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Adjunctive use of tranexamic acid to tourniquet in reducing haemorrhage during abdominal myomectomy - A randomized controlled trial

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ABSTRACT

Background: Uterine fibroids are the commonest tumour of the female genital tract; about one third are symptomatic and require management. The treatment of uterine fibroids may be medical, surgical, conservative or expectant. Myomectomy is the common surgical treatment option for women failing medical management and desiring to preserve fertility and/or their uterus. The tourniquet is shown to be effective in reducing blood loss during myomectomy and tranexamic to a less extent. However, the adjunctive use of tranexamic acid with tourniquet to further reduce blood loss has not been studied.
Aim: The aim of the study was to determine the efficacy of perioperative intravenous tranexamic acid in further reducing blood loss at abdominal myomectomy when used as an adjunct to tourniquet.
Methods: The study was a randomized double-blind controlled study involving women who underwent abdominal myomectomy. Participants were randomized to either tourniquet plus intravenous tranexamic acid or tourniquet plus placebo groups using simple random sampling. The primary outcomes were the intra-operative blood loss, post-operative haematocrit values and need for intra-operative blood transfusion. The data was analyzed using the SPSS software version 23.0 and p value < 0.05 was significant.
Results: The mean intra-operative blood loss (998.72 ± 607.21 ml vs 907.25 ± 529.85 ml, $p = 0.475$), intra-operative blood transfusion rate (45% vs. 30%; $p = 0.166$) and mean unit of blood transfused (1.13 ± 1.64 vs. 0.75 ± 1.28; $p = 0.256$) were higher for tourniquet plus placebo group compared to tourniquet plus tranexamic acid group. The estimated blood loss per 100 g of fibroid removed was reduced significantly in the tranexamic acid plus tourniquet group (139.80 ± 2.28 ml vs 104.09 ± 1.97 ml; $p = 0.001$).
Strength and limitations: : The strength of the study include randomization and blinding. The limitations included non-uniformity of sizes and locations of fibroids, as well as the different surgeons with possibly different skills, techniques and experiences, though they were statistically not significant.
Conclusion: The adjunctive use of tranexamic acid to tourniquet significantly further reduces intraoperative blood loss during abdominal myomectomy when compared to tourniquet alone.
Recommendations: Adjunctive use of tranexamic acid is recommended for further reducing intra-operative blood loss during abdominal myomectomy.

Introduction

The treatment of uterine leiomyoma may be medical, surgical, conservative or expectant. Surgical management consists of hysterectomy and myomectomy, but in some cases less invasive procedures, such as uterine artery embolization are successful [1–4]. For women failing medical management, desiring to preserve fertility and or their uterus, surgical removal of fibroids (myomectomy) is the major option which is the mainstay of treatment in our environment is surgery [3,6,7].

The procedure of myomectomy is associated with haemorrhage [5,6,8], and many interventions such as perioperative vaginal insertion of misoprostol and intraoperative infiltration of vasopressin into the uterine muscle are reported to be effective

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in reducing bleeding during myomectomy [9]. Chemical dissection with mesna, vaginal insertion of dinoprostone and use of tranexamic acid are also employed to reduce blood loss [9,10]. Measures like the intraoperative infusion of vitamin C, infiltration of a mixture of bupivacaine and epinephrine into the uterine muscles, use of fibrin sealant patch and application of Bonney's clamp or a tourniquet around the cervix, and, or infundibulopelvic ligament (triple tourniquet [5]) are in use. Others, like morcellation and temporary clipping of the uterine artery, are other examples of these attempts [9,11].

In previous studies on the Foley catheter form of tourniquet, significant reduction of blood loss among the tourniquet group compared to the no-tourniquet group was demonstrated [7,9,12]. This reduction in blood loss also translates into a reduction in the need for blood transfusion [7]. The amount of blood loss is however dependent on the number, sites and volume of the myoma removed. Therefore, judicious surgical skill to minimize blood loss is also necessary especially in the black population where fibroids are more prevalent, multiple and much larger in volume [13].

Tranexamic acid is a safe non-hormonal medication that significantly reduces abnormal menstrual bleeding [1,14–18]. Tranexamic therefore has become useful in the management of menorrhagia [19,20–24] and now increasingly being tested in blood loss control during myomectomy [10].

Locally, no study has evaluated the use of tranexamic acid in reducing blood loss at myomectomy, and none has studied its usefulness in further reducing blood loss when used as an adjunct to tourniquet either locally or in the world. Hence, the need for this study in confirming the role of Tranexamic acid in reducing blood loss at myomectomy in our locality. If a difference exists, the results of this and future studies/publications would directly impact clinical care locally and internationally.

This study intended to examine the efficacy of perioperative intravenous Tranexamic acid in further reducing blood loss at abdominal myomectomy when used as an adjunct to the haemostatic tourniquet. The objectives include the determination of intra-operative blood loss at abdominal myomectomy in women who had prophylactic intravenous Tranexamic acid plus haemostatic tourniquet and those with haemostatic tourniquet only. Other objectives are the determination of the difference between pre-operative and post-operative packed cell volumes, comparison of intraoperative blood loss, blood transfusion as well as post-operative anaemia in the two groups. After that, based on the findings, make appropriate recommendations on the benefits, advantages, and usefulness or otherwise of adjunctive tranexamic acid in reducing haemorrhage at myomectomy.

We hypothesized (Null) that perioperative intravenous tranexamic acid in combination with haemostatic tourniquet does not further reduce blood loss at myomectomy when compared with tourniquet only. While the alternative hypothesis was that perioperative intravenous tranexamic acid in combination with haemostatic tourniquet further reduces blood loss at myomectomy when compared with tourniquet only.

Methodology

The study population i.e. subjects consisted of non-pregnant women with confirmed diagnosis of uterine leiomyoma seen in the gynaecology clinic already evaluated and are for abdominal myomectomy.

Recruitment of participants for the study was at the gynaecological clinic of the of the University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria. A history of the presenting complaints, any coexisting medical illness, previous surgeries as well as any medication being taken was obtained. The records of these patients were also reviewed at the gynaecological clinic.

The research assistants (four) were resident doctors in each firm of the department trained by the investigators for this study. They were trained a couple of weeks before the commencement of the study and followed up meeting was held for review and to ensure compliance with the study protocols. The researchers and assistants ensured satisfactory completion of the data.

Inclusion criteria were consenting non-pregnant women with a diagnosis of symptomatic fibroid scheduled for abdominal myomectomy, Uterine size less than or equal to 28 weeks, women without pre-operative Anemia (i.e. Haemoglobin concentration $\geq$10 g/dl). The exclusion criteria included women with pre-operative Anemia (i.e. Haemoglobin concentration <10 g/dl), Uterine size greater than 28 weeks, Patients concurrently on medications such as gonadotropin-releasing hormone analogues, mefenamic acid and other hormones, Patients with previous abdominal surgery, cases where haemostatic tourniquet use is impossible, chronic liver diseases, nephropathies, bleeding disorders and past thromboembolic disorders. Other exclusion criteria were known hypersensitivity to Tranexamic Acid, pregnancy and refusal of the patient to consent (Fig. 1).

The study was a randomized, double-blinded controlled study. Participants were randomized into two groups of subjects and controls. The calculation of the sample size used data from previous studies (Appendix A) [13,14]. A sample size of 36.8 patients was obtained for each group. In other to cater for attrition, 10% of the sample size was added to the initial sample size of 36.8 which is approximately 40. Hence the minimum sample size was 40 in each arm of the study. The sampling method was a simple random sampling that used a computer-generated random number. The study involved 80 consenting women scheduled for abdominal myomectomy and who satisfied the inclusion criteria.

The plans of interventions/randomization were put in sealed brown envelopes, numbered by following the randomization tables that were computer generated and coded to reflect the allotted group. Packing, sealing and numbering of the drug and placebo were done by an independent doctor other than the investigator/assistants. The number randomly picked by the patient was given to this independent doctor who picked the appropriately numbered envelope; constituted the injection in privacy based on the type of intervention written in the envelope and handed it over to the investigator who then administered the injection in theatre. The investigator did not know what was constituted. Also, tranexamic acid is a clear fluid and is not distinguishable from water for injection on mere looking. The constitution was done using a 10 ml needle and syringe based on body weight, that is, 10 mg/kg.

The surgeons, the investigators/assistants, and the patients did not know which patient received Tranexamic acid or placebo. The randomization coding tables was concealed from the investigator until the end of the study.

Forty (40) participants received intravenous Tranexamic acid 10–15 min before abdominal incision in combination with tourniquet tying. The other forty (40) received placebo (water for injection) 10–15 min before abdominal incision in combination with tourniquet tying. The first group (Group I) are the study group while the latter group (Group II) served as the control for the study. Also, the participants subsequently had intraoperative haemostatic tourniquet applied at the cervico-isthmic junction intraoperatively. Standard operating techniques were adhered to during all the procedures, and the estimated blood loss was calculated using the Gravimetric method [25].

The data obtained from the study were analyzed using the Statistical Package for Social Sciences software (SPSS) version 23.0 Chicago, Illinois, USA. The data was presented in frequency tables. Chi-square analysis was used to test relationships between

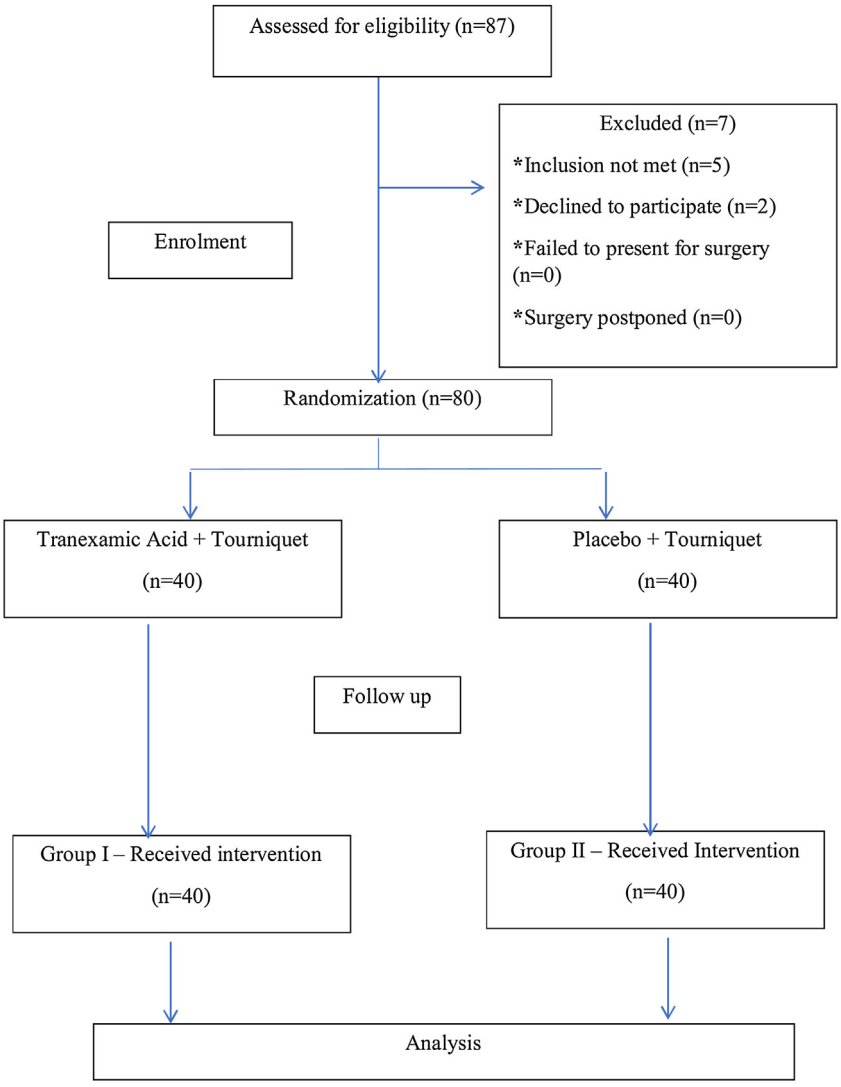

Fig. 1. FLOW OF STUDY PARTICIPANTS.

categorical variables and Student's *t*-test or the parametric test for the difference between continuous data. Probability (p) values less than 0.05 was accepted as statistically significant.

Institutional ethical approval for this study was obtained from the Ethical Review Committee of the University of Ilorin Teaching Hospital before the commencement of the study. Informed written consent was obtained from each participant after adequate counseling.

Results

The study lasted 12 months (26th September 2017 to 11th July 2018). A total of 80 participants were enrolled comprising 40 participants in each group.

The socio-demographic and obstetric features of the participants are as shown in Table 1 there were no statistically significant differences between both groups. The age range of the participants was 26–51 years with a mean age of 34.96 ± 5.09 years. The highest percentage of the participants was in the age group of 31–40 years (59; 73.75%) while the least number of participants were >40 (9; 11.20%). There were 12 participants (15%) in ≤30 years age group. The racial distribution showed the Yorubas (63; 78.75%) as the largest, Igbos (7; 8.75%) was next and Hausas (1; 1.25%) while (9; 11.25%) belong to the group named others. Majority of the participants were married (67; 83.75%), while 13 (16.25%) were single. All participants had some level of education; (57; 71.25%) had tertiary education, 21 (26.25%) secondary education and 2 (2.50%), primary education. The self-employed were Thirty-one (38.75%), 27(33.75%) were civil servants, 17 (21.25%) were artisans while 5 (6.25%) were unemployed or housewives. Majority of the participants were nulliparous (69; 86.25%), 5(6.25%) were primiparous and 6 (7.50%) multiparous.

Table 2 shows the presenting symptoms and the medical history with abdominal swelling (65; 81.25%) been the most frequent presenting symptoms; others were the inability to conceive (58; 72.50%) and excessive/prolonged menstrual flow in 50 (62.50%) participants. Abdominal pain and dysmenorrhea each had 23 (28.75%) and 22 (27.50%) respectively. Seventy-five participants (93.75%) had more than one symptom while 5 (6.25%) had a single symptom. Sixteen participants had chronic hypertension (six and ten in each group) while two patient (one in each group) had diabetes mellitus. The mean body mass indices (BMI) were comparable in both groups (29.31 ± 4.72 vs. 27.88 ± 6.13).

Table 1
Sociodemographic characteristics of the study population.

Variables	Tranexamic n (%)	Placebo n (%)	Total N	χ^2	*p* value
Age group (years)					
≤30	9 (75.0)	3 (25.0)	12(15.0)	3.613^{Y}	0.164
31–40	25 (42.4)	34 (57.6)	59(73.8)		
>40	6 (66.7)	3 (33.3)	9(11.3)		
Mean ± SD		34.95 ± 5.09			
Range		26–51			
Marital status					
Married	32 (47.8)	35 (52.2)	67(83.8)	0.827	0.363
Single	8 (61.5)	5 (38.5)	13(16.2)		
Educational status					
Primary	0 (0.0)	2 (100.0)	2(2.5)	1.893^{Y}	0.388
Secondary	8 (38.1)	13 (61.9)	21(26.3)		
Tertiary	32 (56.1)	25 (43.9)	57(71.3)		
Ethnicity					
Yoruba	34 (54.0)	29 (46.0)	63(78.8)	0.825^{Y}	0.843
Igbo	2 (28.6)	5 (71.4)	7(8.8)		
Hausa	0 (0.0)	1 (100.0)	1(1.3)		
Others	4 (44.4)	5 (55.6)	9(11.3)		
Occupation					
Self Employed	17(54.84)	14 (45.16)	31(38.75)	0.165 ^{Y}	0.983
Civil Servant	13 (48.15)	14 (51.85)	27(33.75)		
Artisans	10 (58.82)	7 (41.18)	17(21.25)		
Unemployed	2 (40)	3 (60)	5(6.25)		
Parity					
0	34 (49.3)	35 (50.7)	69(86.3)	2.300^{Y}	0.317
1	1 (20.0)	4 (80.0)	5(6.3)		
2	5 (83.3)	1 (16.7)	6(7.5)		
Median (range)		0 (0–2)			

χ^2: Chi square; Y: Yates corrected Chi square.

Table 2
Presenting symptoms and medical history of study subjects.

	Tranexamic n (%)	Placebo n (%)	Total N	χ^2	*p* value
Menorrhagia					
Yes	27 (54.0)	23 (46.0)	50(62.5)	0.853	0.356
No	13 (43.3)	17 (56.7)	30(37.5)		
Dysmenorrhea					
Yes	14 (63.6)	8 (36.4)	22(27.5)	2.257	0.133
No	26 (44.8)	32 (55.2)	58(72.5)		
Abdominal swelling					
Yes	32 (49.2)	33 (50.8)	65(81.3)	0.082	0.775
No	8 (53.3)	7 (46.7)	15(18.8)		
Abdominal pain					
Yes	8 (34.8)	15 (65.2)	23(28.8)	2.440^{Y}	0.295
No	32 (57.1)	24 (42.9)	56(70.0)		
Sometimes	0 (0.0)	1 (100.0)	1(1.3)		
Infertility					
Yes	26 (44.8)	32 (55.2)	58(72.5)	2.257	0.133
No	14 (63.6)	8 (36.4)	22(27.5)		
Hypertension					
Yes	10 (62.5)	6 (37.5)	16	1.250	0.264
No	30 (46.9)	34 (53.1)	64		
Diabetes					
Yes	1 (50.0)	1 (50.0)	2	0.513^{Y}	0.474
No	39 (50.0)	39 (50.0)	78		

χ^2: Chi square; Y: Yates corrected Chi square.

Intraoperative findings are shown in Table 3 with the mean intraoperative blood loss was 907.25 ± 529.85mls in the tranexamic group and 998.72 ± 607.21 mls in the placebo group. No statistically significant difference was found between the two groups. The mean unit of blood transfused in the tranexamic group was 0.75 ± 1.28 units and 1.13 ± 1.64 units for the placebo group ($p = 0.256$). The mean fibroid volume in the tranexamic group was 941.75 ± 673.59mls and in placebo group 778.25 ± 609.30mls ($p = 0.258$). The mean fibroid weight of 1027.40 ± 750.45 g in the tranexamic acid group was greater than the 845.72 ± 684.33 g in the placebo group ($p = 0.261$). Statistically, however, the differences were significant between the two groups with regards to thelocation of fibroids, fibroid size (in weeks), volume or weight. Tables 4 shows blood loss per 100 g of fibroid removed using the parametric test between the two groups and it was very close to significant level (p = 0.067). However, when same blood loss per 100 g was converted to logarithm (Table 5), the blood loss reduction in the tranexamic acid group became very significant (P = 0.001).

Tables 6 and 7 contains the haematological indices. The haematocrit change (between preoperative and postoperative) was 3.75 ± 2.54% in the tranexamic group, and 4.03 ± 3.29% in the placebo group; p = 0.493 was not significant. Similarly, the vital signs before the operation and after operation were not different between the cases and controls. The difference between the preoperative and the postoperative platelet count was 0.70 ± 18.56 and 5.93 ± 21.75 (p = 0.101) for the tranexamic acid and the placebo group respectively (Table 8).

Table 9 shows there were no statistically significant differences in the time between the administration of tranexamic acid to skin incision, to the last stitch on the uterus, to the last stitch on the skin and to the mean tourniquet times of 75.85 ± 37.22 min for tranexamic acid group and 92.80 ± 58.38 min for placebo (p = 0.126). Same is true for the duration of surgery which was 89.40 ± 44.82 min and 100.75 ± 62.20 min (p = 0.352) for the tranexamic acid and placebo group respectively. The mean number of days spent in the hospital by the tranexamic group (4.80 ± 0.61 days) was significantly shorter than that of the placebo group (5.55 ± 0.71 days), p = 0.001.

Discussion

Factors associated with increased haemorrhage during myomectomy like myoma location/type (a submucous myoma may bleed more even though the volume is less), patient characteristics, surgeon's skill, duration of surgery and anaesthetic technique [8] were similar in the two groups statistically and therefore did not affect the outcome of the trial which were the similar settings in previous studies [13,25,27].

An earlier study on the benefit of tranexamic acid alone on myomectomy reported an intra-operative blood transfusion rate of 19.7% vs. 34.8% (p = 0.01) [24] which was lower than in this study. Caglar et al, [24] however, reported similar transfusion requirements (p = 0.25). The higher transfusion rate in this study is from the bigger uterine sizes, myoma volume, the multiplicity of the location of the myomas and the longer duration of surgery. Fibroids in this environment are larger and multiple unlike in the studies quoted [20,26]. The number of units transfused in the tranexamic acid group was lower than in the placebo group (mean of 0.75 ± 1.28 vs. 1.13 ± 1.64). Patients were transfused in this study when the calculated maximum allowed blood loss was reached, and, or there were signs of inadequate perfusion and oxygenation of the vital organs. Hence, this subjective clinical decision may partially account for the higher transfusion rate in this study compared to others.

The total tourniquet time in the tranexamic acid group was shorter than in the placebo group (75.85 ± 37.22 vs. 92.80 ± 58.38). A plausible explanation could be that reduced bleeding at the operating field in the tranexamic acid group allowed for more comfortable, faster enucleation of the myomas as well as the reconstruction of the uterus. Caglar et al [24] reported a

Table 3
Comparison of intraoperative findings between the two groups.

	Tranexamic Acid	Placebo	t/U	*p* value
Intraoperative blood loss(ml)	13 (72.2)	5 (27.8)	4.739**	0.094
<500	16 (45.7	19 (54.3)		
500–1000	11 (40.7)	16 (59.3)		
>1000				
Mean ± SD	907.25 ± 529.85	998.72 ± 607.21	0.718 [t]	0.475
Blood transfusion (units)				
Median (IQR)	2 (1-2)	2 (1–2)	680.000	0.169
Mean ± SD	0.75 ± 1.28	1.13 ± 1.64	1.143 [t]	0.256
Number of fibroids(total)	14.88 ± 11.80	14.73 ± 13.31	736.000	0.537
Intramural (Mean)	10.28 ± 7.11	11.23 ± 11.04	735.500	0.534
Median	7.50	6.50	710.000	0.380
Subserosa (Mean)	3.75 ± 5.04	2.83 ± 3.21	712.500	0.352
Median	2.50	2.00	760.000	0.155
Submucous (Mean)	0.85 ± 1.05	0.63 ± 0.87		
Median	3	0		
Others	0.00 ± 0.00	0.05 ± 0.22		
Fibroid Vol. (mls) Mean ± SD	941.75 ± 673.59	778.25 ± 609.30	−1.138 [t]	0.258
Median (IQR)	805.00 (367.50-1387.50)	640.00 (270.00–1025.00)	654.000	0.160
Fibroid weight (g) Median	866.88(430.45–1523.93)	662.52(281.08–1106.25)	677.000	0.237
Mean ± SD	1027.40 ± 750.45	845.72 ± 684.33	−1.131 [t]	0.261

U: Mann Whitney U test; t: *t test***: Chi square was used.; Vol. = Volume.

Table 4
Estimated blood loss per 100 g of fibroid removed (Using non-parametric test for skewed data).

Estimated blood loss per 100 g of fibroid (ml)	Placebo	Tranexamic	U	*p* value
Mean ± SD	191.84 ± 157.59	131.37 ± 98.54		
Median (IQR)	127.39 (86.10 – 270.38)	93.25 (63.61 – 202.08)	610.000	0.067

U: Mann-Whitney U test; *: *p*-value <0.05.

Table 5
Estimated blood loss per 100 g of fibroid removed (Logarithm conversion of skewed to normally distributed data).

Estimated blood loss per 100 g of fibroid (ml)	Placebo	Tranexamic	t	*p* value
Mean ± SD	139.80 ± 2.28	104.09 ± 1.97	74.954	<0.001*

t: Independent Samples t test; *: *p*-value <0.05.

Table 6
Preoperative vital signs and haematological parameters of study participants.

	Tranexamic Acid Mean ± SD	Placebo Mean ± SD	t	*p* value
Hematocrit level (%)	34.30 ± 2.40	34.18 ± 3.47	−0.187	0.852
Hemoglobin level (g/L)	11.40 ± 0.94	11.34 ± 1.28	−0.248	0.805
Platelet count (10^6/L)	295.45 ± 85.36	274.73 ± 68.34	−1.199	0.234
Clotting time (minutes)	4.00 ± 0.91	3.78 ± 0.77	−1.199	0.233
Pulse rate (bpm)	80.60 ± 9.06	83.85 ± 10.39	1.491	0.140
SBP (mmHg)	120.50 ± 11.76	124.25 ± 11.52	1.441	0.154
DBP (mmHg)	75.00 ± 8.17	76.75 ± 7.97	0.970	0.335
Temperature (ºC)	36.62 ± 0.32	36.50 ± 0.35	−1.563	0.122
Respiratory rate (cpm)	21.75 ± 2.84	21.10 ± 2.52	−1.084	0.282

SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; t: Independent Sample *t-test*.

significantly reduced duration of surgery (p = 0.03) while Ngichabe [13] reported no difference.

The effectiveness of tourniquet in reducing blood loss during myomectomy has been studied and established [7,28]. The estimated blood loss from the tourniquet plus placebo group in this study was higher than that reported by Ikechebelu in Nnewi, Nigeria [5]: 515.7 ± 292.81 ml. This observation is possibly due to a likely underestimation of the blood loss in that study because only mops were used during the surgery, which were not weighed but visually estimated depending on the degree of soaking, and even suction was not used [7].

Majority of the women in this study were in the peak period of reproductive age (31-39years) which supports the pathophysiology [28,29] of the disease and is like the reports by other researchers [7,29]. This age of presentation is due to fibroid being stimulated by eostrogen and progesterone (with the peak in this age group) for its growth. The most frequent presenting symptom in this study was abdominal swelling like the findings in Nnewi [7] and Ilorin [8] unlike menorrhagia from another study [13]. The next common presenting symptom was infertility; this underscores the relationship between the higher incidence of fibroids in nulliparous [29] women who constituted most of the study participants. The implication is that myomectomy will continue to be the sought-after surgical management of fibroid to conserve uterus/fertility [29,30].

More subjects in the tranexamic acid and tourniquets group had midline (infra and supraumbilical) incision than Pfannenstiel in the tranexamic group as well as more general anesthesia, epidural

Table 7
Postoperative vital signs and haematological parameters of the study participants.

	Tranexamic Acid Mean ± SD	Placebo Mean ± SD	t	*p* value
Hematocrit level (%)	30.58 ± 2.11	30.15 ± 3.29	−0.688	0.493
Hemoglobin level (g/L)	10.17 ± 0.73	10.06 ± 1.18	−0.506	0.615
Platelet count (10^6/L)	294.75 ± 77.80	268.80 ± 60.90	−1.661	0.101
Clotting time (minutes)	4.35 ± 0.77	4.20 ± 0.56	−0.994	0.323
Pulse rate (bpm)	82.70 ± 9.22	86.40 ± 8.92	1.824	0.072
SBP (mmHg)	119.25 ± 10.95	124.25 ± 11.96	1.950	0.055
DBP (mmHg)	73.50 ± 8.34	76.50 ± 10.01	1.456	0.149
Temperature (ºC)	36.83 ± 0.25	36.81 ± 0.33	−0.425	0.672
Respiratory rate (cpm)	22.75 ± 2.06	22.90 ± 2.68	0.281	0.780

SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure.

and combined spinal/epidural because of larger fibroids. They non the less had less amount of blood loss suggesting a beneficial effect of the combined methods and indeed the difference was statistically significant when conversion to logarithm was done and 't' test conducted. The use of uniform general anaesthesia [13,24] could not be achieved in this study because of the individualized needs based on fibroid sizes. A significant finding in this study was the reduced number of hospitals stay in the tranexamic acid group compared to the placebo group. Contributing factors to the shorter days may have included higher post-operative packed cell volume; better and faster return of normal physical activities; better general feeling of wellness or condition and improved wound healing.

The primary concern in the use of tranexamic acid, an antifibrinolytic, is the possible increased risk of thromboembolic tendency; none of the participants in the study had this complication. There was also no need for additional use of other surgical techniques in controlling haemorrhage such as uterine artery ligation or conversion of abdominal myomectomy to hysterectomy [13,24,26,29].

The major strength of this study is the proper randomization and blinding which helped to yield the real effect of the intervention.

Limitations in this study include the lack of consideration of the additional cost of Tranexamic to treatment, which was not considered. Further studies on its cost-effectiveness at myomectomy will be of value. This study did not compare the effect of different dosages and time interval of administration to incision time of tranexamic acid on blood loss at surgery and may be considered for evaluation in future research. The effect, and, or benefits of oral tranexamic acid (administered days before surgery) in reducing blood loss at myomectomy is opened also to future studies.

Table 8
Time intervals between the administration of Tranexamic acid and placebo specific points during the operation.

Time Intervals	Tranexamic Acid Mean ± SD	Placebo Mean ± SD	t	*p* value
TA to skin incision	12.10 ± 2.26	11.98 ± 2.41	−0.239	0.812
Total tourniquet time	75.85 ± 37.22	92.8 ± 58.38	1.548	0.126
TA to last stitch on uterus	126.53 ± 45.09	131.38 ± 64.07	0.392	0.696
TA to last stich on skin	169.73 ± 47.78	170.65 ± 68.88	0.070	0.945
Duration of surgery*	157.63 ± 47.66	158.43 ± 68.24	0.061	0.952
Duration of surgery**	89.40 ± 44.82	100.75 ± 62.20	0.936	0.352

TA – Tranexamic Acid.
* From skin incision to last stitch on skin.
** From uterine incision to last stitch on uterus.

Table 9
Other intraoperative related events and considerations in both groups.

Variable	Tranexamic n (%)	Placebo n (%)	Total N	χ^2	*p* value
Cadre of surgeon					
Consultant	29 (50.0)	29 (50.0)	58	0.000	1.000
Senior registrar	11 (50.0)	11 (50.0)	5		
Type of skin incision					
Infraumbilical midline	27 (50.9)	26 (49.1)	53	0.419	0.811
Supraumbilical midline	8 (53.30	7 (46.7)	15		
Pffannensteil	5 (41.7)	7 (58.3)	12		
Type of anesthesia					
General anesthesia	20 (58.8)	14 (41.2)	34	11.402	0.010*
Epidural block	15 (53.6)	13 (46.4)	28		
Subarachnoid block	0 (0.0)	11 (100.0)	11		
Spinal-Epidural block	5 (71.4)	2 (28.6)	7	1.841	0.175
Anaesthesia: Subdivided	20 (58.8)	14 (41.2)	34		
General	20 (43.5)	26 (56.5)	46		
Regional					
Number of days spent in the hospital					
Four	12 (85.7)	2 (14.3)	14	15.679[Y]	0.001*
Five	24 (58.5)	17 (41.5)	41		
Six	4 (18.2)	18 (81.8)	22		
Seven	0 (0.0)	3 (100.0)	3		
Mean ± SD	4.80 ± 0.61	5.55 ± 0.71			
Range	4–6	4–7			

Conclusion

Perioperative intravenous tranexamic acid used in addition to tourniquet is safe and further reduces blood loss per 110 g of fibroids removed significantly. The need for blood transfusion and postoperative anaemia were also reduced with the number of days spent in the hospital also significantly reduced.

Declaration of Competing Interest

We confirm that there is no conflict of interest in this manuscript and that there was no significant financial contribution that could have influenced the outcome of the work.

Appendix A.

Sample size calculation

Sample size was determined by data from previous studies on the use of tranexamic acid and placebo to reduce blood loss during myomectomy using the formula below [11,22]:

$N = 2\Sigma\ (z\alpha + Z1/2\beta)/r^2$

Where, N = Total number of patients in each group

Σ = known standard deviation from a previous study [17] which is 460mls

$Z\alpha = 1.96$ at type 1 error of 5%

$Z1/2\beta = 0.84$ at 80% power

r = standard effect size or the difference between two values which in this case was set to detect 300mls mean difference in perioperative blood loss assumed to be clinically significant.

Substituting with figures:

$N = 2 \times 460 \times 460\ (1.96 + 1.282)\ /\ 300 = 36.8$ patients in each group.

To cater for attrition, 10% of the sample size was added to the initial sample size. 10% of 36.8 is 3.68 which added to 36.8 is approximately 40. Hence the minimum sample size was 40 in each arm of the study; hence 40 for the study group and 40 for the control group.

Appendix B.

INFORMATION SHEET

STUDY TITLE: **ADJUNCTIVE USE OF TRANEXAMIC ACID TO TOURNIQUET IN REDUCING HAEMORRHAGE DURING ABDOMINAL MYOMECTOMY AT THEUNIVERSITY OF ILORIN TEACHING HOSPITAL, ILORIN.**

BRIEF DESCRIPTION OF THE STUDY

This study is an experiment to be carried out at the department of obstetrics and gynaecology, University of Ilorin Teaching Hospital, Ilorin, Nigeria.

Blood loss at myomectomy, surgical removal of fibroids, is associated with increased complications, morbidity and mortality. This study intends to determine the efficacy and safety of a drug in reducing blood loss during and after operation which may help in influencing and/or changing clinical practice.

WHAT IS REQUIRED FOR YOUR PARTICIPATION?

You will be eligible to be part of this study if you have clinical or ultrasound diagnosis of fibroids and are scheduled for myomectomy and you meet other inclusion criteria for this study.

Your taking part will involve for example drawing an extra sample of blood to run some investigations, giving an intravenous medication of either tranexamic acid or a placebo.

Your routine care will not be affected negatively in any way.

BENEFITS OF PARTICIPATION.

This study will help to find other ways for reducing blood loss at myomectomy. This will further enhance proper management of patients. Your participation is completely voluntary, and you may choose to withdraw from this study at any time.

ANY DANGER TO THE PATIENT?.

This study poses a risk of thromboembolism in very rare situation.

CONFIDENTIALITY.

The information obtained from you will be handled with confidentiality. The results will be utilized in a dissertation and may also be published in a medical journal but will not include any personal information about you.

CONSENT TO PARTICIPATE AND RIGHT TO WITHDRAW

Your participation is voluntary, and you have the right to withdraw at any stage of the study if you so wish. Withdrawal shall not deny you care or affect the quality of care you will receive.

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Appendix C.

CONSENT FORM

RESEARCH TOPIC: ADJUNCTIVE USE OF TRANEXAMIC ACID TO TOURNIQUETIN REDUCING HAEMORRHAGE DURING ABDOMINAL MYOMECTOMY AT THE UNIVERSITY OF ILORIN TEACHING HOSPITAL, ILORIN.

I . . . . . of . . . . . hereby consent to participate in the above research study after adequate explanation on the nature, risks and benefits of the study have been made to me. I am also aware that I can withdraw this consent anytime during the course of the study without any negative consequence.

Signature or Right thumb print . . . . . .

Date . . . . . .

I confirm that I have explained to you the purpose and nature of this study. All information obtained in this study is confidential and if the study is published, there will be no information that will identify you as a participant.

Signature . . . . . Date . . . .

Witness signature . . . . . .

Date . . . . . .

. . . . . .

. . . . . .

Appendix D.

DATA SHEET

RESEARCH TOPIC- ADJUNCTIVE USE OF TRANEXAMIC ACID TO TOURNIQUET IN REDUCING HAEMORRHAGE DURING ABDOMINAL MYOMECTOMY AT THE UNIVERSITY OF ILORIN TEACHING HOSPITAL, ILORIN.

SOCIO-DEMOGRAPHIC CHARACTERISTICS.

i. Serial number . . . . . .

ii. Hospital no . . . . . .

iii. Age (years) . . . . . .

iv. Address . . . . . .

. . . . . .

v. Occupation:

Civil Servants . . . .Self-Employed . . . . . Artisans . . . .Unemployed/Housewife . . . . . .

Marital status

Married . . . . . Single . . . . . Divorced . . . .Widowed . . . . . .

Educational status.

None . . . . . primary . . . . . secondary . . . . . tertiary . . . . . .

Ethnicity.

Yoruba . . . . . Ibo . . . .Hausa . . . . . .Fulani . . . . . Others . . . . . .

Parity . . . . . (Alive) ; nulliparous . . . .. multiparous . . . . .

Height: . . . . .Weight: . . . . . .BMI(kg/m2) . . . .

(b) GYNAECOLOGICAL HISTORY

i. Last menstrual period . . . . . /cannot remember . . . .

ii. Menorrhagia: Yes . . . . . No . . . . . Sometimes . . . . .

iii. Dysmenorrhea: Yes . . . . . No . . . . . Sometimes . . . . .

iv. Abdominal swelling: Yes . . . . . No . . . . . .

v. Abdominal pain: Yes . . . . . No . . . . . Sometimes . . . . .

vi. Infertility: Yes . . . . . No . . . .

vii. Others . . . . . .

. . . .

(c) PAST MEDICAL HISTORY

i. Hypertension (Yes) (No)

ii. Diabetes (Yes) (No)

iii. Cardiac disease (Yes) (No)

iv. Thromboembolic disease (Yes) (No)

v. Liver disease (Yes) (No)

(d) PRE OPERATIVE CLINICAL CHARACTERISTICS

i. Preoperative hematocrit level (%) . . . . . .

ii. Preoperative hemoglobin level (g/L) . . . .

iii. Preoperative platelet count.. . . . . .

iv. Preoperative Bedside clotting time . . . . . .

(e) SURGICAL OUTCOMES

Intraoperatively:

i. Estimated blood loss (mL) . . . .

ii. Blood transfusion (number of units) . . . .

iii. Fibroid sites: Intramural . . . . . submucous . . . . . .subserosal . . . ..others . . . . . .

iv. Fibroid size: largest . . . . . smallest . . . . . .

v. Fibroid volume: . . . . . .

vi. Fibroid weight: . . . . . .

. . . .

vii. Timings of specific activities . . . . . .

Skin incision time . . . . . .

Time of commencement of tranexamic acid . . . . . .

Tourniquet time . . . .Release time . . . .

Uterine incision time . . . . . .

Time of last stitch on uterus . . . .

Time of last stitch on skin . . . . . .

Duration of surgery . . . . . .

i.Cadre of surgeon: consultant . . . .senior registrar . . . .

ii. Type of anaesthesia . . . . . .

. . . .

iii. Additional uterotonic/anti-haemorrhagic agent and dose . . . . . .

2 h **Postoperatively**

Post-operative vital signs: pulse rate (bpm) . . . .blood pressure (mmHg) . . . . . .temp(^{o}C) . . . . . .respiratory rate . . . .

24 h Postoperatively

Thromboembolic events . . . . . .

Deep venous thrombosis

Pulmonary embolism

Myocardial infarction

Stroke

Post-operative hematocrit level (%) . . . . . .

Post-operative hemoglobin level (g/L) . . . . . .

Post-operative Platelet count . . . . . .

Post-operative Bedside clotting time . . . . . .

Hospital stay . . . . . .

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