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Original Article

Peri-operative administration of tranexamic acid in lower limb arthroplasty: a multicentre, prospective cohort study

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Summary

In the UK, tranexamic acid is recommended for all surgical procedures where expected blood loss exceeds 500 ml. However, the optimal dose, route and timing of administration are not known. This study aimed to evaluate current practice of peri-operative tranexamic acid administration. Patients undergoing primary total hip arthroplasty, total knee arthroplasty or unicompartmental knee arthroplasty during a 2-week period were eligible for inclusion in this prospective study. The primary outcome was the proportion of patients receiving tranexamic acid in the peri-operative period. Secondary outcomes included: dose, route and timing of tranexamic acid administration; prevalence of pre- and postoperative anaemia; estimated blood loss; and red blood cell transfusion rates. In total, we recruited 1701 patients from 56 NHS hospitals. Out of these, 1523 (89.5%) patients received tranexamic acid and of those, 1052 (69.1%) received a single dose of 1000 mg intravenously either pre- or intra-operatively. Out of the 1701 patients, 571 (33.6%) and 1386 (81.5%) patients were anaemic (haemoglobin < 130 $g.l^{-1}$) in the pre- and postoperative period, respectively. Mean (SD) estimated blood loss for all included patients was 792 (453) ml and 54 patients (3.1%) received a red blood cell transfusion postoperatively. The transfusion rate for patients with pre-operative anaemia was 6.5%, compared with 1.5% in patients without anaemia. Current standard of care in the UK is to administer 1000 mg of tranexamic intravenously either pre- or intra-operatively. Approximately one-third of patients present for surgery with anaemia, although the overall red blood cell transfusion rate is low. These data provide useful comparators when assessing the efficacy of tranexamic acid and other patient blood management interventions in future studies.

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Introduction

Primary hip and knee arthroplasty is often associated with blood loss of more than a litre peri-operatively [1]. A significant proportion of patients may require an allogeneic red blood cell transfusion, with rates ranging from 0 to 47% [2]. In addition, both postoperative anaemia and red blood cell transfusion are associated with increased risks of cardiopulmonary morbidity, surgical site infection and

mortality [3, 4]. Therefore, strategies to minimise intra-operative blood loss and promote blood conservation are a priority for improving patient outcomes [5].

Tranexamic acid is a synthetic lysine analogue that inhibits plasminogen activation and promotes clot stabilisation. In patients undergoing total hip or knee arthroplasty, tranexamic acid has been shown to reduce peri-operative blood loss and red blood cell transfusion rates [6]. The National Institute for Health and Care Excellence (NICE) guidelines recommend tranexamic acid is administered to all patients undergoing a surgical procedure with estimated blood loss greater than 500 ml [7]. However, the guidelines did not provide a recommendation on the dose, route or timing of tranexamic administration due to the heterogeneity of studies to date. In order to design an optimal clinical trial an improved understanding of current practice is required, particularly in terms of clinically relevant comparator interventions and outcome measures.

The primary aim of this study was to evaluate current practice of peri-operative tranexamic acid administration in patients undergoing primary hip and knee arthroplasty in the UK. Secondary aims were to identify the prevalence of pre- and postoperative anaemia and to determine estimated blood loss and postoperative red blood cell transfusion rates.

Methods

This study is reported according to STROBE guidelines. A multicentre, prospective, observational study was conducted between 3 September 2018 and 17 September 2018. Collaborators from NHS Trusts within the UK were recruited via the National Orthopaedic Trainee Collaborative network and the British Orthopaedic Trainees Association. Each collaborator registered the audit locally with a clinical lead and the clinical audit and effectiveness department at their respective institution. Research Ethics Committee approval was not required as per the Health Research Authority assessment tool. Collaborators completed and returned locked Excel spreadsheets (Microsoft Corp, NM, USA). No direct or indirect patient identifiable data were collected.

Patients undergoing elective primary total hip arthroplasty, total knee arthroplasty or unicompartmental knee arthroplasty within the study period were eligible for inclusion. The following data were collected on tranexamic administration: dose (mg); timing (pre-operative, intra-operative, or postoperative); and route (oral, intravenous, topical, intramuscular or combined). Additional data included: body mass index ; weight; pre- and postoperative haemoglobin concentration (Hb) and haematocrit (Hct); and postoperative red blood cell transfusion requirements. We calculated the estimated peri-operative blood loss for each patient using the Gross equation (Equation 1). To inform the estimated blood loss calculation, pre-operative estimated blood volume was calculated using the Lemmens-Bernstein-Brodsky equation [8].

$$\text{Estimated blood loss} = \text{estimated blood volume} \times \left(\frac{\text{initial Hct} - \text{final Hct}}{\text{mean Hct}}\right) \quad (1)$$

Patients who were transfused intra-operatively or received an autologous red blood cell transfusion before the first postoperative full blood count were not included in calculations of estimated blood loss.

Pre-operative tranexamic acid administration included doses given between admission and surgical incision. Intra-operative administration included doses given between surgical incision until the recorded end of the procedure. Postoperative administration included doses given from the recorded end of the procedure until patient discharge. Pre-operative Hb and Hct values were recorded from the most recent pre-operative laboratory full blood count. Postoperative Hb and Hct values were recorded from the first laboratory full blood measured postoperatively (and before any red blood cell blood transfusion). Anaemia was defined as a haemoglobin concentration less than 130 $g.l^{-1}$ [9].

Regional variation in practice was explored by country (England, Wales, Scotland, Northern Ireland), and England was subdivided into Public Health England regions (London, South East, South West, East of England, West Midlands, East Midlands, North West, North East, and Yorkshire and Humber).

We did not calculate a sample size for this analysis. Differences between groups were assessed using an unpaired, two-sided t-test for continuous variables and Fisher's exact test for categorical variables. All data analyses were undertaken using STATA v14.2 (StataCorp, TX, USA).

Results

Over the study period, data from 1714 patients undergoing primary hip or knee arthroplasty were included from 56 NHS hospitals in the UK (Fig. 1). Thirteen patients were not included due to incomplete data. Three were not included in the blood loss calculations due to intra-operative transfusion (n = 2) and autologous transfusion (n = 1) (Fig. 2).

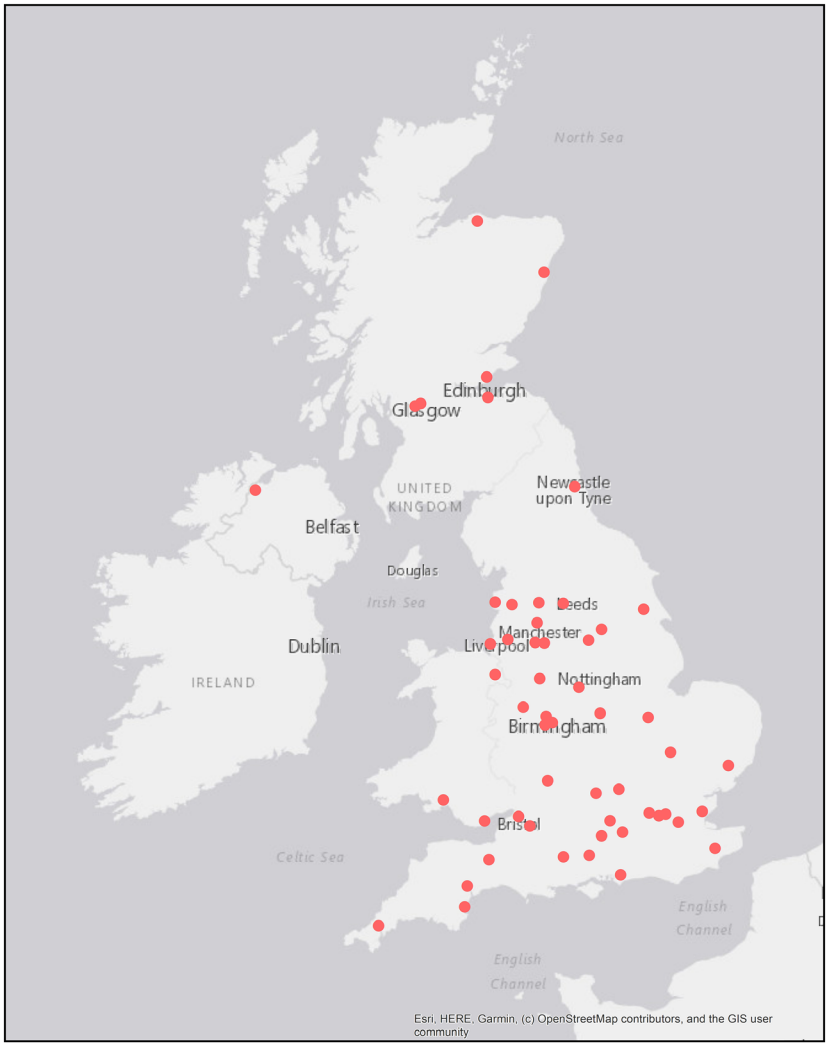

Figure 1 Map of participating centres

Out of the 1701 patients included in the final analysis, 797 (46.9%) underwent total hip arthroplasty, 830 (48.9%) total knee arthroplasty and 74 (4.4%) unicompartmental knee arthroplasty. Mean (SD) weight of included patients was 82.7 (18.3) kg and mean (SD) BMI was 30.2 (5.7) $kg.m^{-2}$. In this study, 1523 out of 1701 (89.5%) received tranexamic acid peri-operatively, with a similar proportion across all three operations (Table 1). Mean (SD) estimated blood loss for patients receiving tranexamic acid was 880.8 (458.6) ml compared with 782.2 (450.8) ml for patients who did not receive tranexamic acid ($p = 0.007$).

The most commonly used tranexamic acid dosing regimen was a single dose of 1000 mg administered intravenously either pre-operatively [n = 547 (36%)] or intra-operatively [n = 505 (33%)] (Fig. 3). Other routes and timing of administration are displayed in Tables 1

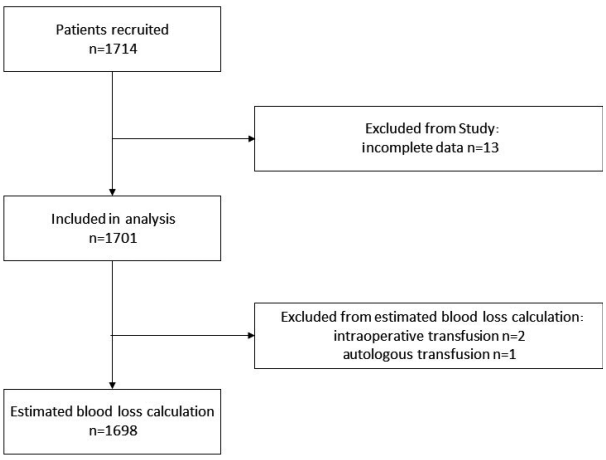

Figure 2 Flow diagram of recruitment and analysis

Table 1 Routes of tranexamic acid administration in all patients and those undergoing total hip arthroplasty, total knee arthroplasty and unicompartmental knee arthroplasty. Values are number (proportion).

Dose	Route	All n = 1701	Total hip arthroplasty n = 797	Total knee arthroplasty n = 830	Unicompartmental knee arthroplasty n = 74
No tranexamic acid		178 (10.4%)	77 (9.6%)	92 (11.1%)	9 (12.2%)
Single dose	i.v.	1227 (72.1%)	614 (77.0%)	565 (68.1%)	48 (64.9%)
	p.o.	1 (0.1%)	0	0	1 (1.4%)
	i.m.	3 (0.2%)	0	3 (0.4%)	0
Multiple doses	i.v. + i.v.	226 (13.3%)	86 (10.8%)	126 (15.2%)	14 (18.9%)
	p.o. + p.o.	2 (0.1%)	1 (0.1%)	1 (0.1%)	0
	i.v. + top	30 (1.8%)	14 (1.8%)	14 (1.7%)	2 (2.7%)
	i.v. + i.m.	3 (0.2%)	0	3 (0.4%)	0
	i.v. + p.o.	31 (1.8%)	5 (0.6%)	26 (3.1%)	0

i.v., intravenous; p.o., oral; i.m., intramuscular; top, topical.

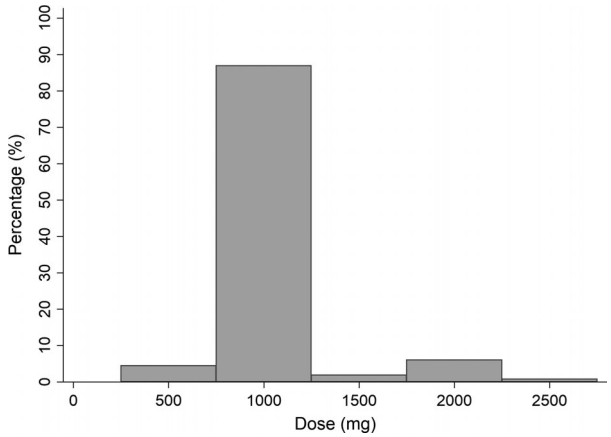

Figure 3 Histogram of single doses of tranexamic acid (n = 1231)

and 2. A total of 1231 (72%) patients received a single dose of tranexamic acid compared with 292 (17%) who received multiple doses (Table 2). The most frequently administered single dose was 1000 mg [n = 1310 (86.1%)] (Fig. 3). Mean (SD) total cumulative dose administered was 1112 (600.5) mg.

In total, 517 out of 1701 (33.6%) patients presented with pre-operative anaemia and 1386 (81.5%) were anaemic postoperatively (Table 3). Data on estimated blood loss and transfusion rates for the overall cohort and according to operation type are in Table 3. The number of patients with an estimated blood loss of greater than 500 ml was 1252 (73.7%). Out of these, 1110 (88.7%) received tranexamic acid. The transfusion rate for patients with pre-operative anaemia was 37/571 (6.5%) compared with 17/1130 (1.5%) in patients without anaemia ($p < 0.0001$). Two patients required intra-operative transfusions and both were anaemic pre-operatively (Hb 109 $g.l^{-1}$ and 107 $g.l^{-1}$).

There was regional variation in practice with the lowest recorded rate of pre-operative anaemia in north-east England (22.0%) and highest in the Yorkshire and Humber

Table 2 Timing of tranexamic acid administration in all patients and those undergoing total hip, knee or unicompartmental knee arthroplasty. Values are number (proportion).

Dose	Peri-operative timing	All n = 1701	Total hip arthroplasty n = 797	Total knee arthroplasty n = 830	Unicompartmental knee arthroplasty n = 74
No tranexamic acid		178 (10.4%)	77 (9.6%)	92 (11.1%)	9 (12.2%)
Single dose	Pre-operative	616 (36.3%)	369 (46.3%)	228 (27.5%)	19 (25.7%)
	Intra-operative	593 (34.9%)	242 (30.4%)	322 (38.7%)	29 (39.2%)
	Postoperative	22 (1.3%)	3 (0.4%)	18 (2.2%)	1 (1.4%)
Multiple doses	Pre-operative	1 (0.1%)	0	1 (0.1%)	0
	Intra-operative	70 (4.1%)	25 (3.1%)	42 (5.1%)	3 (4.1%)
	Postoperative	2 (0.1%)	1 (0.1%)	1 (0.1%)	0
	Pre-operative and intra-operative	117 (6.8%)	44 (5.4%)	65 (7.8%)	8 (10.8%)
	Pre-operative and postoperative	57 (3.4%)	19 (2.4%)	35 (4.2%)	3 (4.1%)
	Intra-operative and postoperative	45 (2.7%)	17 (2.1%)	26 (3.1%)	2 (2.7%)

Table 3 Anaemia prevalence, estimated blood loss and red blood cell transfusion rates in all patients and those undergoing total hip arthroplasty, total knee arthroplasty and unicompartmental knee arthroplasty. Values are number (proportion) or mean (SD).

	All n = 1701	Total hip arthroplasty n = 797	Total knee arthroplasty n = 830	Unicompartmental knee arthroplasty n = 74
Proportion anaemic Hb < 130 $g.l^{-1}$	571 (33.6%)	290 (36.4%)	266 (32.0%)	15 (20.3%)
Pre-operative haemoglobin; $g.l^{-1}$	135.0 (13.5)	134.3 (13.7)	135.5 (13.3)	139 (12.1)
Postoperative haemoglobin; $g.l^{-1}$	115.0 (15.3)	112.4 (15.4)	116.7 (14.8)	127 (11.3)
Estimated blood loss; ml	791.9 (452.5)	862.5 (473.3)	745.1 (423.5)	468.5 (324.8)
Red blood cell transfusion rate	54 (3.1%)	38 (4.7%)	13 (1.6%)	3 (4.1%)

region (49.5%) (Fig. 4, Table S1). The rate of blood transfusion was lowest in Northern Ireland (0%) and highest in the Yorkshire and Humber region (7.6%) (Fig. 5, Table S2).

Discussion

Tranexamic acid was administered in approximately 90% of patients undergoing primary hip or knee arthroplasty. The

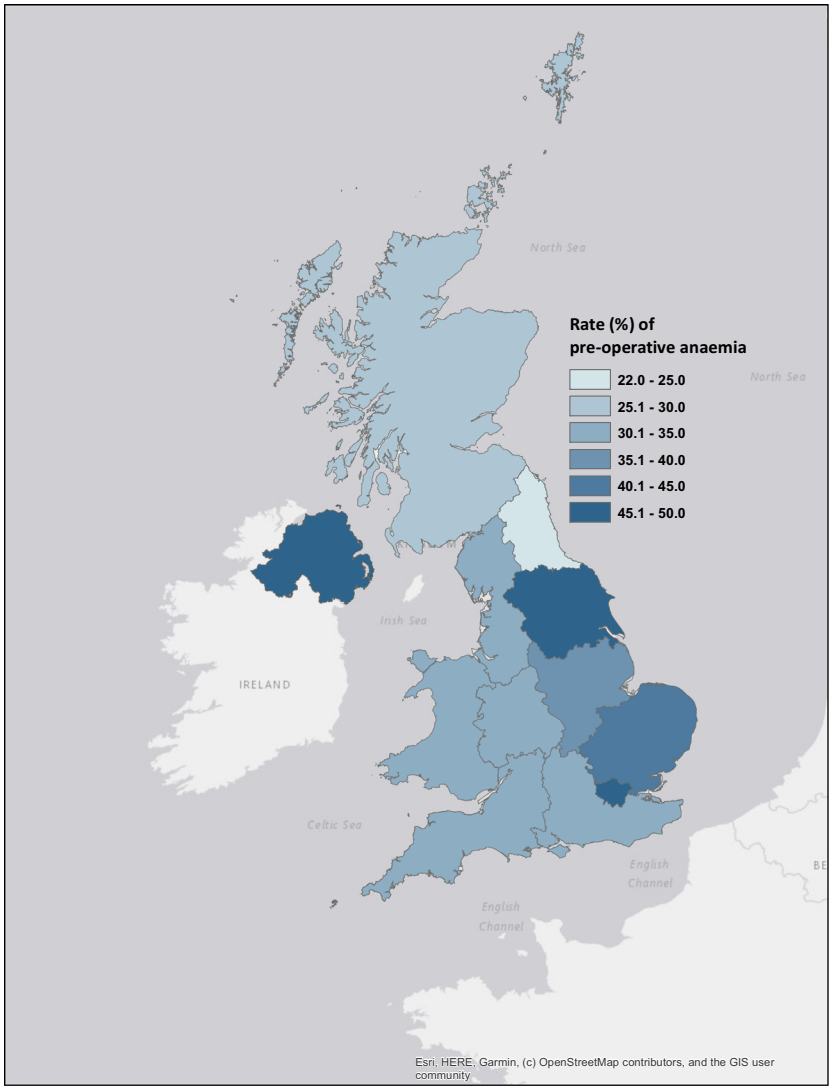

Figure 4 Pre-operative anaemia prevalence by geographical region

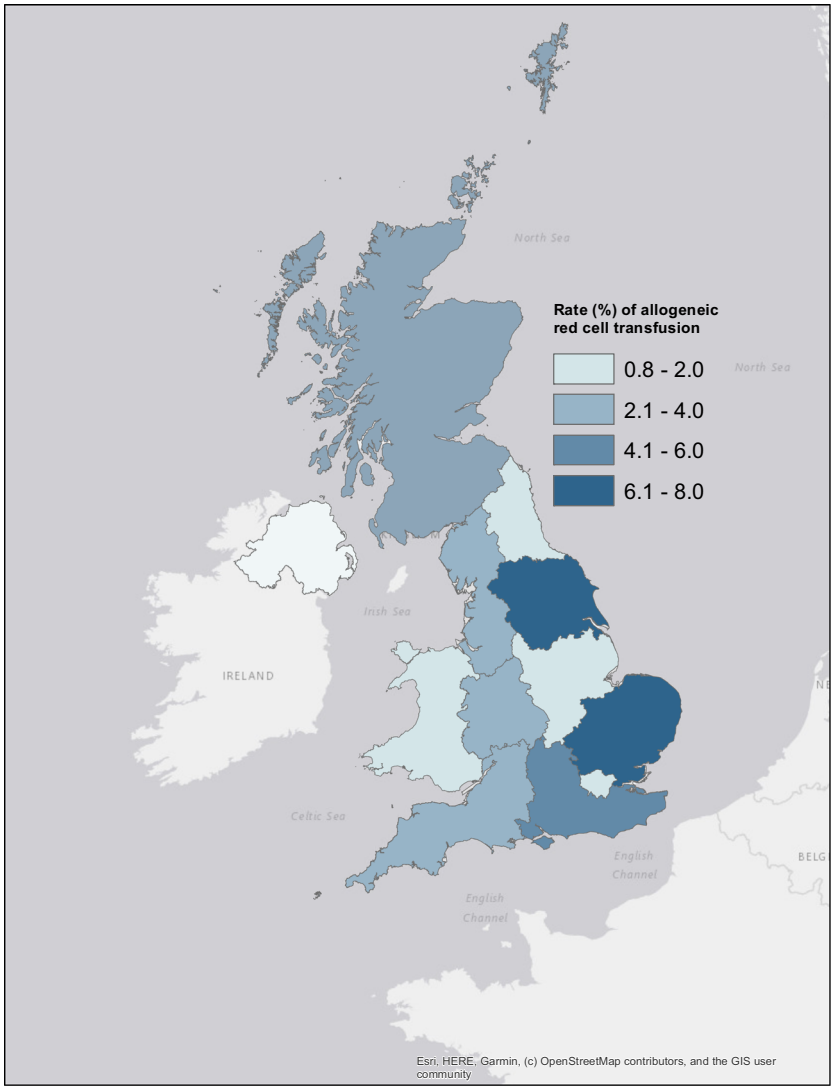

Figure 5 Incidence of allogeneic transfusion by geographical region

most frequently adopted dosing regimen was 1000 mg delivered intravenously as a single dose either pre-operatively or intra-operatively. Approximately one-third of patients presented for surgery with pre-operative anaemia. Mean estimated blood loss exceeded 500 ml for primary total hip and knee arthroplasty in over 70% of patients. The postoperative red blood transfusion rate for our study cohort was 3.1%.

The results of this study demonstrate good compliance with current NICE standards (90% of patients administered tranexamic acid) [7]. This rate of compliance is significantly higher than reported in the 2016 National Comparative Audit of 471 patients undergoing primary total hip arthroplasty and 289 undergoing primary total knee arthroplasty. In this audit, 63% of patients undergoing primary total hip arthroplasty and 51% for primary total knee arthroplasty received tranexamic acid [10].

There was variation in the dose, route and timing of administration, reflecting the absence of a consensus opinion on optimal tranexamic acid dosing regimens. A large number of randomised controlled trials have been performed comparing different routes, doses and timing of administration, but the heterogeneity of these studies makes interpretation difficult in terms of determining an optimal dose [11]. To achieve clarity, future trials examining dosing regimens should be performed against a common comparator that is representative of current practice. We have demonstrated that 1000 mg of tranexamic acid given intravenously as a single dose, either pre-operatively or intra-operatively, would be appropriate whilst also maintaining acceptability to clinicians.

Previous studies show a reduction in blood loss and allogeneic transfusion rates following combined topical and intra-articular tranexamic acid compared with intravenous alone and warrants consideration for routine clinical practice [12]. Topical administration also overcomes potential systemic toxicity in patients with renal failure. Topical application was used in fewer than 2% of patients in this cohort and always in combination with intravenous tranexamic acid. Oral tranexamic acid administration may offer equivalent effectiveness to intravenous and topical administration but AT a much lower cost [13]. A concern from in-vitro studies is potential toxicity to peri-articular tissues when administered topically, which is especially salient in unicompartmental knee arthroplasty and further research is indicated to address this uncertainty [14].

Cumulative doses of tranexamic acid ranged from 500 to 5000 mg given over 1–3 doses in this study. There is inconsistent evidence of reduced blood loss with greater doses of tranexamic acid and concerns over potential toxicity with very high doses [15]. This study found the majority of patients received a 1000 mg dose of tranexamic acid rather than dosing based on patient weight. To optimise the effectiveness of tranexamic acid, optimal blood concentrations should be achieved early and maintained. A 1000-mg bolus of tranexamic acid maintains the minimal target concentration for 1.5 h after administration [16]. While this may be effective at addressing intra-operative blood losses, it is unlikely to account for hidden blood losses postoperatively, which is an important consideration in effective patient blood management [17]. Studies have not demonstrated a benefit from multiple doses of tranexamic acid for primary arthroplasty [6] but may play a role in revision arthroplasty surgery with longer surgical times and greater blood loss. Tranexamic acid was most frequently administered intra-operatively for total knee arthroplasty and pre-operatively for total hip arthroplasty, perhaps because tranexamic acid is usually administered when the tourniquet is released. An ongoing Cochrane network meta-analysis may offer further guidance regarding tranexamic acid administration in total hip arthroplasty and total knee arthroplasty [11].

Approximately one-third of patients in our cohort were anaemic pre-operatively, consistent with studies from other countries [18]. This incidence is lower than the 2016 National Comparative Audit of 726 patients, which found 50% patients were anaemic before primary total hip arthroplasty and 60% before primary total knee arthroplasty (Hb < 130 $g.l^{-1}$ men and Hb < 120 $g.l^{-1}$ women). There is a national quality improvement project underway to optimise pre-operative anaemia in orthopaedic patients [19]. Pre-operative anaemia increases the risk of exposure to red blood cell transfusion and is a significant risk factor for peri-operative morbidity and mortality [20]. Although the World Health Organization defines anaemia as below 120 $g.l^{-1}$ for women and 130 $g.l^{-1}$ for men, consensus guidance is that the threshold should be 130 $g.l^{-1}$ for both sexes [21]. Timely and effective management of pre-operative anaemia may improve peri-operative morbidity and functional outcomes [22, 23].

Postoperative anaemia may have significant implications for patient recovery. Changes in Hb concentration > 50% from baseline or postoperative Hb < 70 gl^{-1} have been shown to be associated with increased risk of postoperative ischaemic events in surgical patients [24]. The association between postoperative anaemia and functional recovery, including patient-reported outcome measures following surgical interventions, remains unclear [22]. Over 80% of patients in our sample were anaemic postoperatively, which demonstrates that a significant proportion of arthroplasty patients are potentially at risk of adverse postoperative recovery [25]. Large-scale observational studies using epidemiological data are required to further investigate whether this association exists.

Red blood cell transfusion rates in our sample (3.1%) were lower than previously reported results from national datasets (18.3–47%) [26], but higher than some institutional cohort studies [2]. Transfusion rates in total joint arthroplasty have changed significantly in the past two decades with development and uptake of patient blood management strategies [27]. Restrictive transfusion thresholds have been demonstrated to reduce rates of allogeneic transfusion with no adverse effect on patient morbidity and mortality [28]. NICE recommends transfusion thresholds of 70 $g.l^{-1}$ except in patients with acute coronary syndrome when the threshold is 80 $g.l^{-1}$ [7]. Transfusion rates following unicompartmental knee arthroplasty (4.1%) were higher than anticipated; however, the cohort included only 74 patients undergoing this procedure with three allogeneic blood transfusions and is likely to represent sampling bias.

There is regional variation in the prevalence of pre-operative anaemia and rate of postoperative transfusion. Conclusions are limited by the small number of patients in some regions; however, the results suggest heterogeneity in the delivery of patient blood management despite national guidelines [7].

Strengths of this study include utilising the power of a trainee collaborative network [29, 30] to collect data on current UK orthopaedic practice covering a wide

geographical area and 56 different NHS hospitals (Fig. 1). Approximately 130,000 primary hip and knee replacements are performed in NHS hospitals in 2018 [31]. Our study is estimated to have captured over a third of procedures performed during the period of study.

Our study also has limitations. Despite widespread collaborator recruitment and data acquisition, it is possible that the participating centres do not represent national practice. Selection bias may favour hospitals with established patient blood management programmes, underestimating allogeneic transfusion rates amongst arthroplasty patients. The calculation of blood loss is an estimation, although Gross' formula is a validated and accurate tool. Compliance with NICE guidance for administering tranexamic acid may be higher than we report, as we did not collect data to explain why tranexamic acid was not administered. Relative contraindications to tranexamic acid administration include thromboembolic events and history of convulsion. Data on modes of anaesthesia and patient comorbidity were not collected as we focused on a small set of variables to enhance recruitment.

In summary, we show good compliance with NICE standards on tranexamic acid administration. The most frequently adopted dosing regimen was 1000 mg delivered intravenously as a single dose either pre-operatively or intra-operatively. Future research studies may wish to adopt this as a comparator to reduce study heterogeneity that currently limits meta-analyses in this field.

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Appendix: collaborators.

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Supporting Information

Additional supporting information may be found online via the journal website.

Table S1. Pre-operative anaemia prevalence by geographical region

Table S2. Incidence of allogeneic transfusion by geographical region