



**Effect of intraoperative use of tranexamic acid on blood transfusion, stone-free rate, and complications in patients with complex kidney stones undergoing percutaneous nephrolithotomy: randomized, double-blind, placebo controlled trial**

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# Disclosure

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✓ **No disclosures**

# Background

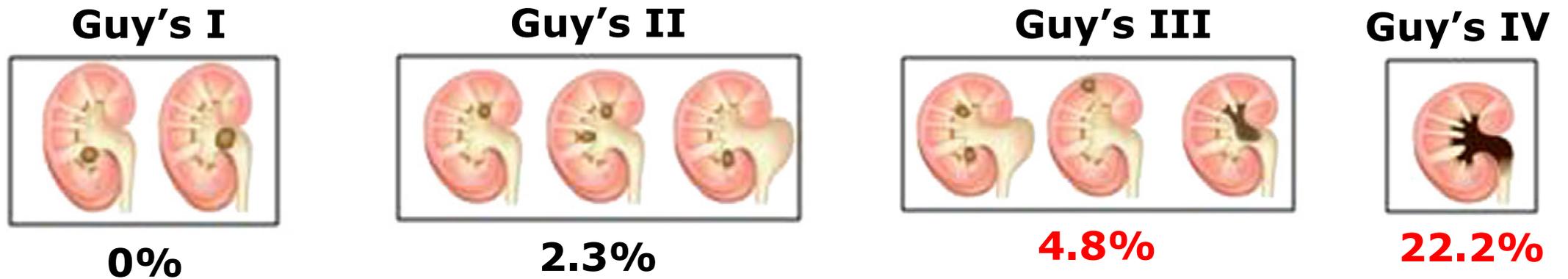


## Bleeding in PCNL:

- ✓ the most dreaded and unpredictable complication
- ✓ PCNL Blood transfusion (CROES): **5.7%**
- ✓ Guy's Stone Score:

Kumar, S. et al.: J Urol 2013  
Desai, M. et al.: J Endourol 2004

de la Rosette, J. et al.: J Endourol 2011



Vicentini, F. C. et al.: Urology 2014



## Strategies to reduce bleeding in PCNL:

1. Renal Access
  - puncture
  - entry of the calix
  - method of dilatation
2. Fibrin sealant
3. Intercostal vessels
4. Small tracts

Brödel, M.. Johns Hopkins Hosp.: Bull, p. 10, 1901

Sampaio FKB et al. J Urol. 1990

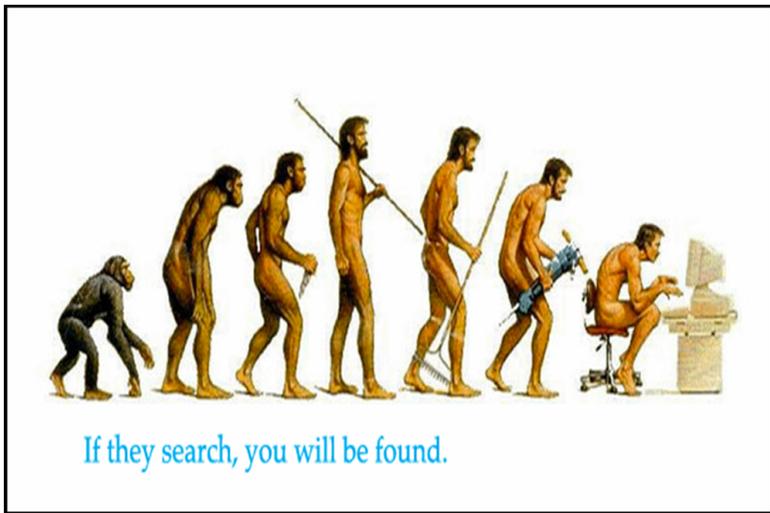
Clayman, R. et al.. J Urol, 132: 228, 1984

Stoller ML.et al. J Urol 152: 1977–1981, 1994

# Background



## Bleeding in PCNL: alternative



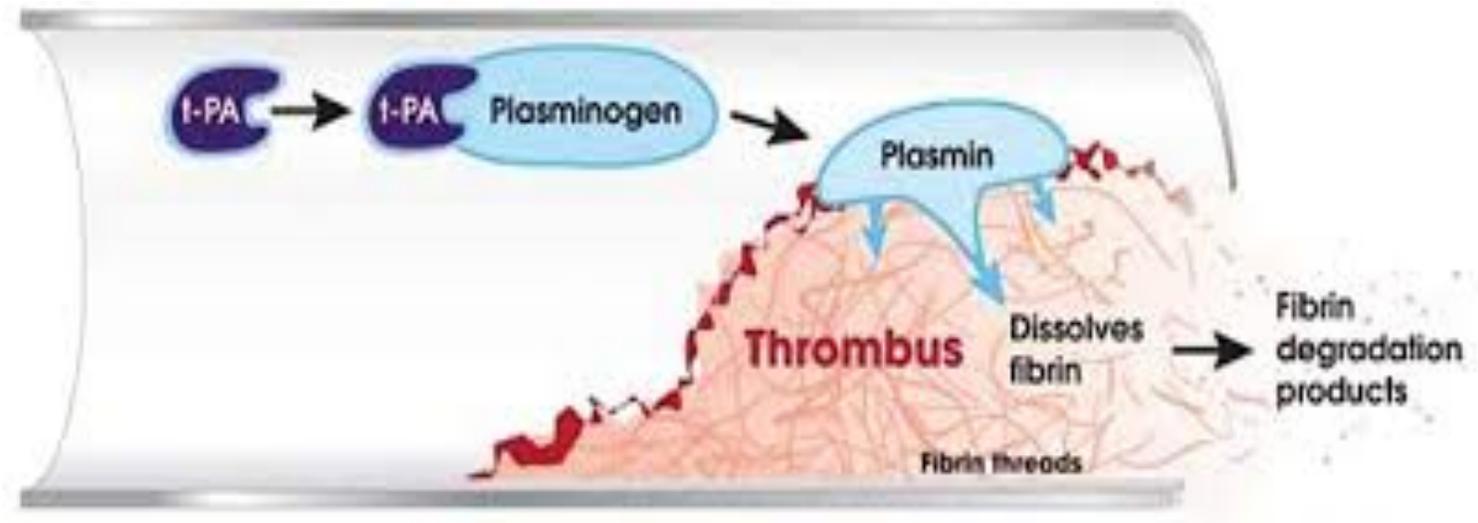
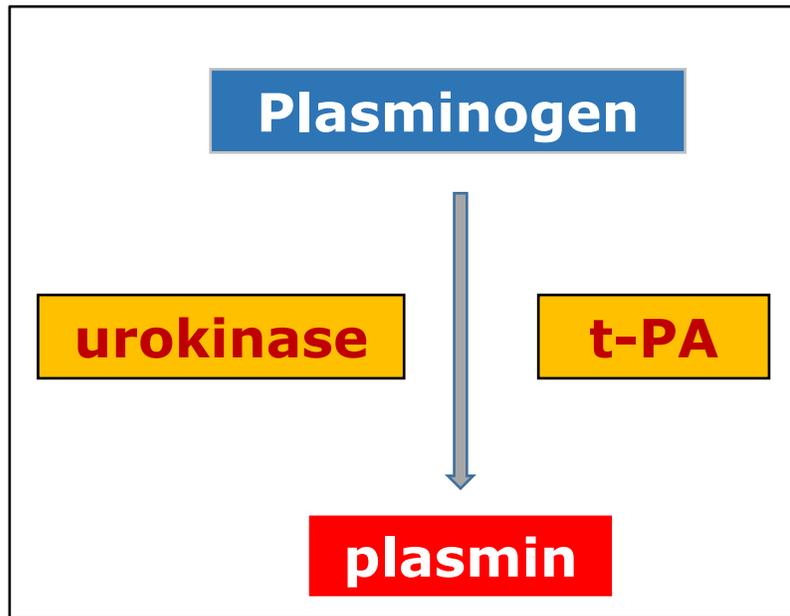
**Tranexamic Acid**

# Background



## Tranexamic acid

- ✓ synthetic antifibrinolytic



Santos, A. T. et al.: Rev Bras Anesthesiol, 57: 549, 2007

Pinosky, M. L. et al.: J Card Surg, 12: 330, 1997

## ➤ Study design:

✓ Prospective, single-center, double-blinded

✓ Randomized (1:1), placebo controlled trial

**Tranexamic Acid**

**Vs.**

**Placebo**

✓ **Inclusion:** adults + complex stones (Guy's III – IV)

✓ **Exclusion:** previous thrombotic event/ MDRD < 30/ allergy



## ➤ Power analysis:

- ✓ **TXA: 5-fold reduction** (blood transfusion rate)
- ✓ Transfusion rate (**Guy's III – IV**)
- ✓ 80% power
- ✓ 2-sided 5% significance level

**N = 96 patients per group  
= 192 (total)**



## ➤ TXA administration:

✓ **1g**

Horrow, J. C. et al.: Anesthesiology, 82: 383, 1995

✓ **Anesthetic induction**

- before incision

Soslau, G., Horrow, J.: Am J Hematol, 38: 113, 1991

- no additional doses

Casati, V. et al.: Anesthesiology, 94: 8, 2001

- t/2: 2h

Santos, A. T. et al.: Rev Bras Anesthesiol, 57: 549, 2007

### *The Dose-Response Relationship of Tranexamic Acid*

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Jonathan L. Parmet, M.D.†

Group	Loading Dose (mg · kg <sup>-1</sup> )	Infusion dose (mg · kg <sup>-1</sup> · h <sup>-1</sup> )
Placebo (P)	0	0
Quarter (Q)	2.5	0.25
Half (H)	5.0	0.50
Whole (W)	10	1.0
Double (D)	20	2.0
Fourfold (F)	40	4.0

# Methods

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## ➤ Endpoints:

**1<sup>st</sup>:** ✓ **blood transfusion rate**

**2<sup>nd</sup>:** ✓ **hemoglobin drop** (immediately after PCNL, 12h, 24h)

✓ **complications**

✓ **Effectiveness: CT POD#1**

# Methods



- **Follow-up:**
  - ✓ POD#7    ✓ POD#30
  - ✓ clinical evaluation

- **Intention-to-treat principle**

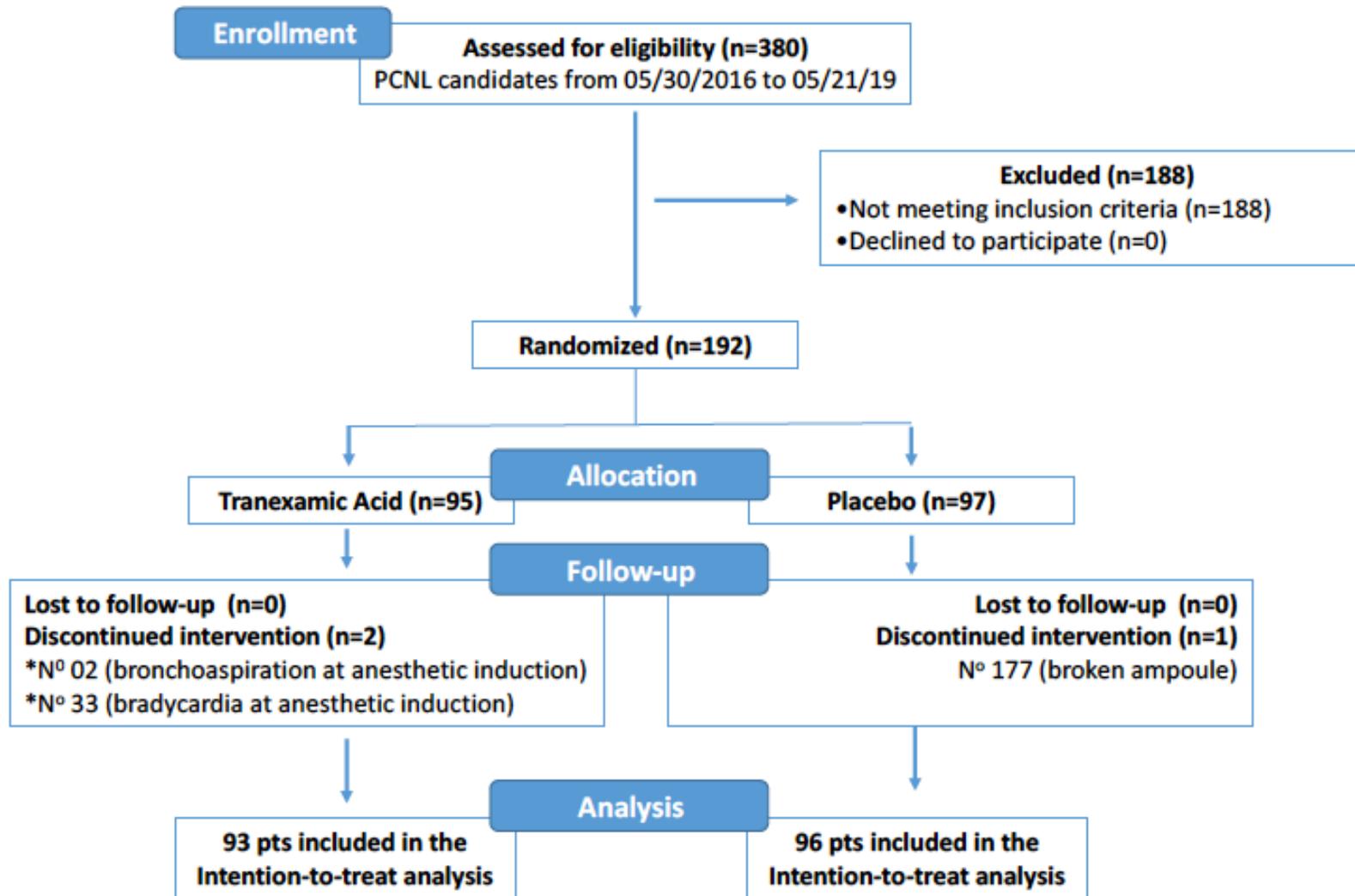
Lachin, J. M.: Statistical considerations in the intent-to-treat principle. *Control Clin Trials*, 21: 167, 2000

- **REDCap TM Software**



- **Clinical Trials (NCT02966236)**





CONSORT Flow diagram

# Results



## ➤ Demographics:

	Placebo (n=96)	Tranexamic acid (n=93)	p - value
<b>Age (y; mean [SE])</b>	45.65 (1.38)	44.16 (1.38)	0.450
<b>Female (n [%])</b>	65 (67.7)	61 (65.6)	0.758
<b>Race (n [%])</b>			0.472
White	39 (40.6)	47 (50.5)	
Black	16 (16.8)	12 (12.9)	
Yellow	1 (1.1)	2 (2.2)	
Brown	40 (42.1)	32 (34.4)	
<b>Symptoms (n [%])</b>			
assymptomatic	3(3.1)	6 (6.5)	0.325
pain	79 (82.3)	80 (86.0)	0.553
hematuria	3(3.1)	2(2.2)	1
UTI	56 (58.3)	53 (57.0)	0.884
<b>Symptoms lenght (mo; min-max [IQ])</b>	1-76 (24)	2-84 (24)	0.909
<b>Comorbidities (n [%])</b>			
HTN	35 (36.5)	27 (29.0)	0.284
DM	17 (17.7)	12 (12.9)	0.359
DLP	13 (13.5)	12 (12.9)	0.897
obesity	33 (33.3)	30 (32.3)	0.878
CKD (30<CrCl<60)	17 (17.7)	14 (15.1)	0.696
<b>ASA (n [%])</b>			0.849
I	29 (30.2)	30 (32.3)	
II	55 (57.3)	54 (58.1)	
III	12 (12.5)	9 (9.7)	
<b>Charlson Index (min-max [IQ])</b>	0-8 (2)	0-6 (2)	0.339

# Results



## ➤ Demographics:

	Placebo (n=96)	Tranexamic acid (n=93)	p - value
<b>Previous Ipsilat Treat (n [%])</b>	48 (50.0)	52 (55.9)	0.467
ESWL	16 (16.7)	21 (22.6)	0.361
URS	11 (11.5)	9 (9.7)	0.814
RIRS	3 (3.1)	2 (2.2)	1.000
PCNL	29 (30.2)	23 (24.7)	0.420
JJ/nephrostomy	11 (11.5)	10 (10.8)	1.000
Anatrophic	1 (1.0)	0 (0.0)	1.000
Open Pyelolithotomy	2 (2.1)	1 (1.1)	1.000
<b>Previous Contralat Treat (n</b>	32 (33.3)	27 (29.0)	0.535
ESWL	12 (12.5)	9 (9.7)	0.645
URS	10 (10.4)	11 (11.8)	0.820
RIRS	1 (1.0)	1 (1.1)	1.000
PCNL	22 (22.9)	16 (17.2)	0.367
JJ/nephrostomy	6 (6.3)	8 (8.6)	0.588
Anatrophic	2 (2.1)	1 (1.1)	1.000
Open Pyelolithotomy	2 (2.1)	2 (2.2)	1.000
Nephrectomy	2 (2.1)	2 (2.2)	1.000

# Results



## ➤ Stone characteristics:

	Placebo (n=96)	Tranexamic acid (n=93)	p - value
<b>Stone features</b>			
right laterality (n [%])	56 (58.3)	48 (51.6)	0.382
Size (mm; mean [SE])	55.38(2.61)	54.28 (2.46)	0.760
density (HU; mean [SE])	916.6 (32.1)	943.4 (32.9)	0.561
<b>Guy's Stone Score (n [%])</b>			0.742
3	72 (75.0)	67 (72.0)	
4	24 (25.0)	26 (28.0)	
<b>Stone composition (n [%])</b>			0.772
Estruvite	47 (50.0)	39 (43.8)	
Calcium oxalate	35 (37.2)	34 (38.2)	
Calcium phosphate	4 (4.3)	6 (6.7)	
Cistine	3 (3.2)	3 (3.4)	
Uric acid	4 (4.3)	7 (7.9)	

# Results



## ➤ Operatory parameters:

	Placebo (n=96)	Tranexamic acid (n=93)	p - value
<b>Patient positioning (n [%])</b>			0.828
Prone	13 (13.5)	11 (11.8)	
Supine	83 (86.5)	82 (88.2)	
<b>Patient positioning (n [%])</b>			0.943
Prone	13 (13.5)	10 (10.8)	
complete supine	12 (12.5)	12 (12.9)	
Galdakao	13 (13.5)	11 (11.8)	
Barts	58 (60.4)	59 (63.4)	
Prone Split-leg	0 (00.0)	1 (1.1)	
<b>Operative time (min) (mean [SE])</b>			
cystoscopy->puncture	22.5 (1.24)	22.6 (1.43)	0.926
puncture->urethral catheter	101.9 (4.79)	98.4 (4.57)	0.599
<b>Anesthesia time (min) (mean [SE])</b>	196.1 (4.94)	200.2 (5.00)	0.556
<b>Operative room time (min) (mean [SE])</b>	246.6 (5.30)	245.9 (5.63)	0.937

# Results



## ➤ Operatory parameters:

	Placebo (n=96)	Tranexamic acid (n=93)	p - value
<b>Number of tracts (n [%])</b>			0.433
one	67 (69.8)	72 (77.4)	
two	27 (28.1)	19 (20.4)	
three	2 (2.1)	2 (2.2)	
<b>Calyx puncture, 1st (n [%])</b>			0.437
lower	62 (64.6)	55 (59.1)	
middle	30 (31.3)	30 (32.3)	
upper	4 (4.2)	8 (8.6)	
<b>Calyx puncture, 2nd (n [%])</b>			0.871
lower	9 (31.0)	6 (28.6)	
middle	14 (48.3)	9 (42.9)	
upper	6 (20.7)	6 (28.6)	
<b>Calyx puncture, 3rd (n [%])</b>			1
middle	1 (50)	1 (50)	
upper	1 (50)	1 (50)	

# Results



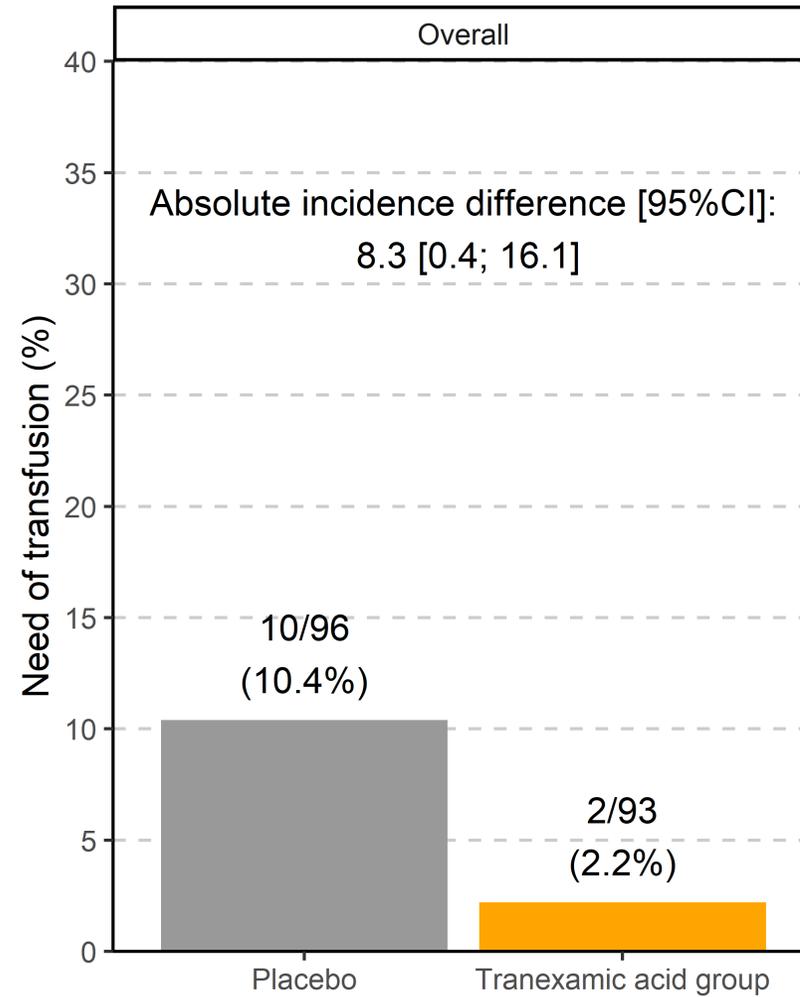
## ➤ Operatory parameters:

	Placebo (n=96)	Tranexamic acid (n=93)	p - value
<b>Access - anterior calyx (n[%])</b>	16 (18.2)	19 (21.8)	0.575
<b>Supra-costal access (n [%])</b>	18 (18.8)	24 (25.8)	0.295
<b>Flexible nephroscopy (n [%])</b>	47 (49.0)	39 (41.9)	0.381
<b>No flexible nephroscopy (n [%])</b>			0.632
no equipment available	6 (12.2)	10 (18.5)	
bleeding	16 (32.7)	17 (31.5)	
prolonged operative time	5 (10.2)	2 (3.7)	
no residual stones	14 (28.6)	18 (33.3)	
many residual stones	8 (16.7)	7 (13.0)	
<b>Kidney drainage (n [%])</b>			0.747
Nephrostomy tube	42 (43.8)	47 (50.5)	
nephro + JJ	19 (19.8)	14 (15.1)	
JJ stent only	22 (22.9)	19 (20.4)	
Ureteral catheter only	13 (13.5)	13 (14.0)	
<b>Radiation</b>			
time (sec; (mean [SE])	700.9 (47.79)	685.5 (37.77)	0.801
intensity (mGy; (mean [SE])	75.11 (6.38)	69.17 (5.31)	0.477
<b>Volume of crystalloids infused (mL) (mean [SE])</b>	1900 (76.7)	2033 (79.4)	0.230
<b>Hospital stay (hours) (mean [SE])</b>	67.23 (4.31)	65.27 (3.34)	0.720

# Results



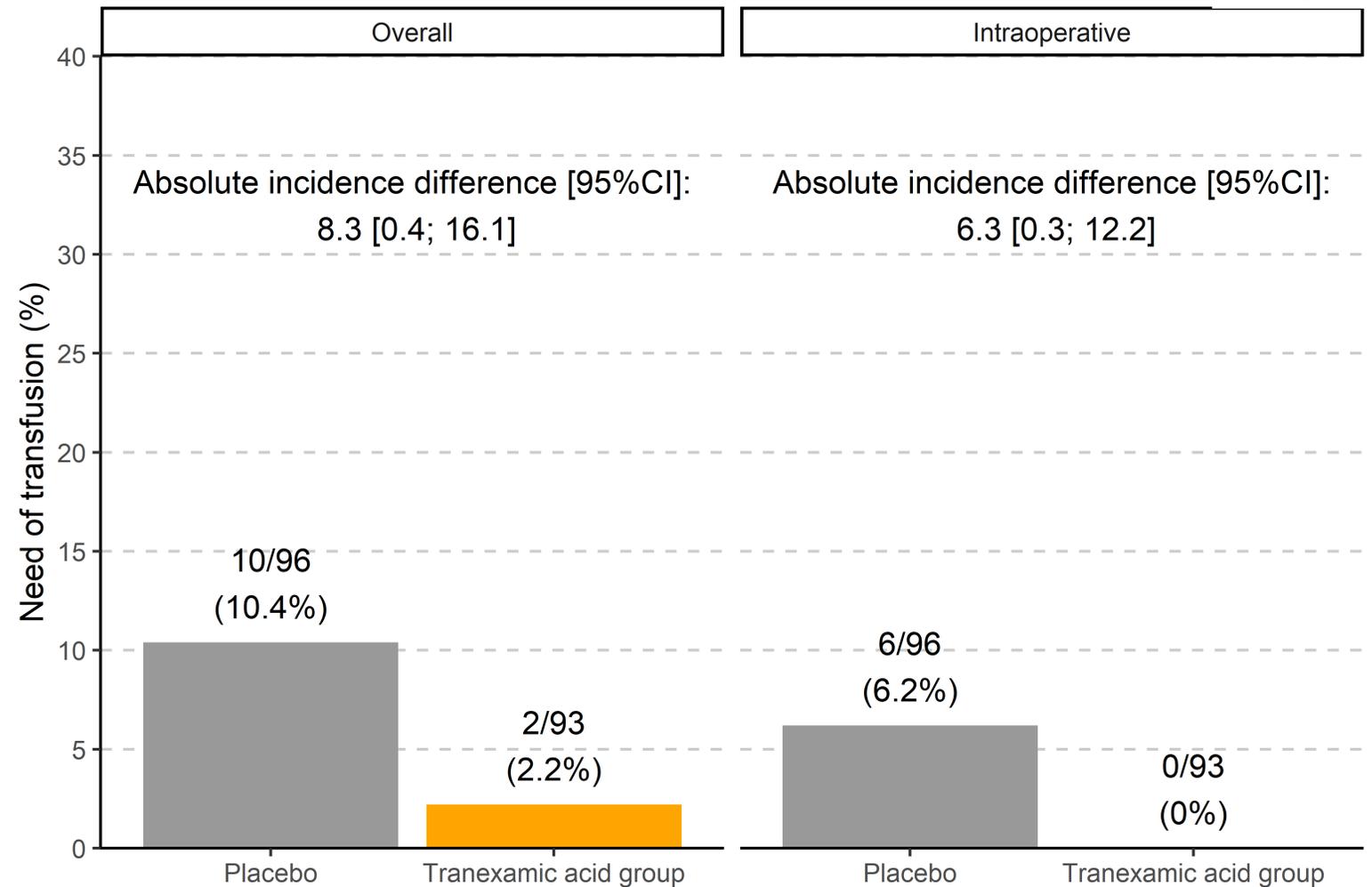
## ➤ Blood transfusion:



# Results



## ➤ Blood transfusion:



# Results



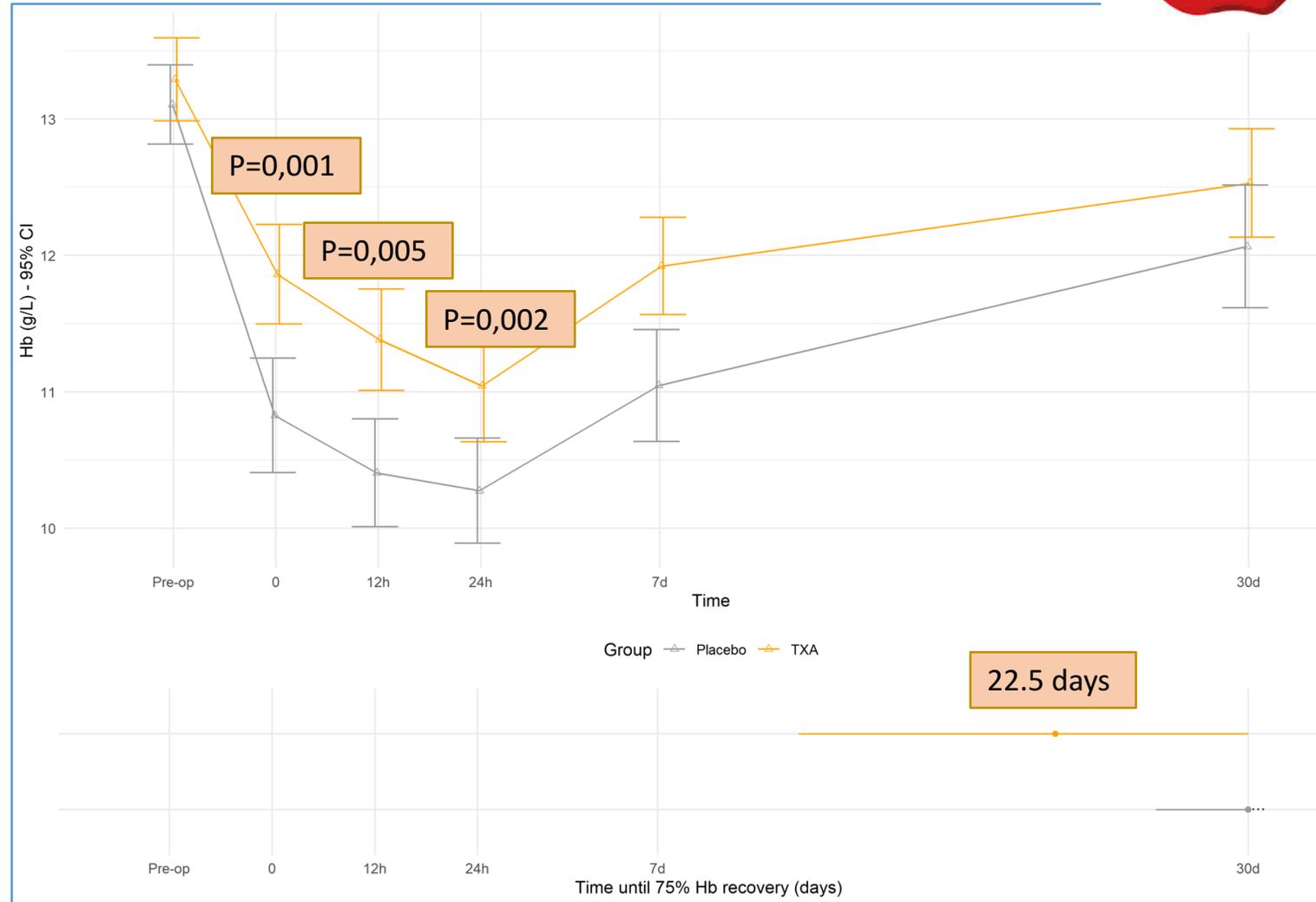
## ➤ Blood transfusion:

	Placebo (n=96)	Tranexamic acid (n=93)	Type of effect estimate	Effect estimate (95% CI)	p - value
<b>Blood transfusion, n (%)</b>					
overall	10 (10.4)	2 (2.2)	AD <sup>1</sup>	8,3 (0.4; 16.1)	0.033
intraoperative	6 (6.25)	0 (0.0)	AD <sup>1</sup>	6.3 (0.3; 12.2)	0.029
<b>Units of blood transfused, n (%)</b>					
1	4 (4.2)	1 (1.1)	-	-	
2	5 (5.2)	1 (1.1)	-	-	
3	1 (1.0)	0 (0.0)	-	-	
mean (SD) per patient	0.18 (0.56)	0.03 (0.23)	MR <sup>2</sup>	0.18 (0.04; 0.54)	0.006

# Results



## ➤ Hemoglobin kinetics:



### Hemoglobin Recovery:

**Tranexamic acid:**

**22.5 days (IQR, 12.5 -> 30+ days)**

# Results



## ➤ Hemodiluted hemoglobin:

	Placebo (n=96)	Tranexamic acid (n=93)	Type of effect estimate	Effect estimate (95% CI)	p - value
<b>Calculated total blood loss immediately after PCNL (mL), mean (SD)</b>	819.9 (828.6)	523.3 (549.3)	MD <sup>6</sup>	296.6 (89.7; 504.5)	0.006
<b>Calculated hemodiluted hemoglobin immediately after PCNL (mg/dL), mean (SD)</b>	10.1 (2.14)	10.6 (2.17)	MD <sup>6</sup>	-0.51 (-1.19; 0.17)	0.142

Ross et al, J Am Coll Surg. 2018

Ward et al, Anesthesiology: The Journal of the American Society of Anesthesiologists. 1980;53(3)



## ➤ Parameters of hemostasy:

	Placebo (n=96)	Tranexamic acid (n=93)	Type of effect estimate	Effect estimate (95% CI)	p - value
<b>D-dimer (<math>\mu\text{g/mL}</math>), mean (SD)</b>					
baseline	393.8 (291.3)	356.7 (177.7)	MD <sup>4</sup>	-0,3 (-88.1; 87.5)	0.997
12h	1723.6 (1705.8)	788.7 (706.0)	MD <sup>4</sup>	30.9 (298.7; 763.1)	<0.001
24h	1176 (1102.3)	806.0 (710.1)	MD <sup>4</sup>	233.7 (40.7; 426.7)	0.039
<b>Fibrinogen (mg/dL), mean (SD)</b>					
baseline	302.2 (80.8)	313 (84.3)	MD <sup>5</sup>	15.6 (-18.5; 49.7)	0.632
12h	287.5 (64.8)	320.4 (84.1)	MD <sup>5</sup>	31.6 (-2.2; 65.5)	0.142
24h	322.1 (83.3)	349.8 (90.2)	MD <sup>5</sup>	22.1 (-11.8; 56.1)	0.379
<b>Platelets (<math>\times 10^3/\text{dL}</math>), mean (SD)</b>					
baseline	266.3 (88.5)	256.1 (66.1)	MD <sup>5</sup>	-11.6 (-32.1; 8.8)	0.483
12h	227.9 (68.9)	220.1 (64.4)	MD <sup>5</sup>	-5.6 (-26.4; 15.2)	0.883
24h	210.5 (65.9)	210.0 (71.4)	MD <sup>5</sup>	-0.10 (-21.0; 20.8)	0.999
<b>Prothrombin time ratio, mean (SD)</b>					
baseline	1.02 (0.06)	1.01 (0.07)	MD <sup>5</sup>	-0.01 (-0.04; 0.02)	0.734
12h	1.08 (0.11)	1.09 (0.10)	MD <sup>5</sup>	0.00 (-0.02; 0.03)	0.982
24h	1.10 (0.13)	1.09 (0.11)	MD <sup>5</sup>	-0.01 (-0.03; 0.02)	0.962

# Results



## ➤ Success and 2<sup>nd</sup> procedure:

	Placebo (n=96)	Tranexamic acid (n=93)	p - value
<b>Single-session SFR, n(%)</b>			
Complete SFR	14 (14.6)	26 (28.0)	0.032
Success (RF≤4mm)	25 (26.0)	39 (41.9)	0.022
<b>3-month SFR, n(%)</b>			
Complete SFR	28 (29.2)	41 (44.1)	0.036
Success (RF≤4mm)	45 (46.9)	58 (62.4)	0.041
<b>Secondary procedure (n [%])</b>	38 (40.0)	45 (48.4)	0.304
PCNL	19 (50.0)	20 (44.4)	
RIRS	10 (26.3)	18 (40.0)	
SWL	7 (18.4)	5 (11.1)	
miniPerc	1 (2.6)	0 (0.0)	
Open pielolitotomy	1(2.6)	2 (4.4)	

# Results



## ➤ Complications:

	Placebo (n=96)	Tranexamic acid (n=93)	p - value
<b>Overall complications (n [%])</b>	21 (21.9)	14 (15.1)	0.264
<b>Clavien-Dindo Score</b>			0.425
minor (Clavien I-IIIa)	15 (15.6)	11 (11.8)	
major (Clavien IIIb-V)	6 (6.3)	3 (3.2)	
<b>Perioperative complications (n[%])</b>			
Blood transfusion	10 (10.4)	2 (2.2)	0.033
Sepsis	5 (5.2)	2 (2.2)	0.445
Acute renal insufficiency	8 (8.3)	5 (5.4)	0.568
Pleural effusion (Chest tube)	0 (0.0)	2 (2.2)	0.241
Ureteral stone (URS)	4 (4.2)	2 (2.2)	0.683
Pulmonary embolism	0 (0.0)	2 (2.2)	0.241
Colonic injury	1 (1.0)	1 (1.1)	1
Death	1 (1.0)	0 (0.0)	1
<b>Readmissions</b>			
yes (n [%])	4 (4.2)	7 (7.5)	0.367
POD, median (min-max)	4 (4-9)	6 (2-19)	0.642
<b>Readmission etiology (n [%])</b>			1.000
pleural effusion	0 (0.0)	1 (1.1)	
sepsis	2 (2.1)	2 (2.2)	
intrarenal pseudoaneurysm	0 (0.0)	1 (1.1)	
ureteral stone	2 (2.1)	1 (1.1)	
ureteral clot	0 (0.0)	1 (1.1)	

# Conclusions

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- **Results:**
  - ✓ Transfusion rate ( $p=0.003$ )
  - ✓ Hb drop ( $p=0.005 - 0.043 - 0.009$ )
  - ✓ Faster Hemoglobin recovery
  - ✓ SFR ( $p=0.03$ )
  - ✓ Complications ( $p=0.36$ )
  
- **Inclusion of Tranexamic acid on PCNL Guidelines**

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