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# Atorvastatin and nitroglycerin ointment in digit replantation: Associations with vascular crisis and circulating biomarkers

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**Abstract**: **Background**: Vascular crisis is a major threat to digit replantation success, leading to substantial failure rates and compromised functional recovery. **Objectives**: To assess the association of combined atorvastatin and nitroglycerin ointment with vascular crisis, circulating biomarkers and clinical outcomes in patients undergoing unilateral digit replantation. **Methods**: 184 patients were prospectively allocated to combination (atorvastatin + nitroglycerin) or control (nitroglycerin alone) groups. Vascular crisis incidence, serum biomarkers (TNF-α, IL-6, CRP, NO, eNOS, ET-1), microcirculation indices and 30-day digit survival were systematically monitored. **Results**: Combination therapy decreased vascular crisis incidence (6.52% vs. 16.30%, P=0.037) and improved 30-day digit survival (90.22% vs. 79.35%, P=0.040). Postoperatively, the combination group exhibited lower levels of TNF-α, IL-6, CRP and ET-1, along with higher NO/eNOS levels and improved microcirculation, with all differences statistically significant after Bonferroni correction (P<0.05). **Conclusion**: Atorvastatin combined with nitroglycerin ointment correlates with reduced vascular crisis and favorable 30-day outcomes, accompanied by beneficial shifts in biomarkers and microcirculation that may underpin the therapeutic effects.

**Keywords**: Atorvastatin; Digit replantation; Microcirculation; Molecular mechanisms; Nitroglycerin; Systemic inflammation; Vascular crisis

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## INTRODUCTION

Digital replantation, since its initial success in 1963, is essential for functional recovery following finger amputation (Gurbuz and Yontar, 2021). Its success, however, is frequently threatened by postoperative vascular crisis, either arterial or venous, contributing to a 10-30% failure rate (Wang *et al.*, 2024). Its etiology is intricate, entailing vasospasm, thrombosis, endothelial damage and systemic inflammatory activation. A pivotal pathophysiological process is the crosstalk between the systemic release of pro-inflammatory factors (tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], etc.) and ensuing microcirculatory impairments (e.g., platelet adhesion/aggregation, blood stasis) (Xiao *et al.*, 2024). Early postoperative management that targets both inflammatory modulation and microcirculatory improvement thus holds promise for mitigating vascular crisis risk and enhancing replant success (Zhou *et al.*, 2024).

Currently, standard treatment for vascular crisis includes local vasodilators (e.g., nitroglycerin ointment), systemic spasmolytics (papaverine) and anticoagulants (low molecular weight heparin), though responses vary considerably among individuals (Georgescu *et al.*, 2025). While nitroglycerin ointment facilitates localized vasodilation through nitric oxide (NO)-mediated mechanisms, its effects remain restricted to the microvasculature and do not directly influence systemic inflammatory processes (Parra-Marquez *et al.*, 2023). Atorvastatin, a classical statin, has been associated with reduced levels of pro-inflammatory biomarkers related to the NF-κB pathway, suggesting potential anti-inflammatory effects and improved endothelial function beyond lipid-lowering actions; yet, oral dosing imposes systemic metabolic burden and lacks precise targeting to localized vascular damage following digital replantation (Yoon *et al.*, 2025a). Most studies address single-drug therapies (Sushko *et al.*, 2021; Garcia-Campa *et al.*, 2024). There is a lack of data on the pharmacodynamics of combination therapy in replantation, especially the simultaneous monitoring of systemic inflammation and microcirculation. Atorvastatin has extensive clinical application, well-documented anti-inflammatory effects beyond lipid-lowering [supported by prior studies (Yoon *et al.*, 2025b; Mousavi *et al.*, 2025)] and a favorable safety profile in perioperative settings, has not been fully validated in digit replantation compared to other statins.

Unlike prior single-drug observational studies, this study is the first to simultaneously monitor systemic inflammatory biomarkers and local microcirculation parameters, providing insights into the potential synergy of systemic anti-inflammatory and local vasodilatory strategies in digit replantation.

## MATERIALS AND METHODS

### *Study cohort*

This was a prospective observational study; treatment allocation was based on clinical decision-making and patient informed consent (non-randomized), which may introduce selection bias. No blinding was performed for patients, investigators, or outcome assessors. The study

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included patients who received unilateral replantation for finger amputations at Yongkang First People's Hospital from April 2024 to June 2025. The incidence of vascular crisis within the first postoperative week was designated as the primary outcome. A prior study (Kobayashi *et al.*, 2024) reported a 25% incidence rate; the research team estimated that the new intervention would reduce it to 15%. Using G*Power with a two-sided α=0.05 and power (1-β) of 80%, the calculated sample size was 76 per group. After adjusting for 10-20% dropouts, 184 patients (92 per group) were enrolled. Ethical clearance was granted by the Yongkang First People's Hospital committee (No. R2024051) and preoperative informed consent was secured from all involved. Treatment allocation was based on clinical decision-making by the attending physician and patient informed consent (non-randomized). The control group received standard treatment, while the combination group received enhanced treatment after patients agreed to additional oral medication. The control group initiated topical nitroglycerin ointment (0.5 g, three times daily; PUMC Pharmaceutical Co., Ltd., H20100195) to the proximal palmar skin of the replanted digit (anastomosis avoided) 6 hours post-surgery. On this basis, the combination group received oral atorvastatin calcium (20 mg, once daily; Hainan Qilu Pharmaceutical Co., Ltd., H20193144). Atorvastatin combined with nitroglycerin ointment is a routine treatment prescribed by physicians for patients at risk of vascular crisis after digit replantation in Yongkang First People's Hospital. The 20 mg daily dose was selected based on its proven efficacy in reducing systemic inflammation and improving endothelial function in perioperative orthopedic patients without excessive metabolic burden (García-Campa *et al*., 2024) and consistent with dosing regimens used in vascular protection studies (Haji Karimi *et al.*, 2025). Postoperative initiation was chosen to avoid potential perioperative bleeding risks while targeting the early inflammatory surge (24-96 h post-surgery) critical for vascular crisis development (Wang *et al.*, 2024). Patient adherence to atorvastatin was monitored via daily nursing records and post-discharge telephone follow-up, with adherence defined as taking ≥80% of prescribed doses. The two study cohorts (control *vs.* combination therapy) were comparable at baseline regarding age, gender and lesion side, as no statistically significant differences were detected for these parameters (P>0.05). All calculated standardized mean differences (SMDs) were less than 0.2, further supporting a minimal imbalance in potential confounders and affirming the groups' comparability (Table 1).

***Patient selection criteria***

*Inclusion criteria*: Patients aged 18–65 years, regardless of sex, presenting with unilateral digital amputation distal to the metacarpophalangeal joint (including at least one interphalangeal joint) were eligible. All the patients had cuts. Successful emergency replantation (anastomosis of at least two arteries and two veins) was required. Participants had to be free of significant systemic conditions (e.g., uncontrolled diabetes, chronic renal insufficiency, or heart failure) and without known allergies to atorvastatin or nitroglycerin.

*Exclusion criteria*: Exclusions comprised prolonged ischemic time of the amputated digit (>12 hours), pre-existing immune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus) or malignancy, recent (3-month) statin/nitrate use and unfavorable replantation conditions (e.g., extensive soft tissue loss >1 $cm^2$ necessitating flaps, or unstable bony fixation due to severe comminution).

***Vascular crisis***

Vascular crisis incidence was documented on postoperative day 7. The arterial type featured pale replanted digits with >2°C temperature drop, absent capillary refill and diminished pulp tension. The venous type was indicated by cyanosis of the digit, temperature reduction, sluggish capillary refill (>2 seconds) and increased pulp tension accompanied by blistering.

***Observation indicators***

Vascular crisis incidence was documented on postoperative day 7. The arterial type featured pale replanted digits with >2°C temperature drop, absent capillary refill and diminished pulp tension. The venous type was indicated by cyanosis of the digit, temperature reduction, sluggish capillary refill (>2 seconds) and increased pulp tension accompanied by blistering.

Venous blood was collected from fasting patients preoperatively and on postoperative day 7 for quantification of serum inflammatory (TNF-α, IL-6, CRP) and vasoactive (NO, eNOS, ET-1) biomarkers using standard laboratory assays. Tissue perfusion and microcirculation were assessed via nail bed transcutaneous oxygen pressure ($TcPO_2$), digital oxygen saturation ($SpO_2$), capillary refill time (CRT) and infrared thermometry. Detailed laboratory protocols are provided in the supplementary material.

Patients were monitored for drug-related adverse events (e.g., headache, gastrointestinal reactions) occurring between treatment initiation and discharge. A follow-up evaluation was conducted 30 days post-surgery to determine the viability of the replanted digit, with outcomes classified as survival (ruddy color, normal temperature and brisk capillary refill), partial necrosis (cyanosis without tissue loss), or complete necrosis (tissue sloughing or dry black eschar formation).

Postoperative day 7 was chosen as the primary time point because it represents a critical window for clinical assessment of vascular crisis, covers the sustained phase of inflammatory response after acute surge (24–96 hours) and allows sufficient time to observe the cumulative effect of combination therapy.

**Table 1**: Baseline demographic and clinical characteristics of the study participants

| Group (92 in each group) | Age (years) | Male [n (%)] | Female [n (%)] | Severed finger in left [n (%)] | Severed finger in right [n (%)] | BMI ($kg/m^2$) | Time of the amputated digit (h) | Smoking [n (%)] |
|---|---|---|---|---|---|---|---|---|
| Control | 41.57±14.09 | 56 (60.87) | 36 (39.13) | 44 (47.83) | 48 (52.17) | 20.18±2.42 | 6.09±3.84 | 42 (45.65) |
| Combination | 41.18±3.94 | 62 (67.39) | 30 (32.61) | 40 (43.48) | 52 (56.52) | 20.49±1.31 | 6.65±3.68 | 37 (40.22) |
| SMD | 0.028 | 0.125 | | 0.100 | | 0.159 | 0.149 | 0.164 |
| t (or $\chi^2$) | 0.184 | 0.851 | | 0.351 | | 1.087 | 1.020 | 0.555 |
| P | 0.854 | 0.356 | | 0.554 | | 0.278 | 0.309 | 0.457 |

Laboratory personnel were not blinded to group allocation, which may introduce detection bias.

***Statistical analysis***

Data were double-entered into an Excel database and verified for accuracy. All statistical evaluations were carried out with GraphPad Prism (Version 9.3). All quantitative variables were tested for normality using the Shapiro-Wilk test. All data conformed to a normal distribution, continuous data (mean ± SD) were compared with independent t-tests (between groups) and paired t-tests (within groups). Bonferroni correction was applied for multiple comparisons of biomarkers and microcirculation parameters to control Type I error. Categorical data [n (%)] were compared with $\chi^2$ or Fisher's exact tests. Results with a P-value below 0.05 were deemed statistically significant.

## RESULTS

***Vascular crisis***

The incidence of postoperative vascular crisis was 16.30% in the control group (5 arterial, 10 venous), compared to 6.52% in the combination group (2 arterial, 4 venous). The incidence of vascular crisis was borderline significantly lower in the combination group than in the control group (P=0.037). The relative risk (RR) of vascular crisis in the combination group was 0.399 (95% CI: 0.168-0.948), absolute risk reduction (ARR) was 9.78% and number needed to treat (NNT) was 10.2.

***Systemic inflammatory response***

No significant differences in preoperative inflammatory marker levels were apparent between the groups (P>0.05). On postoperative day 7, measured levels of TNF-α, IL-6 and CRP were significantly more suppressed in the combination group compared to the control group (P<0.05), despite a general decreasing trend in both groups (P<0.05, Fig. 1).

***Postoperative microcirculatory perfusion***

Preoperative $TcPO_2$, $SpO_2$ and CRT were comparable between the groups (P>0.05). Postoperatively, $TcPO_2$ and $SpO_2$ in the two groups increased and $TcPO_2$ in the combined group was higher than that in the control group (P=0.0023, 0.0031). Meanwhile, CRT was shortened to a greater extent in the combination group than in controls (P=0.018). Preoperative digital skin temperature did not differ between the two groups (P>0.05), though values in both were below those of the healthy digits (P=0.016). After surgery, the temperature of the finger on the affected side in the control group increased compared with that before surgery and was higher than that in the combination group (P=0.012), while there was no change in the temperature of the finger on the affected side in the combination group before and after surgery (P>0.05, Fig. 2).

***Vasoactive performance***

Levels of vasoactive substances did not differ significantly between groups prior to surgery (P>0.05). After the operation, both groups showed a rise in NO and eNOS and a decline in ET-1 (P<0.05). When comparing the groups postoperatively, the combination treatment resulted in greater elevations in NO and eNOS levels and a more marked decrease in ET-1 compared to the controls (P<0.05, Fig. 3).

***Comparable safety profiles between treatment groups***

The safety assessment showed similar adverse event rates between the two groups, with 8.70% in the combination group and 10.87% in the control group. The absence of a statistically significant difference (P=0.620) suggests that the combination therapy is well-tolerated and does not introduce additional drug-induced safety issues (Table 2).

***Improved digital survival quality with combination therapy***

A significant improvement in the survival of replanted digits was achieved in the combination group, with a 30-day survival rate of 84% versus 70% in the control group (P<0.05). While the occurrence of partial or complete necrosis in some digits was comparable between the groups (P>0.05), the combined protocol led to a higher overall rate of digit survival (P=0.040, Table 3).

## DISCUSSION

This pioneering study suggests the synergistic interaction between atorvastatin and nitroglycerin ointment following digital replantation. The observed benefits of combined therapy may be linked to three interrelated phenomena: reduced systemic inflammatory cytokine levels, improved microcirculatory perfusion and favorable shifts in vasoactive mediator balance (increased NO/eNOS, decreased ET-1).

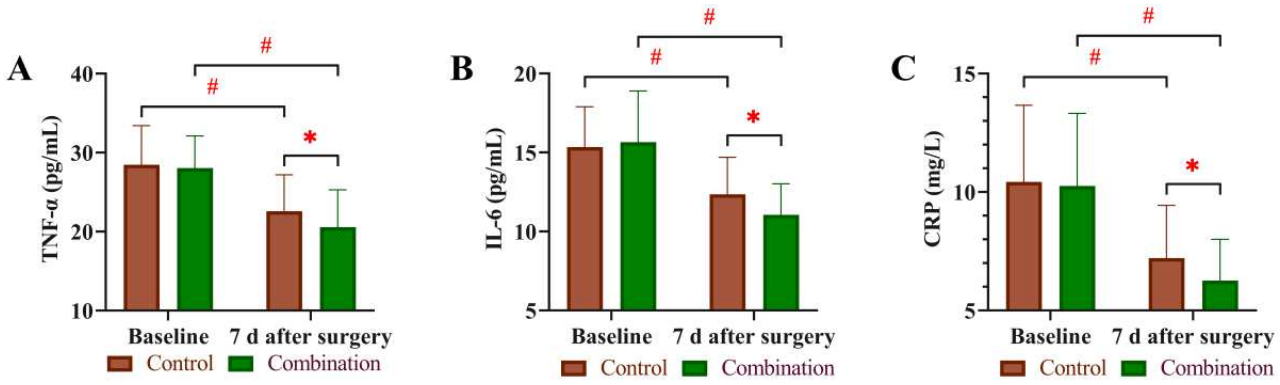


**Fig. 1**: Dynamic changes of serum inflammatory biomarkers (TNF-α, IL-6, CRP) before and 7 days after surgery in the control and combination groups. (A) TNF-α; (B) IL-6; (C) CRP. Note: Within-group comparisons were performed using paired t-tests (#P<0.05 vs. baseline); between-group comparisons were conducted using independent t-tests (*P<0.05 after Bonferroni correction).

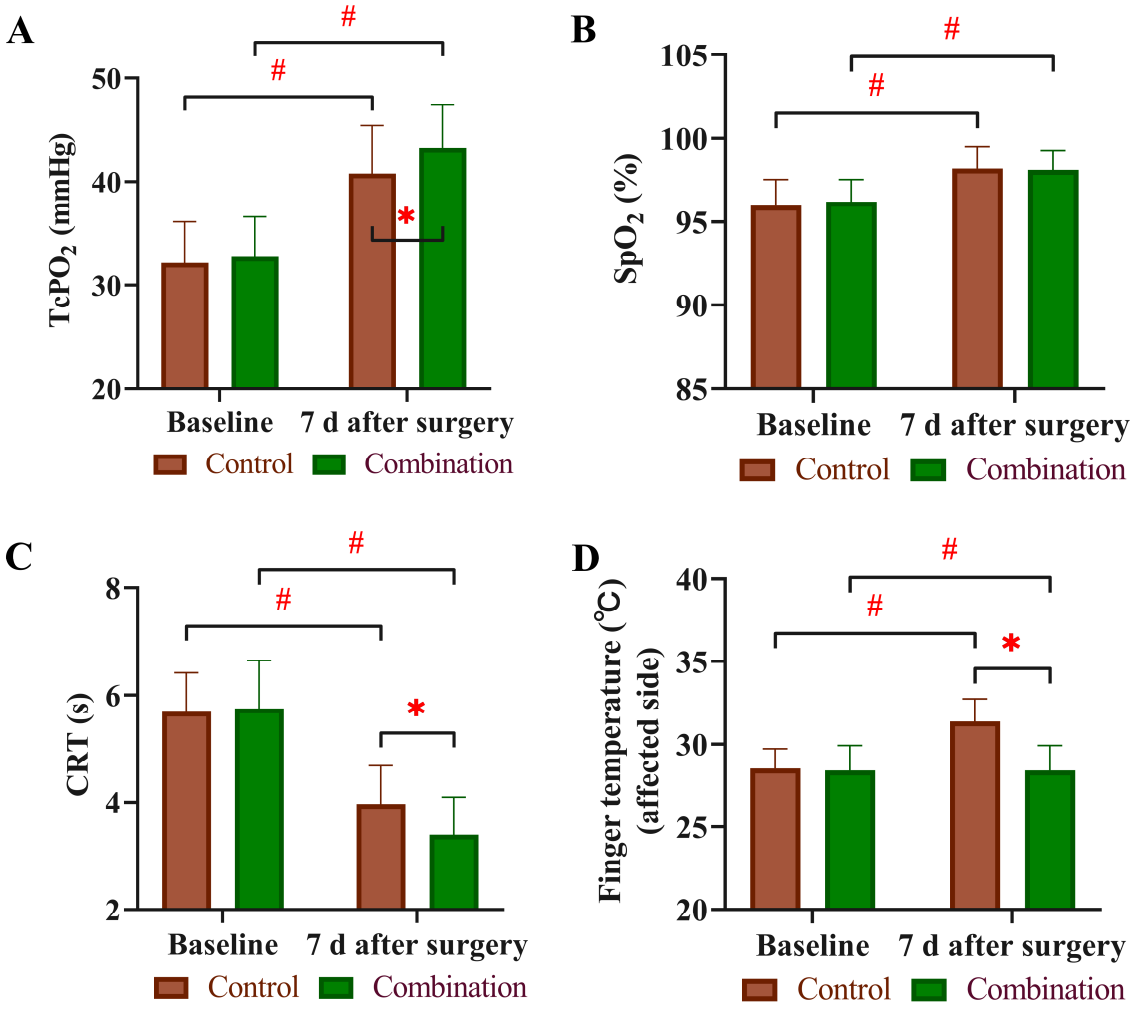


**Fig. 2**: Changes of microcirculation parameters ($TcPO_2$, $SpO_2$, CRT and finger skin temperature) before and 7 days after surgery in the control and combination groups. (A) $TcPO_2$; (B) $SpO_2$; (C) CRT; (D) Finger temperature. Note: Within-group comparisons were performed using paired t-tests (#P<0.05 vs. baseline); between-group comparisons were conducted using independent t-tests (*P<0.05 after Bonferroni correction).

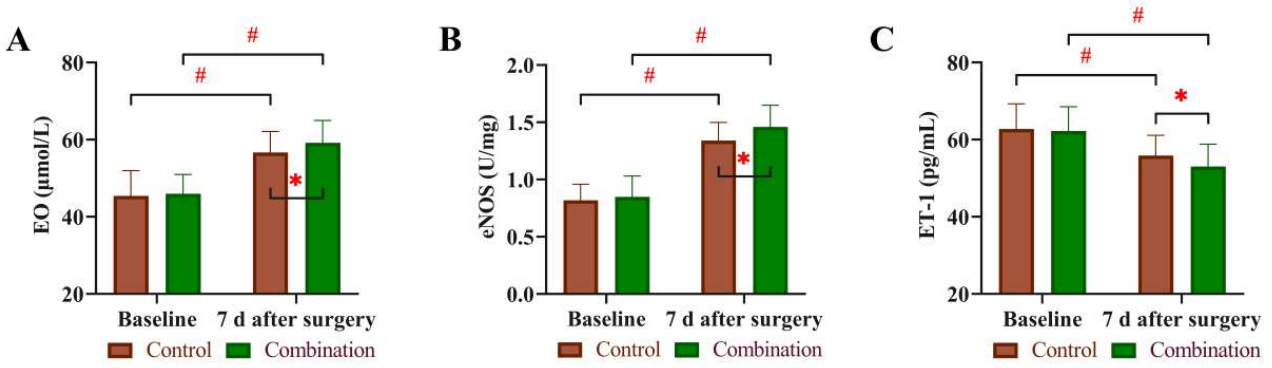


**Fig. 3**: Dynamic changes of vasoactive substances (NO, eNOS, ET-1) before and 7 days after surgery in the control and combination groups. (A) EO; (B) eNOS; (C) ET-1. Note: Within-group comparisons were performed using paired t-tests (#P<0.05 vs. baseline); between-group comparisons were conducted using independent t-tests (*P<0.05 after Bonferroni correction).

**Table 2**: Comparison of adverse effects

| Group (92 in each group) | Headache [n (%)] | Facial flushing [n (%)] | Abnormal liver function [n (%)] | Abdominal pain/ diarrhea/bloating [n (%)] | Nausea/ vomiting [n (%)] | Overall incidence [n (%)] |
|---|---|---|---|---|---|---|
| Control | 3 (3.26) | 1 (1.09) | 1 (1.09) | 3 (3.26) | 2 (2.17) | 10 (10.87) |
| Combination | 3 (3.26) | 1 (1.09) | 0 (0.0) | 1 (1.09) | 3 (3.26) | 8 (8.70) |
| $\chi^2$ | | | | | | 0.246 |
| P | | | | | | 0.620 |

**Table 3**: Comparison of prognostic rehabilitation quality

| Group (92 in each group) | Complete necrosis [n (%)] | Partial necrosis [n (%)] | Survival [n (%)] |
|---|---|---|---|
| Control | 5 (5.43) | 14 (15.22) | 73 (79.35) |
| Combination | 2 (2.17) | 7 (7.61) | 83 (90.22) |
| $\chi^2$ | - | 2.634 | 4.212 |
| P | 0.444 | 0.105 | 0.040 |

This study supports the potential value of combined systemic anti-inflammatory and local vasodilatory strategies for reducing vascular crisis risk compared with nitroglycerin monotherapy. Conventional nitroglycerin ointment exerts localized vasodilation via NO release but lacks systemic anti-inflammatory effects (Safikani Mohammadzadeh *et al.*, 2023), whereas the addition of atorvastatin correlated with lower levels of pro-inflammatory biomarkers associated with the NF-κB pathway (Farrag *et al.*, 2024). These biomarker changes are consistent with potential anti-inflammatory effects, but direct evidence of NF-κB pathway modulation or endothelial homeostasis restoration remains absent due to the lack of tissue-level or molecular measurements. This finding aligns with research by (Jayaram *et al.*, 2022) which demonstrated the ability of statins to reduce postoperative inflammatory cytokine levels in patients undergoing emergency cardiovascular surgery. Additionally, atorvastatin potentially contributes to reduced microthrombosis through plaque stabilization and suppression of platelet-activating factor (PAF) release (Liu and Kang, 2025). Similar studies have explored the synergistic effects of atorvastatin and nitroglycerin in vascular protection. (Haji Karimi *et al.*, 2025) reported that the combination improved microcirculation and reduced ischemia-reperfusion injury in a rat model of digital replantation. However, no prior studies have simultaneously monitored systemic inflammatory biomarkers and local microcirculation parameters to explore the synergy mechanism. The observed differences between the two groups suggest that resolution of inflammation after surgery may be a key mechanism for reducing venous crises. Subsequent measurements revealed a greater increase in $TcPO_2$ in the combination group than in controls. This aligns with previous findings that local NO donors enhance flap survival (Luo *et al.*, 2021). Furthermore, research by (Khalighfard *et al.*, 2021). indicates that statins upregulate eNOS expression pointing to eNOS mRNA stabilization as a mechanism by which atorvastatin boosts endogenous NO synthesis. Meanwhile, ET-1, a core member of the endothelin family, is known to correlate directly with the magnitude of vasoconstriction (Kuczmarski *et al.*, 2021; Allan *et al.*, 2024). Based on the present results, the potential benefit of this drug

combination appears to stem from its concurrent action on two pathways. Firstly, NO relaxes smooth muscle directly by increasing cyclic guanosine monophosphate (cGMP production) via guanylate cyclase (GC) activation. This occurs alongside the inhibition of ET-1, which removes the tonic stimulus on the ET_A receptor, thereby effectively disrupting the vicious cycle of vasoconstriction. However, several critical considerations must be emphasized. All inferences are based on circulating biomarkers and short-term physiological parameters—no direct molecular, pathway-specific, or tissue-level measurements (e.g., NF-κB activity, eNOS expression in digital tissue) were performed.

Second, the clinical relevance of biomarker changes should be interpreted in the context of patient-centered outcomes. The reduced vascular crisis incidence translated to a 10.87% higher 30-day digit survival rate, which is clinically meaningful for reducing treatment failure and avoiding additional surgical interventions. However, the 30-day follow-up window is insufficient to assess sustained digit viability, as delayed necrosis or vascular compromise may occur beyond this period. Critical gaps remain in data on revision surgery rates, long-term functional recovery (e.g., joint range of motion, sensory recovery, daily activity capability) and patient-reported outcomes (e.g., pain scores, quality of life). These limitations restrict the translation of short-term biomarker and survival benefits to real-world clinical practice, where functional recovery is the primary goal of digit replantation.

This study has several key limitations: (1) Non-randomized design with potential selection bias, as treatment allocation was based on clinical decision and patient consent; (2) Lack of blinding for patients, investigators and laboratory personnel, which may introduce performance and detection bias; (3) Short follow-up duration (≤30 days) without functional outcome assessment; (4) No direct molecular or tissue-level measurements to validate pathway modulation—all inferences rely on circulating biomarkers; (5) Biomarkers were only measured at two time points, missing early-phase (24–72 hours) dynamics critical for understanding postoperative inflammation and endothelial responses; (6) Critical confounders including smoking status, ischemia duration of the amputated digit, injury mechanism and intraoperative variables (e.g., anastomosis time, number of anastomosed vessels) were not incorporated into multivariate adjustment or stratified analyses. Although baseline characteristics of the two groups were well balanced, these factors are known to independently affect vascular crisis incidence and digit survival in replantation surgery. The absence of targeted analytical strategies for these confounders weakens the causal interpretation of the association between combination therapy and improved outcomes and may lead to residual confounding that cannot be excluded; (7) No assessment of long-term adverse events of atorvastatin, which is important for systemic therapy; (8) Small number of vascular crisis events (n=15 in control, n=6 in combination) may compromise statistical robustness. To address the above limitations, future research can be improved from the following three key points: recommend three key improvements: First, adopt stratified randomization in randomized controlled trials, with smoking status and ischemia duration as stratification factors. Second, perform stratified analyses and interaction tests to verify the stability of treatment effects across different subgroups. Third, collect comprehensive clinical variables for multivariate adjustment to reduce confounding bias.

## CONCLUSION

This prospective quasi-experimental study suggests that atorvastatin combined with nitroglycerin ointment is associated with reduced vascular crisis incidence and improved 30-day digit survival after unilateral digit replantation, alongside favorable changes in circulating biomarkers and microcirculation. These findings are hypothesis-generating rather than confirmatory, limited to the study population and short-term follow-up. Future multi-center randomized controlled trials with long-term functional outcome assessment are needed to validate the observed associations and confirm therapeutic efficacy.

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None.

***Author's contributions***
All the work for this study was done by Weihua Zhang and agree to be accountable for all aspects of the work.

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There was no funding.

***Data availability statement***
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

***Ethical approval***
Ethical clearance was granted by the Yongkang First People's Hospital committee (No. R2024051) and preoperative informed consent was secured from all involved. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

***Conflict of interest***
The authors declare no conflict of interest.

***Supplementary data***
https://www.pjps.pk/uploads/2026/04/SUP1776930028.pdf

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