

Reviewer #1:

*Language Quality: Grade C (A great deal of language polishing)*

**One of the aspects of language, we believe, did concern the title of the report and we modified the same. The remainder of the manuscript was translated and re-checked by a native speaker and editor of scientific publications (updated statement enclosed).**

*Specific Comments to Authors:*

*1. The authors proposed a new method trying to increase positive LGI bleeding detection rate by intravenous norepinephrine injection in a very small limited case series (4 patients). Although the ideal of increasing systemic blood pressure to unmask the bleeding is reasonable but vasopressors may also induce non-vital organ vasospasm (including kidney, bowel, and extremities... etc) if hypovolemic status persists. Thereafter, simultaneous intravenous fluid supplement (including transfusion) should be important too.*

**We entirely agree with the reviewer in this regard. We have added a statement to the effect that the intensive care treatment of patients – including the intravenous administration of fluid and monitoring of other organs such as the kidneys, bowel and extremities by specialists and experienced physicians – is extremely important in this setting. NE was administered because of cardiovascular instability and we discovered contrast medium extravasation as a byproduct of the same.**

*2. The authors reported the cumulated dose of norepinephrine up to 40µg. What is the maximal dose per bolus injection and the minimal time interval between each injection?*

**Thank you very much for this remark. The maximal dose per bolus was 10 µg and we did not establish a specific time interval. The treatment depended on the observations made during monitoring and intensive care, and achieving a mean pressure above 60 mmHg.**

*4. What's the differences from the pharmacologic point of view between norepinephrine and the other vasopressors (e.g. epinephrine or dopamine)?*

**We did not use different vasopressors so we cannot make a statement in this regard. We used NE because, in the specific shock situation (volume deficiency), it has the most favourable profile compared to other direct sympathomimetics. Due to its alpha-1 receptor affinity, NE has the best profile in terms of achieving an isolated vasoconstrictive effect (and the consequent increase in mean pressure). Especially in comparison with dobutamine, to a lesser extent even adrenaline, the beta-1-mediated cardiac effects of NE are less prominent. Alternatively, one may consider direct alpha-1 receptor agonists.**

**<https://pubmed.ncbi.nlm.nih.gov/26878401/>**

*3. It's not correct of the statement in the 3rd paragraph of the Discussion: "Three of four patients had no complications after embolisation." One patient did not received embolization therapy and one patient had complicated with ischemic bowel.*

**Thank you for this remark. We have revised our statement. Two of four patients had no complications under embolisation unmasked by NE. One patient had bowel ischaemia and one patient did not undergo embolisation.**

*4. 5th paragraph of the “ Discussion ”: 10% ischemic complication can not be regarded as rare.*

**Thanks for this remark. We have omitted the word “rare”. The text now says that bowel ischaemia is a known complication of TAE.**

*5. What’s the CTA findings of the two patients? positive or negative?*

**Patient 1 had no CM extravasation on CTA. We performed a triphasic CT scan and found no signs of previous bleeding. Patient 4 had CM extravasation on CTA. Again, we performed a triphasic CT scan and found active bleeding in the lower gastrointestinal tract.**

**We have changed both points. Thanks for this remark.**

*6. Based on what evidence did you perform prophylactic embolization in those 2 patients and what’s their clinical outcome?*

**Thanks for this justified remark. Prophylactic embolisations have been described in an earlier publication and were not addressed in this report. We are aware of the fact that the body of evidence concerning prophylactic embolization is limited. In both patients described here, the decision was made by the clinician on an individual basis.**

*7. In the current series, 23 patients had negative angiographic findings, but norepinephrine was injected in only 4 patients. What’s the inclusion criteria for this provocative test (angiographic negative patients with systolic blood pressure  $\leq 90$  or 100 mmHg) ? What’s the blood pressure of the other 19 patients during the angiographic study?*

**The other patients have been described in detail in a previous publication. NE was not used in all patients with a negative angiogram, but only in those who would have received NE anyway due to their cardiovascular condition. We have also mentioned that it would be meaningful to perform an angiography at the time of NE administration in order to detect an “accidentally provoked” contrast medium extravasation. We have said this more clearly now. Thanks for drawing our attention to this point.**

*8. patient-1 showed contrast extravasation from the middle colic artery, thereafter, the bleeding site should be hepatic flexure instead of cecum.*

**We noted this error. Contrast extravasation occurred from a branch of the right colic artery. Thanks for mentioning this point.**

*9. Provide the full name of the abbreviation of the coil used in Table1.*

**Tornado Embolization Coil, Cook Medical. This has been added. Thanks.**

Reviewer #2:

**Specific Comments to Authors:** Good work, written by a simple readable language. I have two comments

*First: the title of the manuscript should be modified.*

**We changed the title. Thanks for the remark.**

*Second: being a retrospective study, how do you get the consent from the patients*

The patients' consent to the use of their data for scientific publications was obtained from the individual patients at the start of their stay in the hospital and was also documented (see the filed documents). The retrospective study was approved by the ethics committee of the Regional Medical Society of Hessen (Landesärztekammer Hessen, approval number FF95/2017). We refer to our publication entitled "Endoscopic hemostasis makes the difference: Angiographic treatment in patients with lower gastrointestinal bleeding"; Werner DJ et al., WJG 2021 Jul <https://pubmed.ncbi.nlm.nih.gov/34326943/>

*Reviewer #3:*

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:**

1. *The title to be revised (language error)*

**The title was revised. Thank you for the remark.**

2. *Were the 41 pts with lower gi bleed consecutive pts?*

**Yes. These were all of the patients who underwent radiological treatment for LGIB during this time. We have revised the text. Thanks for the remark.**

3. *Can NE be used in all patients with varying comorbidities?*

**Thank you for the remark. We must state more explicitly that we did not perform provocation with noradrenaline prospectively, but only observed patients who had received noradrenaline for their clinical condition. We have addressed this point again in the text. Noradrenaline must be administered under the supervision of an intensive care specialist and in controlled conditions. Experienced physicians must weigh the side effects and contraindications of noradrenaline against its benefits for the individual patient. We did not administer NE to provoke bleeding prospectively. In patients who needed to be given NE anyway, we observed bleeding that had remained undetected earlier. Relative contraindications of NE include TAA, pheochromocytoma, pulmonary heart disease, or thyrotoxicosis. Intentional provocation – which we did not perform – would potentially cause these side effects.**

4. *What was the dose of NE used? How many times was the NE injected in a single pt?*

NE was given in cumulative doses of 10 ug to maximum 40 ug. Thus, a patient received a maximum of four injections. The time intervals were at the discretion of the intensive care specialist in charge, focused on achieving a mean pressure of 60 mmHg. We have stated this more explicitly in the text.

*5. Can the complication of ischemia requiring hemicolectomy be ruled out as not due to NE?*

Thanks for this remark. The complication may have occurred due to the administration of NE, which was a clinical necessity in these cases. However, bowel ischaemia may also be a complication of non-superselective embolisation. We have addressed both possibilities in the text.

*6. What are the study limitations?*

Thanks for this point. We have addressed the limitations in a longer paragraph. Our study was associated with the known difficulties incumbent upon a retrospective investigation. If further studies show that the suggested approach might be successful, it will be necessary to validate the outcomes prospectively under controlled conditions.

Besides, the data were not collected for the purpose of the present report. Therefore, data collection may have been subject to structural inaccuracies. We observed the described events during data collection. The guidelines have been altered in the meantime and this made it more difficult to interpret the results. The pooling of both data registers, as described in the preceding publication, may have been responsible for a loss of data.

NE is a highly potent substance and should only be used by experienced clinicians. In one of our cases, the complication of bowel ischaemia could have been an effect of NE. Further prospective studies should address this issue. The limitations of the previously published study apply here as well. Many crucial points, such as the fluctuating nature of gastrointestinal bleeding, the time point of endoscopy, the number of endoscopies to be performed, the role of CT diagnosis, and the optimal time of angiography have not been clearly specified yet and must be clarified in future investigations.

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the current series, 23 patients had negative angiographic findings, but norepinephrine was injected in only 4 patients. What's the inclusion criteria for this provocative test (angiographic negative patients with systolic blood pressure  $\leq$  90 or 100 mmHg) ? What's the blood pressure of the other 19 patients during the angiographic study? ---The other patients have been described in detail in a previous publication. NE was not used in all patients with a negative angiogram, but only in those who would have received NE anyway due to their cardiovascular condition. We have also mentioned that it would be meaningful to perform an angiography at the time of NE administration in order to detect an "accidentally provoked" contrast medium extravasation. We have said this more clearly now. Thanks for drawing our attention to this point. 8. patient-1 showed contrast extravasation from the middle colic artery, thereafter, the bleeding site should be hepatic flexure instead of cecum. - --We noted this error. Contrast extravasation occurred from a branch of the right colic artery. Thanks for mentioning this point. 9. Provide the full name of the abbreviation of the coil used in Table1. ---Tornado Embolization Coil, Cook Medical. This has been added. Thanks. ---The manuscript has already been revised. Best regards