Clinical trial results:
Prevention of bleeding and edema in bi-maxillary orthognathic surgery; the effectiveness of tranexamic acid on intraoperative bleeding in orthognathic surgery

Summary

EudraCT number	2013-005473-52
Trial protocol	DK
Global end of trial date	24 October 2016

Results information

Result version number	v1 (current)
This version publication date	23 September 2021
First version publication date	23 September 2021

Trial information

Trial identification

Sponsor protocol code	40964

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hospital of South West Jutland
Sponsor organisation address	Finsensgade 35, Esbjerg, Denmark, 6700
Public contact	Kæbekirurgisk afd., Hospital of South West Jutland, +45 40269517, jesperjaredolsen@gmail.com
Scientific contact	Kæbekirurgisk afd., Hospital of South West Jutland, +45 40269517, jesperjaredolsen@gmail.com

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	14 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 May 2016
Global end of trial reached?	Yes
Global end of trial date	24 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is primarily to evaluate the effectiveness of tranexamic acid (TXA) on intraoperative blood loss - and secondarily postoperative swelling, in patients subjected to bi-maxillary orthognathic surgery. These surgical procedures are performed in anatomic areas rich in vessels, and intraoperative bleeding may pose a significant clinical problem. Tranexamic acid has been shown to significantly reduce intraoperative bleeding across the surgical fields, however within maxillofacial surgery few studies exist, and these are somewhat lacking in consistency and scope. Thus, the effect of TXA on intraoperative bleeding in patients subjected to simultaneous mandibular and maxillary osteotomy is uncertain and a carefully conducted, double-blinded, placebo controlled clinical study is needed.

Protection of trial subjects:

A risk assessment of the potential study subjects was secured by Sponsor and appointed clinical staff prior to trial start through the application of the predetermined selection criteria. The trial was performed according to- and approved by the local Data Monitoring, Ethics Committee as well as the Good Clinical Practice unit in order to monitor and guide the overall progress while protecting the rights and safety of trial patients.As many blood samples as possible were obtained with the trial subjects in full anesthesia, in order to minimize the pain from the needle prick from the collection of venous blood.

Background therapy:

All the study subjects recieved bi-maxillary corrective jaw surgery.

Evidence for comparator:

Tranexamic acid has been shown to significantly reduce intraoperative bleeding across the surgical fields, however within maxillofacial surgery relatively few studies exist, and these are somewhat lacking in consistency and scope. Thus, the effect of TXA on intraoperative bleeding in patients subjected to simultaneous mandibular and maxillary osteotomy is uncertain and a carefully conducted, double-blinded, placebo controlled clinical study is needed.

Actual start date of recruitment	10 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 104
Worldwide total number of subjects	104
EEA total number of subjects	104

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)	104
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This double-blinded placebo-controlled trial recruited patients eligible for orthognathic surgery of upper and lower jaw at the Hospital of South West Denmark (Esbjerg, Denmark) from August 2014 through October 2016.

Pre-assignment

Screening details:

One hundred and fifteen patients were screened for eligibility of which 104 were included of which 96 completed the trial according to protocol.

Period 1

Period 1 title	Intervention (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

The regional hospital pharmacy is responsible for the production of the randomization code and labels for test agents under GCP guidance prior to the start of the trial. During the trial the local hospital pharmacy is responsible for the preparation of the active drug and the placebo including marking the agent with the correct label according to the randomization code document.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

OS patients recieving the active drug consisting of 1 gram bolus intravenous administered tranexamic acid after the induction of general anesthesia

Arm type	Active comparator
Investigational medicinal product name	Tranexamic acid
Investigational medicinal product code	
Other name	TXA
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 gram bolus intravenous administered tranexamic acid

Arm title	Placebo

Arm description:

OS patients recieving inactive placebo agent consisting of 1 gram bolus intravenous administered sterile saline after the induction of anesthesia

Arm type	Placebo
Investigational medicinal product name	Physiological saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 ml of physiologic, sterile saline were administered a single, slow i.v. bolus injection as the placebo treatment.

Number of subjects in period 1	Intervention	Placebo
Started	52	52
Completed	51	45
Not completed	1	7
Consent withdrawn by subject	-	1
Protocol deviation	1	6

Baseline characteristics

Reporting groups

Reporting group title	Intervention

Reporting group description:

OS patients recieving the active drug consisting of 1 gram bolus intravenous administered tranexamic acid after the induction of general anesthesia

Reporting group title	Placebo

Reporting group description:

OS patients recieving inactive placebo agent consisting of 1 gram bolus intravenous administered sterile saline after the induction of anesthesia

Reporting group values	Intervention	Placebo	Total
Number of subjects	52	52	104
Age categorical			
Patients were aged between 18 and 53			
Units: Subjects			
Adults (18-64 years)	52	52	104
Gender categorical Units: Subjects			
Female	25	26	51
Male	27	26	53

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description:	
OS patients recieving the active drug consisting of 1 gram bolus intravenous administered tranexamic acid after the induction of general anesthesia	
Reporting group title	Placebo
Reporting group description:	
OS patients recieving inactive placebo agent consisting of 1 gram bolus intravenous administered sterile saline after the induction of anesthesia	
Subject analysis set title	3D facial scans
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
During the trial an amendment was added in order to measure the postoperative facial swelling in both groups. All other ananlyses incl. blood samples were the same as before the amendment. This results in to populations within the same study - a larger group which analyses the effect of tranexamic acid on bleeding, and a smaller group which concerns both bleeding ad swelling. Thus the 50 participants who are included with scans as well as bleeding measurements are contained in the larger population which pertains to "bleeding only" data. The active arm consisted of 16 males and 13 females and the placebo group consisted of 12males and 9 females. All of these were within same age category as the rest of the study subjects.	

Primary: Intraoperative bleeding

End point title	Intraoperative bleeding
End point description:	
The primary outcome was intraoperative bleeding determined by milliliters of blood in the suction canister and gauzes deducted from the volume of saline used intraoperatively.	
End point type	Primary
End point timeframe:	
Duration of surgery	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	45		
Units: millilitre(s)				
median (inter-quartile range (Q1-Q3))	275 (143 to 408)	403 (215 to 609)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Statistical analysis description:	
The Mann-Whitney U test was applied to compare differences between TXA and placebo. Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.	
Comparison groups	Intervention v Placebo

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Secondary: Platelet count t5 according to intervention group

End point title	Platelet count t5 according to intervention group

End point description:

End point type	Secondary

End point timeframe:

Measured five hours from start of surgery

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	45		
Units: Blood platelets/microlitre(s) of blood				
median (confidence interval 95%)	206 (174 to 252)	198 (169 to 265)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test

Statistical analysis description:

The Mann-Whitney U test was applied to compare differences between TXA and placebo. Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Hemoglobin at t5 according to intervention group

End point title	Hemoglobin at t5 according to intervention group
End point description:	
End point type	Secondary
End point timeframe:	
Five hours after start of surgery.	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	45		
Units: gram(s)/millilitre				
arithmetic mean (confidence interval 95%)	8.0 (7.4 to 8.8)	7.9 (7.3 to 8.6)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Statistical analysis description:	
The Mann-Whitney U test was applied to compare differences between TXA and placebo. Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.	
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Hematocrit at t5 according to intervention group

End point title	Hematocrit at t5 according to intervention group
End point description:	
End point type	Secondary
End point timeframe:	
Five hours after start of surgery.	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	45		
Units: litre(s)/litre(s)				
median (inter-quartile range (Q1-Q3))	0.39 (0.35 to 0.41)	0.37 (0.35 to 0.4)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test

Statistical analysis description:

The Mann-Whitney U test was applied to compare differences between TXA and placebo. Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Postoperative swelling according to intervention group

End point title	Postoperative swelling according to intervention group

End point description:

Subjects were scanned in the DAVID-SLS-2 scanner (SLS-2) [DAVID Vision Systems GmbH, Koblenz, Germany] at 48 hours (t48h) and 4 months (t4 months) postoperatively. At 48 hours the POS was assumed to peak and at four months the majority of POS was expected to have subsided2 serving as the baseline measure for POS. As a consequence, POS is in the current work defined in terms of the difference t48h - t4 months. Subjects were seated with their heads slightly tilted back supported by a headrest, and with teeth in maximal intercuspidal position. No splints were used postoperatively. Three scans (A, B, C) were needed for a full-face scan consisting of A) a frontal scan perpendicular to the facial midline and B, C) bilateral scans spaced approximately 45-55° measured from the facial midline.

End point type	Secondary

End point timeframe:

1st scanning is performed 48 hours postoperatively along with the 3rd blood sample.
2nd scanning is performed 4 months postoperatively along with the 4th blood sample.

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	21		
Units: millimeter(s)				
arithmetic mean (standard deviation)				
1: Neck	2.45 (± 4.14)	2.44 (± 3.07)		
2: Chin	1.67 (± 2.64)	1.92 (± 2.00)		
3: Mouth	2.76 (± 1.86)	3.27 (± 1.26)		
4: Nose	0.28 (± 0.76)	0.21 (± 0.46)		
5: Eyes	0.05 (± 0.49)	0.12 (± 0.54)		
6: Forehead	-0.13 (± 0.26)	-0.03 (± 0.18)		
7: Cheek	3.03 (± 1.39)	3.53 (± 1.29)		

Attachments (see zip file)	Facial scans.pdf

Statistical analyses

Statistical analysis title	Point wise Students t-test

Statistical analysis description:

Values represent spatial differences obtained in the region indicated

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [1]
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - Values equal to or lower than 0.05 are considered significant.
P-values according to facial region:
Neck: 0.99
Chin: 0.72
Mouth: 0.29
Nose:0.72
Eyes: 0.63
Forehead: 0.15
Cheek: 0.20

Secondary: Hemoglobin at t0 according to intervention group

End point title	Hemoglobin at t0 according to intervention group

End point description:

End point type	Secondary

End point timeframe:

At the start of surgery

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	41		
Units: gram(s)/millilitre				
arithmetic mean (confidence interval 95%)	8.3 (7.7 to 8.8)	8.3 (7.5 to 8.9)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Statistical analysis description:	

The Mann-Whitney U test was applied to compare differences between TXA and placebo. Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55 [2]
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[2] - Non significant correlation

Secondary: Hematocrit t0 according to intervention group

End point title	Hematocrit t0 according to intervention group
End point description:	

End point type	Secondary
End point timeframe:	

At the start of surgery

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	45		
Units: litre(s)/litre(s)				
arithmetic mean (confidence interval 95%)	0.39 (0.37 to 0.42)	0.39 (0.36 to 0.41)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test

Statistical analysis description:

The Mann-Whitney U test was applied to compare differences between TXA and placebo. The Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Wilcoxon (Mann-Whitney)
Variability estimate	Standard deviation

Secondary: Platelet count t0 according to intervention group

End point title	Platelet count t0 according to intervention group

End point description:

End point type	Secondary

End point timeframe:

At the start of surgery

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	41		
Units: Blood platelets/microlitre(s) of blood				
arithmetic mean (confidence interval 95%)	216 (174 to 250)	208 (170 to 258)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test

Statistical analysis description:

The Mann-Whitney U test was applied to compare differences between TXA and placebo. The Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.

Comparison groups	Placebo v Intervention

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Age of study subjects according to intervention group

End point title	Age of study subjects according to intervention group

End point description:

End point type	Secondary

End point timeframe:

Date of surgery

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	41		
Units: Years of age				
arithmetic mean (confidence interval 95%)	21 (19.0 to 28.8)	22 (20.0 to 27.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test

Statistical analysis description:

The Mann-Whitney U test was applied to compare differences between TXA and placebo. The Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Procedure length according to intervention group

End point title	Procedure length according to intervention group

End point description:

End point type	Secondary

End point timeframe:

Duration of surgery

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	45		
Units: Minutes				
arithmetic mean (confidence interval 95%)	240 (219 to 272)	254 (218 to 270)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test

Statistical analysis description:

The Mann-Whitney U test was applied to compare differences between TXA and placebo. The Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Weigth of study subjects according to intervention group

End point title	Weigth of study subjects according to intervention group

End point description:

End point type	Secondary

End point timeframe:

On the date of surgery

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	45		
Units: Kg(s)				
arithmetic mean (confidence interval 95%)	75 (65.5 to 82.8)	73.5 (61.0 to 83.0)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Statistical analysis description:	
The Mann-Whitney U test was applied to compare differences between TXA and placebo. The Kolmogorov-Smirnov test was used for the initial evaluation of distribution of data.	
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:	
From start of surgery and 48 hours after the first 3D scan	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Intervention

Reporting group description:

OS patients recieving the active drug consisting of 1 gram bolus intravenous administered tranexamic acid after the induction of general anesthesia

Reporting group title	Placebo

Reporting group description:

OS patients recieving inactive placebo agent consisting of 1 gram bolus intravenous administered sterile saline

Serious adverse events	Intervention	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events		0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Intervention	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 96 (0.00%)	0 / 96 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Only one event occured, which evidently was a consequence from the maxillofaxial surgical procedure. This has been cleared by the local GCP representative. Thus no adverse or serious adverse events are declared.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2014	It was decided to include patients recieving oral contraceptives. This was previously a cause for exclusion. The reason for the inclusion of oral contraceptive users was that the effect of these drugs on the hemostatic response to the surgery was thought to be negligble and by excluding this group a large proportion of the female study population would not represented in the final material.
03 November 2014	3D facial scans was added as a secondary outcome variable. This was done in order to quantify the degree of postoperative facial swelling and identify the possible effect of the active and placebo drug.
17 February 2015	The timing of the facial 3D scans were changed such that the preoperative scan, which initially was thought of as the "baseline" scan was moved to 4 months postoperative. The reason for this was that the movement of the jaw bones during surgery was identified as majo source of error due the concomitant shift in the overlying soft tissues. By scanning postoperatively a unifofm maxillofacial basis was secured and any changes in the surface structure more likely to stem from postoperative swelling alone. The reason for the four month mark was based on the clinical observation, that the majority of the facial edema has subsided at this point in time.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29232560