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Abstract. Orthognathic surgery can cause substantial bleeding. Recent meta-analyses concluded that there is a statistically significant reduction in perioperative blood loss with the preventive use of tranexamic acid (TA). However, the mean reported difference in bleeding was moderate, and the clinical relevance of this blood-sparing effect remains debated. We therefore conducted a prospective, double-blind, randomized, placebo-controlled equivalence study of the effect of TA in patients undergoing Lefort I or bimaxillary osteotomies. Our main outcome measure was total blood loss on postoperative day 1. The equivalence margin was ± 250 ml for the difference in blood loss and its 95% confidence interval. One hundred and forty-seven patients were randomized, of which 122 underwent bimaxillary osteotomies. Blood loss in the treatment group was 682 ± 323 vs. 875 ± 492 ml. The mean difference in bleeding was -132 [-243; -21] ml as per-protocol, but -193 [-329; -57] ml in intention-to-treat: the limits of this confidence interval exceeded the margin of equivalence. Similar results were obtained when analysing only patients undergoing bimaxillary osteotomy. Haemoglobin decreased by 1.8 ± 1.2 g/dl with TA, vs. 2.6 ± 1.1 g/dl with placebo ($p<0.001$). Our study did not demonstrate equivalence between TA and placebo on perioperative blood loss in orthognathic surgery. TA may reduce blood loss but without evidence of clinical consequences.

Orthognathic surgery can cause significant bleeding, sometimes requiring red blood cell (RBC) transfusion[1,2]. Among the many techniques proposed to decrease intraoperative blood loss, the anti-fibrinolytic agent, tranexamic acid (TA), can be an effective preventive treatment with a favourable risk–benefit ratio, as previously established in a wide variety of surgeries[3,4].

Up to 2020, a few randomized controlled trials (all with a relatively small sample sizes) and six meta-analyses have evaluated the effect of TA on blood loss in orthognathic surgery[5–10]. Despite heterogeneity between studies, all meta-analyses concluded that there is statistically significant reduction of surgical blood loss associated with the use of TA. However, the mean reported difference in bleeding between TA and placebo is moderate, ranging between -94 and -265 ml[5,10]. The limits of the 95% confidence interval (CI) indicating the maximal blood-sparing effect range from -133 to -381 ml[5,10]. As elective maxillary osteotomies are mostly performed in otherwise healthy young adults, the clinical relevance of TA-associated decrease in surgical bleeding remains debatable. Indeed, only one meta-analysis suggests a limited effect on reducing the RBC transfusion rate[9]. In addition, when differences in postoperative haematocrit or haemoglobin (Hb) level are observed, they are of minor amplitude. Conversely, the clinical impact of reducing blood loss can also include more refined end-points, such as the need for volume therapy, even without requiring RBC transfusion[11].

Based on the conclusions of the meta-analyses, our primary hypothesis is that blood loss will be reduced using preventive TA versus placebo, but to such an extent that TA will be equivalent to placebo in terms of clinical benefits in patients undergoing orthognathic surgery. We therefore performed a double-blind, randomized, controlled, parallel-arms equivalence study comparing preventive TA versus placebo. Our primary outcome was the effect on total blood loss. Our secondary outcomes included Hb level, transfusion rate, duration of surgery, volume expansion and length of hospital stay.

MATERIALS AND METHODS

This prospective, double-blind, randomized, placebo-controlled, parallel-arms, equivalence study was conducted at Lille University Hospital (France). It was approved by our regional ethics committee (Comité de Protection des Personnes CPP Nord-Ouest IV, 12 January 2016), and registered at Clinicaltrialsregister.eu (EudraCT Number: 2015-002175-24) and Clinicaltrials.gov (NCT02702128) before the first inclusion. All participants, or their legal guardian, provided written informed consent prior to enrollment. The trial was conducted in accordance with the CONSORT statement guidelines.

Population

Patients scheduled for a standard Lefort 1 or bimaxillary osteotomy with a preoperative Hb >12 g/dl and an American Society of Anesthesiologists (ASA) risk classification of I–II were eligible. Patients with any haemostasis disorder, under anticoagulant or anti-platelet therapy, and patients with a history of severe renal failure, seizures, or recent thromboembolic events were not included.

Study design

After inclusion, patients were randomly allocated in a one-to-one ratio to receive either TA or placebo. The randomization sequence was provided by an independent statistician (who did not take part in assessing the patients at any point in the study) using computer-generated random numbers with block sizes of six.

97 The management of general anaesthesia was left to the discretion of the
98 anaesthesiologists, according to their standard practice, with the aim of maintaining
99 mean arterial blood pressure (MBP) between 65 and 75 mmHg, and end-tidal CO_2
100 ($etCO_2$) between 30 and 35 mmHg. All patients remained in the supine position with
101 their head lifted and supported by a gel headrest throughout the procedure. For local
102 anaesthesia, patients received 5–10 ml of 1% lidocaine with epinephrine, as per
103 department's usual practice.

104 The intravenous preventive TA protocol consisted of 1g in 30 min during
105 anaesthetic induction, then 1g over the next 8 h. The study kits thus contained two
106 identical 30-ml syringes filled with a transparent solution, which could be either 2 × 1g
107 of TA or saline according to the patient's group. The patient and the anaesthetic team in
108 charge were blinded to the group allocation. The first syringe was injected over 30 min
109 during anaesthesia induction, and immediately followed by the second, which was
110 administered over the next 8 h. According to our institutional protocol for this type of
111 surgery, patients received RBC transfusion if their Hb level was below 7 g/dl.

112 Acceptable total blood loss (Z) was calculated at the beginning of the procedure
113 as previously described[12]:

114 $Z\ (mL) = TBV \times 2 \times (Hb_i - Hb_t) / (Hb_i + Hb_t)$,

115 where total blood volume (TBV; ml) = weight (kg) × 70 for women; weight (kg) × 75
116 for men; Hb_i = initial Hb level (g/dl), obtained during pre-operative assessment; Hb_t =
117 transfusion threshold for this type of surgery = 7 g/dl.

118 For safety reasons, if estimated intraoperative bleeding was greater than half the
119 acceptable blood loss, the group allocation was unblinded, and patients from the

120 placebo group received a bolus of 1g of TA in 30 min, followed by a maintenance dose
121 of 1 g of TA over 8 h as a curative therapy, according to our routine standard practice.
122 The management of patients from the TA group was unchanged.

123

124 **Data collection**

125 Patient characteristics and Hb_i were recorded preoperatively.

126 The following data were collected during surgery: number and duration of
127 episodes of elevated MBP (>75 mmHg), number and duration of episodes of $etCO_2$
128 outside the 30- to 35-mmHg range, duration of surgery, intraoperative blood loss. Blood
129 loss was calculated by adding the amount of blood in the suction canisters (difference
130 between the total fluid volume in the suction canisters and the irrigation fluid), and the
131 amount of blood in the surgical gauze: in the operating room, the blood-soaked gauzes
132 were weighed before and after use. The difference between wet and dry weight was
133 converted into milliliters of bleeding (1g = 1 ml).

134 On postoperative day 1 (POD1), Hb level was measured (Hb_{POST}), and Hb
135 perioperative variation was calculated ($\Delta Hb = Hb_i - Hb_{POST}$). Postoperative blood loss
136 (drainage) was recorded, and total blood loss was calculated (total blood loss =
137 intraoperative blood loss + postoperative blood loss). Finally, length of hospital stay
138 was recorded at patient's discharge.

139

140 **Aims and outcomes**

141 Our primary aim was to compare blood loss between TA and placebo groups.
142 Our main outcome measure was total blood loss on POD1. The secondary aims were to

compare between the groups: duration of surgery, ΔHb, transfusion rate, and length of hospital stay. The importance of blood loss was also appreciated by comparing intraoperative volume expansion.

Statistical analysis

Our hypothesis was that bleeding in patients receiving placebo would not clinically differ from bleeding with preventive TA in our population and surgical context. We therefore decided to perform an equivalence study. Based on clinical judgment, we decided to set the equivalence margin at 250 ml, and defined an equivalence interval from -250 ml to +250 ml of total blood loss. We believed this was the minimal difference which could potentially lead to therapeutic modifications. As recommended, we planned a per-protocol analysis, secondarily completed by an intention-to-treat (ITT) analysis.

In order to determine the accurate standard deviation (SD) for the main outcome measure (total bleeding) in our centre and our population, we retrospectively reviewed the electronic charts of the patients corresponding to our inclusion criteria over a period of 3 months (unpublished data). Based on this evaluation, the SD of the main outcome measure 'total bleeding' was estimated at 450 ml. Considering two one-sided tests at 0.025 level, equal means in experimental and control arms, a power of 80%, it was necessary to include 140 patients. We decided to include consecutive eligible patients until we reached a total of 140 subjects for the per protocol analysis. Continuous variables are expressed as mean ± SD in the case of normal distribution or medians [interquartile range] otherwise. Normality of distributions was assessed using

histograms and the Shapiro–Wilk test. Categorical variables are expressed as numbers (percentage). Patient characteristics at inclusion are described according to study groups without formal statistical comparisons.

For the main analysis, the difference in total bleeding between groups is expressed as mean [95% CI]. A 95% CI entirely included in the -250 ml to +250 ml interval would lead to reject the null hypothesis and conclude to equivalence. The per protocol analysis (patients without major deviation in protocol as described in the results section) was considered as the primary analysis. A sensitivity analysis was performed on the ITT population including all randomized patients.

Other comparisons between the TA group and the placebo group were performed using Chi-squared tests for categorical variables and Student's *t* or Mann–Whitney U tests (depending on the normality of the distributions) for continuous variables.

Data were analysed using the SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

One hundred and fifty-seven patients were included in the study. Ten patients were excluded prior to surgery (nine because surgical indication was modified, one patient withdrew consent). The remaining 147 patients were randomized and underwent surgery. Bleeding exceeded half the acceptable blood loss in seven patients: two (2.7%) in the TA group and five (6.8%) in the placebo group (p=0.28). For these seven patients, the unblinding procedure was applied. In two of these patients (one in each group), acute bleeding was caused by an accidental vascular wound. No patient was lost to follow-up. Thus, 140 patients completed the trial to its end, and were included in the per protocol (PP) analysis. The ITT analysis was performed on the 147 patients who underwent surgery. The flow-chart is presented in Fig. 1.

Patient characteristics and preoperative data are described in Table 1. All patients were operated by a senior surgeon. Twenty-five percent of the patients in the TA group, and 27% of the patients in the placebo group had a segmentation of the upper jaw. There were no differences between TA and placebo group regarding the duration of surgery, the time spent with a MAP >75 mmHg or outside the 30- to 35-mmHg $etCO_2$ range (Table 2).

Blood loss, volume expansion, and ΔHb are illustrated in Fig. 2 and Table 3. As per protocol, the difference in total bleeding (TA - placebo group) between the groups was -132 [-243; -21] ml, within the pre-specified equivalence margins (± 250 ml). These results were not confirmed in the ITT analysis: difference -193 [-329; -57] ml. Volume expansion was not different between the groups. ΔHb was lower in the TA group. To further characterize the interest of prophylactic TA on surgical bleeding, we calculated, as a post hoc analysis, the proportion of patients with a blood loss exceeding

1200 ml in each group: incidence was higher in the Placebo group than in the TA group in the ITT analysis (Table 3).

As a post hoc analysis, we studied total blood loss in the patients who underwent bimaxillary osteotomies. As per protocol, blood loss in the treatment group (n = 58) was 707 ± 278 vs. 843 ± 368 ml in the placebo group (n = 58). The difference in total bleeding (TA - placebo group) between the groups was -135 [-255 to -15] ml. The lower limit of the confidence interval was close but outside the pre-specified equivalence margins. These results were confirmed in the ITT analysis: blood loss was 734 ± 320 (treatment group; n = 60) vs. 906 ± 439 ml (placebo group; n = 62); difference: -172 [-309; -34] ml.

Length of hospital stay was similar in both groups (ITT: 5 [4–5] vs. 5 [5–5] days, p=0.15; PP: 5 [4–5] vs. 5 [5–5] days, p=0.30). No patient had any thromboembolic complication.

One patient required a blood transfusion. This 16-year-old female undergoing bimaxillary osteotomy was one of two patients whose surgery was complicated by a vascular wound with acute massive bleeding. Total bleeding was 1834 ml. After having lost more than half the acceptable blood loss, group allocation was unblinded: the patient was in the placebo group, and therefore received curative TA.

A detailed table with the blood loss per patient, type and duration of surgery is available in the Supplementary Material.

DISCUSSION

Our trial could not demonstrate that in standard Lefort I or bimaxillary osteotomy, total blood loss with preventive TA (1g in 30 min followed by 1g over 8 h) was equivalent to total bleeding with placebo. Our results also indicated that preventive TA was not associated with clinically significant postoperative benefits. This trial was the first to include more than 100 patients undergoing this specific type of surgery, and the first to test an equivalence hypothesis.

From a methodologic point of view, failure to demonstrate equivalence does not rule out equivalence, but does not either allow conclusion of a difference. Nevertheless, the incidence of surgical bleeding >1200 ml was three times higher in the placebo group than in the TA group. This amount of blood loss was chosen as it represents 20–25% of TBV in young adult patients, close to the 30% threshold indicating that transfusion is 'probably necessary'[11]. In the conditions of the study, this was however not accompanied by an increased intraoperative fluid administration in the placebo versus TA group nor a greater number of patients in whom intraoperative blood loss exceeded half the calculated acceptable blood loss. We also report a lower ΔHb in the TA group, but this difference was of little clinical relevance. Apart from one patient, no subject required transfusion. Several reasons might explain these results: our patients had no major comorbidities, the pre-operative Hb level was relatively high in both groups, and surgical procedures were expected to be standard. Thus, lack of equivalence on total bleeding and ΔHb had no consequences for the patients in terms of volume expansion, transfusion and hospital length of stay.

We chose to perform an equivalence trial to specifically assess the clinical relevance of TA in maxillary osteotomies, instead of an additional superiority trial,

254 which would probably have yielded similar results to the already published reports,
255 showing a statistically significant difference in surgical bleeding. The advantage of the
256 equivalence design was that the limits of 'equivalence' are pre-specified and based on
257 clinical considerations. The choice of a 250-ml equivalence margin might however be
258 questioned and may be considered as a limitation of our study. The preliminary 3
259 months' retrospective review we performed prior to designing this trial revealed that
260 mean blood loss in our target population was around 700 ml (unpublished data). These
261 results were discussed within our medical team: for this procedure, surgical bleeding
262 would be considered clinically equivalent if it remained between 500 and 1000 ml.
263 Based on these observations and conclusions, we decided to set the equivalence margin
264 at 250 ml. The interpretation of our results might have been different with another
265 definition of the clinically relevant equivalence interval.

266 The discrepancy between the results obtained with the per-protocol and the ITT
267 analyses is likely due to the design of the study. Indeed, the seven patients excluded
268 from the per-protocol analysis, but not from the ITT, were those who had a surgical
269 blood loss exceeding half the acceptable bleeding calculated before the procedure, thus
270 directly affecting our main outcome measure. Although it might be considered as
271 another limitation of this study, the decision to unblind the allocation group for these
272 patients was based on safety and ethical concerns. Indeed, at this stage, we believed the
273 situation required TA as a curative treatment: exceeding this bleeding threshold might
274 have increased the morbidity in the placebo group. It is worth noting that this situation
275 occurred in fewer than 10% of patients, even in the placebo group.

276 The TA-related difference in bleeding reported in our study was close to the
277 conclusions of two former meta-analyses, which calculated an overall difference of 94

278 [55–133] and 171 [100–235] ml[5,6]. The lower ΔHb in the TA group was also in line
279 with the conclusions of the meta-analyses. No clinical trial investigating surgical
280 bleeding in orthognathic surgery could actually demonstrate an effect of TA on the risk
281 of allogenic blood transfusion. One of the six recent meta-analyses suggested a limited
282 effect of TA on transfusion rate but the total transfusion rate in the pooled control
283 groups was 7%, which appears to be higher than in our study (1%)[9].

284 Among the available data on preventive TA in orthognathic surgery, only two
285 randomized controlled superiority trials report a difference in bleeding exceeding 250
286 ml[13,14]. However, in both studies, mean intraoperative bleeding in the control group was
287 around 1200 ml, well above what was observed in our patients. These studies, although
288 reporting the largest TA-related difference in bleeding, could not demonstrate the
289 clinical relevance of their results, and neither could any of the meta-analyses.

290 Our analysis mixed single- and double-jaw surgeries. However, bimaxillary
291 surgery generally results in greater blood loss than standard Lefort 1. We therefore
292 repeated the main analysis in the 122 of our 147 patients who had undergone
293 bimaxillary surgery. Restriction to this population was indeed associated with a slight
294 increase in mean bleeding, but did not change the result of the main analysis: the limits
295 of the 95% CI of the difference in total bleeding still exceeded the equivalence margin.

296 Although it exceeded our preset equivalence margin and does not allow the
297 conclusion of equivalence, the difference in surgical bleeding between TA and placebo
298 remained modest. As a first hypothesis to explain this finding, it is possible that our
299 study lacked the sufficient power to demonstrate equivalence. But our main hypothesis
300 was that the moderate bleeding associated with this surgery might not lead to rapid or
301 major fibrinolysis, thus limiting the impact of a preventive infusion of TA. Another

hypothesis would be that, on the contrary, our TA dosage might have been too low: a higher dose might have induced a larger difference between the groups. However, several arguments make this latter hypothesis unlikely. There is a wide variety in the doses used in the available published studies, and no firm recommendations indicating the optimal dosage for prophylactic TA. We therefore chose the dosage used in the international multicentre CRASH-2 study[15], in which this TA dose proved effective in reducing bleeding in trauma patients. We believed that if it was effective and safe in severe trauma patients, this dosage would be sufficient in uncomplicated orthognathic surgery. This dosage was also described in recent European guidelines[16]. Moreover, positive results were obtained with smaller TA doses ranging from 10 to 20 mg/kg, or with only a single bolus (1 g)[13,14,17,18]. Finally, the dosage we chose for preventive TA was similar to the one we routinely use when curative TA is administered for major bleeding in our department: it is thus unlikely that TA may have been underdosed.

Our study has several other limitations. The 'equivalence margins' (± 250 ml) which were used in this study were chosen with regard to the potential increase in the risk of RBC transfusion. This is classically one of the final endpoints used in the meta-analyses to assess the clinical relevance of blood-sparing strategies. However, the quality of the surgical field may be altered by bleeding, even if the amount of blood is less than 250 ml. Most of the published studies provide data on the duration of surgery, a criterion that depends in part on the quality of the surgical field. In our study, the duration of surgery was not different between the groups.

In conclusion, our study could not demonstrate equivalence between TA and placebo on perioperative blood loss in orthognathic surgery. TA use may reduce blood loss and the decrease in Hb level, but without evidence of clinical consequences. This is

326 probably due to the characteristics of this surgical procedure, and of the population
327 undergoing this type of surgery, specifically young patients with no major comorbidity
328 and normal pre-operative Hb level. Investigations focused on more fragile patients or
329 more hemorrhagic procedures, preventive protocols combining TA with other blood-
330 sparing strategies might demonstrate clinically meaningful results.

331

332

333

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None.

Competing interests

None.

Ethical approval

This study was approved by our regional ethics committee (Comité de Protection des Personnes CPP Nord-Ouest IV – 12 January 2016), and registered at Clinicaltrialsregister.eu (EudraCT Number: 2015-002175-24) and Clinicaltrials.gov (NCT02702128) before the first inclusion.

Patient consent

All participants, or their legal guardian, provided written informed consent prior to enrolment.

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Supplementary material

Supplementary material related to this article can be found in the online version at:

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420

421

422 *Table 1.* Patient characteristics and preoperative data.

	TA group (n = 72)	Placebo group (n = 68)
Age (years)	28 ± 11	24 ± 10
Sex (M/F)	28/44	30/38
BMI (kg/m^2)	23 ± 5	22 ± 4
Palatal expansion in the year before surgery	2	3
Surgery (Lefort I/bimaxillary osteotomy)	14/58	10/58
Hb_i (g/dl)	14.3 ± 1.2	14.3 ± 1.2

423 BMI, body mass index; Hbi, preoperative haemoglobin level; TA, tranexamic acid.

424 Values are presented as mean ± standard deviation or numbers of subjects.

425

426 *Table 2.* Duration of surgery; intraoperative mean blood pressure and end-tidal CO_2.

		TA group	Placebo group	p
Duration of surgery	PP	182 ± 51	188 ± 59	0.56
(min)	ITT	183 ± 51	191 ± 61	0.43
Number of episodes with	PP	2 [1–3]	2 [1–4]	0.26
MBP >75 mmHg	ITT	2 [1–3]	2 [1–4]	0.32
Duration of episodes with	PP	13 [4–40]	20 [5–40]	0.51
MBP >75 mmHg (min)	ITT	15 [5–40]	20 [5–40]	0.50
Number of episodes with	PP	1 [0–2]	1 [1–2]	0.19
$etCO_2$ <30 or >35 mmHg	ITT	1 [0–2]	1 [1–2]	0.31
Duration of episodes with	PP	17 [0–38]	24 [4–56]	0.16
$etCO_2$ <30 or >35 mmHg (min)	ITT	20 [0–45]	24 [4–53]	0.31

427 $etCO_2$, end-tidal CO_2; ITT, intention-to-treat analysis (TA: n = 74; placebo: n = 73);
428 MBP, mean blood pressure; PP, per protocol analysis (TA: n = 72; placebo: n = 68);
429 TA, tranexamic acid. Values are presented as mean ± standard deviation or median
430 [interquartile range].

431

Table 3. Total blood loss and main clinical impact.

		TA group	Placebo group	p
Total blood loss	PP	660 ± 287	791 ± 370	*
(ml)	ITT	682 ± 323	875 ± 492	
Volume expansion	PP	1500 [1010–1745]	1500 [1020–1755]	0.63
(ml)	ITT	1500 [1010–1750]	1500 [1100–2000]	0.31
Δ Hb	PP	1.8 ± 1.2	2.5 ± 1.1	<0.001
(g/dl)	ITT	1.8 ± 1.2	2.6 ± 1.1	<0.001
Blood loss >1200 ml	PP	4 (5.6)	9 (13.2)	0.12
Number of subjects (%)	ITT	5 (6.8)	14 (19.2)	0.025
Blood transfusion	PP	0 (0)	0 (0)	NA
Number of subjects (%)	ITT	0 (0)	1 (1.4)	NA

ITT, intention-to-treat analysis (TA: $n = 74$, placebo: $n = 73$); NA, not applicable; PP, per protocol analysis (TA: $n = 72$, placebo: $n = 68$); TA, tranexamic acid. Values are presented as mean ± standard deviation, median [interquartile range] or numbers (percentage).

*p-Value not computed (primary analysis performed using confidence intervals).

439 **CAPTIONS**

440 *Fig. 1.* Study flow chart.

441

442 *Fig. 2.* Difference in mean surgical bleeding (tranexamic Acid (TA) - placebo) (ml).
443 Vertical marks on the arrows represent mean differences. [-250; +250] ml represents
444 pre-specified equivalence margins. Broken line: 95% confidence interval – intention-to-
445 treat analysis. Solid line: 95% confidence interval – per-protocol analysis.

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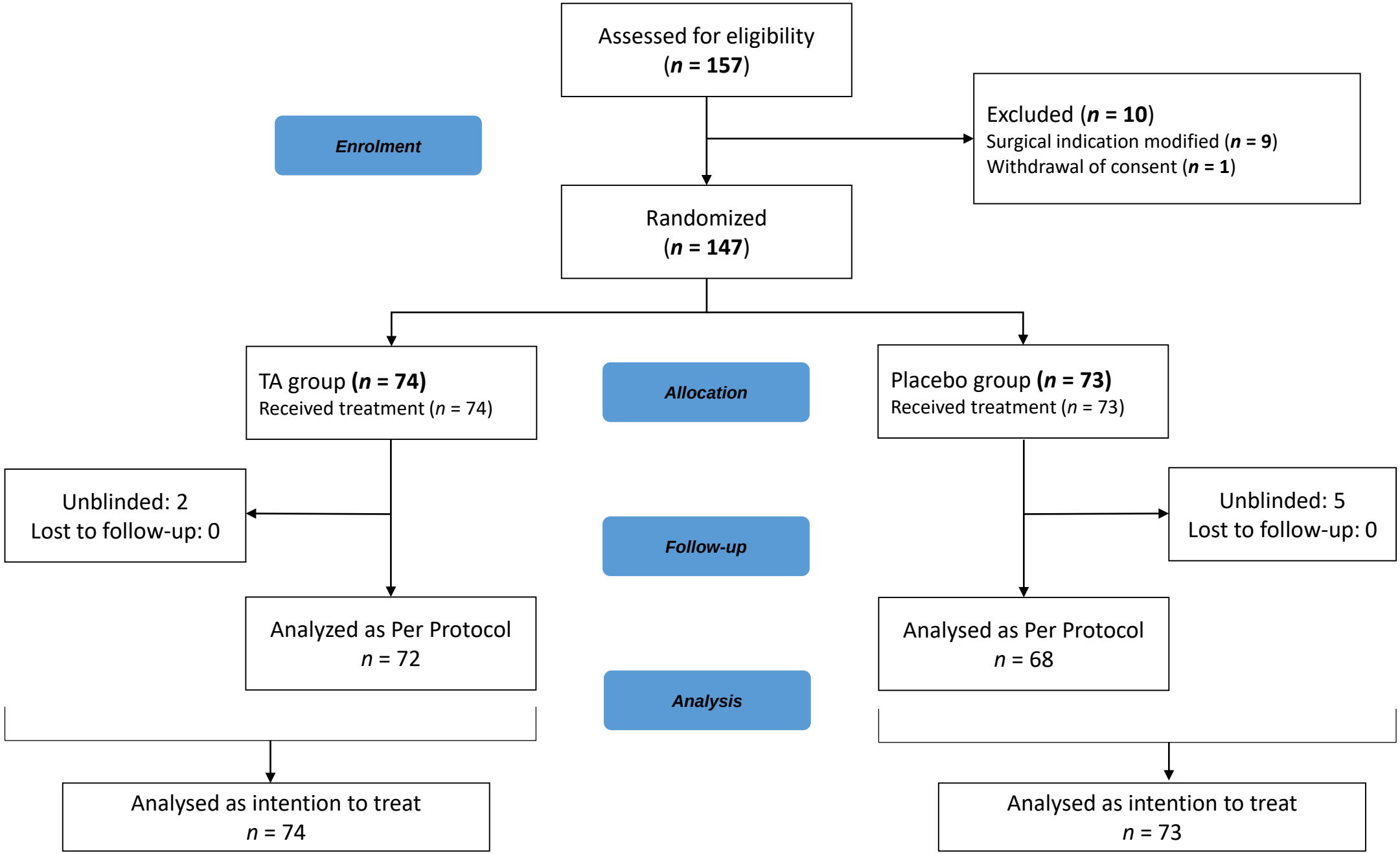
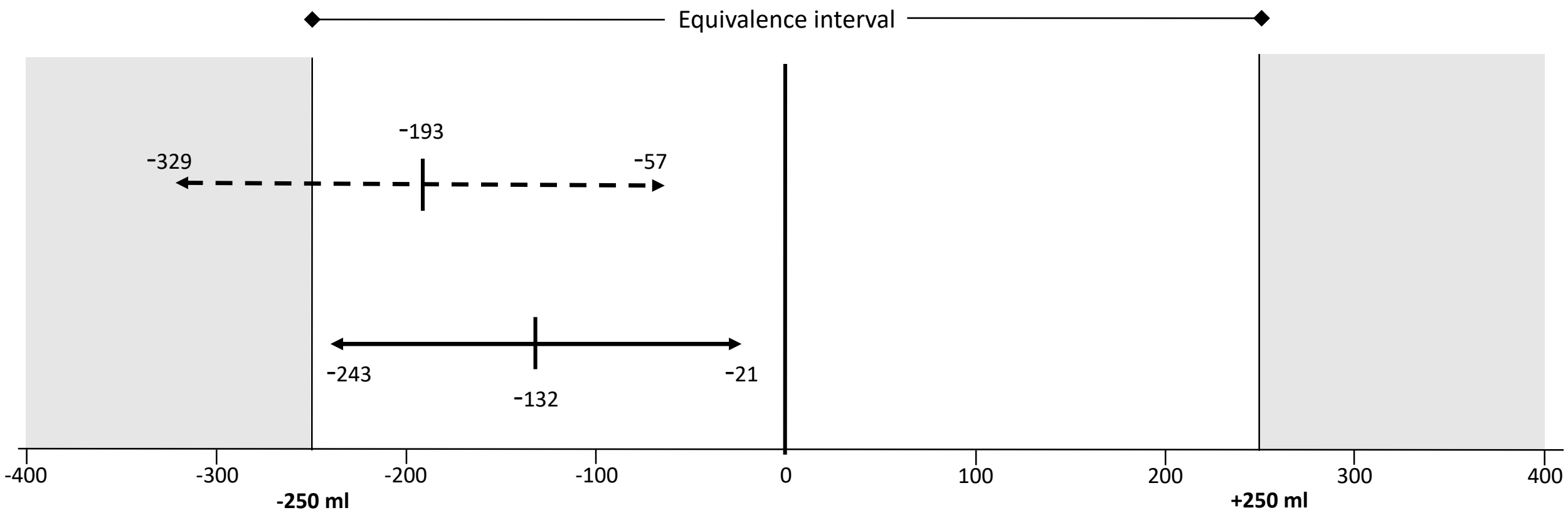

Assessed for eligibility
(n = 157)
Enrolment
Excluded (n = 10)
Surgical indication modified (n = 9)
Withdrawal of consent (n = 1)
Randomized
(n = 147)
TA group (n = 74)
Received treatment (n = 74)
Allocation
Placebo group (n = 73)
Received treatment (n = 73)
Unblinded: 2
Lost to follow-up: 0
Follow-up
Unblinded: 5
Lost to follow-up: 0
Analyzed as Per Protocol
n = 72
Analysed as Per Protocol
n = 68
Analysis
Analysed as intention to treat
n = 74
Analysed as intention to treat
n = 73


Equivalence interval
-193
-329
-57
-243
-21
-132
-400
-300
-200
-100
0
100
200
300
400
-250 ml
+250 ml