surgery (325 [213–770] vs. 715 [475–1,175] ml, respectively; $P$ 0.014; corrected $P$ significant). In contrast, 5G/5G patients receiving TA had significantly lower blood loss compared with the placebo group at 0 h (55 [25–70] vs. 160 [98–250] ml, respectively; $P$ 0.028; corrected $P$ nonsignificant), at 4 h (140 [100–152] vs. 661 [505–1,045] ml, respectively; $P$ 0.008; corrected $P$ significant), and at 24 h (293 [160–357] vs. 1,220 [1,045–1,855] ml, respectively; $P$ 0.004; corrected $P$ significant) after surgery (fig. 2). Fifty-five percent of 5G/G patients in the placebo group received fresh frozen plasma during their intensive care unit stay compared with no patients in the TA group ($P$ 0.014; corrected $P$ significant). There were no differences in platelet requirements.

Discussion

Our results show that the efficacy of TA prophylaxis for reducing postoperative chest tube blood loss was dependent on patient PAI-1 genotype. 5G carriers treated with TA had significantly lower blood loss than those receiving placebo; however, homozygous 5G patients showed the greatest descent in blood loss. In contrast, the efficacy of TA prophylaxis to reduce blood loss compared with placebo was not observed in homozygous 4G patients.
Table 2. Characteristics of Patients Not Receiving Tranexamic Acid Grouped According to Plasminogen Activator Inhibitor-1 (4G/5G) Polymorphism

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>5G/G (n = 9)</th>
<th>4G/SG (n = 12)</th>
<th>4G/G (n = 5)</th>
<th>P Value</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
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<tr>
<td>Age, yr</td>
<td>67 (59–74)</td>
<td>70 (63–75)</td>
<td>64 (50–71)</td>
<td>0.84</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>6 (67)</td>
<td>6 (50)</td>
<td>2 (40)</td>
<td>0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.1 (24.8–29.3)</td>
<td>27.7 (25.2–29.3)</td>
<td>32.3 (29.3–32.8)</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Parsonnet</td>
<td>15.5 (8.5–18)</td>
<td>17 (14–23)</td>
<td>19 (16–24)</td>
<td>0.27</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Surgical data</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Type of surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.47</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary</td>
<td>5 (56)</td>
<td>4 (33)</td>
<td>3 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve</td>
<td>2 (22)</td>
<td>7 (59)</td>
<td>1 (20)</td>
<td></td>
<td></td>
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<tr>
<td>Mixed</td>
<td>2 (22)</td>
<td>1 (8)</td>
<td>1 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redo, n (%)</td>
<td>1 (11.1)</td>
<td>3 (25)</td>
<td>0 (0)</td>
<td>0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>108 (71–110)</td>
<td>84 (74–117)</td>
<td>89 (70–100)</td>
<td>0.78</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic clamping time, min</td>
<td>64 (47–82)</td>
<td>63 (48–69)</td>
<td>51 (27–65)</td>
<td>0.36</td>
<td>NS</td>
</tr>
<tr>
<td>Total heparin dose, mg/kg</td>
<td>4.3 (3.9–4.4)</td>
<td>4.1 (3.8–4.5)</td>
<td>4.3 (4.2–4.4)</td>
<td>0.74</td>
<td>NS</td>
</tr>
<tr>
<td>Total protamine dose, mg/kg</td>
<td>2.7 (2.6–2.9)</td>
<td>2.7 (2.5–2.9)</td>
<td>2.6 (2.3–2.7)</td>
<td>0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Blood salvage device, ml</td>
<td>675 (570–855)</td>
<td>750 (675–950)</td>
<td>800 (600–810)</td>
<td>0.51</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Perioperative parameters</strong></td>
<td></td>
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<tr>
<td>Hematocrit preoperative</td>
<td>40.8 (39.6–45.6)</td>
<td>40.8 (35.7–46)</td>
<td>37.2 (33.8–37.6)</td>
<td>0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit 0 h</td>
<td>29.8 (26.4–31.4)</td>
<td>32.5 (29.6–33.3)</td>
<td>31.8 (31.5–35.5)</td>
<td>0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Prothrombin time 0 h, %</td>
<td>63 (53–71)</td>
<td>74 (65–79)</td>
<td>77 (75–83)</td>
<td>0.009</td>
<td>S</td>
</tr>
<tr>
<td>Fibrinogen 0 h, mg/dl</td>
<td>230 (163–304)</td>
<td>292 (262–432)</td>
<td>357 (313–422)</td>
<td>0.005</td>
<td>S</td>
</tr>
<tr>
<td>Fibrinogen 4 h, mg/dl</td>
<td>252 (193–319)</td>
<td>240 (249–378)</td>
<td>357 (334–467)</td>
<td>0.006</td>
<td>S</td>
</tr>
<tr>
<td>Antithrombin 0 h</td>
<td>21 (17–25)</td>
<td>27 (22–33)</td>
<td>40 (40–42)</td>
<td>0.001</td>
<td>S</td>
</tr>
<tr>
<td>tPA preoperative, ng/ml</td>
<td>16 (11–18)</td>
<td>18 (11.5–24)</td>
<td>16.8 (9.8–20)</td>
<td>0.78</td>
<td>NS</td>
</tr>
<tr>
<td>tPA 0 h, ng/ml</td>
<td>17.7 (14–24)</td>
<td>19 (16–25)</td>
<td>20 (17–26)</td>
<td>0.23</td>
<td>NS</td>
</tr>
<tr>
<td>Chest tube blood loss at ICU admission, ml</td>
<td>160 (98–250)</td>
<td>114 (88–215)</td>
<td>30 (28–45)</td>
<td>0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Chest tube blood loss at 4 h, ml</td>
<td>661 (505–1,045)</td>
<td>253 (185–574)</td>
<td>160 (98–210)</td>
<td>0.001</td>
<td>S</td>
</tr>
<tr>
<td>Chest tube blood loss at 24 h, ml</td>
<td>1,220 (1,045–1,855)</td>
<td>715 (475–1,175)</td>
<td>428 (313–548)</td>
<td>0.009</td>
<td>S</td>
</tr>
</tbody>
</table>

Values are expressed as median and interquartile range, or frequency and percentage.

* P value corrected according to correction of Bonferroni.

0 h = intensive care unit admission; ICU = intensive care unit; NS = not significant; S = significant; tPA = tissue plasminogen activator.

Fig. 2. Accumulative postoperative chest tube blood loss according to plasminogen activator inhibitor type 1 genotypes, comparing placebo with tranexamic acid: 4G/G homozygotes (blue box plots), 4G/5G heterozygotes (green box plots), and 5G/G homozygotes (red box plots). Horizontal line represents the median, box encompasses the 25th–75th percentiles, and whiskers encompass the minimum and maximum values. A corrected P value less than 0.017 according to the Bonferroni test was significant.
BLEEDING AND POLYMORPHISMS OF THE PAI-1 GENE

Bleeding after CPB surgery is multifactorial. However, there is growing evidence that genetic factors influence postoperative bleeding. The fact that certain patients have disorders in hemostasis that only manifest in response to major insults such as cardiac surgical procedures supports this view.

Many studies demonstrate that the 4G allele in the 4G/5G polymorphism of the PAI-1 gene is associated with higher plasma PAI-1 levels, whereas patients with 5G alleles have low PAI-1 levels. In the current study, PAI-1 levels were measured by a validated method.

We found differences between the three PAI-1 genotypes in the levels of PAI-1, although these differences were not significant. Recently, a correlation has been demonstrated between PAI-1 genotype and messenger RNA transcription in CPB surgery. 4G homozygotes had the highest plasma PAI-1 levels, heterozygote subjects were intermediate, and 5G homozygotes had the lowest levels of PAI-1. It seems that PAI-1 polymorphism is a determinant factor with respect to serum PAI-1 levels. Thus 5G homozygotes may be predisposed to greater bleeding due to insufficient inhibition of fibrinolysis. It remains possible, however, that the association of the 4G/5G polymorphism with the observed phenotype reflects only the role of an unknown gene nearby, in linkage disequilibrium with PAI-1.

Antifibrinolytic drugs have been used as prophylaxis for postoperative bleeding, but there is no universally accepted consensus on what strategy to use and in which patients. A relevant finding of the current study was the identification of patients with greater tendency to bleeding (5G carriers, particularly homozygotes) who benefit most from antifibrinolytic prophylaxis.

This study has limitations. Because of the sample size, multivariable models could not be adequately conducted, and this renders several confounding scenarios as potential explanations. Body mass index has been associated with postoperative bleeding, and this renders several confounding scenarios as potential explanations. Body mass index has been associated with postoperative bleeding, and this renders several confounding scenarios as potential explanations.

Conclusion

5G carriers showed greater tendency to post-CPB chest tube blood loss. 5G homozygotes, not receiving TA, showed significantly more postoperative bleeding than patients with other PAI-1 genotypes. 5G homozygotes who received TA showed the greatest blood-sparing benefit.

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