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TOPICAL USE OF ANTIFIBRINOLYTIC AGENTS

REDUCES POSTOPERATIVE BLEEDING:

A DOUBLE-BLIND, PROSPECTIVE, RANDOMIZED STUDY

SHORT TITLE: Topical Use of Antifibrinolytic Agents

AUTHORS:

Davor Baric[1], Bojan Biocina[1], Daniel Unic[1], Zeljko Sutlic[1], Igor Rudez[1], Vesna Bacic Vrca[2],

Kristina Brkic[1], Mira Ivkovic[1]

[1] Department of Cardiac Surgery, University Hospital Dubrava, Zagreb, Croatia

[2] Department of Pharmacy, University Hospital Dubrava, Zagreb, Croatia

CORRESPONDING AUTHOR:

Dr. Davor Baric

Department of Cardiac Surgery

University Hospital Dubrava

10000 Zagreb, Croatia

Tel: +385 1 290 2530

Fax: +385 1 290 3819

Email: dbaric@kbd.hr

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ABSTRACT

Objectives:

Postoperative bleeding is still one of the most common complications of cardiac surgery. Antifibrinolytic agents successfully reduce bleeding, but there are controversies concerning adverse effects after their systemic use. By topical application of antifibrinolytic agents in pericardial cavity, most of these effects are avoided. We compared the effects of topically applied aprotinin, tranexamic acid and placebo on postoperative bleeding and transfusion requirements.

Methods:

In this single-center prospective, randomized, double-blind trial, 300 adult cardiac patients were randomized into 3 groups to receive one million IU of aprotinin (AP group), 2.5g of tranexamic acid (TA group) or placebo (PL group) topically before sternal closure. Groups were comparable with respect to all preoperative and intraoperative variables. Postoperative bleeding, transfusion requirements and hematologic parameters were evaluated.

Results:

Postoperative bleeding within first 12-hour period (AP group 433 ± 294 [350; 360] mL, TA group 391 ± 255 [350; 305] mL, PL group 613 ± 505 [525; 348] mL), as well as cumulative blood loss within 24h (AP group 726 ± 432 [640; 525] mL, TA group 633 ± 343 [545; 335] mL, PL group 903 ± 733 [800; 445] mL), showed statistically significant inter-group differences (both p<0.001). Bleeding rates values were significantly higher in placebo group compared to the groups treated with antifibrinolytic agents (AP and TA groups) concerning both variables. Although TA group showed the lowest values, no statistical differences between TA and AP groups were found. Inter-group difference of blood product requirements was not statistically significant.

Conclusions:

Topical use of either tranexamic acid or aprotinin efficiently reduces postoperative bleeding. TA seems to be at least as potent as aprotinin, but potentially safer and with better cost-effectiveness ratio.

KEYWORDS:

1. INTRODUCTION

In time when systemic use of antifibrinolytic agents is highly controversial, with conflicting evidence of both benefits and adverse effects [1,2,3], topical application of these agents in pericardial cavity could provide alternative means to effectively reduce postoperative bleeding.

Although the topical use of antifibrinolytic agents, such as aprotinin and tranexamic acid (TA), is not a novel method [4,5], it has not been widely accepted as a routine part of cardiac procedure. One of the main reasons is lack of evidence to support regular topical use of antifibrinolytic agents [6]. Only one randomized controlled trial by De Bonnis [7] demonstrated a clinically small benefit in favor of topical TA application over placebo in a group of low risk coronary patients.

The aim of this study was to compare the effects of topically applied aprotinin with TA and placebo on postoperative bleeding and transfusion requirements.

2. MATERIAL AND METHODS

After institutional approval was obtained, 300 patients scheduled for first-time elective cardiac procedure between May 2003 and April 2005 were enrolled in the study. The demographic data of our study groups is displayed in **Table1**. The study was carried out as a prospective, randomized, double-blind investigation with parallel groups.

Exclusion criteria were as follows: procedures of thoracic aorta, redo procedures, active endocarditis, emergent procedures and known preexisting coagulation defects or abnormal platelet count.

2.1. Pharmacological protocol

After the enrollment, patients were randomized into three groups using random-number tables. The independent pharmacologist in hospital pharmacy prepared coded solutions with the study drugs or placebo and was not directly involved in the clinical treatment of randomized patients. Solutions contained one million IU of aprotinin (Trasylol; Bayer Pharma d.o.o., Ljubljana, Slovenia) in 250 mL of saline solution (AP group), 2.5 g of TA (Cyklokapron; Pharmacia AB, Stockholm, Sweden) in 250 mL of saline solution (TA group) or 250 mL of saline as placebo (PL group), without any other additives or preservatives. Identical bottles marked with a study number of patient were delivered to the operating theaters. Both the operation theater staff and that of the intensive care unit were blinded regarding the study drug and codes were disclosed at the end of the study.

In all patients, antiaggregative therapy was discontinued for at least 5 days and anticoagulant therapy was continued up to 24 hours prior to surgery. There was no systemic appliance of either aprotinin or tranexamic acid in any patient.

2.2. Surgical procedures and drug administration

Different cardiac procedures were performed in this study (**Table 2**), reflecting the usual case-mix performed at our Department. Patients with operations both with and without use of cardiopulmonary bypass (CPB) were included in study.

After thorough surgical hemostasis and before closure of the median sternotomy, study solution at room temperature was poured into the pericardial cavity and over the mediastinal tissues. After chest closure, study solution was suctioned out through chest tubes. After the patient was transferred to the intensive care unit (ICU), continuous suction (20 cm H_2O) was applied, which was supplemented with periodic milking of the drains.

2.3. Anesthetic protocol and cardiopulmonary bypass management

Same anesthetic protocols were used for all patients. All patients were premedicated with morphine in the dose of 0.1 mg/kg IM (Morphine Merck; Merck KgaA, Darmstadt, Germany) one hour before surgery. Anesthesia was induced by 0.1 mg/kg IV midazolam (Dormicum; F. Hoffman-La Roche Ltd., Basel, Switzerland), 5-7 g/kg IV fentanyl (Fentanyl; Janssen Pharmaceutica, Beerse, Belgium), and 0.1 mg/kg IV pancuronium-bromide (Pavulon; N.V. Organon, Oss, the Netherlands). After endotracheal intubation, the lungs were mechanically ventilated by positive pressure (tidal volume of 8 mL/kg and ventilatory frequency of 12/min) (Cato; Dräger, Lübeck, Germany). Tidal volume and respiratory rate were adjusted to maintain acid-base status and arterial CO_2 pressure within physiological limits. Anesthesia was maintained with a nitrous-oxide mixture (60% oxygen and 40% nitrous oxide) and sevoflurane (Sevorane; Abbott Laboratories S.A., Abbott Park, IL, USA) in doses of 1.0-1.3 minimal alveolar concentration (MAC). Additional doses of pancuronium-bromide (0.1 mg/kg) were administered as required to maintain neuromuscular blockade during surgery.

All cases which required CPB were performed in moderate hypothermia with cardiac arrest achieved with a single antegrade dose of blood cardioplegia followed by a continuous retrograde application of blood potassium cardioplegic solution.

2.4. Anticoagulation during operation

Heparin-sodium (Heparin; Belupo, Koprivnica, Croatia) was administered to achieve activated clotting time (ACT) of >480 seconds for patients undergoing the procedure with the use of CPB, and was checked every 20 minutes and re-administered according to the ACT values measured.

For patients undergoing the procedure without CPB (off-pump), heparin was administered to achieve ACT time of at least 200 seconds.

In patients undergoing coronary revascularization (both on- and off-pump) heparin was administered at the end of LIMA takedown. In valvular patients heparin was administered upon placing the cannulation stitches.

At the end of the procedure heparin was fully reversed with protamine-hydrochloridum (Protamin ICN; ICN Pharmaceuticals, Birsfelden, Switzerland) in all patients. In patients undergoing surgery with the use of CPB heparin reversal started upon the removal of the venous cannula, and in patients undergoing off-pump surgery upon the completion of the last anastomosis.

2.5. Transfusion policy

Criteria for transfusion of packed red blood cells were as follows: hematocrit value less than 30% and haemoglobin value less than 90 g/dL accompanied by signs or symptoms of hypovolemia after CPB and during the ICU stay. The criterion for transfusion of fresh frozen plasma was a prothrombin time greater than 1.5 (international normalized ratio) with excessive bleeding, defined as greater than 200 mL/h for 2 consecutive hours. The criterion for transfusion of platelet concentrates was a platelet count less than 50,000/mm3 with excessive bleeding (>200 mL/h for 2 consecutive hours). Surgical re-exploration was performed if bleeding in the first 2 hours was greater than 300 mL/h or greater than 200 mL/h for 4 consecutive hours with normal coagulation parameters.

2.6. Data collection and laboratory analysis

Postoperatively, blood loss from the mediastinal chest tubes was recorded at 12 and 24 hours from the time patient arrived in the ICU. Blood product transfusions were documented for the entire postoperative hospital stay. All clinical data was harvested from CardioBase, custom-made database of cardiac patients that is routinely used at our Department.

Plasma concentration of hemoglobin, hematocrit level, platelet count, prothrombin time, activated partial thromboplastin time (aPTT) and fibrinogen levels were measured before operation and after patient's arrival in the ICU.

2.7. Statistical analysis

Continuous variables are presented as mean ± standard deviation and, for variables with a skew distribution, additionally median with interquartile range was given.

Test of normality (Kolmogorov-Smirnov statistic, with a Lilliefors significance level) has been performed for all continuous variables. For variables with a normal distribution (pre- and postoperative hematologic characteristics), statistical comparison of groups was carried out using analysis of variance (ANOVA) and, for significant inter-group differences, Sidak's and Dunnett's post hoc tests were applied to locate the between-group differences. For variables with a skew distribution (all bleeding results and transfusion requirements), Kruskal-Wallis test was used and, for statistically significant differences, Mann-Whitney test with Bonferoroni correction was used for post-hoc comparisons.

The χ^2 test or Fisher exact test was used to compare categoric data.

All statistical tests were evaluated at significant level of 0.05. Statistical analysis was performed using SPSS, version 11.0 (SPSS, Inc., Chicago, IL, USA)

3. RESULTS

Six patients were withdrawn from the study due to the postoperative reopening for bleeding where an evident surgical source of bleeding was discovered. One patient dropped-out from the study due to the technical mistake. A total of 293 patients were assessed in the study: 100 patients in AP group, 97 in TA group and 96 in PL group.

The three groups were comparable with regard to age, sex, diabetes and EuroSCORE (both additive and logistic), as shown in **Table 1**. There were no inter-group differences concerning both CPB use (p=0.27) and percentage of isolated coronary surgery (p=0.29). Laboratory analyses showed not differences between the three groups, both pre- (**Table**) and postoperatively (**Table**).

From 293 enrolled patients, 6 of them (2%) died: 2 in AP group, 1 in TA group, 3 in PL group (p=0.59). Three patients died of cardiac reasons (perioperative myocardial infarction - 2, malignant arrhythmia - 1) and 3 from non-cardiac reasons (sepsis - 2, stroke - 1).

3.1. Postoperative blood loss

Postoperative blood loss for first and second 12- hour periods, as well as cumulative blood loss at 24h is presented in **Figure 1 (a-c)**. Postoperative bleeding within first 12-hour period (AP group 433 ± 294 [350; 360] mL, TA group 391 ± 255 [350; 305] mL, PL group 613 ± 505 [525; 348] mL), as well as cumulative blood loss within 24h (AP group 726 ± 432 [640; 525] mL, TA group 633 ± 343 [545; 335] mL, PL group 903 ± 733 [800; 445] mL), showed statistically significant inter-group differences (both p<0.001). In both cases, placebo group bleeding was significantly higher than bleeding in groups treated with antifibrinolytic agents. Although TA group showed the lowest values, no statistical differences were found between TA and AP groups. Decrease of mean cumulative blood loss at 24h was about 30% (270 mL) in TA group, and 20% (169 mL) in AP group, when compared to placebo. There was no inter-group difference in blood loss during second 12-hour period (p=0.46; AP group 293 ± 228 [225; 223] mL, TA group 242 ± 144 [200; 140] mL, PL group 290 ± 275 [250; 140] mL).

3.2. Transfusion requirements

In AP group, 53 patients (53%) received packed red blood cells, in TA group 51 (53%) and in PL group 51 (53%), with no differences between groups (p=0.99). Total amount of packed red blood cells transfused was highest in PL group (AP group 596 ± 803 [300; 755] mL, TA group 423 ± 483 [320; 690] mL, PL group 647 ± 1137 [370; 805] mL), but no significant inter-group differences (p=0.44) were found. Results are presented in Figure 1 (d)

3.3. Subgroups analyses

Statistical analysis of 2 subgroups of our study population has been performed. CPB subgroup included patients operated only with CPB support and OPCAB subgroup included patients operated without using CPB.

Results of CPB subgroup are displayed in **Table** . Again, significant inter-group differences were observed, concerning postoperative blood loss during first 12-hour period and cumulative blood loss within 24 hours. Posthoc analyses revealed that PL group differs significantly from both AP and TA groups, with no differences between later two. Decrease of mean cumulative blood loss at 24h was 37% (308 mL) in TA group, and 20% (163 mL) in AP group, when compared to placebo.

Results of OPCAB subgroup are displayed in **Table** . In this subgroup, inter-group difference was significant concerning only postoperative bleeding during first 12-hour period. Posthoc analyses revealed significant difference only between AP and PL group, with reduction of bleeding of 170ml (28%) in AP group.

4. DISCUSSION

This study reveals favorable effect of topically applied antifibrinolytic agents after cardiac operation: both aprotinin and TA efficiently reduce blood loss in first 12 hours in a large and heterogeneous group of cardiac patients. Cumulative blood loss at 24h after surgery was significantly lower compared to placebo - by 20% in AP group and 30% in TA group. Although evident, the difference between two antifibrinolytic agents in favor of TA was not statistically significant. The fact that there is no difference between groups in blood loss during second 12-h period is anticipated and is in accordance with results from De Bonis and colleagues, who demonstrated that hemostatic effect of 1% solution of TA lasted for 3-4 hours [7].

First study of topical application of antifibrinolytic agents was reported back in 1993, when Tatar and colleagues demonstrated evident reduction of both postoperative bleeding and the need for transfusion after topical use of aprotinin in 25 coronary patients [4]. Their results were further verified by double-blind, randomized trial on 100 patients undergoing cardiac operations with CPB published in 1995 by O'Regan and his group [5]. Cicek et al. [8] showed in 1995 that topically applied aprotinin could not be detected in blood and proposed that it locally relieves fibrinolytic state present in thoracic cavity after cardiopulmonary bypass. The same author year later raised a concern that aprotinin application in thoracic cavity may enhance postoperative mediastinal adhesion formation through its antifibrinolytic effects [9]

De Bonis and colleagues [7] published in 2000 a double blinded controlled trial with 40 patients undergoing primary CABG with 25% reduction of bleeding after 24 hours in group treated with TA, but with no reduction in allogenic transfusions. No systemic absorption of TA was noted. Proposed action of TA is a stabilization of formed cloths by removal of plasminogen from their fibrin surface and therefore inhibition of plasmin-induced resolution of fibrin

Our intention was to compare effects of both antifibrinolytic agents in larger RCT and to find out if their effects justify regular use in cardiac surgery. Decision to include both patients with and without CPB use in our study reflects regular high percent of off-pump surgery at our department. The potential influence of CPB on results is neutralized by the fact that there are no statistical differences between groups concerning CPB use. Patients at higher risk for postoperative bleeding,

such as aortic dissections or reoperations, were excluded from the study because of expected systemic applications of aprotinin.

Although the amount of transfused blood products was almost 250 mL lower in TA group compared to placebo, our study failed to show statistically significant decrease of transfusion requirements. Despite reduction of postoperative bleeding, there was still a relatively high percentage of patients receiving transfusions. This fact is most probably due to flexible adherence to transfusion criteria. Several other studies of either topical or systemic application of different antifibrinolytic agents also failed to show differences in blood products transfusions [7,10,11,12].

Additional statistical analysis showed the same results in a subgroup of patients operated with use of CPB. On the other hand, in the subgroup of patients operated without use of CPB (OPCAB subgroup), significant difference was shown only concerning bleeding during first 12-hour periods, with only AP group being considerably lower then placebo! This result suggests that aprotinin is more potent then tranexamic acid when no CPB is being used. However, these results must be interpreted with caution, because of the smaller sample sizes of mentioned subgroups.

We also have to mention impressive differences regarding the cost of the 2 drugs: at our institution the aprotinin protocol costs round 71€ per patient, whereas the TA application costs only 23€ per patient.

Based on the results of this double blinded randomized trial, we can conclude that topical application of both aprotinin and TA efficiently reduces postoperative bleeding. TA seems to be at least as potent as aprotinin, but potentially safer and with better cost-effectiveness ratio.

5. TABLES

Table 1. Baseline characteristics of study groups.

	AP group (n=100)	TA group (n=97)	PL group (n=96)	P-value
Age (years)	61.1 ± 9.3 [63; 14]	61.2 ± 10.7 [63; 16]	61.2 ± 10.3 [62.5, 15]	0,99
Female patients	27 (27%)	20 (20.6%)	26 (27.1%)	0,49
Diabetes mellitus	19 (19%)	18 (18.6%)	14 (14.6%)	0,58
CPB used	49 (49%)	52 (53.6%)	58 (60.4%)	0,27
Coronary surgery only	66 (66%)	72 (74.2%)	62 (64.6%)	0,30
EuroScore (additive)	3.4 ± 2.2 [3; 3]	3.3 ± 2.2 [3; 3]	3.7 ± 2.4 [3; 3]	0,47
EuroScore (logistic, %)	3.0 ± 2.2 [2.3; 2.5]	3.0 ± 2.4 [2.3; 1.2]	3.7 ± 4.8 [2.3; 2.8]	0,22

Results are presented as n (%) or mean ± SD [median; interquartile range].

Table 2. Surgical procedures performed, according to the study groups

	AP group (n=100)	TA group (n=97)	PL group (n=96)	Total	%
OPCAB	50	46	38	134	45,7
CABG	16	26	24	66	22,5
AV	11	16	8	35	11,9
CABG & AV	6	4	7	17	5,8
MV	5	2	3	10	3,4
CABG & other	3		4	7	2,4
other	5	1	1	7	2,4
CABG & MV	1	1	3	5	1,7
MV & other	2		2	4	1,4
AV & MV			3	3	1,0
AV & other	1	1		2	0,7
AV & MV & other			1	1	0,3
CABG & AV & MV			1	1	0,3
CABG & MV & other			1	1	0,3

OPCAB – off pump coronary artery bypass, CABG – coronary artery bypass grafting, AV – aortic valve procedure, MV – mitral valve procedure, other – other cardiac procedure

Table 3. Preoperative hematologic characteristics of study groups.

	AP group (n=100)	TA group (n=97)	PL group (n=96)	P-value
Hematocrit (%)	40.7 ± 5	41.3 ± 4.1	40.9 ± 5.1	0.77
Hemoglobin (g/dL)	140 ± 16	156 ± 143	139 ± 19	0.35
Platelet count (10^9/L)	195 ± 49	214 ± 54	205 ± 67	0.14
INR	1.050 ± 0.109	1.039 ± 0.102	1.098 ± 0.453	0.39
aPTT (sec.)	32.8 ± 4.8	32.7 ± 4.9	32.7 ± 5	0.98
Fibrinogen (g/L)	3.766 ± 1.038	3.948 ± 1.117	3.94 ± 1.148	0.52

Results are presented as mean ± SD (all variables show normal distribution).

Table 4. Postoperative hematologic characteristics of study groups

	AP group (n=100)	TA group (n=97)	PL group (n=96)	P-value
Hematocrit (%)	32.2 ± 3.4	32.3 ± 3.2	32.6 ± 3.2	0.74
Hemoglobin (g/dL)	112 ± 13	112 ± 13	113 ± 13	0.93
Platelet count (10^9/L)	128 ± 46	136 ± 53	134 ± 47	0.52
INR	1.710 ± 0.869	1.642 ± 0.623	1.822 ± 0.775	0.69
aPTT (sec.)	52.1 ± 24.8	75 ± 61.5	42.2 ± 15.9	0.21
Fibrinogen (g/L)	3.086 ± 1.478	3.883 ± 0.512	3.4 ± 1.679	0.59

Results are presented as mean ± SD (all variables show normal distribution).

Table 5. CPB subgroup results

	AP group (n=51)				TA group (n=51)				PL group (n=58)				P-value
	mean	SD	median	interqartile range	mean	SD	median	interqartile range	mean	SD	median	interqartile range	
Bleeding 0-12h (ml)	411	323	300	310	311	179	260	208	552	297	500	320	<0.001
Bleeding 12-24h (ml)	259	201	180	220	214	97	200	93	281	236	250	150	0.17
Bleeding 0-24h (ml)	670	441	600	340	525	222	460	235	833	440	800	410	<0.001
PRBC transfusion (ml)	853	969	600	1385	476	479	365	698	782	1403	380	960	0.51
Postoperative hospital stay (days)	12.3	9.6	10.0	5.0	10.0	2.8	9.5	4.3	12.8	8.1	10.0	5.0	0.19

Table 6. OPCAB subgroup results

	AP group (n=49)				TA group (n=48)				PL group (n=38)				P-value
	mean	SD	median	interqartile range	mean	SD	median	interq. range	mean	SD	median	interq. range	
Bleeding 0-12h (ml)	435	257	370	360	481	312	400	428	605	344	550	310	0.042
Bleeding 12-24h (ml)	336	239	280	243	291	196	230	175	251	131	230	110	0.69
Bleeding 0-24h (ml)	771	402	685	513	772	446	690	545	856	423	800	415	0.35
PRBC transfusion (ml)	309	451	135	540	321	437	0	553	391	365	350	690	0.20
Postoperative hospital stay (days)	9.7	4.2	9.0	4.0	8.9	1.9	8.0	2.3	11.7	6.1	9.0	5.0	0.22

6. FIGURES

Figure 1. Boxplots representing: blood loss during the first 12-hour period (a), the second 12-hour

period (b), cumulative blood loss at 24h (c) and packet red blood cells transfusions (d).
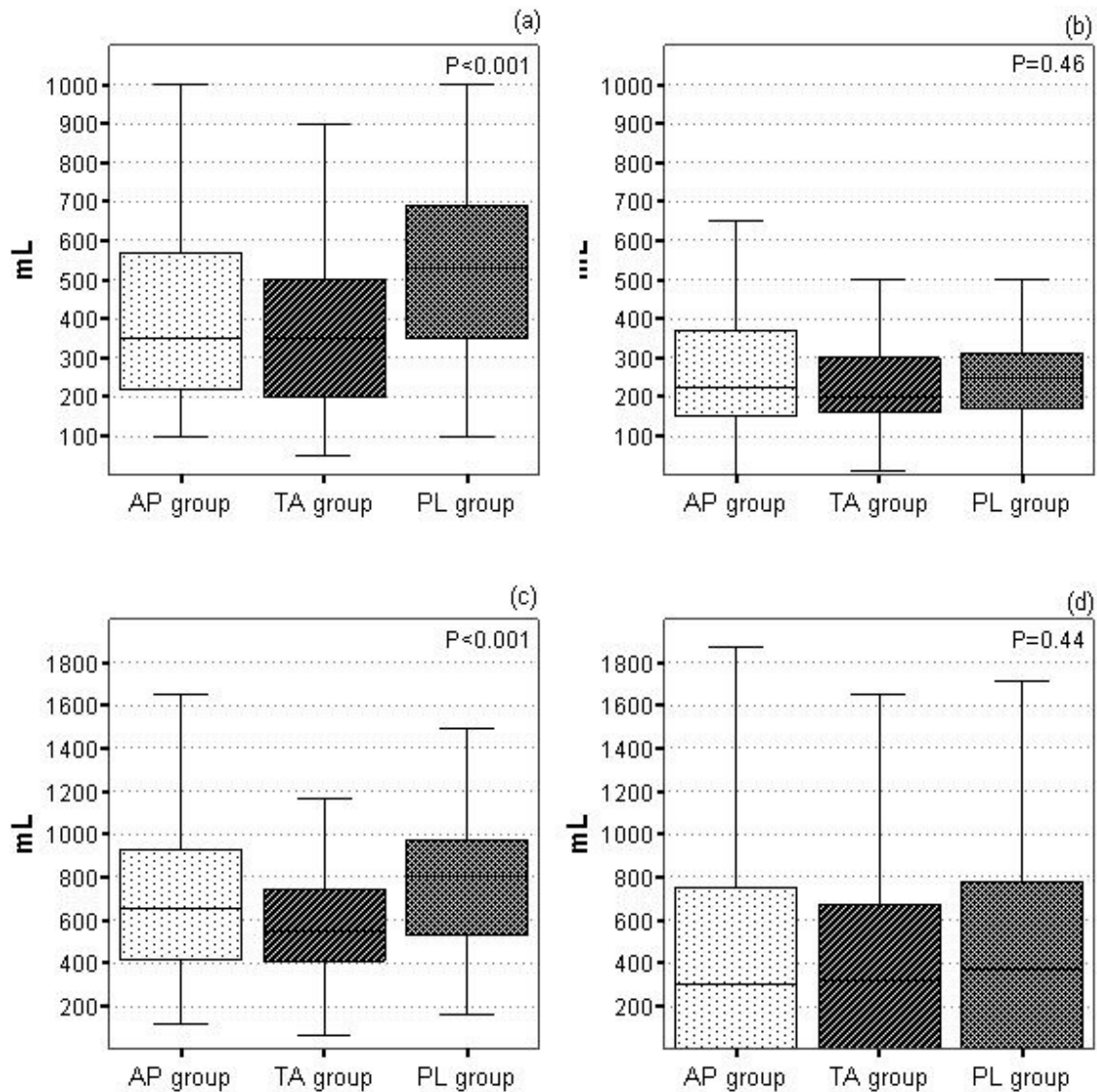
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