

ANNALS OF PALLIATIVE MEDICINE

Peer Review File

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Round 1

Detailed Responses to Review Comments

Comment 1:

Please delete the patient's personal information in the figure.

Reply:

We appreciate the Reviewer for pointing out this issue. As suggested, we have deleted the patient's personal information in figure 1.

Comment 2:

Please draw a timeline figure. Make sure it stands alone which covers what's done when it's done, what's found, what's the outcome with definite time.

Reply:

We thank the Reviewer for the constructive suggestion about our study. As suggested, we have showed the timeline of the treatment and follow-up of this patient in Table 1. Meanwhile, we have added the statements as follows: Timeline of the treatment and follow-up of this patient is presented in Table 1.

Round 2

Detailed Responses to Review Comments

General Comments:

It is no exaggeration to say that when hypocoagulation and ischemic stroke coincide in a patient, it is an art to restore blood flow while avoiding bleeding. The authors should be congratulated as they made it. The full experience is beneficial to peers. To further make it more impactful, here are some minor concerns.

Reply:

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We thank the Reviewer for the positive comments on our study. We have followed your suggestions and made every possible effort to address the concerns. Detailed responses are below.

Comment 1:

In the abstract, what's unique of this case report needs highlighting. This should be based on comparison with similar situation and previous therapy and outcomes. How's this case different from others? What's the most significant difference?

Reply:

We appreciate the Reviewer for pointing out this issue. As suggested, we have improved the statements in the abstract section as follows: It is essential for acute ischemic stroke (AIS) patients to receive timely revascularization. However, intravenous thrombolysis (IVT) is not recommended for AIS patients with warfarin associated hypocoagulability. Meanwhile, monotherapy of coagulation factors or vitamin K is unable to reverse anticoagulation of warfarin in emergency. Thus, developing an effective IVT strategy poses a challenging task for these fragile population. For normalizing INR, combination of 4 factor prothrombin complex concentrate, fresh frozen plasma and vitamin K1 were administrated. Finally, the patient successfully received recombinant tissue plasminogen activator (rt-PA), with an obviously neurological improvement.

Comment 2:

In the introduction, more literature/evidence introduction is needed. This is also applied to prove WHY this case is unique. Therefore, peers could learn something new.

Reply:

We thank the Reviewer for the constructive suggestion about our case report. As mentioned above, we have added the statements in the introduction section as follows: Goldstein JN et al. revealed that rapid INR reduction (INR \leq 1.3 at 30min after the end of infusion) was achieved in 55% (48/87) patients using vitamin K and 4-factor prothrombin complex concentrate (4F-PCC) compared with 10% (8/81) of patients receiving vitamin K and fresh frozen plasma (FFP). Insufficient normalization of INR inevitably limits the application of IVT, making a poor outcome in these patients.

Comment 3:

The timeline. Add additional precise time (year, month/day) in both the timeline and the manuscript accordingly.

Reply:

As suggested, we added additional precise time in both timeline and the manuscript.

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In case presentation section: An 82-year-old male (weight of 57 kg) was admitted to our emergency department within 90 minutes after experiencing sudden onset of dysarthria and left-sided hemiparesis on Mar 10, 2017, with an initial National Institutes of Health Stroke Scale (NIHSS) score of 40 (very severe stroke), indicating a poor prognosis and necessity for thrombolytic or mechanical intervention; After 24 hours of the thrombolysis (Mar 11, 2017), the patient's NIHSS score markedly improved from 40 to 33, and the CT scan showed a mild hemorrhagic transformation of parenchymal hematoma (PH) type 1 (Fig. 1b). Warfarin at the dosage of 3.75mg resumed on day 14 post-IVT (Mar 24, 2017) and the patient's NIHSS score was gradually improved to 11 during three-month follow-up (Jun 15, 2017). A CT scan one year later (Mar 15, 2018) showed a low-density area due to old ischemic stroke without hemorrhage (Fig. 1c).

In table 1:

Table 1 Timeline of the treatment and follow-up in the present patient

Time course	Date	Events
Stroke onset	Mar 10, 2017	Dysarthria and left-sided hemiparesis
90 minutes	Mar 10, 2017	Admitted to emergency department (NIHSS score: 44; INR: 1.72; PT: 18.2s)
110 minutes	Mar 10, 2017	Reversal of anticoagulation: 4F-PCC 200 IU, FFP 380ml, vitamin K ₁ 10mg
159 minutes	Mar 10, 2017	IVT: rt-PA 51.3mg
24 hours after IVT	Mar 11, 2017	Mild hemorrhagic transformation; NIHSS score: 33
14 days	Mar 24, 2017	Warfarin resumed (3.75mg)
3 months	Jun 15, 2017	NIHSS score: 11
12 months	Mar 15, 2018	CT scan showed a low-density area due to old ischemic stroke without hemorrhage

NIHSS: National Institutes of Health Stroke Scale; INR: international normalized ratio; PT: prothrombin time; 4F-PCC: 4-factor prothrombin complex concentrate; FFP: fresh frozen plasma; IVT: intravenous thrombolysis; rt-PA: recombinant tissue plasminogen activator; CT: computed tomography.

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Comment 4:

In the discussion, one separate paragraph to show both strengths and limitations is needed.

Reply:

We thank the Reviewer for the suggestive comments about our study. As suggested, we have added a separate paragraph to stress both strengths and limitations in discussion section: In the present AIS patient, his significantly elevated INR and prolonged PT at initial blood examination was immediately normalized with the combination of vitamin K, PCC and FFP. Since the thrombolysis was timely carried out within 3 hours from our patient's onset of stroke, sufficient dosage of rt-PA (0.9 mg/kg) was administrated, resulting in a satisfactory outcome. We believe that this case report provides useful information regarding IVT strategy in AIS patients with warfarin-associated hypocoagulability. However, no RCTs have been conducted to evaluate the reversal strategy for these patients, thus further high-quality real-world studies on evaluation of this issue are necessary.

