Lian-Sheng Ma
Science Editor, Company Editor-in-Chief
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Dear editor,

We appreciate the opportunity to respond to the reviewers' comments and believe that the manuscript has been improved considerably based on the suggestions and recommendations provided. We have carefully considered each issue that was raised by the reviewers and have addressed them point-by-point in the attached letter and revised manuscript. We thank the reviewers for their constructive criticism. We hope that you will find the revised manuscript suitable for publication in the ***World Journal of Clinical Cases***.

Thank you for your consideration.
Sincerely,

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Response to Reviewers' Comments

Manuscript: 61717

To Reviewer 1:

Comments to the Author

This is a case report showing that the use of mannitol combined with furosemide can be effective to treat refractory lymphedema. Such treatment was given in a patient for intracranial hemorrhage who had also lower limb refractory lymphedema post cervical cancer. The case report provides an effective treatment option for refractory lymphedema, but there are some concerns made mostly from the decision to extent treatment and the monitoring tools used to provide safety that should be clarified better.

Author response: We appreciate your in-depth review, which has assisted us in revising our manuscript. Please see our line-by-line responses to the comments below.

Comment 1: Please clarify better clinical status of patient admitted with intracranial hypertension. What treatment strategy has been followed? Intubation?Sedation? Intracranial pressure monitoring (ICP)?

Author response 1: We agree with the reviewer's opinion. We described in more detail the patient's clinical condition and treatment strategy. First, the patient was intubated due to stuporous mentality at the time of admission, and her initial GCS score was 8, showing severe neurologic impairment. Although accurate ICP measurement and monitoring could not be performed because no invasive procedures were performed, hemorrhage was seen brain CT and, considering her neurologic symptoms (mental changes, etc.), ICP elevation was considered the cause of the patient's symptoms. On follow-up brain CT performed on 3/12, hemorrhage continued, and neurologic symptoms did not improve. This suggested that ICP elevation continued, and we decided to continue using drugs for ICP control. We described the clinical status of the patient in more detail as follows.

CASE PRESENTATION	
Before	*History of present illness* Three hours prior to acute mental change, the patient reported a severe

	headache and right hemiplegia. Her mental state was stupor when she arrived at hospital.
After	*History of present illness* Three hours prior to acute mental change, the patient reported a severe headache and right hemiplegia. Her mental state was stupor when she arrived at the hospital. Tracheal intubation was performed due to stuporous mentality.

CASE PRESENTATION	
Before	*History of past illness* The patient had a history of refractory lymphedema of the left lower extremity since 1998 after total abdominal hysterectomy for cervical cancer in 1987, and she had been treated with a pneumatic compression device and short-stretch bandaging at home. She was repeatedly admitted into the rehabilitation department to receive complete decongestive therapy (CDT) with intermittent pneumatic compression treatment (IPC), and her family stated that the lymphedema had become aggravated while she was living at home.
After	*History of past illness* The patient had a history of refractory lymphedema of the left lower extremity since 1998 after total abdominal hysterectomy for cervical cancer in 1987, and she had been treated with a pneumatic compression device and short-stretch bandaging at home. She was repeatedly admitted into the rehabilitation department to receive complete decongestive therapy (CDT) with intermittent pneumatic compression treatment (IPC), and her family stated that the lymphedema had become aggravated while she was living at home. She also had a history of hospitalization for chronic kidney disease (CKD) in 2017, and was managed with candesartan 4 mg/day through the outpatient department. Baseline estimated glomerular filtration rate

	(eGFR) before admission was 77mL/min/1.73m^2 and serum creatinine level was 0.7 mg/dL.
TREATMENT	
Before	The patient's family refused a surgical procedure for intracranial hemorrhage, so she was admitted to the intensive care unit for conservative treatment. Upon admission, she immediately received mannitol (0.2 g/ml, 50 ml every 6 hours) and furosemide (5 mg every 6 hours) for intracranial pressure control.
After	Tracheostomy was performed on the 8th hospital day for prevention of aspiration pneumonia and removal from intubation. The patient's family refused a surgical procedure for intracranial hemorrhage, so she was admitted to the intensive care unit for conservative treatment. Considering the brain CT and physical examination findings, her neurologic symptoms were attributed to increased intracranial pressure (ICP). Upon admission, she immediately received mannitol (0.2 g/ml, 50 ml every 6 hours) and furosemide (5 mg every 6 hours) for intracranial pressure control. Sedation was not required due to stuporous mentality. Since no invasive procedures were performed, direct ICP monitoring was not possible. However, persistent hemorrhage was confirmed on follow-up brain CT on the 8th hospital day. Thus, ongoing ICP elevation was suspected and ICP control agents were continued.

Comment 2: Did you use only mannitol and furosemide and why? How did you monitor mannitol effects? ICP? CT or MRI scan? Osmolality gap? Osmolarity variations may be harmful causing in extremis the fatal central pontine myelinolysis. How did you monitor this syndrome? What was the daily fluid balance for the patient? Please provide clinical course laboratory (blood gas/kidney function/electrolytes) and imaging applied (table and figure).

Author response 2: We appreciate the reviewer's valuable comments and have revised the manuscript accordingly. Mannitol and furosemide were used for ICP control, and direct ICP monitoring was not possible because invasive procedures were not performed. The effect on

ICP was evaluated through brain CT and worsening of neurologic symptoms. In addition, osmolarity and electrolyte concentrations were checked through periodic laboratory studies. Brain CT, blood gas, kidney function, and electrolyte data are provided as a figure and table below.

CASE PRESENTATION	
Before	*Imaging examinations* Computed tomography (CT) of the brain revealed an intracranial hemorrhage in the left hemisphere.
After	*Imaging examinations* Computed tomography (CT) of the brain revealed an intracranial hemorrhage and brain edema in the left parieto-occipital lobe (Fig 1A).

OUTCOME AND FOLLOW-UP	
Before	On the 21st hospital day, the patient's vital signs had stabilized, and she was transferred to the general ward. Mannitol and furosemide were applied until the 27th hospital day.
After	The effects of mannitol and furosemide on ICP were assessed indirectly through brain CT and changes in neurologic symptoms. In addition, due to concerns about side effects of osmolarity variation, laboratory evaluation of blood gas, electrolyte, osmolarity, and kidney function was performed during hospitalization (Table 1). On the 21st hospital day, the patient's vital signs had stabilized, and she was transferred to the general ward. Mannitol and furosemide were applied until the 27th hospital day.

OUTCOME AND FOLLOW-UP	
Before	
After	Intracranial hemorrhage and brain edema were followed using brain CT during hospitalization. Ongoing resolution of hemorrhage and

improvement in brain edema were demonstrated (Fig 1).

FIGURE LEGENDS

Before

After

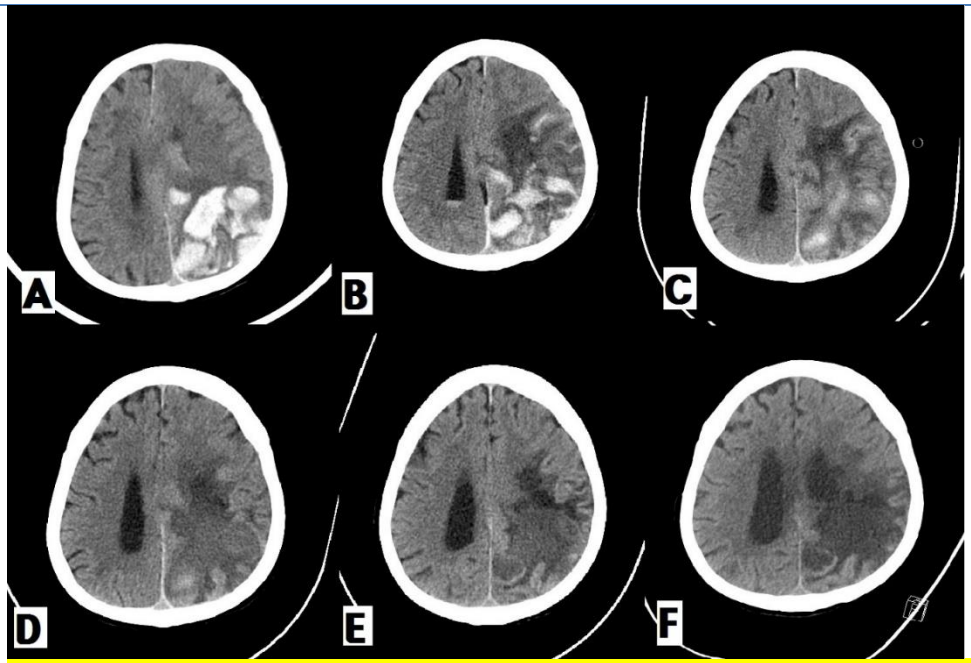

Figure 1. Change in brain computed tomography during hospitalization

A. Brain CT at admission. Intracranial hemorrhage in the parieto-occipital lobe was confirmed, and midline shift was observed due to brain edema.

B. Brain CT on the 8th hospital day. Intracranial hemorrhage persists and concomitant IVH is confirmed.

C. Brain CT on the 17th hospital day. Intracranial hemorrhage has begun to resolve and improvement of IVH is shown.

D. Brain CT on the 28th hospital day. Intracranial hemorrhage shows ongoing resolution, and brain edema has also decreased.

E. Brain CT on the 57th hospital day. Improvement in brain edema has resulted in dilatation of the ventricle and resolution of midline shift.

F. Brain CT on the 82nd hospital day. Encephalomalacic change in the left parietal lobe is confirmed, and there is no evidence of new intracranial hemorrhage.

Table
Befor e
After

Table 1. Laboratory findings during hospitalization

	Baseline	HD 1	HD 2	HD 3	HD 4	HD 5	HD 7	HD 9	HD 11	HD 13	HD 15	HD 17	HD 19	HD 21	HD 48	HD 58	HD 65	HD 77	HD 85	HD 95	HD 108	HD 1
Na (mEq/L)	-	140	140	139	145	150	144	142	144	145	140	135	138	138	142	145	148	139	142	136	139	135
K (mEq/L)	-	3.0	3.0	2.9	3.1	2.8	2.9	2.8	3.4	3.5	3.6	3.6	3.9	3.8	3.8	3.3	3.9	3.0	4.1	4.3	4.1	4.5
Cl (mEq/L)		105	105	106	111	114	111	105	107	110	108	106	108	104	110	107	117	110	114	108	107	102
Cr (mg/dL)	0.7	0.82	0.83	0.84	0.77	0.68	0.68	0.67	0.74	0.64	0.57	0.54	0.53	0.52	0.51	0.58	0.59	0.57	0.55	0.78	0.65	0.68
eGFR(mL/min/1.73m^2)	77	63	62	61	68	77	77	78	72	79	82	83	84	84	85	81	81	82	83	67	78	77
BUN(mg/dL)	-	25.2	21.2	40.5	45.1	38	26.1	24	27.8	24.9	31.3	27.1	30	30.4	23.8	16.1	25.9	15.3	17.5	29.5	20.3	19.3
sOsm (mOsm)	-	302	302	309	323	325	305	308	308	313	305	295	294	296								
pH	-	-	7.356	7.492	7.465	7.491	7.508	7.505	7.492	7.513	7.477	7.473	7.456	7.457								
pCO2 (mmHg)	-	-	33.3	30.5	35.6	36.3	37.3	38.2	39.0	35.1	35.3	34.8	36.6	38.2								
pO2 (mmHg)	-	-	117	108	84.6	109	71.1	137	122	97.1	129	146	100	102								
HCO3- (mmol/L)	-	-	18.1	23.1	25.2	27.5	29.3	29.9	29.6	28.0	25.8	25.2	25.4	26.6								
BE (mmol/L)	-	-	-6.1	0.7	2.1	4.4	6.3	6.7	6.2	5.3	2.8	2.1	2.0	3								
SaO2 (%)	-	-	98.5	98.8	96.9	98.7	95.7	99.0	98.8	97.6	98.7	99.2	97.9	98.2								

Abbreviations: Na= sodium, K= potassium, Cl= chloride, Cr= creatinine, eGFR= estimated glomerular filtration rate, BUN= blood urea nitrogen, sOsm= serum osmolarity, pCO2= partial pressure of carbon dioxide, pO2= partial pressure of oxygen, HCO3-= bicarbonate, BE= base excess, SaO2= oxygen saturation

Comment 3: Why did you use mannitol for such a long period? Mannitol use is mostly limited in a short period and restricted for intracranial pressure control. Hypertonic saline (3-5%) infusion could also be used as an alternative agent as shown in previous studies. Furosemide can be also effective in some cases. Further study is required to assess superiority of mannitol.

Author response 3: We appreciate the reviewer's comments. As mentioned, mannitol is typically used for a short period, and hypertonic saline (3-5%) can be used as a substitute. In this case, it was incidentally observed that mannitol and furosemide administered for ICP control also improved lymphedema of the lower extremity. However, in this case, it was not possible to compare the effects of hypertonic saline, and those effects should be compared using a control group to hypertonic saline in a further study. Please see our responses to your comments below.

DISCUSSION
Before

After

Mannitol therapy might cause electrolyte imbalance, rebound cerebral edema, and kidney failure[12,13,14]. Mannitol use for ICP control in acute stroke is generally short-term (1-2 weeks), but we used the above agents for longer to identify the effects of mannitol on lymphedema. One report found no significant difference in the fatality or severe disability rate between short-term use (1 week) and long-term use (1 month) of mannitol, based on limited data[15]. Since mannitol was applied for a long period in this case, the patients was carefully monitored for complications during hospitalization, including laboratory tests such as blood gas, electrolyte, serum osmolarity, creatinine and BUN (Table 1). Although eGFR decreased to 20% of baseline during the first week after admission, it recovered to the baseline level and was maintained until discharge. Except for this mild, temporary decrease in renal function, no serious complications occurred during hospitalization.

In this case, mannitol was used for 27 days (hospital days 1-27) after admission and then used for an additional 7 days (hospital days 52-58) under close monitoring. Considering that serious side effects are unlikely to occur when used in this way, it is considered appropriate to use within 1 month. However, since these results represent administration in only on patient, it is necessary to verify the appropriate period of use through additional large-scale studies.

Intravenous hypertonic saline solution was reported to have a similar effect to mannitol in ICP control[16]. However, in this case, it was not possible to compare the effects of mannitol with hypertonic saline, and the superior effect of mannitol over hypertonic saline should be confirmed in large-scale, long-term study.

[References]

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Comment 4: Based on this case report what is the suggested refractory lymphedema treatment period according to the authors?

Author response 4: We appreciate the reviewer's comments. As mentioned above, there is a report that serious side effects do not differ significantly between short-term use and long-term use of mannitol, but the evidence is limited [12]. In this case, mannitol was used for 27 days (hospital day 1-27) after admission and then additionally used for 7 days (hospital day 52-58). Considering that serious side effects will not occur when used in this way, it is considered appropriate to use within 1 month. However, since close monitoring is required, it should be used only in the hospitalized state. Also, since it may be effective only in this patient, the effect of mannitol cannot be generalized, and additional large-scale studies are needed to prove it. Please see our responses to your comments below.

DISCUSSION	
Before	
After	In this case, mannitol was used for 27 days (hospital days 1-27) after admission and then used for an additional 7 days (hospital days 52-58) under close monitoring. Considering that serious side effects are unlikely to occur when used in this way, it is considered appropriate to use within 1 month. However, since these results represent administration in only on patient, it is necessary to verify the appropriate period of use through additional large-scale studies.

Comment 5: Treating lymphedema by mannitol and furosemide might be useful; however the harmful effects (brain/heart/kidneys ecc.) cannot be excluded from the provided clinical information. Please give us more information for the patient`s general clinical status at discharge apart from the lymphedema improvement.

Author response 5: We appreciate your comments. During the period of mannitol administration, eGFR temporarily decreased by 20% from the baseline, but soon returned to baseline. At the time of discharge, the patient's laboratory values were Na 133mEg/L, K 4.4mEg/L, Cl 100mEg/L, eGFR 78, Creatinine 0.66 mg/dL, BUN 24.6mg/dL with no severe electrolyte imbalance or acute renal failure. Tracheostomy performed at the early phase of hospitalization was successfully decannulated. However, hemorrhage findings on brain CT persisted, and the patient's state of consciousness had not improved significantly at discharge. Please see our responses to your comments below.

OUTCOME AND FOLLOW-UP	
Before	
After	At the time of discharge, the patient's laboratory values were sodium 133 mEg/L, potassium 4.4 mEg/L, chloride 100 mEg/L, eGFR 78 mL/min/1.73m^2, creatinine 0.66 mg/dL, and BUN 24.6 mg/dL, with no severe electrolyte imbalance or acute renal failure. Tracheostomy performed during the early phase of hospitalization was successfully decannulated. The patient's state of consciousness had not improved significantly at discharge, despite improvement of intracranial hemorrhage and brain edema findings on CT.

To Reviewer: 2

This paper reported an intersting case of refractory lymphedema, which was improved by a combination of mannitol and furosemide. As to this patient, her lower extremity lymphedema improved dramatically after receiving the mannitol and furosemide, but subsequently worsened after the mannitol and furosemide were discontinued. Even though, the conclusion that a combination of mannitol and furosemide could be considered as another effective therapeutic option for refractory lymphedema ineffective on CDT and IPC should be taken cautionally.

Author response: We appreciate the reviewer's valuable comments and have revised the manuscript accordingly. Please see our responses to your comments below.

Comment: For one thing, it is a case report. Secondly, it is a special patient of a 90-year-old female diagnosed with intracranial hemorrhage and refractory lymphedema of the left lower extremity since 1998. It is true that the intervention is effective specially to this patient. However, its efficacy and safety remains unknown to others. In this regard, the conclusion should be adjusted, and the discussion should be modified accordingly.

Author response: We appreciate your comments. As mentioned, this manuscript is a case report describing one patient. In other words, the findings of this manuscript cannot be generalized to larger populations. Additional research is needed to confirm the effectiveness and appropriate period of use of mannitol. Please see our line-by-line responses to your comments below.

DISCUSSION	
Before	There are a few limitations to consider in our case report. First, since pharmacologic agents and CDT were co-administered, the results should be compared only to the effect of mannitol and furosemide. Second, high-dose mannitol therapy necessitates close monitoring because of its side effects, such as congestive heart failure, hyperosmolality, hyponatremia, hypokalemia, and acute renal failure.[8] In the present case, there were no significant complications with mannitol use, but its side effects would need close monitoring in the outpatient setting.

After	There are a few limitations to consider in our case report. First, this manuscript is a case report of one patient. In other word, mannitol may be effective only for this particular patient, and there is a limitation to generalizing it to all patients with lymphedema. Second, since pharmacologic agents and CDT were co-administered, the results should be compared only to the effect of mannitol and furosemide. Thrid, high-dose mannitol therapy necessitates close monitoring because of its side effects, such as congestive heart failure, hyperosmolality, hyponatremia, hypokalemia, and acute renal failure.[8] In the present case, there were no significant complications with mannitol use, but its side effects would need close monitoring in the outpatient setting.

CONCLUSION	
Before	The present case suggests that a combination of mannitol and furosemide could be considered as another effective therapeutic option for refractory lymphedema when CDT and IPC are ineffective. It is a noninvasive treatment option and could be combined with conventional physical therapy. However, further large-scale studies should be followed to clarify the effect of mannitol and furosemide on lymphedema.
After	Although our findings cannot be generalized to a larger population, the present case raises the possibility that a combination of mannitol and furosemide might be an effective therapeutic option for refractory lymphedema when CDT and IPC are ineffective. It is a noninvasive treatment option and could be combined with conventional physical therapy. However, further large-scale studies should be performed to clarify the effect of mannitol and furosemide on lymphedema.