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ORIGINAL RESEARCH

The Impact of Intra-Operative Heparin on Thromboembolism and Death in a Matched Cohort of Patients with a Ruptured Abdominal Aortic Aneurysm

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Objective: Portuguese nationwide estimates indicate that 20% of abdominal aortic aneurysms (AAAs) are treated when ruptured. In these cases, intra-operative unfractionated heparin (UFH) usage rates vary widely. Evidence on this topic is scarce and focused on patients treated by open repair (OSR). The aim was to determine the influence of UFH on peri-operative thromboembolic events (TEs) and death in a cohort of ruptured AAA (rAAA).
Methods: Retrospective, single-centre, comparative study. From 2011 to April 2023, all consecutive rAAAs (endovascular repair [EVAR] and OSR) were considered. Primary outcomes were 30-day TE free survival and TE rates. The secondary outcome was 30-day death. Safety endpoints were procedural blood loss, blood product requirements, and secondary interventions due to haemorrhage. Using propensity score matching (PSM) each UFH patient was matched with one no UFH patient in a 1:1 ratio.
Results: The study included 250 patients. After PSM, 190 patients were analysed (EVAR: 60.0% no-UFH vs. 64.4% UFH). TE free survival estimates favoured the UFH group (67.3% vs. 47.2%, $p = .009$; UFH adjusted odds ratio [aOR] 2.01, 95% confidence interval [CI] 1.04—4.17). TEs were more frequent in the no UFH group (20.0% vs. 44.2% patients, $p < .001$; UFH aOR 0.31, 95% CI 0.15—0.65 for any TE), driven by an increase in bowel ischaemia (17.9% no UFH vs. 3.2% UFH, $p = .001$). Most events occurred in the first 72 hours. EVAR was associated with reduced TE and improved TE free survival (aOR 0.20, 95% CI 0.09—0.45 and aOR 5.54, 95% CI 2.34—13.08, respectively). No significant differences in 30-day survival were noted (75% no-UFH vs. 83% UFH, $p = .26$; aOR 1.08, 95% CI 0.48—2.43) nor in blood loss, peri-operative red blood cell and fresh frozen plasma requirements, or secondary interventions due to haemorrhage ($p = .10$; $p = .11$; $p = .13$ and $p = .18$ respectively).
Conclusion: In this cohort, intra-operative UFH was safe and associated with improved TE free survival, driven by a reduction in bowel ischaemia. Conversely, mortality remained unaffected. Randomised controlled trials are required to confirm these findings.

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INTRODUCTION

Portuguese estimates indicate that 20% of abdominal aortic aneurysms (AAA) are treated when ruptured.[1] Throughout 2000—2015, in hospital mortality reached 30% and 50% after endovascular aneurysm repair (EVAR) and open repair (OSR), respectively.[2]

During elective AAA repair, unfractionated heparin (UFH) is the norm, before aortic cross clamping in OSR or after obtaining access in EVAR.[3] International surveys have shown that most physicians choose a standardised 5 000 IU UFH bolus for these procedures.[4—6]

The major advantage of UFH is the prevention of peri-operative thromboembolic complications.[7] An increase in blood product requirements or the need for re-exploration can offset this benefit, particularly when treating ruptured AAA (rAAA). In addition to haemorrhagic shock, rAAAs are associated with significant rates of thromboembolic events (TEs), TE related secondary interventions and cardiovascular death.[8—12] In this scenario, UFH usage rates have varied widely over time (16—76.9%).[4,13,14] This reflects the absence of evidence regarding this topic, particularly after EVAR. Notwithstanding, a survival benefit after OSR with intra-operative UFH has been reported previously.[14,15]

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The authors aim was to investigate whether intra-operative UFH during primary rAAA repair reduces TE and or death. Also, safety outcomes, namely bleeding complications, were assessed.

MATERIALS AND METHODS

A single centre, retrospective, comparative study following the principles outlined by the Declaration of Helsinki and STROBE guidelines was performed.[16] Institutional review board approval was waived due to the retrospective, observational nature of this study.

Patient population

All consecutive patients treated for rAAA (OSR or EVAR), from January 2011 to April 2023, at a tertiary academic centre were considered. Infrarenal and juxtarenal pathologies were considered. Suprarenal, thoracic, thoracoabdominal aneurysms, secondary ruptures, and symptomatic, non-ruptured cases were excluded. Two groups were defined: an UFH group, including patients treated with intra-operative UFH, and a no-UFH group, including patients treated without UFH.

Definitions

Cut off values for age >76 years, creatinine >160 μmol/L, haemoglobin <5.6 g/dL and lowest systolic blood pressure ≤80 mmHg were selected according to mortality prediction models in rAAA.[17,18]

TEs were defined as any complication caused, at least partly, by thrombus or embolus including, but not exclusively, deep venous thrombosis, pulmonary embolism, bowel ischaemia, stroke, graft thrombosis, thrombus or embolus in organs or lower limbs, and other peripheral thromboses.[19] Bowel ischaemia was defined as colon and or small bowel ischaemia requiring surgical resection.

AAA rupture was documented by computed tomography angiography and confirmed by the attending physicians before the procedure. The aneurysm was defined as juxtarenal or infrarenal aortic aneurysm.[3] Remaining definitions on baseline variables and data collection strategy are shown in Supplementary Material S1 and S2, respectively.

Outcomes

Primary outcomes were 30 day TE free survival and TE rates. Secondary outcome was 30 day survival. Safety endpoints were procedural blood loss, 24 h red blood cell and fresh frozen plasma (RBC and FFP) requirements, and 30-day secondary interventions due to haemorrhage.

Unfractionated heparin

In OSR, UFH was administered after proximal aortic cross clamping. During EVAR, timing was more variable. Activated coagulation time was not routinely measured during the procedure. UFH and respective dosage were chosen at the surgeon's discretion. Some surgeons routinely administered UFH while others did not. Patients resumed prophylactic anticoagulation on the first post-operative day.

Statistical analysis

Continuous data are presented as mean ± standard deviation for Gaussian distributed variables or median ± interquartile range for non-Gaussian distributed variables and compared with Student's *t* test or Mann−Whitney U test, respectively. Dichotomous variables were expressed as counts and percentages and differences assessed using Pearson's χ^2 test or Fisher's exact test.

Kaplan−Meier analyses with the log rank test were conducted to assess the effect of UFH on TE free and overall survival. A multivariable logistic regression analysis examined the association between intra-operative UFH and the outcomes. Variables returning $p < .05$ on univariable analysis and or considered clinically relevant were added to the multivariable analysis. Odds ratios with 95% confidence interval are presented. The level of statistical significance was set at a $p < .05$. Statistical analysis was performed using SPSS software (version 26.0; SPSS, Chicago, IL, USA).

Missing data management and propensity score matching

Data pertaining this group of patients contained missing values. No patterns of missing data were found. Therefore, data were assumed to be missing completely at random, allowing to impute missing data using the method of multiple imputation.[20] To account for the variation in completing the dataset, 10 imputed datasets per group were created. Then, results were combined to produce a final dataset. Patients in the UFH group underwent propensity score matching (PSM) with patients in the no UFH group in a 1:1 ratio to reduce bias posed by differences in surgical technique and patient related data. When calculating the propensity score, pre-specified sets of covariables were included as confounders in a logistic regression model to predict the treatment of interest. Introduced covariables included baseline (age, comorbidities, medications), aneurysm extent, and peri-operative characteristics (haemoglobin <5.6 d/dL, creatinine >160 μmol/L, cardiac arrest, loss of consciousness, lowest SBP ≤80 mmHg, EVAR *vs.* OSR, adjunctive procedures). PSM was performed using nearest neighbour matching and the calliper method with a threshold of 0.20 standard deviations of the difference in the propensity score. Finally, multivariable logistic regression analysis using complete case analysis was performed.

RESULTS

Baseline characteristics

From a total of 1 354 aortic procedures, 250 (103 UFH *vs.* 147 no UFH) were for primary rAAA (Fig. 1). Missing data and baseline characteristics before and after PSM are shown in (Table 1). Before PSM, the UFH group had higher rates of pulmonary disease ($p = .036$). After PSM, two comparable cohorts (95 patients per group) were identified

for final analysis, and no significant baseline differences were found (Table 1).

Peri-operative characteristics

Before PSM, the no UFH group had higher creatinine levels ($p = .043$), more frequently presented with a lowest SBP ≤80 mmHg ($p = .022$) and loss of consciousness ($p < .001$) and more frequently underwent OST ($p < .001$) (Table 1). After PSM, no significant differences were found.

The most frequently used UFH dosage was 5 000 IU, in 73.5% patients (median 5 000 IU, range 3000—9000 IU). Aortic balloon occlusion was used in 1.8% EVAR (1 no-UFH *vs.* 1 UFH) and a supracoeliac clamp in 20.5% OSR (8 no-UFH *vs.* 8 UFH).

Patients excluded from the PSM cohort presented higher rates of cardiac arrest ($p < .001$), loss of consciousness ($p < .001$), lowest SBP ≤80 mmHg ($p < .001$), creatinine >160 µmol/L ($p < .001$), and underwent OSR more frequently ($p = .003$) (Supplementary Material S3).

PSM cohort survival and thromboembolic events

Sixty-two TE occurred in 54 (28.4%) patients and were significantly more common in the no-UFH group (40.0% *vs.* 16.8%, $p < .001$) (Table 2). Most TE (72%) occurred in the first 72 hours (71% no UFH *vs.* 80.1% UFH). Bowel ischaemia (10.5% overall) was more common in the no UFH group (17.9% *vs.* 3.2%, $p = .001$) and the main cause of death in 20% ($n = 4$) of this subgroup. No association with cross clamp site was noted ($p = .80$). No significant differences between groups in the remaining TE were noted (Table 2). On multivariable analysis, intra-operative UFH presented an adjusted odds ratio (aOR) 0.31 (95% confidence interval [CI] 0.15—0.65) for any TE (Table 3). EVAR was associated with reduced risk of any TE (aOR 0.20, 95% CI 0.09—0.45). When depicted by surgical technique, no UFH patients had significantly increased rates of bowel ischaemia (OSR: 26.8% *vs.* 5.4%, $p = .032$; EVAR: 11.1% *vs.* 1.7%, $p = .041$) (Supplementary Material S4).

TE free survival estimates favoured the UFH group up to post-operative day 30 (70.5% UFH *vs.* 49.5% no UFH, $p = .005$) (Fig. 2A). On multivariable analysis, UFH was associated with a significantly increased 30 day TE free survival (aOR 2.01, 95% CI 1.03—4.17), as was EVAR (aOR 5.54, 95% CI 2.34—13.08) (Table 3).

Overall, 30 day mortality rate was 20.5% ($n = 39$). No significant differences in 30 day survival were noted between groups (75.8% no UFH *vs.* 83.2% UFH, $p = .26$; aOR 1.08, 95% CI 0.48—2.43) (Fig. 2B). Age >76 years (aOR 0.44; 95% CI 0.20—0.99) creatinine >160 µmol/L (OR 0.26; 95% CI 0.12—0.58), and haemoglobin <5.6 g/dL (aOR 0.27, 95% CI 0.12—0.61) were associated with reduced 30 day survival. Most deaths (64%) occurred in the first 72 hours (13 no UFH *vs.* 12 UFH).

PSM cohort safety outcomes

No significant differences in blood loss and peri-operative RBC and FFP requirements were noted (no UFH *vs.* UFH: 1 080 *vs.* 850 mL, $p = .10$; 3.8 *vs.* 3.2 RBC, $p = .11$ and 2.2 *vs.* 1.8 FFP, $p = .13$, respectively). All secondary interventions due to haemorrhage occurred within 72 hours (3.2% no UFH *vs.* 1.1% UFH, $p = .28$) (Supplementary Material S5).

DISCUSSION

In this cohort, intra-operative UFH during rAAA repair was associated with a significantly increased probability of 30

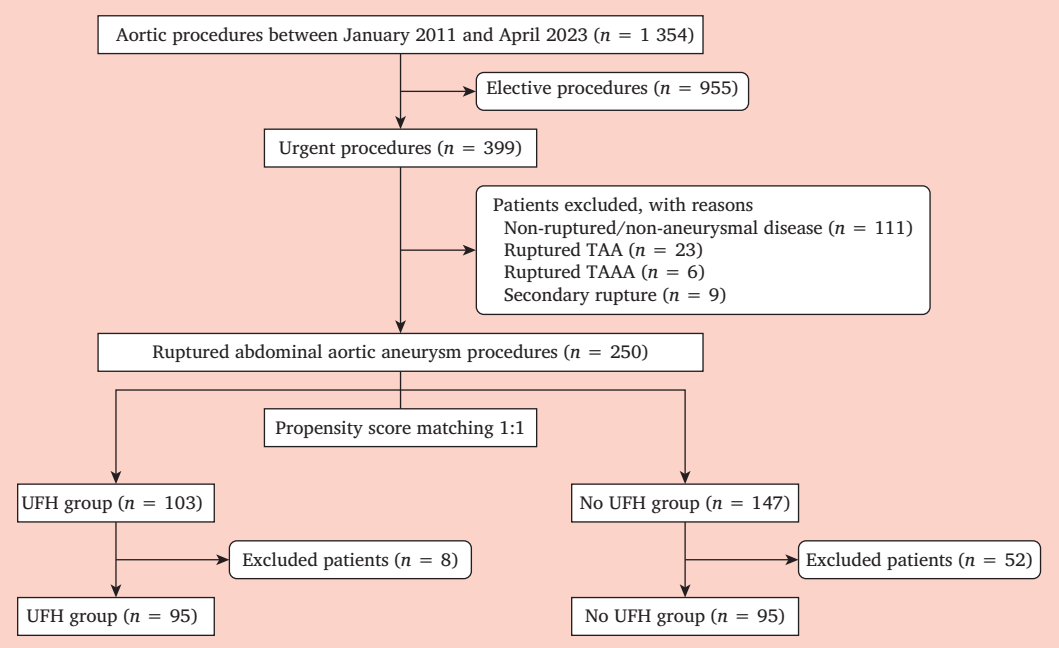


Figure 1. Study flowchart of patient selection. The flowchart shows inclusion and exclusion of patients with ruptured aortic aneurysms who underwent intra-operative administration of unfractionated heparin (UFH) or no UFH, according to the criteria mentioned in the methodology section and after propensity score matching. TAA = thoracic aortic aneurysm; TAAA = thoraco-abdominal aortic aneurysm.

Table 1. Baseline and clinical presentation characteristics.

		Before PSM			PSM cohort		
Baseline characteristics	Missing data	No UFH ($n = 147$)	UFH ($n = 103$)	p value	No UFH ($n = 95$)	UFH ($n = 95$)	p value
Age	0	73 ± 11	72 ± 10	.26	72 ± 12	72 ± 10	.48
Male	0	137 (93.2)	89 (86.4)	.07	88 (92.6)	84 (88.4)	.32
Smoking history	16 (6.4)	96 (69.6)	75 (78.1)	.15	67 (70.5)	75 (78.9)	.18
Hyperlipidaemia	8 (3.2)	74 (52.5)	62 (61.4)	.17	50 (52.6)	56 (58.9)	.38
Hypertension	5 (2.0)	110 (77.5)	85 (82.5)	.33	72 (75.8)	77 (81.1)	.38
Diabetes mellitus	7 (2.8)	19 (13.5)	13 (12.7)	.87	9 (9.5)	13 (13.7)	.36
CKD	9 (3.6)	24 (17.1)	21 (20.8)	.47	16 (16.8)	18 (18.9)	.71
Heart disease	9 (3.6)	52 (36.6)	44 (44.4)	.22	33 (34.7)	40 (42.1)	.29
Cerebrovascular disease	7 (2.8)	25 (17.7)	15 (14.7)	.53	15 (15.8)	13 (13.7)	.68
Pulmonary disease	8 (3.2)	28 (19.9)	32 (31.7)	.036	22 (23.2)	30 (31.6)	.19
PAD	10 (4.0)	19 (13.7)	18 (17.8)	.38	14 (14.7)	17 (17.9)	.56
Statin	24 (9.6)	67 (52.3)	54 (55.1)	.68	45 (47.4)	49 (51.6)	.56
Anticoagulant	10 (4.0)	17 (11.6)	14 (13.6)	.83	10 (10.5)	11 (11.6)	.86
Antiplatelet	20 (8.0)	58 (44.3)	37 (37.4)	.29	36 (37.9)	36 (37.9)	
Aneurysm diameter	30 (12.0)	81±22	79±22	.51	79±20	79±20	.80
Aneurysm extent	0			.19			.61
Infrarenal		105 (70.4)	80 (77.7)		71 (74.7)	74 (77.9)	
Juxtarenal		42 (28.6)	23 (22.3)		24 (25.3)	21 (22.1)	
Peri-operative characteristics							
Creatinine >160 μmol/L	13 (5.2)	56 (40.3)	27 (27.6)	.043	27 (28.4)	25 (26.3)	.65
Haemoglobin <5.6 g/dL	13 (5.2)	44 (31.7)	24 (24.5)	.23	27 (28.4)	21 (22.1)	.32
Cardiac arrest	10 (4.0)	10 (7.3)	2 (1.9)	.059	2 (2.1)	2 (2.1)	
Loss of consciousness	11 (4.4)	51 (37.5)	12 (11.7)	<.001	19 (20.0)	12 (12.6)	.17
Lowest SBP ≤80 mmHg	36 (14.4)	64 (52.0)	33 (36.3)	.022	41 (43.2)	31 (32.6)	.14
Endovascular repair	0	65 (44.2)	70 (68.0)	<.001	54 (60.0)	58 (64.4)	.27

Data is presented as n (%) or mean ± standard deviation. Missing data analysis and baseline characteristics before (250 patients) and after (190 patients) PSM. CKD = chronic kidney disease; PAD = peripheral artery disease; PSM = propensity score matching; SBP = systolic blood pressure; UFH = unfractionated heparin.

Table 2. PSM cohort 30 day thromboembolic event rates.

Thromboembolic events	No-UFH ($n = 95$)	UFH ($n = 95$)	p value
Bowel ischaemia	17 (17.9)	3 (3.2)	.001
Intra-operative thrombectomy	13 (13.7)	8 (8.4)	.25
Acute limb ischaemia	4 (4.2)	2 (2.1)	.68
TIA or stroke	3 (3.2)	2 (2.1)	
Limb or graft thrombosis	3 (3.2)	0 (0)	.25
Other[a]	5 (5.3)	2 (2.1)	.44

Data is presented as n (%). PSM = propensity score matched; TIA = transient ischaemic attack; UFH = unfractionated heparin. Myocardial infarction (5.3% no UFH *vs.* 4.2% UFH, $p = 1.0$) was not considered as TE most likely due to the type 2 mechanism.
[a] Other: renal ischaemia, pulmonary embolism, pelvic ischaemia.

day TE free survival (aOR 2.01, 95% CI 1.04—4.17). Conversely, death remained unaffected.

Guideline indications on intra-operative UFH during rAAA are often omissive.[21—23] The European Society for Vascular Surgery AAA guidelines provide a chapter on this topic, stating that although controversial, UFH should be considered, particularly during EVAR.[3] References are scarce and describe OSR patients.[24] Understandably, they were not able to provide a recommendation, but rather a suggestion.[4].

Although data in clinical practice is limited, there is evidence for a theoretical physiological benefit. A systematic review and pooled analysis (seven studies) found coagulopathy in 6% and disseminated intravascular coagulation in 2.4% of rAAA.[25] In the remainder, no abnormally low values (fibrinogen, platelets) were observed and D-dimers were frequently elevated (46.2%).[25] Comparative studies found thrombin generation and fibrinolysis inhibition markers significantly augmented in rAAA, lasting through the first 24 post-operative hours.[26,27] Fransson et al. found reduced rates of coagulopathy related deaths and elevated rates of thrombosis related deaths in a rAAA cohort.[28] This suggests that haemorrhagic derangement is rather uncommon and that a prothrombotic state may even ensue, contrary to post-traumatic haemorrhagic shock.[29]

The rationale for UFH relies in its ability to reduce peri-operative TE. A 2008 prospective, non-randomised study of 131 patients with rAAA who underwent OSR, compared 63 receiving UFH (5 000 IU) with 68 controls.[15] UFH patients had improved 30 day survival (84% *vs.* 67%, $p = .001$). Non-significant differences in intra-operative thrombectomy or blood product use were noted. The authors concluded that UFH was safe and speculated that this drug is the cornerstone in preventing thromboembolism in this setting.

Recently, Cuen-Ojeda et al. performed a retrospective analysis of rAAA in the Vascular Quality Initiative Database (2003—2020). After PSM 519 OSR pairs, a significantly reduced death risk in the UFH group (risk ratio (RR) 0.74, 95% CI 0.66—0.84) was found. Notwithstanding, blood loss and RBC requirements were higher in the no UFH group.[14] In our cohort, we did not find significant differences in 30 day mortality. This could be partly explained by a significant proportion of EVAR procedures, which were associated with a reduced mortality rate. Also, PSM in this cohort not only accounted for demographic and clinical presentation data, but also aneurysm extent and some procedural features were included. These balanced, at least in part, the technical complexity between groups.[14] As the decision to administer UFH is intra-operative, it is believed this is relevant when matching. Conversely, a benefit in blood loss and RBC and FFP transfusion was not observed, which may have resulted from balancing the procedural complexity.[14] Ultimately, the exclusion of patients with a worse pre-operative condition may have balanced mortality rates between PSM groups, which is a limitation of this study.

This cohort presented elevated rates of TE, particularly the need for intra-operative thrombectomy and bowel ischaemia. Bowel ischaemia was significantly reduced in those treated with UFH, even when analysed per mode of operation. Most TE occurred in the first 72 post-operative hours, suggesting a time frame for maximum benefit of UFH.

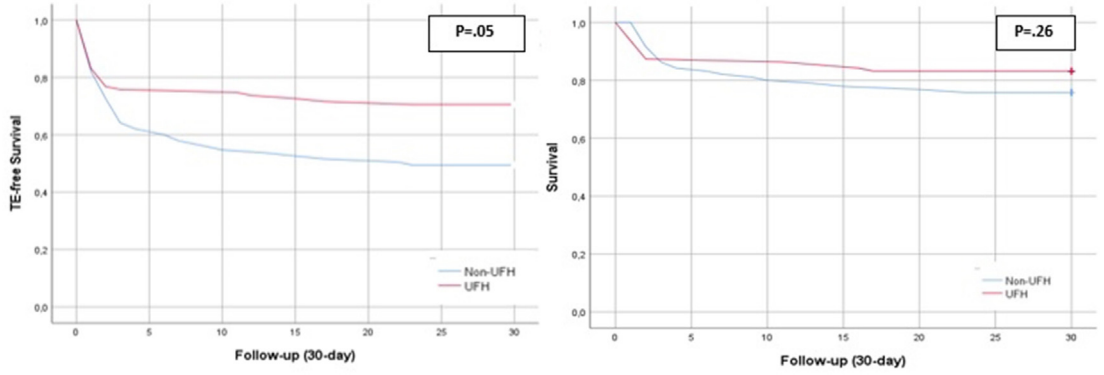
Notably, bowel ischaemia is not the sole result of emboli or *in situ* thrombosis. Bowel ischaemia is multifactorial and favoured by mesenteric and or hypogastric coverage or embolisation, hypotension, splanchnic vasoconstriction, and microvascular thrombosis.[8,30] Some of these mechanisms may be reduced with UFH.

The findings suggest that rAAA management presents serious thrombotic risks superimposed on a major haemorrhagic scenario. Interestingly, in the literature, coagulopathy and disseminated intravascular coagulation are infrequent, and a significant number can even present a procoagulant state. After aortic clamping or aortic balloon

Table 3. PSM cohort multivariable logistic regression analysis for any 30-day thromboembolic event (TE) and TE free survival.

	Multivariable analysis
Any thromboembolic event	
Intra-operative UFH	0.31 (0.15—0.65)
EVAR	0.20 (0.09—0.45)
TE free survival	
Intra-operative UFH	2.01 (1.04—4.17)
EVAR	5.54 (2.34—13.08)
Creatinine >160 µmol/L	0.43 (0.21—0.89)
Haemoglobin <5.6 g/dL	0.19 (0.09—0.44)

Complete case analysis of 190 patients in the PSM cohort up to 30 days. Adjusted OR are presented as OR (95% CI). Adjusted OR with a $p < .05$ are presented. UFH = unfractionated heparin; CI = confidence interval; OR = odds ratio; PSM = propensity score matched; TE = thromboembolic event.



UFH	Day 0	Day 10	Day 20	Day 30
Number at risk	95	72	68	67
KM estimate (SE)	____	75.8% (0.044)	71.6% (0.046)	70.5% (0.047)
Non-UFH	Day 0	Day 10	Day 20	Day 30
Number at risk	95	52	49	47
KM estimate (SE)	____	54.7% (0.051)	51.6% (0.051)	49.5% (0.051)

UFH	Day 0	Day 10	Day 20	Day 30
Number at risk	95	83	79	79
KM estimate (SE)	____	87.4% (0.034)	83.2% (0.038)	83.2% (0.038)
Non-UFH	Day 0	Day 10	Day 20	Day 30
Number at risk	95	76	73	72
KM estimate (SE)	____	80.0% (0.041)	76.8% (0.043)	75.8% (0.044)

Figure 2. Cumulative Kaplan—Meier (KM) estimates for TE free survival and overall survival after treatment of ruptured aortic aneurysm in patients who received intra-operative unfractionated heparin (UFH) *vs.* no UFH. (A) TE-free survival and (B) overall survival in the PSM cohort. KM survival estimates are depicted as percentages (standard error). SE = standard error; TE = thromboembolic event.

occlusion, UFH can potentially diminish the risk of TE with limited impact on haemorrhage. Ultimately, this reduction in vascular morbidity, in particular bowel ischaemia, should lead the surgeon to systematically consider the intra-operative administration of UFH in this scenario.

This study has limitations to be noted. First, it is a single centre retrospective study, which has unavoidable biases, although statistical methods were performed to mitigate them in the best way possible. Second, there was no standardised protocol for UFH administration. In addition, saline diluted heparin administered through sheaths during EVAR or the iliac and or femoral arteries during OSR could not be accounted for. Activated coagulation time measurements were unavailable, and these could have clarified the therapeutic decisions and individual biological variation in response.

Contrary to the above described limitations, the authors provide one of the biggest samples studied on this topic and, as far as known, the first to include endovascular procedures in a matched cohort, thus minimising potential bias generated by a worse clinical presentation or a procedure of increased complexity.

Conclusions

In this cohort of rAAAs, intra-operative UFH was safe and associated with increased TE free survival, driven by a reduction in bowel ischaemia. This benefit appears to occur in the early post-operative period. Conversely, mortality rate remained unaffected. Randomised controlled trials are required to confirm these findings.

FUNDING

None.

CONFLICT OF INTEREST

Frederico Bastos Gonçalves has received speaker and proctoring fees from W.L. Gore, Medtronic, and Cook Medical.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejvsvf.2023.11.004.

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