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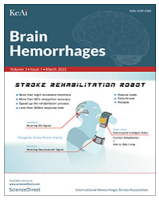

Short Review

Could clazosentan, first approved in Japan, improve neurological prognosis after subarachnoid hemorrhage in combination with modified water-electrolyte management?

Eiji Shikata [a,b,*], Izumi Yamaguchi [a], Masaaki Korai [a], Takeshi Miyamoto [a], Tadashi Yamaguchi [a], Hiroshi Kagusa [a], Kenji Shimada [a], Yoshiteru Tada [a], Keiko T. Kitazato [a], Yasuhisa Kanematsu [a], Yasushi Takagi [a]

[a] Department of Neurosurgery, Graduate School of Biomedical Sciences, Tokushima University, Kuramoto-cho, Tokushima, Japan
[b] Department of Neurosurgery, Takamatsu Municipal Hospital, Busshozan-cho, Kagawa, Japan

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ABSTRACT

An aneurysmal subarachnoid hemorrhage (aSAH) is a devastating event associated with a high mortality and morbidity rate. Though numerous medications are used to prevent cerebral vasospasm and vasospasm-related cerebral infarction after aSAH, no effective pharmacological treatment has been established. Clazosentan, a highly selective endothelin receptor type A antagonist, was approved for use in Japan in April 2022 based on results of two pivotal randomized, placebo-controlled phase 3 studies (JapicCTI-163369, JapicCTI-163368). These studies indicated that clazosentan significantly reduced the incidence of vasospasm-related morbidity and all-cause mortality after aneurysm coiling and clipping. Clazosentan is thus expected to become a "game changer" for improving the neurological prognosis after aSAH. However, other reports indicate that even when clazosentan or nimodipine are administered for prophylaxis against delayed neurological decline, patients treated with increased colloid administration or hypertonic saline (3% sodium chloride) load exhibit poor functional outcome and higher mortality, suggesting that extra fluid and sodium derived from prophylactic colloid administration contribute to negative outcomes after aSAH. Pharmacological treatments such as clazosentan in addition to perioperative management involving delivery of less water and sodium might be crucial for achieving better outcomes than conventional therapy. Based on a literature review, we present here the future perspectives regarding clazosentan and the necessity for modifying management of the water-electrolyte balance by focusing on endothelin-1 and blood–brain barrier disruption.

1. Introduction

An aneurysmal subarachnoid hemorrhage (aSAH) is an uncommon but severe subtype of stroke. Although the survival rate after aSAH has increased due to better diagnosis and advances in intensive care, the daily life of aSAH survivors and their ability to work are strongly impacted.[1] To elucidate the pathophysiologic mechanism of aSAH, an increasing number of studies are examining early brain injury (EBI).[2,3] EBI occurs immediately after bleeding begins. A sudden increase in intracranial pressure (IICP) caused by the extravasation of bleeding in the subarachnoid space results in endothelial damage and neuronal death, in turn leading to the release of various damaged-associated molecular patterns (DAMPs). The released DAMPs are bound by pattern recognition receptors such as Toll-like receptor 4 (TLR4), which leads to recruitment of neutrophils and macrophages to the subarachnoid space. These inflammatory cells destroy erythrocytes and promote inflammatory reactions leading to the release of vasoactive substances such as endothelin-1 (ET-1) and oxyhemoglobin (OxyHb).

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; ET_A, endothelin receptor type A; ET-1, endothelin-1; BBB, blood–brain barrier; EBI, early brain injury; IICP, increase in intracranial pressure; DAMPs, damaged-associated molecular patterns; OxyHb, oxyhemoglobin; CVS, cerebral vasospasm; DCI, delayed cerebral ischemia; ET_B, Endothelin receptor type B; MLC, myosin light chain; TNF-α, tumor necrosis factor–α; PMN-MDSCs, polymorphonuclear myeloid-derived suppressor cells; IL, interleukin; ATP1α3, Na^+/K^+ ATPase.

* Corresponding author at: Department of Neurosurgery, Graduate School of Biomedical Sciences, Tokushima University, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan (E. Shikata).

E-mail address: ninth4kata@yahoo.co.jp (E. Shikata).

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OxyHb directly induces ET-1 production in endothelial cells and vascular smooth muscle cells via protein kinase C–cyclic adenosine monophosphate signaling. ET-1 is a strong vasoconstrictor associated with the pathogenesis of cerebral vasospasm (CVS) and neuroinflammation recognized as delayed cerebral ischemia (DCI).[4]

IICP also complicates blood–brain barrier (BBB) disruption. In response to degradation of the extracellular matrix, matrix metalloproteinases (MMPs) are induced. Although essential for normal biological function, inflammatory activation of these enzymes can promote the breakdown of proteins forming tight junctions between capillary endothelial cells, leading to BBB disruption.[5] Subarachnoid hemorrhaging significantly upregulates both the expression and activity of MMP-9 in the blood and cerebrospinal fluid.[6,7] Deleterious changes in the brain parenchyma due to BBB disruption, such as vasogenic edema, cytotoxic edema, and peripheral innate cell infiltration into interstitial spaces, are easily exacerbated by external impacts such as fluid and sodium infusion, resulting in neuroinflammation.[5,8] Therefore, the blockade of ET-1 receptors and perioperative management practices that will not aggravate the brain damage induced by BBB disruption are essential for increasing the chances of good neurological outcomes after aSAH.

2. Association between ET-1 in early brain injury and CVS and neuroinflammation in DCI

CVS decreases perfusion in the distal tissues due to narrowing, in turn causing ischemic symptoms and cerebral infarction. ET-1–induced vasoconstriction is mediated by two G-protein–coupled receptors: endothelin receptor type A (ET_A) and endothelin receptor type B (ET_B).[9] ET_A in smooth muscle cells actives phospholipase-C, generating diacylglycerol and inositol triphosphate, which in turn stimulate Ca^{2+} release from intracellular stores, ultimately leading to vasoconstriction. In the Ca^{2+}–independent pathway, ET_A in smooth muscle cells also stimulates the small G-protein RhoA. RhoA activates Rho kinase, which then phosphorylates and inactivates myosin light chain (MLC) phosphatase. This in turn increases the proportion of phosphorylated MLC (MLC-P) and thereby promotes further vascular smooth muscle contraction (Fig. 1). In contrast, activation of ET_B in endothelial cells stimulates nitric oxide synthase and prostacyclin synthase to release the vasodilators nitric oxide and/or prostacyclin, respectively.[10,11]

In addition to its adverse effect on vasoconstriction, ET-1 also stimulates interleukin (IL) and tumor necrosis factor (TNF)-α expression in monocytes, leukocyte adherence, platelet aggregation, and adhesion molecule expression, in turn leading to neuroinflammation and microthrombus formation, which are also involved in DCI (Fig. 1).[12–14] Therefore, blockade of the ET-1 receptor using an ET_A antagonist such as clazosentan could avoid the complication of DCI development.

3. Perspectives on clazosentan, first approved in Japan

Clazosentan is a highly selective ET_A antagonist with approximately 1000-fold greater binding affinity for ET_A than ET_B. Clazosentan is highly soluble in aqueous solutions, making it suitable for intravenous (iv) use.[15] Due to the ability to block ET_A, clazosentan has been widely investigated for use in preventing cerebral vasospasm in patients with aSAH (Fig. 1).[16–18] Clazosentan was approved for use in Japan in April 2022 for the prevention of cerebral vasospasm, vasospasm-related cerebral infarction, and cerebral ischemic symptoms after aSAH, based on the results of two pivotal randomized, placebo-controlled phase 3 studies (JapicCTI-163369, JapicCTI-163368).[19]

In addition to the rescue of cerebral vasospasm, blockade of the ET-1 receptor by clazosentan might also attenuate neuroinflammation after aSAH, as ET-1 stimulates IL and TNF-α expression in monocytes and platelets aggregation, leading to neuroinflammation (Fig. 1).[12–14] Zhang et al. reported that the ET_A antagonist BQ123, which exhibits high binding affinity for ET_A similar to clazosentan, suppresses allergic airway inflammation by decreasing the production of type 2 cytokines, the expression of which is

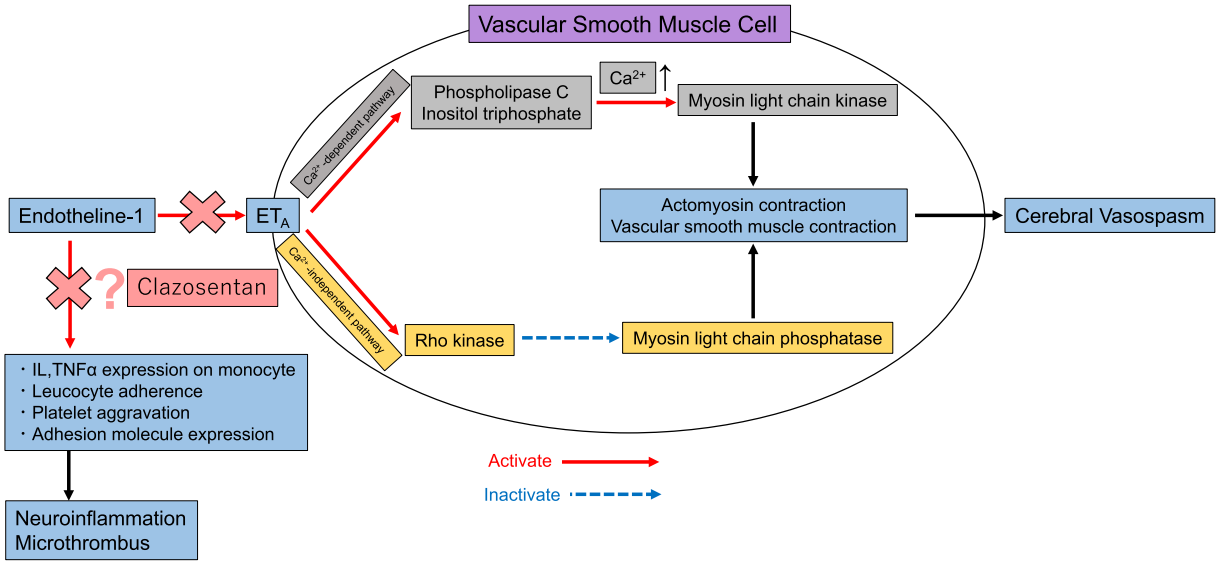

Fig. 1. Possible mechanism of cerebral vasospasm, neuroinflammation, and microthrombus formation caused by endothelin-1 and the possible effect of clazosentan. Vasoconstriction induced by ET-1 in smooth muscle cells is mediated via both Ca^{2+}-dependent and Ca^{2+}-independent pathways. In the Ca^{2+}-dependent pathway, phospholipase-C and inositol triphosphate activated by ET_A receptor increase intracellular Ca^{2+} levels, which activate myosin light chain (MLC) kinase, leading to vascular smooth muscle cell contraction. In the Ca^{2+}-independent pathway, ET-1 also activates Rho kinase, which in turn inactivates MLC phosphatase, leading to vascular smooth muscle cell contraction. Clazosentan probably suppresses not only vasospasms but also neuroinflammation and microthrombus formation by competing with ET-1, which stimulates IL and TNF-α expression in monocytes, leukocyte adherence, platelet aggregation, and adhesion molecule expression. ET-1: endothelin-1; MLC: myosin light chain; IL: interleukin; TNF-α: tumor necrosis factor–α.

increased by group 2 innate lymphoid cells.[20] Another study reported that the accumulation of T-cell–dependent polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) activated by BQ123 in the colon, lung, and liver attenuate inflammation in mice.[21] As the number of PMN-MDSCs is also increased in the ischemic hemisphere 72 h after transient middle cerebral artery occlusion in mice, treatment with an ET_A antagonist could restrain the development of neuroinflammation in the cerebral parenchyma with hypoperfusion under IICP after aSAH.[22]

However, clazosentan can notably increase the risk of pulmonary edema in addition to the neurologic pulmonary edema caused by aSAH, which reportedly occurs in 2–31 % of cases.[23] An updated *meta*-analysis of 6 randomized controlled trials directly comparing the use of clazosentan and placebo for the treatment of cerebral vasospasm after aSAH suggested that the incidence of pulmonary adverse events was significantly increased by clazosentan compared with placebo.[24] Lung fluid balance is actively regulated by the distal lung epithelium under both normal and pathological conditions. Sodium ions in alveolar fluid are taken up into epithelial cells (type I and type II alveolar cells) via apical epithelial sodium channels and actively transported to the interstitium by basolateral Na^+-K^+ ATPase. Water (H_2O) moves down the osmotic gradient through aquaporin channels, such as aquaporin 5, to the interstitium (Fig. 2a).[25] In models of lung injury, ET-1 binds to ET_B in pulmonary microvascular endothelial cells, releasing nitric oxide, which downregulates Na^+-K^+ ATPase function in alveolar epithelial type I and type II cells. As a result of decreased alveolar reabsorption, high-altitude pulmonary edema is induced.[26] Though ET_A blockade by ET_A antagonists conversely activates ET_B, it might indirectly increase vascular permeability and induce exaggerated fluid retention (Fig. 2b).[27] These observations could explain the mechanism by which clazosentan aggravates pulmonary edema.

4. The risk of excessive fluid and sodium administration to the brain associated with BBB disruption and pulmonary edema after aSAH

Excessive fluid and sodium administration can exacerbate EBI as well as systemic complications such as pulmonary edema. Through BBB disruption, excessive water floods into interstitial spaces, resulting in exacerbation of vasogenic and cytotoxic edema.[5] Not only the inflow of water but also inflow of sodium into the interstitial spaces can aggravate cytotoxic edema and neuroinflammation. We reported that in rat brain parenchyma harboring cerebral aneurysms prone to rupture, a high-salt diet is associated with down-regulation of ATP1α3, a neuronal subtype of the Na^+ efflux pump, resulting in accumulation of water-free sodium. Down-regulation of ATP1α3 is similarly observed in the brain parenchyma with a ruptured aneurysm.[28] This may indicate that brain cells under aSAH exhibit impaired exclusion of intracellular sodium into the extracellular space and that sodium administration can easily aggravate the cytotoxic edema. Further, disruption of the BBB, unlike typical vessel walls, allows peripheral lymphocytes to infiltrate into interstitial spaces with activation of microglia in the central nervous system, leading to release of proinflammatory cytokines such as IL-6 and TNF-α and ultimately neuroinflammation (Fig. 3).[12–14] Hucke et al. reported that a high-salt diet significantly increases macrophage infiltration in the central nervous system (CNS) and affects the activation status of CNS myeloid cells (monocytes/macrophage) in an animal model of multiple sclerosis, in which BBB disruption was induced by immunization with myelin oligodendrocyte glycoprotein(MOG) peptide and pertussis toxin.[29]

The toxicity of increased fluid and sodium administration after aSAH has been reported in both fundamental research and clinical practice. Ibrahim et al. reported an unfavorable

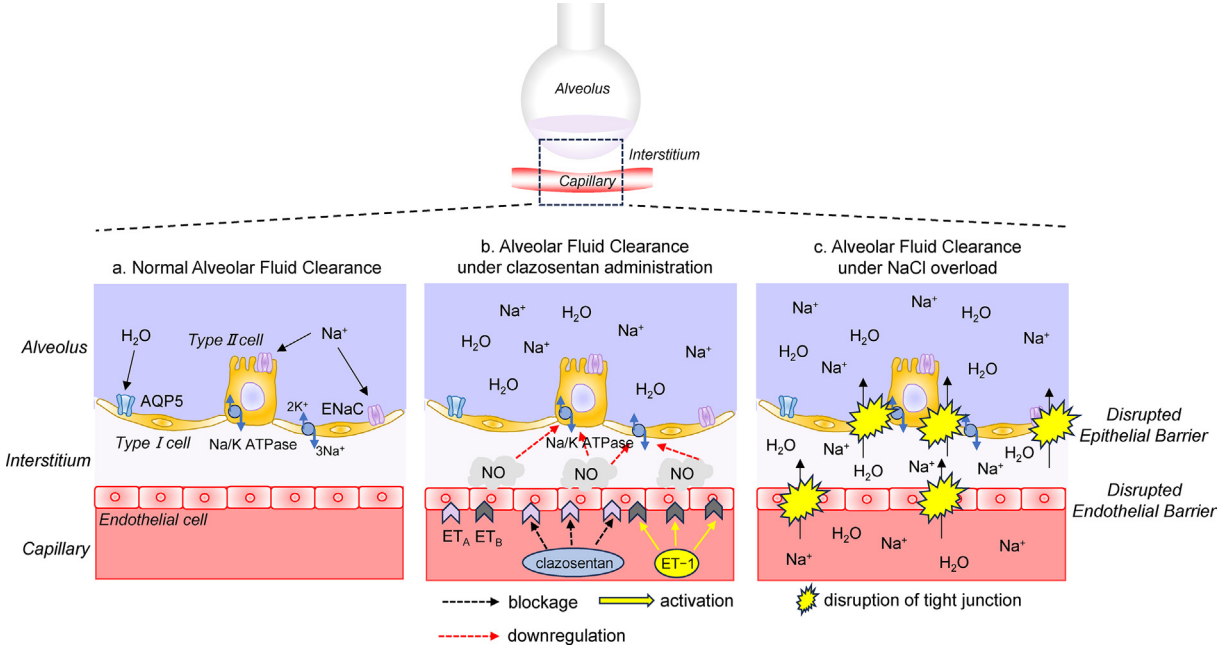

Fig. 2. Normal alveolar fluid clearance and the possible mechanism of pulmonary edema induced by clazosentan and sodium overload In normal alveolar clearance, sodium ions in alveolar fluid are absorbed into type I and type II alveolar cells via apical epithelial sodium channels (ENaCs) and actively transported to the interstitium by basolateral Na^+/K^+ ATPase. Additional cation channels also transport ions across the alveolar epithelium (not shown). Water (H_2O) moves down through aquaporin 5 to the interstitium according to the osmotic gradient. ENaC: epithelial sodium channel Clazosentan could increase the risk of pulmonary edema. Blockage of ET_A by clazosentan might indirectly activate ET_B. ET-1 binds to ET_B in pulmonary microvascular endothelial cells, releasing nitric oxide (NO), which downregulates Na^+/K^+ ATPase function in type I and type II alveolar cells. Decreased alveolar reabsorption could induce high-altitude pulmonary edema. ET_A: endothelin receptor type A; ET_B: endothelin receptor type B; NO: nitric oxide Disruption of the microvascular endothelial barrier from exposure to high levels of sodium increases permeability to fluids, which then fill the interstitium. Disruption of the alveolar epithelial barrier also increases the permeability to interstitial fluid that floods the alveolus, resulting in pulmonary edema.

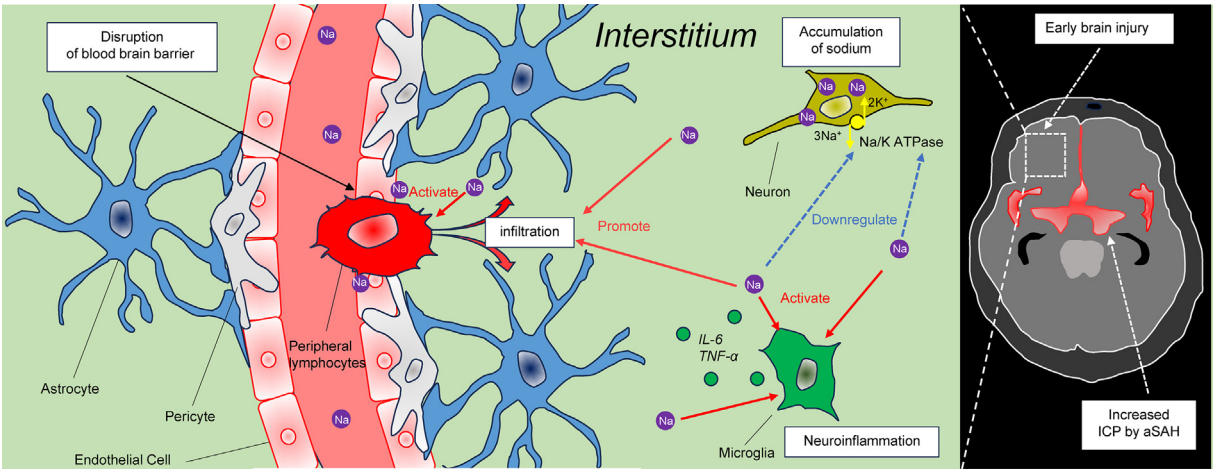

Fig. 3. The impact of sodium overload in the brain with early brain injury Through disruption of the BBB caused by IICP, peripheral lymphocytes infiltrate into the interstitial spaces. Though water as well as sodium also flood into interstitial spaces, sodium activates peripheral lymphocytes and promotes their infiltration. Sodium also stimulates microglia in the CNS, which release IL-6 and TNF-α, leading to neuroinflammation. In the brain cells including neurons under aSAH, Na^+/K^+ ATPase is down-regulated in association with sodium accumulation. These cells exhibit difficulty in excluding intracellular sodium into the extracellular space, which aggravates cytotoxic edema. Sodium overload can exacerbate such pathological conditions as neuroinflammation and cytotoxic edema.

opinion of the effect of clazosentan under a positive fluid balance and excessive colloid administration. In patients treated with clazosentan, a positive fluid balance and excessive colloid administration were associated with poor functional outcomes.[30] Other reports also supported a relationship between poor outcome and positive fluid balance and high fluid intake after aSAH.[31–35] These studies highlight the importance of fluid management involving delivery of less water than previously recommended in order not to exacerbate cytotoxic and vasogenic edema following disruption of the BBB, keeping a distance from pharmacological management.

With regard to sodium, Hoffman et al. reported that hypernatremia was associated with poorer outcomes regardless of aSAH severity in a nationwide inpatient sample analysis. Patients with hypernatremia had a significantly higher rate of pulmonary complications and acute kidney injury.[36] Chua et al. also reported that overall mean serum sodium levels were significantly higher in patients who had neurological deterioration and poor functional outcome (mRS 3–6), even if they had received nimodipine for prophylaxis against delayed neurological decline, despite administration of isotonic saline and hypertonic saline (3 % sodium chloride) to manage fluids and electrolytes.[37] Regarding hydrocephalus, higher serum sodium, lower serum potassium, and higher glucose levels from postoperative days 1 to 12–16 were shown to be related to higher shunt-dependent hydrocephalus in univariate and multivariate Cox regression analyses to calculate hazard ratios for shunt-dependent hydrocephalus based on clinical and laboratory data.[38] In terms of impact on pulmonary edema, microvascular endothelial barrier permeability and alveolar epithelial barrier permeability from exposure to high levels of sodium in the lungs potentially increases the risk of edematous fluid influx, hypoxia, and death (Fig. 2c).[39] Even in healthy volunteers, bolus intravenous 0.9 % saline caused interstitial permeability pulmonary edema.[40,41] Therefore, sodium load potently exacerbates pulmonary edema, which is particularly problematic given that both aSAH and clazosentan easily cause pulmonary edema. Sodium toxicity can be highly stressful both to the brain following BBB disruption and to the systemic organs after aSAH.

Treatment protocol	Water management		Serum sodium management
	Daily drip Infusion comprised of saline (S), Ringer's acetate (RA) and maintenance fluid (MF)	**Additive infusion for water balance**	
Protocol 1. Group 1 (n=33)	Median amount Water 3.0 l NaCl 17.5 g (S+RA:MF=2.5~5:1)	Ringer's acetate	drip infusion of 10% NaCl
Protocol 2. Group 2 (n=22)	Median amount Water 2.0 l NaCl 9.5 g (S+RA:MF=1~2:1)	Maintenance fluid	oral administration of salt

Components of infusion; Saline; Na^+ 154 mEq/l, Cl^- 154 mEq/l;
Ringer's acetate; Na^+ 131 mEq/l, K^+ 4 mEq//l, Cl^- 109 mEq/l;
Maintenance fluid; Na^+ 35 mEq/l, K^+ 20 mEq/l, Cl^- 35 mEq/l

Fig. 4. Description of the protocols All 55 operated aSAH patients were treated under protocol 1 (group 1, n = 33) or protocol 2 (group 2, n = 22) postoperatively. In protocol 1, Ringer's acetate was added for water balance. NaCl (10 %) was drip-infused for hyponatremia. In protocol 2, maintenance fluid was delivered for water balance, and NaCl (salt) was administered orally for hyponatremia. In protocol 2, the amount of NaCl used was based on the following equation: body weight (kg) × 0.6 × (last recorded – current serum sodium concentration [mEq/L])/17Na: sodium; K: potassium; NaCl: sodium chloride Revised from Fig. 1 of our publication World Neurosurg. 2019;129:e352-e360.

In summary, the unnecessary administration of fluid and sodium strongly exacerbates neuroinflammation and systemic complications simultaneously, even if pharmacological treatment is properly applied after aSAH.

5. Modified water-electrolyte management by delivery of an optimal minimum amount of water and sodium to prevent DCI after aSAH

Overall, current data indicate a critical need to manage water-electrolyte balance by delivery of the optimal minimum amount of water and sodium after aSAH to maximize the effectiveness of clazosentan. However, it is rather difficult to maintain euvolemia and eunatremia simultaneously by administering less water and sodium than before. To resolve this issue, we previously showed that the independent delivery of the required amount of water and sodium could improve neurological prognosis, maintaining euvolemia and eunatremia at the same time.[42] We recruited 55 consecutive patients who had undergone clipping or endovascular coil embolization after aSAH. Group 1 (n = 33) received conventional therapy based on triple H. Group 2 (n = 22) received the optimal amount of water and sodium separately (Fig. 4). Patient background characteristics, including severity of aSAH, did not differ significantly between the two groups. Both groups were treated with fasudil hydrochloride and ozagrel sodium. Group 2 exhibited a significantly lower median total of drip infusion and sodium chloride contained in it through postoperative day 8 compared to group 1 ($p < 0.01$) (Fig. 5), resulting in a much lower rate of symptomatic vasospasm and/or shunt-dependent hydrocephaly ($p < 0.005$) (Table 1). The modified Rankin scale score at discharge was 0–2 in 21 patients (95 %) in group 2 and 18 patients (55 %) in group 1 ($p < 0.001$) (Table 1). This indicated that the separate delivery of optimal amounts of water and sodium could be a promising therapeutic strategy to increase the chances of a good outcome after aSAH. Water-electrolyte management strategies such as this might be compatible with clazosentan because clazosentan could be ineffective under conditions of increased fluid administration.

6. Conclusion

Clazosentan could become a ‘‘game changer” for improving the neurological prognosis after aSAH. However, perioperative management aimed at not compounding EBI is also important, apart from pharmacological approaches.

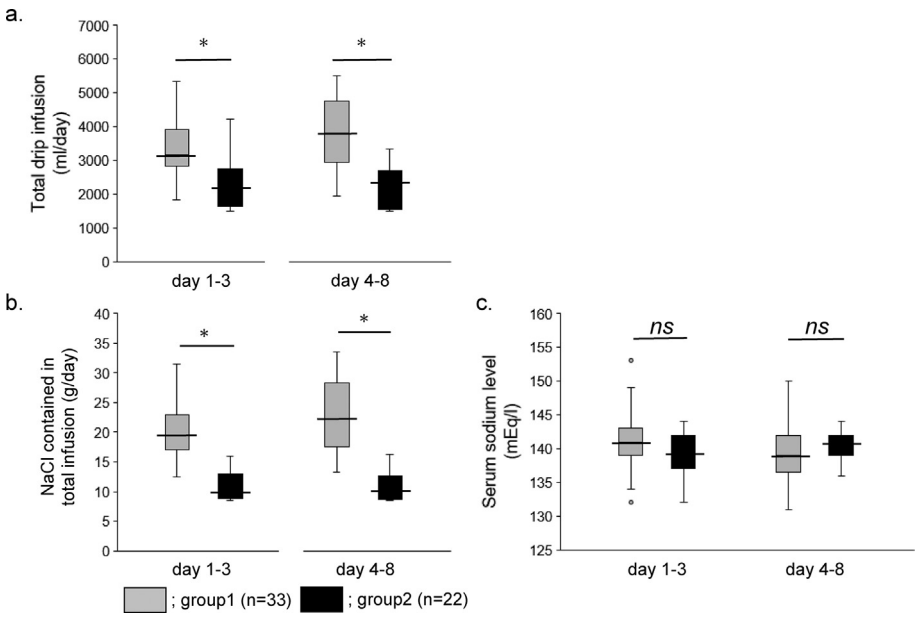

Fig. 5. Total infusion volume (a) and amount of sodium chloride (b) included in the total infusion delivered on days 1–3 and 4–8 In both groups, the serum sodium level was similar and within the normal range throughout the 8-day observation period (c). Horizontal bars and columns show the median and interquartile range, respectively, in (a), (b), and (c). *: $p < 0.001$ by the Wilcoxon rank sum test. Serum sodium levels on days 1–3 and 4–8 were compared using the Student's *t*-test. Na: sodium; NaCl: sodium chloride Revised from Fig. 3 of our publication World Neurosurg. 2019;129:e352-e360.

Table 1
Incidence of symptomatic cerebral vasospasm, shunt-dependent hydrocephalus, and modified Rankin scale at discharge.

		Group 1 (n = 33)	Group 2 (n = 22)	p-value
(a) Symptomatic vasospasm, n (%)		6 (18 %)	0 (0 %)	0.071
(b) Shunt dependent hydrocephalus, n (%)		8 (24 %)	0 (0 %)	0.016*
(a) and/or (b)		11 (33 %)	0 (0 %)	0.002*
Modified Rankin Scale, n (%)				
	0–2	18 (55 %)	21 (95 %)	
	3–6	15 (45 %)	1 (5 %)	<0.001*

*: $p < 0.05$.
p-values: Fisher's exact test.
Revised of our publication: Table 2. World Neurosurg. 2019;129: e352-e360.

CRediT authorship contribution statement

Izumi Yamaguchi: Data curation. **Tadashi Yamaguchi:** Investigation. **Hiroshi Kagusa:** Formal analysis. **Kenji Shimada:** Investigation. **Yoshiteru Tada:** Investigation. **Keiko T. Kitazato:** Conceptualization. **Yasuhisa Kanematsu:** Supervision. **Yasushi Takagi:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Statement

This review article does not contain any studies with human participants or animals performed by any of the authors.

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