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Communication

Periprocedural outcomes of protamine administration after catheter ablation of atrial fibrillation

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Abstract

Background: Perioperative anticoagulation management with uninterrupted or minimally interrupted anticoagulation during atrial fibrillation (AF) ablation is thought to be critical to minimize thromboembolic complications. Protamine is often administered to neutralize the effects of heparin and expedite vascular hemostasis post-procedure. **Objective**: We performed a systematic review and meta-analysis to determine the effectiveness of protamine to expedite vascular hemostasis and ambulation in patients undergoing AF ablation. **Methods**: Electronic searches on PubMed, The Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases from the inception through August 7, 2021, were performed. The primary outcomes included—time to hemostasis (minutes) and time to ambulation (minutes). The secondary outcomes included - any vascular complications (excluding minor hematoma), minor hematoma, or cerebrovascular accidents (CVA). **Results**: A total of 5 eligible studies (3 retrospective cohort studies and two randomized trials) consisting of 1012 patients (515 patients received protamine group and 497 patients did not receive protamine group) were included in the meta-analysis. There was a significant reduction in time to ambulation [weighted mean difference (WMD) –176.6 minutes, 95% Confidence interval (CI) –266.9 to –86.3; $p < 0.01$] and time to hemostasis (WMD –13.72 minutes, 95% CI –22 to –5.4, $p < 0.01$) in the protamine group compared to the contrary. At a follow-up up to 3 months, there was no statistical difference between the two groups with regards to vascular complications (2.9% vs. 7.4%; Risk ratio (RR) 0.46 95% CI 0.17 to 1.24; $p = 0.12$), minor hematoma (2.1% vs. 5.8%; RR 0.43, 95% CI 0.16 to 1.2; $p = 0.11$) or CVA (0 vs. 0.3%; RR 0.62, 95% CI 0.08 to 4.98; $p = 0.65$). **Conclusion**: Protamine administration was associated with reduced time to ambulation (176 minutes reduction) and time to hemostasis (13 minutes reduction) without an increase in any adverse events.

Keywords: Atrial fibrillation ablation; Protamine; Anticoagulation

1. Introduction

Therapeutic anticoagulation with unfractionated heparin (UFH) during atrial fibrillation (AF) ablation is critical to minimize procedure-related thromboembolic complications [1]. The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE, an expert consensus statement on catheter ablation of AF, recommends protamine to neutralize effects of heparin and hasten hemostasis to avoid vascular complications such as aneurysm, fistula, and hematoma (Class IIa, based on moderate quality of evidence) [1]. However, its safety profile and efficacy in promoting faster patient recovery are still unclear. We performed a systematic review and meta-analysis to determine the effectiveness of protamine to expedite vascular hemostasis and ambulation in patients undergoing AF ablation.

2. Methods

A systematic search on PubMed, The Cochrane Library, EMBASE was done using the keywords: "protamine" and "atrial fibrillation ablation". Two investigators (JK and KS) independently performed the literature search (using PubMed, EMBASE, SCOPUS, Google Scholar, and ClinicalTrials.gov from inception to October 20th, 2021) and screened all titles and full-text versions of all relevant studies that met study inclusion criteria (**Supplementary Fig. 1**).

We used the following keywords and medical subject heading: "Protamine", "atrial fibrillation ablation", "AF ablation". This meta-analysis was performed according to the PRISMA guidelines and was prospectively enrolled in the PROSPERO database (*ID* 288480).

The eligibility criteria for our systematic review and meta-analysis included: (1) all studies reporting outcomes of the use of protamine in patients with AF ablation (2) studies that included human subjects. We included studies only

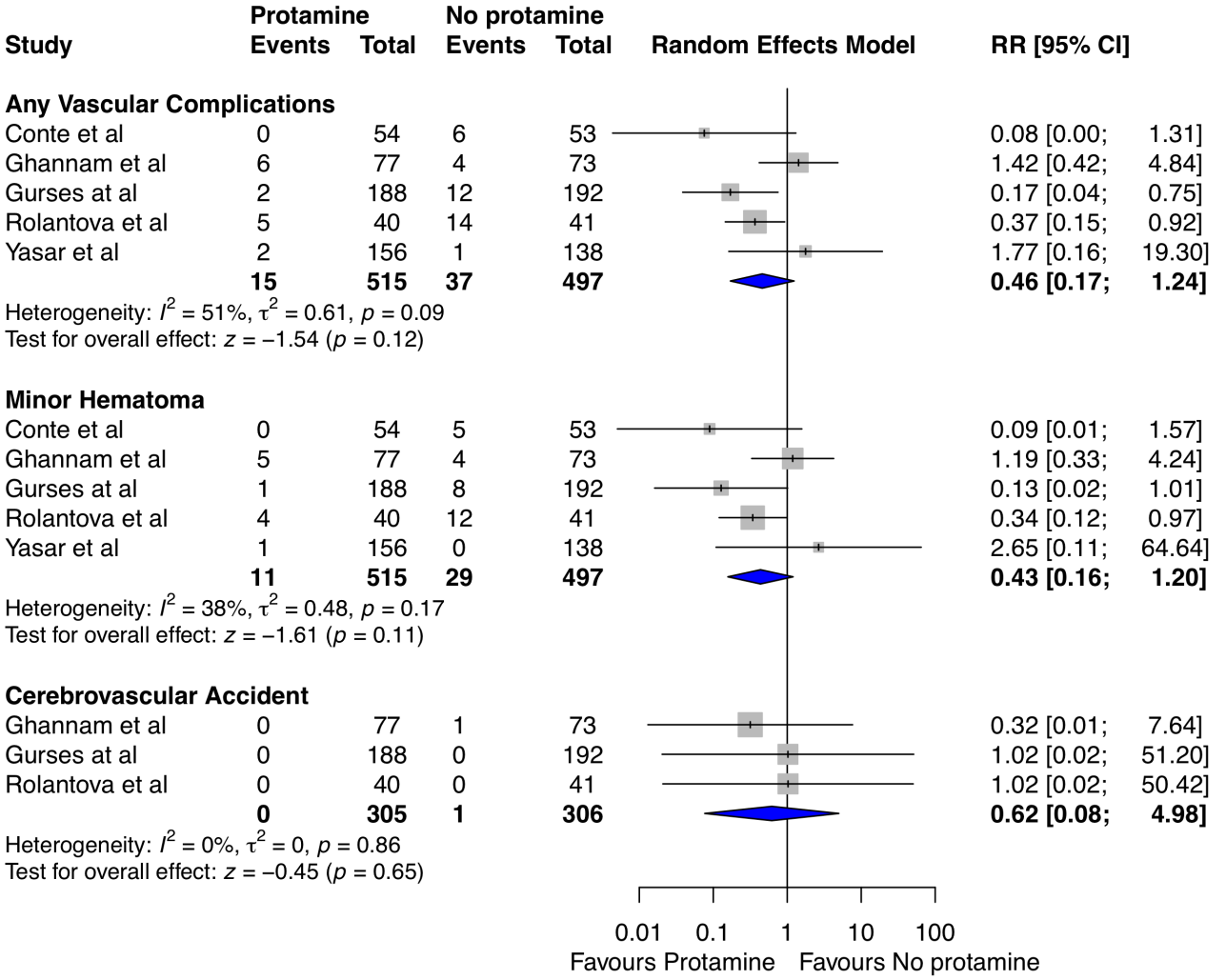


Fig. 1. Forest plot demonstrating the WMD of time to ambulate and time to hemostasis post-procedure between patients who received protamine and patients who did not. The total number of participants mean and SD for time to ambulation and time to hemostasis are reported for each study individually. Square with horizontal line represents WMD and 95% CI for each individual study, with square size reflecting the statistical weight of the study using the random-effects model. The diamond represents pooled WMD and 95% CI for each outcome. Heterogeneity (I^2) and between-study variance (T^2) with p-value, and overall effect size (z) with p-value are reported below each of their respective forest plot. CI, Confidence interval; SD, Standard deviation, WMD, Weight mean difference.

in the English language. Case reports, abstracts, editorial, or systematic reviews were excluded. The data from the included studies were extracted using a standardized protocol and a data extraction form. Any discrepancies between the two investigators were resolved with a consultation with the co-senior investigators (DL and JG). The following data was extracted from the eligible studies: author name, study design, publication year, follow-up duration, number of patients, age, gender, co-morbid conditions, anticoagulation type, ablation strategy, procedural characteristics and post ablation management. The Cochrane – Risk bias assessment tool was used to appraise the quality of randomized studies (**Supplementary Table 1**), while the Newcastle Ottawa Risk bias assessment tool was used to appraise the quality of the included studies (**Supplementary Table 2**). Studies' quality was rated as good, fair, and poor by awarding stars in each domain. A "good" quality score required 3 or 4 stars in the selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A "fair" quality score required two stars in the selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A "poor" quality score reflected 0 or 1 star(s) in selection, or 0 stars in comparability, or 0 or 1 star(s) in outcomes.

Statistical analysis was performed using *meta-package* for R version 4.0 and Rstudio version 1.2. Mantel-Haenszel risk ratio (RR) random-effects model was used to summarize data between two groups. Heterogeneity of the effect size among the included studies was assessed by Higgins I-squared (I^2) statistic. A value of I^2 of 0–25% represented insignificant heterogeneity, 26–50% represented low heterogeneity, 51–75% represented moderate heterogeneity, and more than 75% represented high

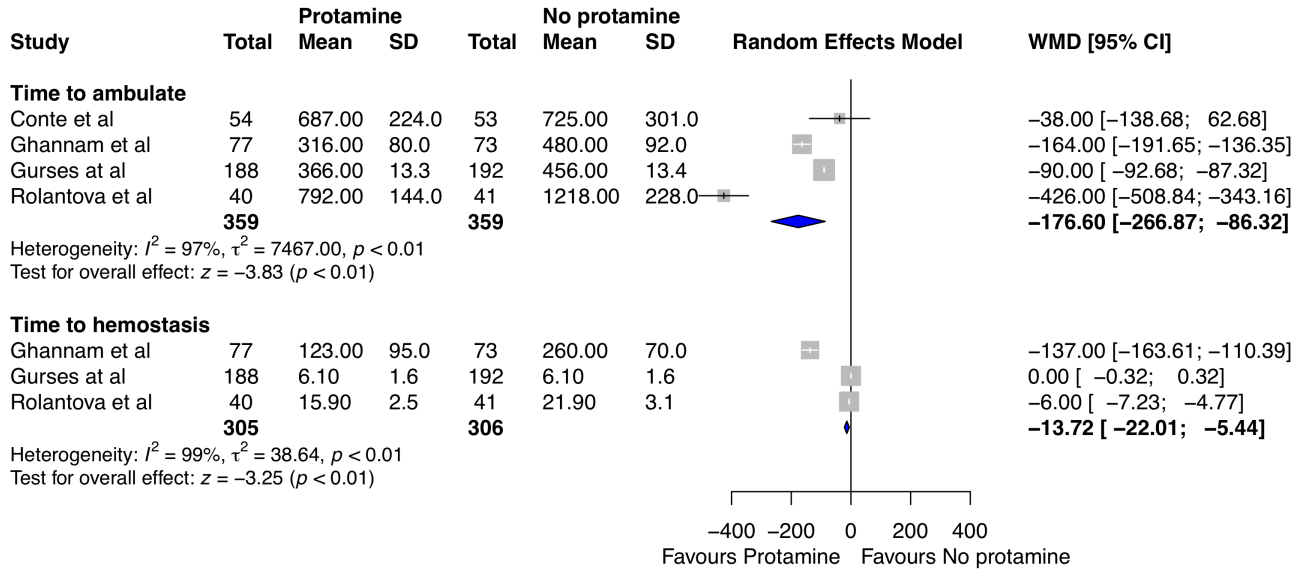


Fig. 2. Forest plot demonstrating risk ratio of adverse events post-procedure between patients who received protamine and patients who did not. The total number of participants and number of events for any vascular complications, minor hematoma, and cerebrovascular accident are reported for each study individually. Square with horizontal line represents RR and 95% CI for each individual study with square size reflecting the statistical weight of the study using the random-effects model. Diamond demonstrates pooled RR and 95% CI for each outcome. Heterogeneity (I^2) and between-study variance (T^2) with p-value, and overall effect size (z) with p-value are reported below each of their respective forest plot. CI, Confidence interval; RR, Risk ratio.

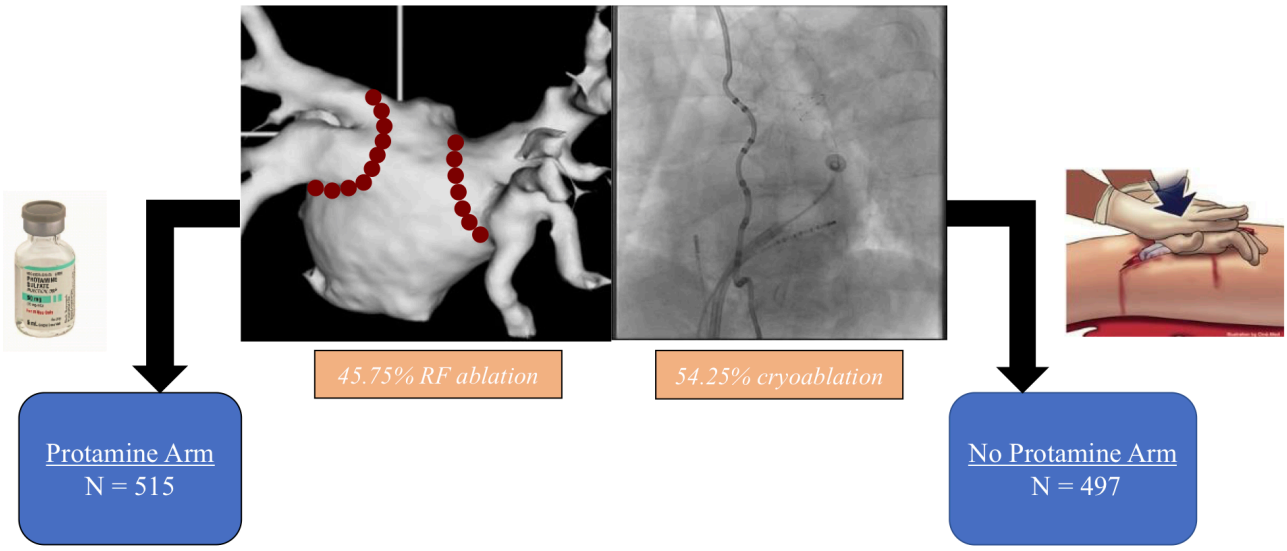
heterogeneity, as set forth by the Cochrane Collaboration. Publication bias was not assessed when the number of studies was less than 10.

The primary outcomes included—time to hemostasis (minutes) and time to ambulation (minutes). The secondary outcomes included—any vascular complications (composite of any major hematoma, hematomas requiring blood transfusion, pseudoaneurysm, arteriovenous fistula excluding minor hematoma), minor hematoma, or cerebrovascular accidents (CVA).

3. Results

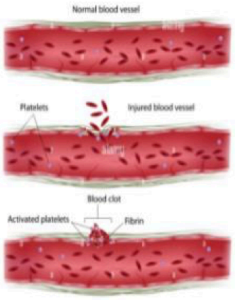
A total of 5 eligible studies (3 retrospective cohort studies and two randomized trials) consisting of 1012 patients (515 patients received protamine group and 497 patients did not receive protamine group) were included in the meta-analysis [2–6]. Overall, the mean age was 62.9 ± 15.6 years, the mean left ventricular ejection fraction was 64.1 ± 5.9%, and 56.8% (n = 575) patients were men. About 67.9% (n = 687) patients had paroxysmal AF, 31% (n = 314) persistent AF, and 1.1% (n = 11) were unknown AF duration. Pre-ablation anticoagulation strategies differed amongst studies—from uninterrupted warfarin or minimally interrupted direct oral anticoagulants [4,6] to discontinuing oral anticoagulants or warfarin at least 48 hours before and bridging with low molecular weight heparin if indicated [3,5]. 54.25% (n = 549) patients underwent cryoablation, while 45.75% (n = 463) underwent radiofrequency ablation. The ablation strategy included pulmonary vein isolation and additional ablation at the operator's discretion. In the protamine group, protamine was administered at the end of the procedure with a dose of 1 mg per 100 U of heparin given over 5 minutes, or dosage at the operator's discretion. The sheaths were removed after protamine administration in the protamine group; in contrast, in the no-protamine group, the activated clotting time (ACT) must fall below a target range or after a certain prespecified time period per study protocol. Manual compression and bed rest protocol was implemented in both groups in all studies (Table 1 (Ref. [2–6]) highlights the details on post-procedure management). The two groups were well balanced with respect to baseline demographics and clinical characteristics (p-value > 0.05 for all). Baseline characteristics of the study population have been detailed in the Table 1.

There was a significant reduction in time to ambulation [weighted mean difference (WMD) –176.6 minutes, 95% CI –266.9 to –86.3; p < 0.01] and time to hemostasis (WMD –13.72 minutes, 95% CI –22 to –5.4, p < 0.01) in the protamine group compared to the contrary (Fig. 1). Test of heterogeneity was significant (I^2 97% and 99%, respectively)—primarily due to differences in post-procedure protocols across studies. At a follow-up up to 3 months, there was no statistical difference between the two groups with regards to vascular complications, minor hematoma or CVA. However, protamine group had a numerically lower rates of any vascular complications (2.9% vs. 7.4%; RR 0.46, 95% CI 0.17 to 1.24; p = 0.12), mi-



Mean age 62.9 ± 15.6 years, Mean ejection fraction = 64.1 ± 5.9%
Paroxysmal Atrial Fibrillation = 67.9%, Persistent Atrial fibrillation = 31%

Time to hemostasis



Time to ambulation

Mean Weighted Difference -176.6 minutes with *Protamine*

Mean Weighted Difference -13.7 minutes with *Protamine*

Clinical Outcomes	*Protamine*	*No Protamine*	*Risk Ratio*	*95% CI*
Any vascular complication	2.9% (15/515)	7.4% (37/497)	0.46	0.17-1.24
Minor hematoma	2.1% (11/515)	5.8% (29/497)	0.43	0.16-1.20
Cerebrovascular accident	0	0.3% (1/306)	0.62	0.08-4.98

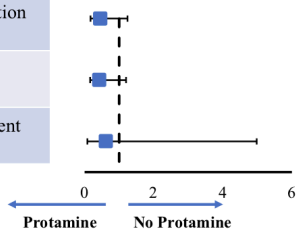


Fig. 3. Protamine administration after catheter ablation of atrial fibrillation.

nor hematoma (2.1% vs. 5.8%; RR 0.43, 95% CI 0.16 to 1.2; p = 0.11) and CVA (0 vs. 0.3%; RR 0.62, 95% CI 0.08 to 4.98; p = 0.65) when compared with no-protamine group, but the difference did not reach statistical significance (Fig. 2). Reaction to protamine occurred in 3 (0.6%) patients—two patients had hypotension that resolved with fluid administration, and the authors did not define one patient's symptoms.

4. Discussion

The results of our pooled analysis demonstrate a significant reduction in time to hemostasis and time to ambulation with a mean of 13 minutes and 176 minutes, respectively, with the use of protamine following AF ablation. There was a positive trend in decreasing the risk of vascular complications and CVA with protamine administration, although this difference did not reach statistical significance due to inadequate power and low event rates (Fig. 3).

Table 1. Baseline characteristics of the included studies.

Variables	Conte *et al.* [2], 2014 (n = 107)		Ghannam *et al.* [4], 2018 (n = 150)		Gurses *et al.* [3], 2015 (n = 380)		Rolantova *et al.* [5], 2018 (n = 81)		Yasar *et al.* [6], 2019 (n = 294)	
	Protamine (n = 54)	No protamine (n = 53)	Protamine (n = 77)	No protamine (n = 73)	Protamine (n = 188)	No protamine (n = 192)	Protamine (n = 40)	No protamine (n = 41)	Protamine (n = 156)	No protamine (n = 138)
Study design	Retrospective cohort		Randomized controlled trial		Retrospective cohort		Randomized controlled trial		Multicenter retrospective cohort	
Age, years (mean ± SD or median (SD))	60 ± 11	58 ± 14	63 ± 12	66 ± 9	55 (27–76)	57 (20–86)	61.2 ± 5.6	64.5 ± 6.2	64.2 ± 11.4	63 ± 11.1
Male, n (%)	33 (61%)	31 (58%)	46 (60%)	48 (66%)	95 (50.5%)	88 (45.8%)	23 (58%)	22 (54%)	100 (64.1%)	89 (64.5%)
Diabetes mellitus, n (%)	4 (7%)	5 (9%)	n/a	n/a	31 (16.5%)	25 (13%)	5 (13%)	7 (17%)	24 (19.8%)	32 (23.2%)
Hypertension, n (%)	21 (39%)	23 (43%)	n/a	n/a	81 (43.1%)	94 (49%)	25 (63%)	33 (81%)	91 (75.2%)	106 (76.8%)
Coronary artery disease, n (%)	7 (13%)	6 (11%)	n/a	n/a	17 (9%)	29 (15.1%)	5 (13%)	5 (13%)	33 (27.3%)	27 (19.6%)
Type of atrial fibrillation										
Paroxysmal, n (%)	100%	100%	40 (52%)	34 (46%)	146 (88%)	163 (85%)	28 (70%)	23 (56%)	92 (59%)	54 (39%)
Persistent, n (%)	-	-	34 (44%)	31 (42%)	42 (22%)	29 (15%)	12 (30%)	18 (44%)	64 (41%)	84 (61%)
Anticoagulation use					52 (27.7%)	60 (31.3%)				
Warfarin	31 (57%)	32 (60%)	14 (18%)	14 (19%)	n/a	n/a	40 (100%)	41 (100%)	22 (14.1%)	30 (21.7%)
NOAC	9 (17%)	9 (17%)	63 (82%)	59 (81%)	n/a	n/a			116 (74.4%)	95 (68.8%)
Aspirin	14 (26%)	12 (23%)	-	-	n/a	n/a			n/a	n/a
LVEF (mean ± SD)	58 ± 7	55 ± 8	n/a	n/a	65.9 ± 3.1	65.9 ± 3.5	66.3 ± 5.2	66 ± 4.9	n/a	n/a
LA size, mm (mean ± SD)	41 ± 6	42 ± 4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
CHA2DS2-VASc score (mean ± SD)	1.8 ± 1.5	1.6 ± 1.4	2.1 ± 1.2	2.2 ± 1.2	n/a	n/a	2.2 ± 1.3	2.1 ± 1.1	n/a	n/a
HAS-BLED score (mean ± SD)	1.0 ± 1.9	0.9 ± 0.9	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pre-ablation anticoagulation strategies	-		uninterrupted warfarin or minimally interrupted oral anticoagulants		discontinuing oral anticoagulants or warfarin 48 hours before; bridging with low molecular weight heparin		discontinuing oral anticoagulants or warfarin 48 hours before; bridging with low molecular weight heparin		uninterrupted warfarin or minimally interrupted oral anticoagulants	
Ablation type										
Radiofrequency, n (%)	-	-	57 (74%)	55 (75%)	-	-	100%	100%	132 (85%)	100%
Cryoballoon, n (%)	100%	100%	20 (26%)	18 (25%)	100%	100%	-	-	24 (15%)	-
Total heparin dose, U (mean ± SD)	8900 ± 2500	8700 ± 2600	23724 ± 13977	21541 ± 13649	7808 ± 1281	7827 ± 1270	19500 ± 2700	18900 ± 3200	239 ± 69 (U/kg)	208 ± 56 (U/kg)
Protamine administration	1 mg/100 U of heparin given at the end of procedure	-	1 mg/100 U of heparin given at the end of procedure	-	1 mg/100 U of heparin given at the end of procedure	-	Fixed dose per total heparin and last ACT given at the end of procedure	-	Dose at operator's discretion	-

Table 1. Continued.

Variables	Conte *et al.* [2], 2014 (n = 107)		Ghannam *et al.* [4], 2018 (n = 150)		Gurses *et al.* [3], 2015 (n = 380)		Rolantova *et al.* [5], 2018 (n = 81)		Yasar *et al.* [6], 2019 (n = 294)	
	Protamine (n = 54)	No protamine (n = 53)	Protamine (n = 77)	No protamine (n = 73)	Protamine (n = 188)	No protamine (n = 192)	Protamine (n = 40)	No protamine (n = 41)	Protamine (n = 156)	No protamine (n = 138)
Sheath removal process	At the end of protamine administration	After ACT <150	After ACT <200 or pre-procedural baseline		At the end of protamine administration	90 minutes after last heparin dose without ACT	At the end of protamine administration	After ACT <1.5 times upper normal limit	After ACT <200 or at the end of protamine administration	Suture with F8S or SCT prior to sheath removal
Hemostasis-to-ambulation protocol	Manual compression and 10-hr bed rest and groin bandage		Manual compression and 4-hr bed rest		Manual compression and 6-hr bed rest and 12-hr groin bandage		Manual compression and 12-hr bed rest		Manual compression and 4-hr bedrest for both group	
Procedural time (minutes)										
Total time (mean ± SD)	93 ± 8	89 ± 12	199 ± 74	214 ± 40	73.6 ± 12.6	71.3 ± 12.1	111 ± 13	104 ± 14	177.1 ± 48.1	213.2 ± 57.3
Fluoroscopy time (mean ± SD)	14 ± 6	13 ± 6	n/a	n/a	15 ± 2.5	15.1 ± 2.7	4.8 ± 1.1	5.1 ± 1.3	n/a	n/a
Post-procedural time (minutes)										
Time to sheath removal (mean ± SD)	n/a	n/a	n/a	n/a	6.3 ± 2.4	96.3 ± 2.4	n/a	n/a	n/a	n/a
Time to hemostasis (mean ± SD)	n/a	n/a	123 ± 95	260 ± 70	6.1 ± 1.6	6.1 ± 1.6	15.9 ± 2.5	21.9 ± 3.1	n/a	n/a
Time to ambulation (mean ± SD)	687 ± 224	725 ± 301	316 ± 80	480 ± 92	366.3 ± 13.3	456.3 ± 13.4	792 ± 144	1218 ± 228	n/a	n/a
Reported vascular complications	Hematoma, bleeding		Bleeding, hematoma		Hematoma, pseudoaneurysm, AVF		Hematoma, pseudoaneurysm, AVF, bleeding		Hematoma, pseudoaneurysm, AVF, suture failure	
Adverse events										
Any Vascular complication, n (%)	0	6 (11%)	6 (8%)	4 (5%)	2 (1.1%)	12 (6.3%)	5 (12.5%)	14 (34%)	2 (1%)	1 (0.6%)
Minor hematoma, n (%)	0	5 (9%)	5 (6%)	4 (5%)	1 (0.5%)	8 (4%)	4 (10%)	12 (29.2%)	1 (0.6%)	0
Cerebrovascular accident, n (%)	n/a	n/a	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	n/a	n/a
Adverse reaction to protamine	0	-	1 (1%)	-	1 (0.5%)	-	0	-	1 (0.6%)	-

ACT, Activated clotting time; AVF, Arteriovenous fistula; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category; F, Figure-of-eight; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; LA, Left atrium; LVEF, Left ventricular ejection fraction; NOAC, Novel oral anticoagulation; SCT, Three-way stopcock technique; SD, Standard deviation.

Vascular access complications, including bleeding, hematoma, arteriovenous fistula, or pseudoaneurysm, are major adverse events in patients undergoing AF ablation due to an aggressive anticoagulation protocol [7–9]. To reduce the risk of bleeding events, ACT must return from ACT goal during the procedure (300–350 s) to normal range (<180 s) before femoral sheath removal [1]. However, this process can take up to several hours due to a 90-min half-life of UFH, thus creating a negative experience for the patients. Furthermore, the risk of vascular complications increases the longer the sheath remains in the femoral vein [10]. Protamine sulfate binds with heparin to form inactive complexes and rapidly negates the antithrombotic effect of heparin [11]. Despite the long history of its utilization in other specialties, including cardiothoracic surgery and interventional cardiology [12,13], the evidence of its safety and efficacy in AF ablation is limited. This is the first systematic review and meta-analysis to evaluate the effectiveness and safety of protamine in this patient population.

Taken together, our study provides the best available evidence to date regarding the effect of protamine administration on sheath removal time, immobilization time, and the risk of adverse clinical events—finding which might be clinically relevant and can reduce intensive care monitoring time, and consequently health care cost utilization. This meta-analysis is limited by possible patient-physician selection bias, lack of patient-level data, heterogeneous study design (different preablation anticoagulation management strategies) and follow-up period, and lack of long-term outcomes and imaging data. Finally, these results cannot be extrapolated to groins closed with commercially available vascular closure devices.

Author contributions

Conceptualization: JK, KS, MT; methodology, JK, KS, MT, JG; software, JK, KS; validation, KS, MT, JG; formal analysis, RB, RM, TC; investigation, MT, RB, JG; resources, KS, JG; data curation, JK, KS; writing—original draft preparation, JK, TC, DL; writing—review and editing, DL, JG; visualization, RB, TC, RM; supervision, DL, JG; project administration RM, DL, JG. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://www.imrpress.com/journal/RCM/23/1/10.31083/j.rcm2301034.

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