Clinical Study on Nicotinic Acid for Injection as Adjuvant Therapy to Improve Microcirculatory Perfusion After Digital Replantation

Ann. Ital. Chir., 2026 97, 6: 1080–1087
https://doi.org/10.62713/aic.4466

Yuan Yang[1], Yang Zhao[1], Xuhong Wang[2]

[1]Department of Pharmacy, Zhuji Sixth People's Hospital, 311801 Shaoxing, Zhejiang, China
[2]Department of Hand Surgery, Zhuji Sixth People's Hospital, 311801 Shaoxing, Zhejiang, China

AIM: This study aimed to evaluate the impact of injectable nicotinic acid as adjuvant therapy on microcirculatory perfusion and digit survival rate after digital replantation.
METHODS: This single-center retrospective cohort study included 200 patients who underwent digital replantation. Based on the treatment regimen, patients were divided into two groups: the nicotinic acid group (n = 102) and the control group (n = 98). The primary outcome was the relative perfusion ratio (PU ratio), calculated by normalizing the perfusion value of the replanted digit to that of an intact and uninjured reference digit from the same patient, measured using a laser Doppler flowmeter. Secondary outcomes included the incidence of vascular crisis, digit survival rate, postoperative hospital stay, and adverse reactions.
RESULTS: On postoperative day 1, the perfusion ratio did not differ between the two groups. However, on postoperative days 3, 5, and 7, the perfusion ratios in the nicotinic acid group were significantly higher than those in the control group (all $p < 0.001$). In the nicotinic acid group, the total incidence of vascular crisis was significantly lower ($p = 0.029$), and the digit survival rate was significantly higher ($p = 0.030$), along with shorter postoperative hospital stay compared with the control group ($p < 0.001$). Subgroup analysis indicated that the therapeutic benefit of nicotinic acid was particularly pronounced in the subgroup with more severe "crush/avulsion" injuries. The incidence of facial flushing was higher in the nicotinic acid group ($p < 0.001$).
CONCLUSIONS: Adjuvant use of injectable nicotinic acid, in addition to conventional therapy, was associated with improved microcirculatory perfusion, reduced incidence of vascular crisis, and increased digit survival rate. The treatment was generally well tolerated with no serious safety concerns identified. Due to the retrospective and non-randomized nature of this study, these findings should be interpreted as associations rather than definitive treatment effects.

Keywords: nicotinic acid; digital replantation; microcirculatory perfusion

Introduction

Digital amputation is a common severe trauma in hand surgery, often leading to significant functional impairment along with substantial psychological and socioeconomic effects [1]. The development of digital replantation is a landmark achievement in microsurgery, aiming to restore anatomical continuity and functional capacity of the injured digit, and remains an important reconstructive option for carefully selected patients with complete digital amputation [2,3]. However, the success of replantation surgery extends beyond successful anastomosis of blood vessels. During the postoperative period, the viability of the replanted digit relies largely on the maintenance of sustained and effective microcirculatory perfusion, which is one of the most critical factors determining long-term survival [4]. The survival of a replanted digit is essentially a blood supply-dependent process; even when the major vessels remain patent, inadequate perfusion within the distal microcirculatory network can lead to secondary necrosis due to hypoxia and the accumulation of metabolites. Therefore, the status of postoperative microcirculation is regarded as a key predictor of replantation outcomes.

Postoperative microcirculatory disturbance after digital replantation is a multifactorial and dynamic pathological process. The principal mechanisms include vasospasm and thrombosis. Tissue trauma, surgical manipulation, and postoperative pain can stimulate sympathetic excitation, resulting in increased intracellular calcium concentration in vascular smooth muscle cells. This process causes persistent, rhythmic, and intense vasoconstriction, which increases peripheral vascular resistance and reduces blood flow [5,6]. Vascular endothelial cell injury occurring during amputation and anastomosis exposes subendothelial collagen, activating platelet adhesion and aggregation and initiating the coagulation cascade. These events may promote thrombus formation at the anastomosis site or within dam-

Submitted: 27 November 2025 Revised: 3 March 2026 Accepted: 12 March 2026 Published: 10 June 2026
Correspondence to: Yuan Yang, Department of Pharmacy, Zhuji Sixth People's Hospital, 311801 Shaoxing, Zhejiang, China (e-mail: yangyuan87210003@163.com).
Editor: Hui Lu

aged microvessels, ultimately causing lumen occlusion [7]. Furthermore, changes in hemorheological properties, such as increased blood viscosity, combined with oxidative stress and inflammatory cytokine storm induced by ischemia-reperfusion injury, and microvascular compression associated with tissue edema, collectively exacerbate the deterioration of microcirculation, ultimately reducing perfusion efficiency [4,8]. These processes form a viscous cycle that increases the risk of inadequate blood supply in the replanted digit.

Therefore, improving postoperative microcirculatory perfusion is an important therapeutic strategy for enhancing the success rate of digital replantation. Currently, clinical management frequently uses a postoperative "triple-antagonistic" therapy comprising antispasmodic, anticoagulant, and anti-infection agents. Among these components, antispasmodic drugs (e.g., papaverine) directly target one of the core mechanisms underlying microcirculatory disturbance. However, identifying more effective and safer vasodilators to further optimize microcirculatory perfusion remains an ongoing pursuit in hand surgery. Nicotinic acid (niacin, Vitamin B3) is a water-soluble vitamin with pharmacological effects that extend far beyond its nutritional role. It is a potent peripheral vasodilator, a property primarily responsible for its well-recognized side effect of cutaneous flushing [9]. This vasodilatory mechanism is primarily mediated through activation of the G protein-coupled receptor 109A (GPR109A), expressed on skin cells and microvessels. Activation of this receptor promotes the release of prostaglandin D_2 (PGD_2) and E_2 (PGE_2) from Langerhans cells and related cell types, subsequently relaxing vascular smooth muscle and significantly increasing local blood flow [10,11].

Based on these potent vasodilatory properties, we hypothesized that nicotinic acid might counteract the refractory microvascular spasm caused by sympathetic excitation, endothelial injury, and inflammatory responses after digital replantation, thereby offering a new adjuvant therapeutic strategy to interrupt the vicious cycle of microcirculatory disturbance. Although nicotinic acid is widely used in the treatment of lipid metabolism disorders, its role in improving local tissue perfusion, particularly within microsurgical settings, has not been systematically evaluated. Moreover, while the conventional "triple-antagonistic" therapy is standard, the management of severe microcirculatory disturbance remains challenging, particularly following complex injuries such as crush or avulsion amputations. Identification of additional adjuvant strategies to optimize perfusion, therefore, remains a pertinent clinical pursuit.

Therefore, this retrospective cohort study aimed to objectively evaluate the adjuvant therapeutic effect of injectable nicotinic acid on postoperative microcirculatory function. The primary objective was to investigate whether adjuvant use of nicotinic acid could significantly improve standardized microcirculatory perfusion indices, specifically the relative perfusion ratio (PU ratio), compared with the corresponding healthy digit. Additionally, the study examined its effect on clinically meaningful outcomes, such as digit survival rate and vascular crisis.

Methods

Study Design

This single-center retrospective cohort study analyzed the clinical records of 228 patients who underwent digital replantation at Zhuji Sixth People's Hospital between January 2024 and June 2025. Based on predefined inclusion and exclusion criteria, 15 patients with incomplete clinical data, 8 individuals lost to follow-up, and 5 with severe underlying diseases were excluded. Hence, a total of 200 participants were enrolled in the final study cohort for analysis. Based on the postoperative treatment regimen, patients were divided into two groups. The nicotinic acid group (n = 102) received conventional postoperative therapy in combination with intravenous nicotinic acid (50 mg/day for 7–10 days), whereas the control group (n = 98) received conventional therapy alone. The study protocol was approved by the Ethics Committee of Zhuji Sixth People's Hospital (approval number: 2025-05) and was conducted in compliance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants for the use of their anonymized clinical data for research purposes.

Inclusion criteria for patient selection were as follows: (1) age $\geq$18 years; (2) complete single or multiple digital amputation due to trauma, with at least one intact and unaffected digit on the same hand serving as an internal reference for relative perfusion ratio measurement; and (3) availability of complete postoperative medical records. Exclusion criteria included: (1) pre-existing severe hepatic or renal dysfunction; (2) coagulation disorders or active bleeding; (3) documented hypersensitivity to nicotinic acid; (4) concurrent use of other potent vasodilators (e.g., prostaglandin E_1) during the study period; and (5) occurrence of major systemic complications within the first 24 hours after surgery.

Treatment Protocol

Patients were allocated to either the nicotinic acid group or the control group based on the actual postoperative medication regimen applied in the routine clinical practice. The decision to administer nicotinic acid was made by the attending surgeon based on routine postoperative evaluation, including assessment of vascular status and overall clinical judgment of the risk of vasospasm or impaired perfusion.

Patients in the nicotinic acid group (n = 102) received standard postoperative care in combination with injectable nicotinic acid (50 mg/vial, manufacturer: Jilin Jinsheng Pharmaceutical Co., Ltd., Meihekou, China, batch No. 202004032). Each dose of 50 mg nicotinic acid was diluted in 250 mL of 0.9% sodium chloride or 5% glucose solution and administered once daily by intravenous infu-

sion. Treatment was initiated on the first postoperative day in all patients and continued for 7–10 days, depending on individual clinical response and the stability of microcirculatory perfusion. However, Patients in the control group (n = 98) received standard postoperative care without nicotinic acid.

During standard postoperative management, all digital replantation procedures were performed by the same team of senior hand surgeons using uniform microsurgical techniques. Postoperative management followed a unified institutional protocol designed to support vascular patency and tissue viability. Antispasmodic therapy included intramuscular papaverine administered at a dose of 30 mg every 6–8 hours. Anticoagulation therapy was administered using subcutaneous low molecular weight heparin sodium (4000 AXaIU) once daily. Prophylactic antibiotics were initiated intraoperatively and continued postoperatively in accordance with institutional infection control guidelines. Limb management consisted of immobilization of the affected limb with splint fixation, elevation to promote venous return, and maintenance of ambient ward temperature to support peripheral perfusion. Supportive care, such as analgesia, fluid management, and hemodynamic stabilization, was provided as needed.

To avoid potential confounding effects on microcirculatory outcomes, additional vasodilators or microcirculation-modulating agents, including prostaglandin E_1, dexmedetomidine, or leech therapy, were not permitted during the postoperative period. Patient group allocation ultimately indicated the attending surgeon's intraoperative assessments and postoperative management approach. Particular consideration was given to intraoperative indicators of microcirculatory status, such as vascular tone and capillary refill after reperfusion and complexity of injury. Nicotinic acid was used prophylactically in patients perceived to be at higher risk of postoperative microcirculatory impairment, especially in cases involving crush or avulsion injuries.

Data Collection

Postoperative microcirculatory perfusion was expressed as the relative perfusion ratio (PU Ratio), calculated as the perfusion unit (PU) value of the replanted digit divided by the PU value of an intact and uninjured reference digit from the same patient. Measurements were obtained at the midpoint of the pulp of the replanted digit at predefined time points (postoperative days 1, 3, 5, and 7) using a laser Doppler flowmeter (PeriFlux System 5000, Perimed). All measurements were conducted by trained technicians who were blinded to group allocation.

Patient baseline characteristics, such as age, body mass index (BMI), diabetes mellitus, and hypertension, were confirmed by systematically reviewing admission records, patient self-reported medical history, and long-term medication use. Surgical variables, such as the number of vascular anastomoses and the use of vein graft, were directly extracted from the detailed operative notes and anesthesia records. The incidence of vascular crisis was determined by two senior attending physicians who were blinded to group allocation. Evaluation was based on clinical manifestations, such as digit color, skin temperature, tissue turgor, capillary refill, and bleeding upon pinprick testing. Survival rate of the replanted digit was assessed at 3 months postoperatively, with a successful outcome defined as complete survival of the digit accompanied by primary wound healing. Postoperative hospital stay was defined as the number of days from the date of surgery to the date of discharge and was obtained from inpatient medical records.

Adverse events occurring in both groups were recorded throughout the observation period. The observation indicators included bleeding complications, transient facial flushing, and abnormalities in liver and kidney function.

Statistical Analysis

Statistical analysis was performed using SPSS (version 27.0, IBM Corp., Armonk, NY, USA). Normality of continuous data was assessed using the Shapiro-Wilk test, and homogeneity of variances was evaluated with Levene's test. Normally distributed variables were presented as mean ± standard deviation ($\bar{x} \pm SD$), and intergroup comparisons were performed using an independent samples *t*-test. Non-normally distributed variables were presented as median (interquartile range) [M (Q_1, Q_3)], and intergroup comparisons were performed using the Mann-Whitney U test. Count data were presented as frequencies and percentages [n (%)], with intergroup comparisons performed using the χ^2 test or Fisher's exact test, as appropriate. Repeated measurements were analyzed using repeated measures analysis of variance (ANOVA). Mauchly's test of sphericity was performed, and when the assumption was violated, the Greenhouse–Geisser correction was applied. To decompose a significant interaction effect, post hoc pairwise comparisons between groups at each postoperative time point were performed using the Least Significant Difference (LSD) approach. A p-value of < 0.05 was considered statistically significant.

Results

Comparison of Baseline Characteristics Between the Two Groups

This study ultimately included 200 patients, with 102 in the nicotinic acid group and 98 in the control group (Table 1). There were no statistically significant differences between the two groups in baseline characteristics, such as age, gender, ischemia time, smoking history, injury type, amputation level, or thumb injury (all $p > 0.05$), indicating good comparability between the groups.

Table 1. Clinical baseline characteristics of the two groups of patients.

Variable	Total (n = 200)	Control (n = 98)	Nicotinic acid (n = 102)	Statistic	*p*-value
Ischemia time (h), Mean ± SD	5.97 ± 1.75	6.17 ± 1.82	5.78 ± 1.67	$t = 1.57$	0.118
Age (years), M (Q_1, Q_3)	38.00 (32.00, 47.00)	37.00 (29.00, 47.75)	39.50 (33.25, 46.00)	Z = –1.31	0.189
Gender, n (%)				$\chi^2 = 1.75$	0.185
Male	153 (76.50)	71 (72.45)	82 (80.39)		
Female	47 (23.50)	27 (27.55)	20 (19.61)		
Smoking, n (%)				$\chi^2 = 1.59$	0.207
No	95 (47.50)	51 (52.04)	44 (43.14)		
Yes	105 (52.50)	47 (47.96)	58 (56.86)		
Injury type, n (%)				$\chi^2 = 1.71$	0.425
Crush	53 (26.50)	29 (29.59)	24 (23.53)		
Laceration	126 (63.00)	61 (62.24)	65 (63.73)		
Avulsion	21 (10.50)	8 (8.16)	13 (12.75)		
Amputation level, n (%)				$\chi^2 = 1.24$	0.538
I zone	58 (29.00)	31 (31.63)	27 (26.47)		
II zone	126 (63.00)	58 (59.18)	68 (66.67)		
III zone	16 (8.00)	9 (9.18)	7 (6.86)		
Thumb injury, n (%)				$\chi^2 = 0.09$	0.763
No	145 (72.50)	72 (73.47)	73 (71.57)		
Yes	55 (27.50)	26 (26.53)	29 (28.43)		
Number of vascular anastomoses, M (Q_1, Q_3)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	Z = –0.29	0.770
Diabetes mellitus, n (%)				$\chi^2 = 0.14$	0.705
No	189 (94.50)	92 (93.88)	97 (95.10)		
Yes	11 (5.50)	6 (6.12)	5 (4.90)		
Hypertension, n (%)				$\chi^2 = 0.10$	0.746
No	177 (88.50)	86 (87.76)	91 (89.22)		
Yes	23 (11.50)	12 (12.24)	11 (10.78)		
Use of vein graft, n (%)				$\chi^2 = 0.06$	0.814
No	164 (82.00)	81 (82.65)	83 (81.37)		
Yes	36 (18.00)	17 (17.35)	19 (18.63)		

Table 2. Comparison of relative perfusion ratios at different postoperative time points between the two groups.

Variable	Total (n = 200)	Control (n = 98)	Nicotinic acid (n = 102)	Statistic	*p*-value
Pu ratio day1	0.47 ± 0.04	0.47 ± 0.04	0.47 ± 0.05	$t = –0.52$	0.602
Pu ratio day 3	0.64 ± 0.07	0.60 ± 0.05	0.67 ± 0.06	$t = –9.31$	<0.001
Pu ratio day 5	0.77 ± 0.08	0.71 ± 0.06	0.82 ± 0.06	$t = –13.10$	<0.001
Pu ratio day 7	0.84 ± 0.09	0.77 ± 0.07	0.90 ± 0.07	$t = –12.32$	<0.001
F		1024.90	720.42		
p-value		<0.001	<0.001		
Between-group effect			$F = 4467.99$, $p < 0.001$		
Time effect			$F = 1312.58$, $p < 0.001$		
Interaction effect			$F = 12.91$, $p < 0.001$		

Note: The values have been rounded to two decimal places; minor differences may not be reflected.

Comparison of Microcirculatory Perfusion Between the Two Groups

On postoperative day 1, the relative perfusion ratio (PU ratio) of the replanted digits did not differ substantially between the two groups ($p = 0.602$). Starting from postoperative day 3, patients receiving nicotinic acid showed significantly higher perfusion ratios than those in the control group ($p < 0.001$). This difference remained persistent on postoperative days 5 and 7, with the nicotinic acid group exhibiting significantly better microcirculatory perfusion ($p < 0.001$). Repeated measures ANOVA further confirmed significant group effects, time effects, and interaction effects (all $p < 0.001$), suggesting that alterations in the perfusion over the postoperative period differed considerably between the two groups (Table 2).

Postoperative Recovery Outcomes Between the Two Groups

The postoperative hospital stay was significantly shorter in patients who received nicotinic acid compared with those

Table 3. Comparison of postoperative recovery outcomes between the two groups.

Variable	Total (n = 200)	Control (n = 98)	Nicotinic acid (n = 102)	Statistic	*p*-value
Hospital stay (days), M (Q_1, Q_3)	14.00 (12.00, 16.00)	15.00 (12.25, 17.00)	13.00 (11.00, 14.00)	Z = –4.45	<0.001
Vascular crisis, n (%)				χ^2 = 4.751	0.029
Arterial crisis	7 (3.50)	4 (4.08)	3 (2.94)	χ^2 = 0.00	0.975
Venous crisis	20 (10.00)	15 (15.31)	5 (4.90)	χ^2 = 6.01	0.014
None	173 (86.50)	79 (80.61)	94 (92.16)		
Survival, n (%)				χ^2 = 4.70	0.030
Survived	184 (92.00)	86 (87.76)	98 (96.08)		
Failed	16 (8.00)	12 (12.24)	4 (3.92)		

Table 4. Comparison of adverse reactions between the two groups.

Variable	Total (n = 200)	Control (n = 98)	Nicotinic acid (n = 102)	Statistic	*p*-value
Facial flush, n (%)				χ^2 = 27.45	<0.001
No	175 (87.50)	98 (100.00)	77 (75.49)		
Yes	25 (12.50)	0 (0.00)	25 (24.51)		
Bleeding, n (%)				χ^2 = 0.02	0.894
No	179 (89.50)	88 (89.80)	91 (89.22)		
Yes	21 (10.50)	10 (10.20)	11 (10.78)		
Liver kidney dysfunction, n (%)				χ^2 = 2.03	0.154
No	191 (95.50)	91 (92.86)	100 (98.04)		
Yes	9 (4.50)	7 (7.14)	2 (1.96)		

Table 5. Subgroup analysis for laceration injuries.

Variable	Total (n = 126)	Control (n = 61)	Nicotinic acid (n = 65)	Statistic	*p*-value
Pu ratio day1, Mean ± SD	0.47 ± 0.04	0.47 ± 0.04	0.47 ± 0.05	*t* = 0.24	0.812
Pu ratio day3, Mean ± SD	0.64 ± 0.07	0.60 ± 0.05	0.67 ± 0.06	*t* = –7.24	<0.001
Pu ratio day5, Mean ± SD	0.77 ± 0.09	0.71 ± 0.07	0.83 ± 0.06	*t* = –10.14	<0.001
Pu ratio day7, Mean ± SD	0.84 ± 0.09	0.78 ± 0.07	0.90 ± 0.07	*t* = –9.51	<0.001
F		642.65	1192.88		
p-value		<0.001	<0.001		
Between-group effect			F = 85.58, $p < 0.001$		
Time effect			F = 1298.23, $p < 0.001$		
Interaction effect			F = 41.35, $p < 0.001$		
Survival, n (%)				χ^2 = 0.00	0.956
Survived	123 (97.62)	59 (96.72)	64 (98.46)		
Failed	3 (2.38)	2 (3.28)	1 (1.54)		

Table 6. Subgroup analysis for crush and avulsion injuries.

Variable	Total (n = 74)	Control (n = 37)	Nicotinic acid (n = 37)	Statistic	*p*-value
Pu ratio day1, Mean ± SD	0.46 ± 0.04	0.47 ± 0.04	0.46 ± 0.05	*t* = 0.96	0.338
Pu ratio day3, Mean ± SD	0.63 ± 0.07	0.59 ± 0.05	0.67 ± 0.07	*t* = –5.79	<0.001
Pu ratio day5, Mean ± SD	0.76 ± 0.08	0.70 ± 0.05	0.81 ± 0.06	*t* = –8.31	<0.001
Pu ratio day7, Mean ± SD	0.83 ± 0.09	0.77 ± 0.07	0.89 ± 0.07	*t* = –7.76	<0.001
F		374.24	447.04		
p-value		<0.001	<0.001		
Between-group effect			F = 54.96, $p < 0.001$		
Time effect			F = 872.04, $p < 0.001$		
Interaction effect			F = 31.51, $p < 0.001$		
Survival, n (%)				χ^2 = 4.57	0.032
Survived	61 (82.43)	27 (72.97)	34 (91.89)		
Failed	13 (17.57)	10 (27.03)	3 (8.11)		

in the control group ($p < 0.001$). At 3-month follow-up, the digit survival rate of replanted digits was significantly higher in the nicotinic acid group ($p = 0.030$). Furthermore, the overall incidence of vascular crisis was significantly lower in the nicotinic acid group ($p = 0.029$), with a significantly reduced incidence of venous crisis ($p = 0.014$). In contrast, there was no significant difference in the incidence of arterial crisis between the two groups ($p = 0.975$, Table 3).

Comparison of Adverse Reactions Between the Two Groups

Transient facial flushing was found in 25 patients (24.51%) in the nicotinic acid group, representing a significantly higher incidence compared to the control group ($p < 0.001$). The flushing resolved spontaneously after decreasing the infusion rate, without requiring discontinuation of treatment. There were no significant differences between the two groups in the incidence of serious adverse reactions, such as bleeding complications ($p = 0.894$) or liver/kidney dysfunction ($p = 0.154$, Table 4).

Subgroup Analysis

An exploratory subgroup analysis based on injury mechanism showed that in the laceration injury subgroup (n = 126), both groups had similarly high digit survival rates ($p = 0.956$). However, the perfusion ratios on postoperative days 3, 5, and 7 were consistently higher in the nicotinic acid group (all $p < 0.001$). Conversely, the therapeutic effect of nicotinic acid was more pronounced in the crush or avulsion injury subgroup (n = 74). Within this subgroup, those receiving nicotinic acid showed a significantly higher digit survival rate compared with the control group ($p = 0.032$). Additionally, perfusion ratios on postoperative days 3, 5, and 7 were significantly improved in the nicotinic acid group than those in the control group (all $p < 0.001$, Tables 5,6).

Discussion

This retrospective cohort study systematically evaluated the potential impact of injectable nicotinic acid as an adjuvant to standard therapy on microcirculatory perfusion and clinical outcomes in patients undergoing digital replantation. The findings indicate that patients who received nicotinic acid showed improved postoperative microcirculatory perfusion compared with those treated with conventional therapy alone. Higher perfusion ratios were observed from postoperative day 3 onward, and this improvement was accompanied by a lower incidence of vascular crisis, higher digit survival at 3 months, and a shorter postoperative hospitalization.

We observed that by postoperative day 7, the PU ratio in the nicotinic acid group approached 1, indicating restoration of perfusion levels similar to those found in unaffected digits. This result may show improvement in microvascular flow during the early postoperative period. Traditional antispasmodic drugs such as papaverine primarily restore baseline blood flow by relieving abnormal contraction of vascular smooth muscle [12]. Nicotinic acid, one of the most potent peripheral vasodilators, acts mainly by activating the G-protein-coupled receptor 109A (GPR109A), which promotes the release of prostaglandins (such as PGD_2 and PGE_2), thereby efficiently dilating microvessels [10,11]. During postoperative tissue stress and relative hypoxia, enhanced vasodilation may theoretically support compensatory increases in local blood flow, which could contribute to the observed improvement in perfusion ratios over time. However, direct assessment of tissue oxygenation, metabolic activity, or endothelial function was not performed in this study, and therefore, mechanistic interpretations remain speculative. Pharmacological evidence supports that nicotinic acid induces vasodilation primarily via activation of the GPR109A–prostaglandin signaling pathway [13]. Additionally, a previous clinical and experimental study have suggested that nicotinic acid may influence metabolic responses in ischemic tissues [14]. Whether similar mechanisms operate in replanted digital tissue requires further investigation. The observed reduction in the incidence of venous crisis in the nicotinic acid group may suggest improved microvascular flow dynamics, as adequate perfusion pressure and high-flow blood may reduce microcirculatory stasis and secondary thrombosis.

The present study contributes to the limited clinical evidence assessing the potential application of nicotinic acid in microsurgical settings. Even when combined with standard antispasmodic therapy, nicotinic acid was associated with improved microcirculatory perfusion parameters, suggesting that these two agents may exert complementary effects. Papaverine is a non-specific phosphodiesterase inhibitor that increases intracellular cyclic adenosine monophosphate (cAMP), thereby relaxing vascular smooth muscle [15], whereas nicotinic acid exerts vasodilatory effects through activation of the GPR109A–prostaglandin signaling pathway. Acting through distinct pharmacological mechanisms, these agents may provide additive microvascular dilation. Our observations are broadly consistent with previous reports suggesting that nicotinic acid can enhance peripheral blood flow in clinical conditions such as peripheral vascular disease [16], while a experimental study suggest potential benefits in improving flap survival [17]. Notably, the decrease in vascular complications observed in the present study was more pronounced for venous crisis than arterial crisis. While arterial crisis is often closely related to technical factors at the anastomotic site, venous insufficiency may be more strongly influenced by microcirculatory stasis, hypercoagulability, and tissue edema—processes that could theoretically be modulated by enhanced microvascular perfusion.

Subgroup analysis is exploratory in nature and should not be interpreted as confirmatory evidence due to limited sta-

tistical power. Future studies with larger, prospectively enrolled cohorts are needed to validate these preliminary subgroup findings. Subgroup analysis revealed heterogeneity in the efficacy of nicotinic acid across different injury types. In relatively simple laceration injuries, both groups had high survival rates, and the advantage of nicotinic acid was mainly reflected in the faster recovery of the perfusion ratio. However, in the more complex "crush/avulsion" injury subgroup with more severe microcirculatory disruption, nicotinic acid demonstrated a particularly significant advantage in improving survival. These avulsion injuries are particularly challenging because of extensive endothelial disruption, intimal injury, and severe vasospasm, all of which contribute to microvascular instability [18]. The potent vasodilatory effect of nicotinic acid may help maintain residual perfusion through partially preserved microvascular networks, which support tissue viability during the early postoperative period. This finding shows that nicotinic acid adjuvant therapy may be valuable in complex digital replantation, warranting confirmation in prospective studies. However, these subgroup findings are exploratory and should be interpreted with caution, given the modest sample size and retrospective design.

The therapeutic rationale for nicotinic acid shares certain mechanistic similarities with prostacyclin (PGI_2) analogues used in the management of critical limb ischemia [19], although direct comparative evidence in digital replantation is lacking. Both approaches aim to promote perfusion through prostaglandin-mediated vasodilation and inhibition of platelet aggregation. It is worth noting that nicotinamide, a metabolite of nicotinic acid, has recently been confirmed in a study to have effects on improving blood pressure and promoting placental-fetal growth [20]. This suggests that the benefits of nicotinic acid and its metabolites may extend beyond traditional vasodilation, and their actions might align with emerging strategies aimed at comprehensively improving vascular endothelial function by regulating key targets such as SIRT1 [21]. Therefore, the therapeutic logic of nicotinic acid can be compared not only to classic prostacyclin drugs but also to the forefront of current vascular protection research, which aims to achieve antioxidant, anti-inflammatory, and endothelial protection through multiple targets (e.g., SIRT1). Compared with expensive prostacyclin drugs, nicotinic acid, as a classic, economical, and readily available drug, holds significant potential clinical application value that may have practical clinical relevance in microsurgical settings. The higher incidence of facial flushing in the nicotinic acid group is an expected pharmacological response due to its activation of the GPR109A receptor and subsequent prostaglandin release [22]. This effect was generally mild and manageable with infusion rate adjustment. More importantly, there were no significant differences between the groups in the incidence of serious adverse reactions such as bleeding and liver/kidney dysfunction. This indicates that at therapeutic doses, when combined with anticoagulants post digital replantation, nicotinic acid did not increase the risk of serious bleeding, demonstrating a favorable clinical safety profile.

This study has several limitations. First, as a retrospective study, treatment allocation was based on clinical judgement rather than randomization, which may have introduced indication bias (e.g., a tendency to administer nicotinic acid to more complex cases). Although baseline characteristics were comparable between groups, unmeasured confounders (such as subtle surgical nuances or unrecorded comorbidities) cannot be excluded. Second, as a single-center study, the generalizability of the findings needs further validation. Third, despite adjusting for several key baseline factors, residual confounding factors (e.g., subtle differences in surgical technique or unrecorded comorbidities) may persist due to the non-randomized design. Moreover, multiple comparisons were conducted without formal adjustment for multiplicity, which increases the possibility of type I error. Importantly, because of the observational design and the absence of randomization, the findings should be interpreted as associations rather than evidence of causal therapeutic effects. Furthermore, we did not measure indicators such as plasma prostaglandin levels to directly confirm its mechanism of action. Therefore, the statistical significance of secondary and subgroup findings should be interpreted cautiously.

Future studies should focus on multicenter, prospective, randomized controlled trials (RCTs) to elucidate whether nicotinic acid offers a true therapeutic effect in digital replantation. Therefore, investigation of optimal dosing approaches, treatment duration and timing of administration may also help optimize clinical management protocols. Experimental studies examining molecular mechanisms underlying ischemia-reperfusion damage, endothelial protection, and inflammatory regulation may offer insights into the role of nicotinic acid in microvascular healing.

Conclusions

In this retrospective cohort study, adjuvant use of nicotinic acid was associated with enhanced postoperative microcirculatory perfusion, reduced incidence of vascular crises, and increased digit survival rate compared with conventional therapy alone. The association appeared more pronounced in patients with crush or avulsion injuries. However, due to the observational and non-randomized design, these findings should be interpreted as associations rather than evidence of therapeutic efficacy. Further prospective, randomized controlled trials are necessary to determine whether nicotinic acid confers a true therapeutic benefit in digital replantation.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

YY and YZ designed the research study. YY and XHW performed the research. YZ and XHW analyzed the data. YY drafted this article. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Zhuji Sixth People's Hospital (approval number: 2025-05), and all procedures followed the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants for the use of their anonymized clinical data in this research.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Sabapathy SR, Venkatramani H, Bharathi RR, Bhardwaj P. Replantation surgery. The Journal of Hand Surgery. 2011; 36: 1104–1110. https://doi.org/10.1016/j.jhsa.2011.03.039.

[2] Dec W. A meta-analysis of success rates for digit replantation. Techniques in Hand & Upper Extremity Surgery. 2006; 10: 124–129. https://doi.org/10.1097/01.bth.0000225005.64605.17.

[3] Bueno RA, Jr, Battiston B, Ciclamini D, Titolo P, Panero B, Tos P. Replantation: current concepts and outcomes. Clinics in Plastic Surgery. 2014; 41: 385–395. https://doi.org/10.1016/j.cps.2014.03.010.

[4] Allen DM, Chen LE, Seaber AV, Urbaniak JR. Pathophysiology and related studies of the no reflow phenomenon in skeletal muscle. Clinical Orthopaedics and Related Research. 1995; 122–133.

[5] Povlsen B. Cold-induced vasospasm after finger replantation; abnormal sensory regeneration and sensitisation of cold nociceptors. Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery. 1996; 30: 63–66. https://doi.org/10.3109/02844319609072406.

[6] Ince B, Uyanik O, Ismayilzade M, Yildirim MEC, Dadaci M. The effect of dobutamine treatment on salvage of digital replantation and revascularization. European Journal of Trauma and Emergency Surgery. 2023; 49: 2113–2120. https://doi.org/10.1007/s00068-023-02312-x.

[7] Reissis D, Geoghegan L, Sarsam R, Young Sing Q, Nikkhah D. Perioperative thromboprophylaxis in digital replantation: a systematic review. Plastic and Reconstructive Surgery–Global Open. 2020; 8: e2806. https://doi.org/10.1097/gox.0000000000002806.

[8] Siemionow M, Arslan E. Ischemia/reperfusion injury: a review in relation to free tissue transfers. Microsurgery: Official Journal of the International Microsurgical Society and the European Federation of Societies for Microsurgery. 2004; 24: 468–475. https://doi.org/10.1002/micr.20060.

[9] Carlson LA. Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. Journal of Internal Medicine. 2005; 258: 94–114. https://doi.org/10.1111/j.1365-2796.2005.01528.x.

[10] Benyó Z, Gille A, Kero J, Csiky M, Suchánková MC, Nüsing RM, *et al*. GPR109A (PUMA-G/HM74A) mediates nicotinic acid-induced flushing. The Journal of Clinical Investigation. 2005; 115: 3634–3640. https://doi.org/10.1172/JCI23626.

[11] Maciejewski-Lenoir D, Richman JG, Hakak Y, Gaidarov I, Behan DP, Connolly DT. Langerhans cells release prostaglandin D2 in response to nicotinic acid. The Journal of Investigative Dermatology. 2006; 126: 2637–2646. https://doi.org/10.1038/sj.jid.5700586.

[12] Ashrafi S, Alam S, Sultana A, Raj A, Emon NU, Richi FT, *et al*. Papaverine: A Miraculous Alkaloid from Opium and Its Multimedicinal Application. Molecules (Basel, Switzerland). 2023; 28: 3149. https://doi.org/10.3390/molecules28073149.

[13] Gille A, Bodor ET, Ahmed K, Offermanns S. Nicotinic acid: pharmacological effects and mechanisms of action. Annual Review of Pharmacology and Toxicology. 2008; 48: 79–106. https://doi.org/10.1146/annurev.pharmtox.48.113006.094746.

[14] Lassers BW, Wahlqvist ML, Kaijser L, Carlson LA. Effect of nicotinic acid on myocardial metabolism in man at rest and during exercise. Journal of Applied Physiology. 1972; 33: 72–80. https://doi.org/10.1152/jappl.1972.33.1.72.

[15] Hocking KM, Putumbaka G, Wise ES, Cheung-Flynn J, Brophy CM, Komalavilas P. Papaverine prevents vasospasm by regulation of myosin light chain phosphorylation and actin polymerization in human saphenous vein. PloS one. 2016; 11: e0154460. https://doi.org/10.1371/journal.pone.0154460.

[16] Hiatt WR, Hirsch AT, Creager MA, Rajagopalan S, Mohler ER, Ballantyne CM, *et al*. Effect of niacin ER/lovastatin on claudication symptoms in patients with peripheral artery disease. Vascular Medicine (London, England). 2010; 15: 171–179. https://doi.org/10.1177/1358863X09360579.

[17] Collins TM, Denish A, Sheffield J, Mitra A, Stueber K, Smith YR. Nicotinamide enhances skin flap survival. Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery. 1989; 23: 177–179. https://doi.org/10.3109/02844318909075114.

[18] Sears ED, Chung KC. Replantation of finger avulsion injuries: a systematic review of survival and functional outcomes. The Journal of Hand Surgery. 2011; 36: 686–694. https://doi.org/10.1016/j.jhsa.2010.12.023.

[19] Vietto V, Franco JV, Saenz V, Cytryn D, Chas J, Ciapponi A. Prostanoids for critical limb ischaemia. The Cochrane Database of Systematic Reviews. 2018; 1: CD006544. https://doi.org/10.1002/14651858.CD006544.pub3.

[20] Takahashi N, Li F, Fushima T, Oyanagi G, Sato E, Oe Y, *et al*. Vitamin B_3 Nicotinamide: A Promising Candidate for Treating Preeclampsia and Improving Fetal Growth. The Tohoku Journal of Experimental Medicine. 2018; 244: 243–248. https://doi.org/10.1620/tjem.244.243.

[21] Domi E, Hoxha M. Natural Compounds Targeting SIRT1 and Beyond: Promising Nutraceutical Strategies Against Atherosclerosis. Nutrients. 2025; 17: 3316. https://doi.org/10.3390/nu17213316.

[22] Kamanna VS, Ganji SH, Kashyap ML. The mechanism and mitigation of niacin-induced flushing. International Journal of Clinical Practice. 2009; 63: 1369–1377. https://doi.org/10.1111/j.1742-1241.2009.02099.x.