Clinical trial results:
Efficacy of topical tranexamic acid versus intravenous administration to reduce blood transfusion rate in total knee arthroplasty surgery: phase III, unicentric, controlled, double-blind, randomized non-inferiority clinical trial.

Summary

EudraCT number	2011-003218-17
Trial protocol	ES
Global end of trial date	28 October 2013

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	JBJ article (00004623-201412030-00001.pdf)

Trial information

Trial identification

Sponsor protocol code	TRANEX1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01881568
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hospital Universitario La Paz-Cantoblanco
Sponsor organisation address	Pso. de la Castellana 261, Madrid, Spain, 28046
Public contact	PharmD. MPH Norma G. Padilla Eguiluz, Universidad Autónoma de Madrid-Hospital Universitario La Paz-IdiPAZ, 34 654807102, norma.padilla@uam.es
Scientific contact	Prof. Enrique Gómez Barrena, Department of Orthopaedic Surgery and Traumatology, Hospital Universitario La Paz, 34 917277085, egomezb@salud.madrid.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of topical intra-articular application of 3 g of TXA compared with IV administration of two 15-mg/kg doses during primary unilateral total knee replacement with cemented implants.

Protection of trial subjects:

Patients with preoperative anaemia (haemoglobin, <13 g/dL) were not excluded; instead, they were offered the current standard preoperative protocol at our institution (IV administration of iron and/or subcutaneous administration of 40,000 IU of erythropoietin), and surgery was postponed until the haemoglobin level was ‡13 g/dL. All patients were instructed to discontinue aspirin, anti-platelet agents, and nonselective cyclooxygenase inhibitors at least seven days prior to surgery. T

Background therapy: -

Evidence for comparator:

The use of tranexamic acid (TXA) in primary total knee replacement with cemented implants is supported by studies with a level of evidence of I that confirm its efficacy for decreasing blood loss(1-4), although safety concerns have not been confirmed in studies comparing TXA treatment against placebo, which showed equivalent safety(3,5-8). Although blood loss prevention protocols have been adopted at many institutions, there are concerns regarding intravenous (IV) administration of TXA in some settings, and topical administration may be considered an appealing alternative that is potentially less risky than systemic administration.

1. Tan J et al. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. J Surg Res. 2013 Oct;184(2):880-7.
2. Kim TK et al. Practical issues for the use of tranexamic acid in total knee arthroplasty: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2013 Mar 31.
3. Gandhi R et al. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. BMC Res Notes. 2013;6(1):184.
4. Yang ZG et al. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am. 2012 Jul 3;94(13):1153-9.
5. Alshryda S et al. Tranexamic acid in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br. 2011 Dec;93(12):1577-85.
6. Dunn CJ et al. Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999 Jun;57(6):1005-32.
7. Engel JM et al. Regional hemostatic status and blood requirements after total knee arthroplasty with and without tranexamic acid or aprotinin. Anesth Analg. 2001 Mar;92(3):775-80.
8. Gillette BP et al. Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty. Clin Orthop Relat Res. 2013 Jan;471(1):150-4.

Actual start date of recruitment	08 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 78
Worldwide total number of subjects	78
EEA total number of subjects	78

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	58
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

All adult patients scheduled to undergo primary unilateral total knee replacement with cemented implants in Cantoblanco University Hospital of Madrid, Spain, from January to October 2013 were eligible for inclusion.

Pre-assignment

Screening details:

Of the 93 candidate patients screened, 15 were excluded, and 78 were randomized in the control (n=39) or experimental (n=39) arm. None lost during follow up were observed in any arm of treatment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Patient assignments were prepared by a research statistician and were placed into sequentially numbered opaque sealed envelopes, only opened before each surgery. Uninvolved anesthesiologists prepared study medication and placebo (both identical in appearance) under the supervision of a research pharmacist not involved in patient care. Patients, surgeons, and health care participating in treatment and evaluation were blinded to the group allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Patients in the control group received a slow IV infusion of 100 mL of physiological saline solution containing a 15 mg/kg dose of TXA fifteen to twenty minutes before tourniquet release and a second identical dose three hours after surgery, on the basis of previous efficacy studies. In addition, patients in this group received a topical intra-articular placebo (100 mL of physiological saline solution).

Arm type	Active comparator
Investigational medicinal product name	Tranexamic Acid
Investigational medicinal product code	
Other name	Amchafibrin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

slow IV infusion of 100 mL of physiological saline solution containing a 15 mg/kg dose of TXA fifteen to twenty minutes before tourniquet release and a second identical dose three hours after surgery

Arm title	Experimental

Arm description:

The experimental group received a topical intra-articular dose of 3 g of TXA (Amchafibrin; Rottapharm) in 100 mL of physiological saline solution (0.9% sodium chloride solution; Grifols). Half of the volume was administered by irrigation to achieve tissue impregnation before joint closure, and the other half was administered intra-articularly after skin closure (through a 12-mm drain tube with the knee in a fully extended position after stapling and before tourniquet release). In addition, patients in this group received 100 mL of an IV placebo solution (physiological saline solution) fifteen to twenty minutes before tourniquet release and 100 mL three hours later. P

Arm type	Experimental

Investigational medicinal product name	Tranexamic Acid
Investigational medicinal product code	
Other name	Amchafibrin
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use, Topical

Dosage and administration details:

3 g of TXA (Amchafibrin; Rottapharm) in 100 mL of physiological saline solution (0.9% sodium chloride solution; Grifols). Half of the volume was administered by irrigation to achieve tissue impregnation before joint closure, and the other half was administered intra-articularly after skin closure (through a 12-mm drain tube with the knee in a fully extended position after stapling and before tourniquet release)

Number of subjects in period 1	Control	Experimental
Started	39	39
Completed	39	39

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Patients in the control group received a slow IV infusion of 100 mL of physiological saline solution containing a 15 mg/kg dose of TXA fifteen to twenty minutes before tourniquet release and a second identical dose three hours after surgery, on the basis of previous efficacy studies. In addition, patients in this group received a topical intra-articular placebo (100 mL of physiological saline solution).	
Reporting group title	Experimental
Reporting group description:	
The experimental group received a topical intra-articular dose of 3 g of TXA (Amchafibrin; Rottapharm) in 100 mL of physiological saline solution (0.9% sodium chloride solution; Grifols). Half of the volume was administered by irrigation to achieve tissue impregnation before joint closure, and the other half was administered intra-articularly after skin closure (through a 12-mm drain tube with the knee in a fully extended position after stapling and before tourniquet release). In addition, patients in this group received 100 mL of an IV placebo solution (physiological saline solution) fifteen to twenty minutes before tourniquet release and 100 mL three hours later. P	

Reporting group values	Control	Experimental	Total
Number of subjects	39	39	78
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	71.8	70.1	
standard deviation	± 10.3	± 9.1	-
Gender categorical Units: Subjects			
Female	25	26	51
Male	14	13	27

End points

End points reporting groups

Reporting group title	Control

Reporting group description:

Patients in the control group received a slow IV infusion of 100 mL of physiological saline solution containing a 15 mg/kg dose of TXA fifteen to twenty minutes before tourniquet release and a second identical dose three hours after surgery, on the basis of previous efficacy studies. In addition, patients in this group received a topical intra-articular placebo (100 mL of physiological saline solution).

Reporting group title	Experimental

Reporting group description:

The experimental group received a topical intra-articular dose of 3 g of TXA (Amchafibrin; Rottapharm) in 100 mL of physiological saline solution (0.9% sodium chloride solution; Grifols). Half of the volume was administered by irrigation to achieve tissue impregnation before joint closure, and the other half was administered intra-articularly after skin closure (through a 12-mm drain tube with the knee in a fully extended position after stapling and before tourniquet release). In addition, patients in this group received 100 mL of an IV placebo solution (physiological saline solution) fifteen to twenty minutes before tourniquet release and 100 mL three hours later. P

Primary: Transfusion rate

End point title	Transfusion rate

End point description:

End point type	Primary

End point timeframe:

48h post surgery

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: rate	0	0		

Statistical analyses

Statistical analysis title	Non-inferiority
Comparison groups	Control v Experimental
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	> 0.05 [1]
Method	Wilson
Parameter estimate	proportion

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.9
Variability estimate	Standard deviation

Notes:

[1] - No transfusion was performed in either group, confirming noninferiority for the primary efficacy endpoint (transfusion rate) and suggesting equivalence (95% CI according to the Wilson test, 29% to 9%).

Secondary: Total blood loss

End point title	Total blood loss

End point description:

The estimated total blood loss was calculated using the Nadler formula

End point type	Secondary

End point timeframe:

48h post-operative

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: ml				
arithmetic mean (standard deviation)	1626.0 (± 519.2)	1574.5 (± 542.9)		

Statistical analyses

Statistical analysis title	Non-inferiority
Comparison groups	Control v Experimental
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.205
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: During hospital stay and post-operative	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	0
Reporting groups	
Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Serious adverse events	Experimental	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
deep vein thrombosis	Additional description: a seventy-two-year-old woman had Doppler confirmation of a superficial venous thrombosis in the femoral vein at postoperative day 30, which was treated with therapeutic enoxaparin dose of 100mg/24 hr for three months and was no longer visible		
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Experimental	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 39 (10.26%)	8 / 39 (20.51%)	
Vascular disorders			
deep venous thrombosis suspected			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Hypertension subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 39 (5.13%) 2	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 39 (2.56%) 1	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2 0 / 39 (0.00%) 0	3 / 39 (7.69%) 3 1 / 39 (2.56%) 1	
Infections and infestations superficial injury infection subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	1 / 39 (2.56%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As no transfusion was needed in either group, the analysis was likely underpowered for confirming the superiority of either treatment with respect to blood loss, and larger studies may be warranted.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25471907