ANGIOLOGIA E CIRURGIA VASCULAR
PUBLICAÇÃO OFICIAL SPACV

REVIEW ARTICLE

Unfractionated heparin in ruptured aortic aneurysms – narrative review

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Submitted: May 14, 2023; **Reviewed:** June 19, 2023; **Accepted:** September 2, 2023.
Presented at: 22nd Annual Meeting of the Portuguese Society of Angiology and Vascular Surgery

ABSTRACT

INTRODUCTION: Portuguese estimates point out that nearly 20% of aortic aneurysms are treated in a ruptured setting, with in-hospital mortality reaching up to 50%. Although unfractionated heparin (UFH) is routine during elective surgery, this technical point is debatable when treating ruptured aneurysms. The authors aimed to review the literature on the topic of intraoperative heparinization with UFH within the intraoperative period of ruptured aortic aneurysms.

METHODS: A *MEDLINE* and Scopus database search using the terms “unfractionated heparin," “aortic aneurysm," and “ruptured aortic aneurysm” was performed. No time or language limitations were imposed. The last search was run in July 2023. Manuscripts were considered irrespective of study design. Additional articles of scientific interest for the purpose of this non-systematic review were included by cross-referencing.

RESULTS: In the rupture setting, UFH usage rates have widely varied throughout time and geographical sites, and they are reported to be as low as 16%. Overall, the evidence of UFH in clinical practice in this scenario is limited. Notwithstanding, there is some evidence from observational studies of an increased pro-coagulant activity in this clinical scenario, favoring a theoretical physiologic benefit. A prospective, non-randomized study of 131 OSR patients found that patients treated with UFH had improved 30-day survival (84% vs 67%, P=0.001). Non-significant differences in blood product usage were noted. Therefore, societal guideline recommendations about intraoperative UFH in ruptured aortic aneurysms are often missing.

CONCLUSION: UFH may potentially reduce death after open repair of rAAA. These findings should be carefully interpreted, as the evidence is scarce and heterogeneous and only portrays open repair.

Keywords: Abdominal Aortic Aneurysms; Unfractionated Heparin; Ruptured Aortic Aneurysms.

INTRODUCTION

Portuguese estimates point out that nearly 20% of aneurysms are treated in a ruptured setting.[1,2] Throughout 2000-2015, these also point towards one-third dying before hospital admission, and amongst those who underwent surgery, in-hospital mortality could reach up to 50%.[3] In elective surgery, the use of unfractionated heparin (UFH) is routine, as most physicians opt for a standardized 5000 International Units (IU) bolus.[4,5] The advantage of intraoperative UFH use is preventing adverse events caused by in situ thrombosis or emboli. On the other hand, an increase in clinically relevant hemorrhagic events, particularly when treating ruptured aneurysms, can offset this benefit. The authors aimed to review the literature on the topic of systemic heparinization

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Angiol Vasc Surg 2024;20(1):25-27
DOI: https://doi.org/10.48750/acv.564

with UFH in the intraoperative period of primary ruptured aortic aneurysms.

METHODS

A search using the terms “unfractionated heparin," “aortic aneurysm," and “ruptured aortic aneurysm” was performed using the MEDLINE and Scopus databases. No time or language limitations were imposed. The last search was run in July 2023. Manuscripts were considered irrespective of study design. Additional articles of scientific interest for the purpose of this non-systematic review were included by cross-referencing. Relevant publications were analyzed, and data was extracted and tabled.

RESULTS

Unfractionated heparin in aortic aneurysm surgery:
The basis for the use of UFH in aortic aneurysm surgery was established in 1996 by Thomson et al.[6] They performed a randomized controlled clinical trial, including 248 patients, to assess the rates of thromboembolic complications after elective open aortic aneurysm surgery. Patients were allocated to intraoperative unfractionated heparin vs. no heparin at all group. Patients under acetylsalicylic acid, non-steroidal anti-inflammatory drugs, and those who had a bleeding tendency (not disclosed how this was analyzed) were excluded. Hemoglobin, hematocrit, and platelet counts were obtained pre-operatively, one day, and one week after surgery. Complications included lower limb embolism/thrombosis, pulmonary embolism, and renal, respiratory, and cardiac complications. Heparin was administered before cross-clamping at a standard dosage of 5000IU. They noted a significant reduction in post-operative fatal myocardial infarction. At the same time, no increased blood loss nor hemorrhagic complications were identified. Although the use of heparin is standard in elective repair, there is much debate regarding its use during emergent repairs. In the rupture setting, UFH usage rates have widely varied throughout time and at different geographical sites. A 1994 survey showed that UFH was used in 34% of cases across Europe, compared to 53% in the USA.[4] Afterwards, a Scottish survey showed that only 16% of surgeons administered UFH to patients with ruptured aortic aneurysms.[7]

Coagulation in ruptured aortic aneurysms:
The evidence of UFH in clinical practice is limited in this scenario. Notwithstanding, there is some evidence for a theoretical physiologic benefit. A 1997 observational prospective study compared the coagulation and fibrin pathways in ruptured and non-ruptured aortic aneurysms.[8] The authors found a statistically significant increase in thrombin generation markers (thrombin-antithrombin III complex and prothrombin fragment 1 + 2) in the ruptured aneurysms, which lasted through the first 24 hours. In addition, a marked inhibition of systemic fibrinolysis due to the elevated tissue plasminogen activator (t-PA) antigen, reduced t-PA activity, and elevated plasminogen activator inhibitor activity.

A systematic review and pooled analysis of 7 studies (461 patients) found an overall weighted prevalence of coagulopathy of 12.3% (95% CI 10.7-13.9), 11.7% for INR (95% CI 1-31.6), 10.1% for platelet count (95% CI 1-26.8), and 11.1% for aPTT (95% CI 0.78-31). Fibrinogen serum concentration level was normal in 97%, and 46.2% (n=55) of patients had elevated D-dimer. Six percent of ruptured AAA demonstrated significant coagulopathy, and 2.4% showed disseminated intravascular coagulation (DIC).[9] In the remaining ones, no abnormally low values (fibrinogen, platelets) were observed. D-dimers were frequently elevated (46.2%). These data suggest that hemorrhagic derangement is relatively uncommon and that a prothrombotic state may even ensue, contrary to post-traumatic hemorrhagic shock.[10]

Thromboembolism after ruptured AAA repair:
Thromboembolic events are frequently observed in the post-operative period of ruptured AAA. Clamp-induced and access-related thrombotic injuries are encountered in up to 10% of cases.[11] Ischemic colitis is more frequent (up to 26% of patients) if grade 1 and 2 colonic ischemia are considered. Grade 3 (transmural) ischemia occurs in nearly 10% of patients.[12] Myocardial infarction develops in 37-42% of OSR patients. Less frequent is spinal cord ischemia, which occurs in 1.2% after OSR and 0.5 to 11.5% after EVAR for ruptured AAA.[13]

Evidence of unfractionated heparin in ruptured aortic aneurysms:
The aim of administering UFH in ruptured AAA is the reduction of adverse cardiovascular events and thromboembolic complications (intra-operative or post-operative). Lammy et al. performed a systematic review of intravenous heparin during ruptured abdominal aneurysmal repair. They aimed to include randomized controlled trials or controlled clinical trials. No studies satisfied the inclusion criteria, so high-level evidence on this topic is scarce.[14] A 2008 prospective, non-randomized study of 131 OSR patients with ruptured AAA compared 63 who received UFH (5000IU at proximal aortic clamping) with 68 controls. Patients treated with UFH had improved 30-day survival (84% vs 67%, P=.001). Non-significant differences in intraoperative thrombectomy rates or blood product usage were noted. In the non-UFH group, four patients expired due to DIC. The authors concluded that UFH was safe and speculated that, in this setting, prevention of ischemic complications represents this drug cornerstone.[15] Recently, two papers have been published on this topic after the open rAAA repair.[16,17] Cuen-Ojeda et al. performed a retrospective analysis of 2410 patients in the Vascular Quality Initiative database (2003-2020). After propensity-score matching 59 pairs, they found a significantly reduced 30-day death risk in the UFH group (risk ratio 0.74, 95% CI 0.66-0.84). In-hospital mortality was also reduced (risk ratio: 0.68; 95% CI: 0.60–0.77). They also found no increased risk of bleeding. This benefit lasted up to 10 years (hazard ratio: 0.62; 95% CI, 0.53–0.72; P < 0.0001). Later, Zarrintan et al. analyzed the same database for OSR (2011-2021) and found reduced mortality and re-exploration for bleeding in the UFH group. Ultimately, there are no papers stating the ideal indications for this drug in this scenario.

Guidelines of unfractionated heparin in ruptured aortic aneurysms:

Recommendations for intraoperative UFH in ruptured aortic aneurysms are often omissive.[18-20] SVS guidelines for managing patients with AAA state that "heparin may be omitted or administered in lower doses in special circumstances of a ruptured aneurysm (...)." However, they provide no references.[18] ESVS guidelines for managing AAA state that despite being controversial, serious consideration should be given to UFH administration, particularly in EVAR, after the aneurysm is excluded. [21] References available were scarce and only portrayed OSR patients. Understandably, current guidelines cannot provide a recommendation but a suggestion regarding this topic.

CONCLUSION

For the time being, unfractionated heparin in ruptured aortic aneurysms may pose the potential of reducing death after open repair of abdominal aortic aneurysms without significantly increasing hemorrhagic risk. These findings should be carefully interpreted, as the evidence is scarce and needs confirmation in adequately designed trials. Evidence during endovascular repair needs to be improved.

Acknowledgments: None

Conflicts of interest: None

Funding None

REFERENCES

1. Bastos Gonçalves F, Sousa P, Abreu D, Menezes JD, Mansilha A. Treatment of arterial pathology in the Portuguese Health Service - a report of the years 2009-2017. Angiol Cir Vasc 2021; 17:1-6.

2. Bastos Goncalves F, Menezes JD, Mansilha A, Vieira M, Sousa J, Quintas A, et al. The first year of the abdominal aortic module of the Portuguese National Registry of Vascular Procedures. Angiol Cir Vasc 2021; 17:72-80.

3. Dias-Neto M, Castro-Ferreira R, Mani K, Freitas A, Leite-Moreira A, Sampaio SM Nationwide Analysis of Ruptured Abdominal Aortic Aneurysm in Portugal (2000-2015), Eur J Vasc Endovasc Surg 2020; 60:27-35.

4. Wakefield TW, Lindblad B, Stanley TJ, Nichol BJ, Stanley JC, Bergqvist D et al. Heparin and protamine use in peripheral vascular surgery: a comparison between surgeons of the society for vascular surgery and the european society for vascular surgery. Eur J Vasc Surg 1994; 8:193–8.

5. Wiersema AM, Vos JA, Bruijninckx CMA, van Delden OM, Reijnen MMP, Vahl A et al. Periprocedural prophylactic antithrombotic strategies in interventional radiology: current practice in the Netherlands and comparison with the United Kingdom. Cardiovasc and Interv Rad 2013; 36:1477–92.

6. Thompson JF, Mullee MA, Bell PR, Campbell WB, Chant AD, Darke SG, et al. Intraoperative heparinisation, blood loss and myocardial infarction during aortic aneurysm surgery: a Joint Vascular Research Group study. Eur J Vasc Surg 1996; 12:86-90.

7. Milne AA, Murphy WG. Current blood transfusion practice in aortic aneurysm surgery in Scotland. The Scottish Vascular Audit Group. J R Coll Surg Edinb 1995; 40:104–8.

8. Adam DJ, Ludlam CA, Ruckley V, Bradbury AW. Coagulation and fibrinolysis in patients undergoing an operation for ruptured and unruptured infrarenal abdominal aortic aneurysms. J Vasc Surg 1999;30:641–50

9. Kordzadeh A, Parsa AD, Askari A, Maddison B, Panayiotopoulos YP. Presenting Baseline Coagulation of Infra Renal Ruptured Abdominal Aortic Aneurysm: A Systematic Review and Pooled Analysis. Eur J Vasc Endovasc Surg 2016 51:682-9.

10. Kornblith LZ, Moore HB, Cohen MJ. Trauma-induced coagulopathy: The past, present, and future. J Thromb Haemost. 2019 Jun;17:852-62.

11. Mehta M, Byrne J, Darling 3rd JC, Paty P, Roddy SP, Kreienberg PB et al. Endovascular repair of ruptured infrarenal abdominal aortic aneurysm is associated with lower 30-day mortality and better 5-year survival rates than open surgical repair. J Vasc Surg 2013; 57:368-75.

12. Tottrup M, Fedder AM, Jensen RH, Tottrup A and Laustsen J. The value of routine flexible sigmoidoscopy within 48 hours after surgical repair of ruptured abdominal aortic aneurysms. Ann Vasc Surg 2013; 27:714-8.

13. Peppelenbosch AG, Windsant V, Jacobs MJ, Tordoir J, Schurink G. Open repair for ruptured abdominal aortic aneurysm and the risk of spinal cord ischemia: Review of the literature and risk-factor analysis. Eur J Vasc Endovasc Surg 2010; 40:589-99

14. Lammy S, Blakmur JP, Perkins JMT. Intravenous heparin during ruptured abdominal aortic aneurysmal repair. Cochrane Database Syst Rev. 2016;8:CD011486)

15. Chinien G, Waltham M, Abisi S, Smith A, Taylor P, Burnand KG. Systemic administration of heparin intraoperatively in patients undergoing open repair of leaking abdominal aortic aneurysm may be beneficial and does not cause problems. Vascular 2008;16:189-93

16. Zarrintan S, Chow CY, Mathlouthi A, Cajas-Monson LC, Malas M. Use of Heparin during Open Repair of Ruptured Abdominal Aortic Aneurysm is Safe and Reduces Mortality (Abstract). J Am Coll Surg 2022;235: 102-3.

17. Cuen-Ojeda C, Li B, Tam DY, Dharma C, Feridooni T, Eisenberg N, Roche-Nagle G. The Impact of Heparin on Mortality Following Open Ruptured Abdominal Aortic Aneurysm Repair. Ann Vasc Surg. 2023;96:147-54

18. Upchurch GR, Escobar GA, Azizzadeh A, Beck AW, Conrad MF, Matsumura JS et al. Society for Vascular Surgery clinical practice guidelines of thoracic endovascular aortic repair for descending thoracic aortic aneurysms. J Vasc Surg 2021;73:55s-83s.

19. Riambau V, Böckler D, Brunkwall J, Cao P, Chiesa R, Coppi G, et al. Editor's Choice e Management of Descending Thoracic Aorta Diseases Clinical Practice Guidelines of the European Society for Vascular Surgery. Eur J Vasc Endovasc Surg. 2017;53:4–52.

20. NICE. NG156. Abdominal aortic aneurysm: diagnosis and management. (Available at https://www.nice.org.uk/guidance/ng156).

21. Wanhainen A, Verzini F, Herzeele IV, Allaire E, Brown M, Cohnert T et al. European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg 2019;57:8-93.