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Review

Efficacy of the anti-seizure medications in acute symptomatic neonatal seizures caused by stroke. A systematic review

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Abstract. *Background and aim:* Neonatal stroke is the second cause of acute symptomatic neonatal seizures after hypoxic-ischemic encephalopathy. The aim of this systematic review is to determine which drug among those available represents the best therapeutic choice for treatment of secondary seizures due to neonatal stroke. *Methods:* We performed a systematic review searching on PubMed the keywords "Neonatal", "Stroke", "Seizures" and "Treatment". Search was limited only to English language with no time limit. Last literature search was done on May 30, 2022. *Results:* We selected 5 articles involving a total of 52 full-term neonates. In 96.1% the first line treatment was phenobarbital and in 3.9% was used phenobarbital associated with midazolam from the seizure onset but in all of these cases it was necessary to introduce further medications for controlling the seizures. As second line treatment was used lidocaine (response rate of 53.3%), midazolam (response rate of 15.38%) bumetanide (response rate of 100%), and fosphenytoin (no response). As third line treatment was used lidocaine (response rate of 87.5%), Midazolam (response rate of 60%), levetiracetam and clonazepam (response rate of 100%). *Conclusions:* Our review shows that the use of ASMs that act throughout a gabaergic mechanism are inadequate in controlling seizures secondary to neonatal stroke in full-term newborns. Very effective seems to be lidocaine and levetiracetam with an apparent safer profile in short and long term. Bumetanide shows promising results, but they need to be confirmed by phase 3 studies. (www.actabiomedica.it)

Key words: Neonatal seizures, Stroke, Seizures, Anti-seizure medication

Introduction

Acute symptomatic neonatal seizures represent the most important and frequent acute neurological disorder in neonatal intensive care units. Neonatal stroke is the second etiology of neonatal seizures after hypoxic–ischemic encephalopathy in term infant (1). The usual clinical presentation is with focal motor clonic seizures during the first 12-72 hours of life that can be recognized up to 90% of patients and typically resolve during the neonatal age but post-neonatal epilepsy develops in about 70% of them in the later ages (2). Of interest, neonatal stroke can happen with an incidence reported of about 1:1600-4000 neonates at birth (2). Neonatal

stroke is also classified as neonatal arterial ischemic stroke, neonatal hemorrhagic stroke, and cerebral sinovenous thrombosis. In about of 80% of cases, stroke is secondary to ischemic damage (arterial or venous) and in 20% stroke is caused by cerebral sinovenus thrombosis or parenchymal hemorrhage (2). Neonatal stroke can be associated to several conditions: 1) maternal factors such as infection, thrombophilia, preeclampsia, cocaine use or smoking; 2) fetal/infant factors such as infection thrombophilia, congenital heart disease, low APGAR score at birth, use of forces on head and neck; 3) placental factors like infarction, abruption, insufficiency and chorioamnionitis (2). However, in many patients the etiology may remain unknown and the precise mechanisms with which the several risk factors above mentioned cause stroke are not completely understood yet. Acute symptomatic neonatal seizures can be provoked by perinatal stroke and sometimes evolve in status epilepticus (3). It is unknown if treatment of the neonatal seizures could improve the outcome (4), and if neonatal seizures can increase the long-term effects of their underlying cause (5). In the acute phase of the stroke, recurrent seizures increase the metabolic demand in ischemic penumbra worsening the brain injury (6). Several studies suggest that neonatal seizures per se can be harmful to the immature brain especially those prolonged (5). Prolonged acute symptomatic seizures likely contribute to long-term outcomes by independently adding further injury to the initial insults (7,8). Therefore, the treatment of the seizures especially of the status epilepticus can play a potential role in minimizing the injury in affected neurons (9,10). Currently anti-seizure medications (ASM) used in these patients are phenobarbital (PB), midazolam (MDZ) and lidocaine (LD) however, in literature no clear indications about the use of one specific ASM are reported (11).

The purpose of this systematic review is to determine whether there are some evidences of a better efficacy and safety of a specific ASM in the treatment of neonatal seizures due to neonatal stroke.

Methods

We performed a systematic review searching on PubMed the keywords "Neonatal", "Stroke", "Seizures" and "Treatment". Search was limited only to English language manuscripts with no time limit. The literature search was last done in June 2022. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed while conducting the study.

The full texts examined after the first screening of the abstracts were read by the Authors and data were extracted and discussed to assess the quality of the studies. Articles were included if they fully reported cases of neonatal stroke in full-term newborns with complete information about perinatal history, seizure development and type of ASM used and dosages. We included case reports, retrospective studies, and a randomized-controlled double-blind trials. We excluded studies describing only clinical features of the seizures with incomplete information about ASM or with incomplete information about perinatal clinical history (Fig. 1).

Results

We selected a total of 5 articles, namely one double blind trial, two retrospective studies and two case reports, regarding a total of 52 full-term newborns with a diagnosis of neonatal stroke and acute symptomatic seizures that occurred during the first days of life. To define if an ASM has shown a better efficacy in the control of neonatal seizures, we analysed the type of ASM used as either first, second or third line, its dosage and efficacy. Efficacy was considered as total when seizures completely stopped, partial when seizures were still present after first line ASM and require the use of a second line ASM, and absent when the seizures where either controlled or not after the introduction of a third line ASM. Furthermore, the presence of side effects due to ASM was noted when the datum was available.

The results are summarized in Table 1.

1. *First line treatment and efficacy*

   In 50/52 (96.1%) the first line treatment was PB with a dosage between ≥ 20 mg/kg and 40 mg/kg (12,13,15) and in two cases (3.9%) was used PB at dosage between ≥ 20 mg/kg

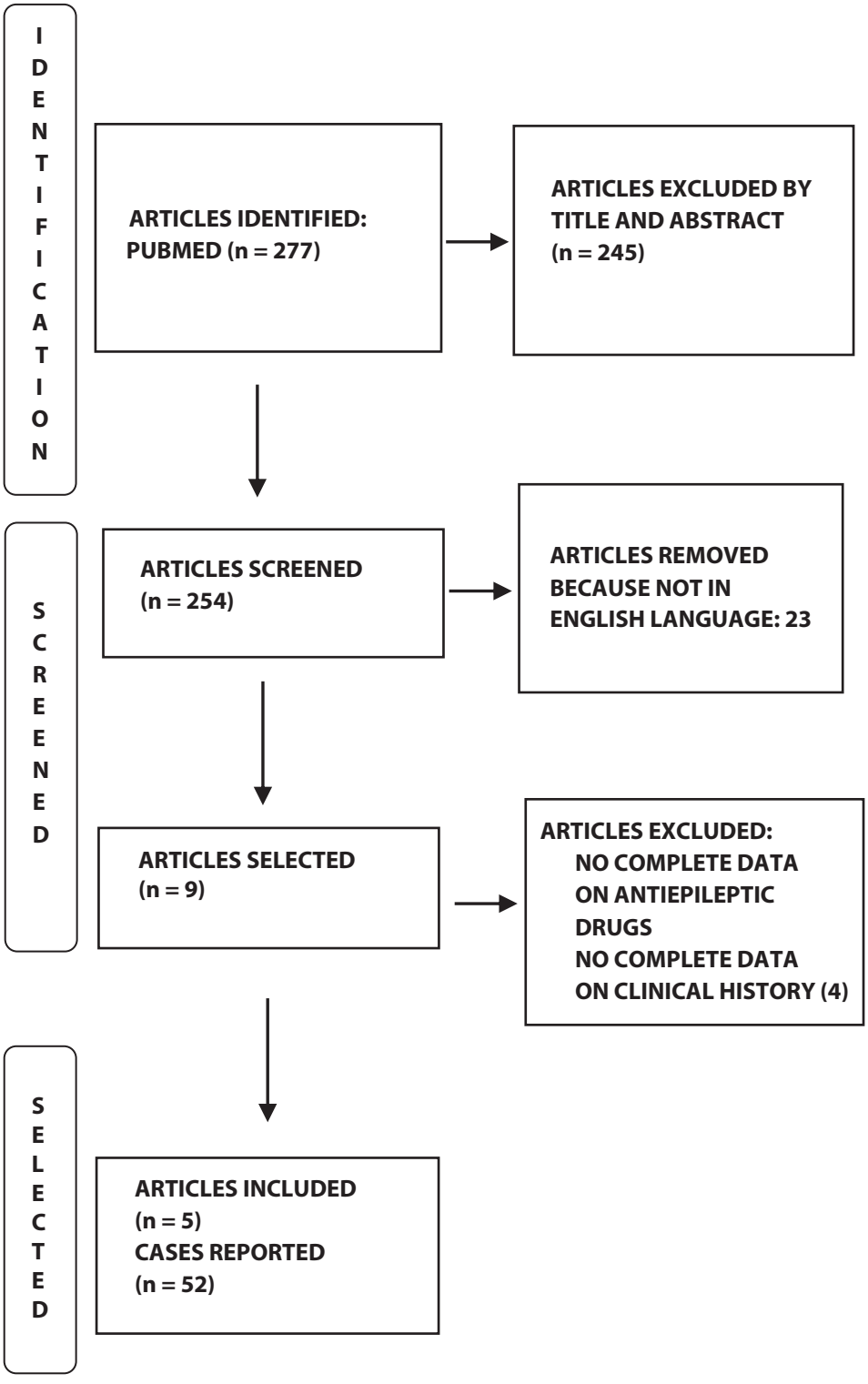

Figure 1. Full text selection.

Table 1. Articles examined.

Authors	Year	Type of study	Number of patients	First line treatment	2nd or 3th line treatment: (n=patient treated)	Dosage of the drug (n=patient treated)	Response rate to second or third line drugs	Side effects
Janet et al. (12)	2021	Randomized Controlled Double-Blind Trial	7	Phenobarbital 20-40 mg/kg	Bumetanide (2nd): N=7	Bumetanide 0.1mg/kg (N=4) Bumetanide 0.2mg/kg (N=3)	100% 100%	No
Weeke et al. (13)	2016	Retrospective study	32	Phenobarbital 20 mg/kg	Lidocaine (2nd): N=11 Lidocaine (3th): N=26 Midazolam (2nd): N=18 Midazolam (3th): N=5	Midazolam 0.05 mg/kg than 0.15-0.5 mg/kg/h Lidocaine: 2 mg/Kg than 6 mg/kg/h (6h), than 4 mg/kg/h (12h); than 2 mg/kg /h (12 h)	Lidocaine 2nd: 45.5% Lidocaine 3th: 84.6% Midazolam 2nd: 11.1% Midazolam 3th: 60%	No
Shoemaker et al. (14)	2007	Case report	1	Phenobarbital 20 mg/Kg and Midazolam 0.1 mg/kg	fosphenytoin (2nd) Levetiracetam (3th)	fosphenytoin 12.5 mg/Kg Levetiracetam 60 mg/kg	Fosphenytoin: 0% Leveritacetam 100%	No
Jennekens et al. (15)	2012	Retrospective	11	Phenobarbital 20-30 mg/Kg	Midazolam (2nd): 8 Lidocaine (2nd): 3 Lidocaine (3th): 6	Midazolam 0.05 mg/kg than 0.15-0.2 mg/kg Lidocaina 2 mg/Kg than 6-4-2 per 6-12-12	Midazolam: 25% Lidocaina 2nd: 100% Lidocaina 3th: 100%	No
Govaert et al. (16)	2008	Case report	1	Phenobarbital 40 mg/Kg and Midazolam 0.1 mg/kg	Lidocaine (2nd) Clonazepam (3th):	Lidocaine 4 mg/kg/h Clonazepam 0.3 mg/d	Lidocaine 0% Clonazepam 100%	No

and 40 mg/kg together with MDZ at a dosage of 0.1 mg/kg (14,16) from the seizure onset. In all patients, first line treatment was ineffective and further ASMs were necessary to control seizures (Fig. 2).

2. *Second line treatment and efficacy*

In 7/52 (13.5%) patients, bumetanide was used with a total efficacy (12). In 15/52 (28.8%), LD was used at a loading dose of 2 mg/kg then 6 mg/kg/h for the next six hours. After this time period, discontinuation of LD was started with a reduction of 2 mg/kg/h every 12 hrs. This therapy showed a total efficacy in 8/15 patients (53.3%) (13,15,16). In 26/52 patients, (50%) MDZ was used with a loading dose of 0.05 mg/kg then 0.15-0.5 mg/kg/h with a total efficacy in 4/26 newborns (15.38%) (13,15). Fosphenytoin was used in one newborn at the dosage of 12.5 mg/kg without efficacy (14) (Fig. 2).

3. *Third line treatment and efficacy*

Lidocaine was used as third line ASM in 32/52 (61.5%) newborns with the following scheme: 2 mg/kg then 6 mg/kg/h per 6 hrs, then with a reduction of 2 mk/kg every 12 hrs and in one case at the dosage of intravenous infusion of 4 mg/Kg/h with a total seizure control in 28/32 newborns (87.5%) (13,15). Midazolam was used in 5 subjects (9.62%) at the loading dose of 0.05 mg/kg

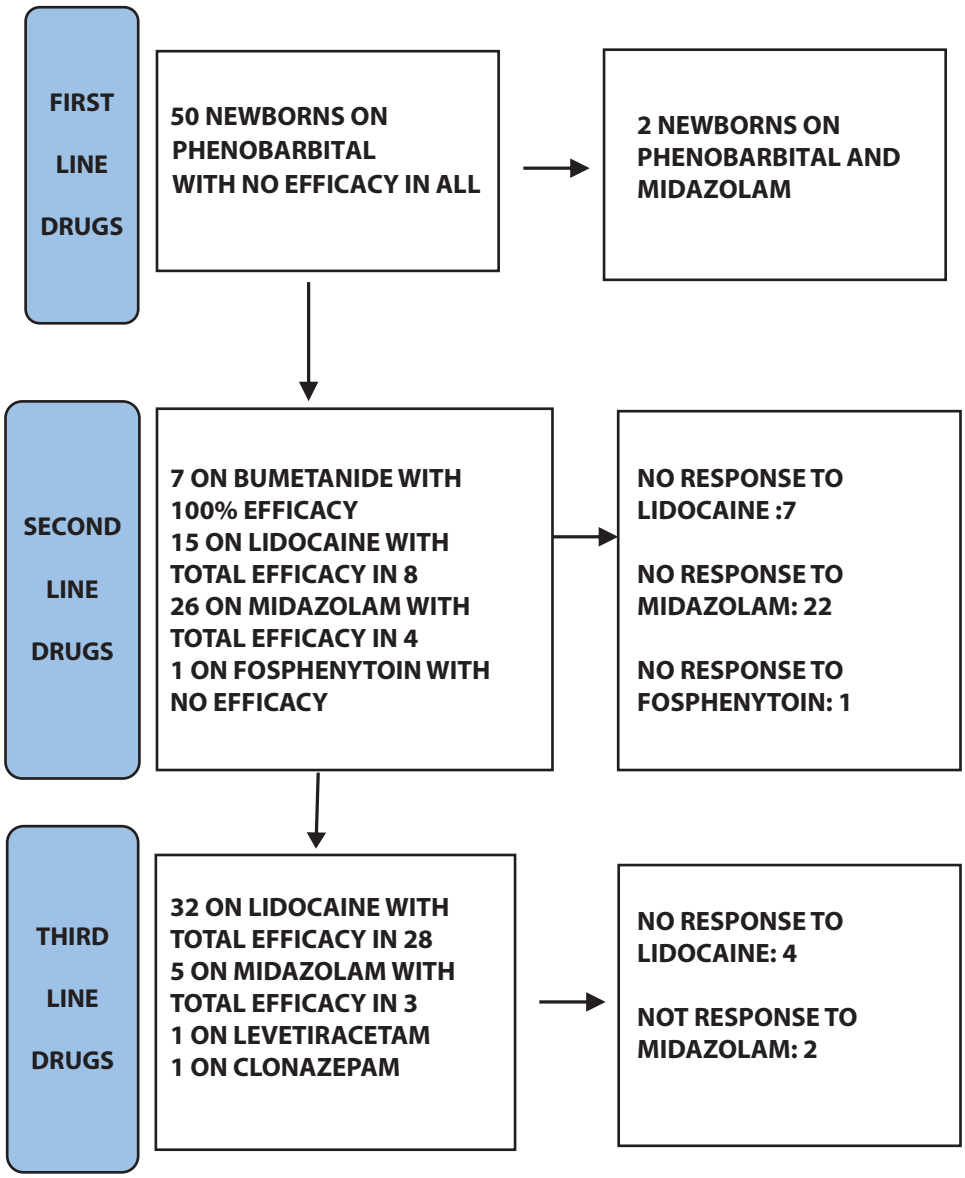

Figure 2. Antiseizure medications used.

then 0.15-0.5 mg/kg/h with a total efficacy in 3 cases (60%) (13). In one newborn, levetiracetam (LEV) at 60 mg/kg determined a control of the seizures (14) and in another patient the same efficacy was obtained with clonazepam at 0.3 mg/d i.v. (16) (Fig. 2).

4. *Side effects of Anti-seizure Medications*

In all studies evaluated, there were no reported side effects related to the use of ASM.

Discussion

Control of seizures in neonatal intensive care units is one of the most important challenge for physicians in order to reduced short and long-term consequences on the brain development. Worldwide, PB is the most used ASM (17) regardless of the etiology of seizures. For those seizures that do not respond to first line treatment, phenytoin (18,19), MDZ (18,20-23), LD (20,24,21), clonazepam (20) and LEV (25,26)

are used as either second or third line drugs. However, the most frequently used ASMs as third line are MDZ (21,27,22) and LD (28,29–31,32,33). The aim of our work was to establish from the published reports selected which of these drugs was the most effective in the treatment of the seizures in full-term newborns with stroke. In all patients selected from our systematic review, PB has always been ineffective and the use of a second line ASM for controlling the seizures was needed. Phenobarbital is a positive allosteric modulator of GABA-A receptors and its action is due to increases the flow of ione Cl into the post synaptic neurons. In addition, several studies have shown that PB may have long-term side effects on neurocognitive development (33,34,35) and preclinical studies have shown the poor efficacy of drugs acting on the GABA system such as PB and benzodiazepine due to the poor development of inhibitory systems in the immature brain (36,37). When PB is used as first line therapy its response rate is between 43.3 and 50% (19,20). In only two cases, PB and MDZ were used together from the seizure onset as first-line drugs but without achieving seizure control (16). Therefore, our analysis confirms the partial efficacy of PB in the treatment of seizures due to stroke in term newborns because an additional treatment was required in all patients.

Lidocaine and MDZ were used as second-line treatments with a better response for LD in controlling neonatal seizures compared to MDZ (53.3% vs 15.3%) and the same greater efficacy was confirmed when LD was used as third-line treatment (87,5% vs 60%). Lidocaine is a common anesthetic that acting blocking the sodium channel on the neuronal membrane and can be used to treat seizures. On literature its response rate is between 40% and 50% (20,21,24) when it is used as second line treatment and 62-91% when it is used as third line (28, 32). Midazolam is a benzodiazepine that acts on GABA-A receptors increasing the ione Cl flow into the neurons to determinate hyperpolarization. The response rate in seizure control is between 0% an 100% when it is used as second line treatment (20,18) and 50%-73.3% when it is used as third line medication (21,27). The higher rate in seizure control of LD when it is used either as second or third line treatment can be due to a synergistic mechanism where the hyperpolarization of the neuron due to its effect on GABA-A receptors and the block of sodium channels determines a prolonged refractory period (13).

In only one study, fosphenytoin was used as second line treatment but without stopping the seizures. This drug is the precursor of phenytoin, an agent that can act blocking the Na channels in neurons membranes, and it is usually used intravenously to treat seizures as first line medication with a response rate of 44.8% (19). However, when it is used as second line drug a response rate between 26.6 and 53.1% was reported (19,18).

Of interest, either LEV and clonazepam resulted in a full seizure control but their used was reported only in one patient respectively. However, the clonazepam is rarely used because of its potential side effects with coughing, difficulty breathing, increasing salivation. Furthermore, animal models demonstrate how the administration of clonazepam may lead to changes in the expression of GABA-A channel during life especially in hippocampus and it may represent the neurobiological base of emotional behavior and cognitive dysfunction and development of anxiety (38).

LEV is becoming increasingly used and this is mainly due to its availability for the intravenous administration and because apparently without severe adverse effects. In fact, a recent study demonstrates a better short-term neurological outcome in neonates treated with LEV compared to newborns treated with PB evaluated using the Hammersmith Neonatal Neurological Examination (39).

In contrast to PB, LEV has not any pro-apoptotic action on developing brain and its use is safe also at high dosage (40). So, it is becoming increasingly used even as a first-line treatment but its efficacy is still unclear. In fact, in an open labeled, randomized controlled trial realized to compare the efficacy and safety of LEV versus PB in the treatment of neonatal seizures (41), a better efficacy of LEV was seen. However, in another multicenter, randomized, blinded, controlled, phase IIb trial investigating the efficacy, and safety of LEV compared with PB as a first-line treatment for neonatal seizures of any cause (NEOLEV2) (42), PB demonstrates to be more effective in controlling neonatal seizures compared to LEV. The limitations of these studies were the small sample size, the short-term

outcome and the lack of homogeneity in the protocols used for the pharmacological seizures treatment. So, further studies are needed before making definitive guidelines on the use of these two drugs.

Janett et al. in their trail (12), proposed the use of bumetanide, a diuretic that blocks Na-K-Cl cotransporter NKCC1 and is highly expressed in the developing cortical neurons (43) as a second-line drug after conventional use of PB with a total efficacy. However, these results are coming from a phase II controlled trial study and further confirming data are therefore needed. Furthermore, bumetanide has already been used for the treatment of the neonatal seizures in the NEMO trial, but the study was stopped because of the severe side effects especially due to ototoxicity (44).

Another interesting aspect is the interaction of ASMs with the EEG background activity. Jennekens at al. analyzed the spectral aEEG after the ASMs administration and they found that MDZ caused moderate suppression of EEG activity after the first administration. Instead, LD generated a milder suppression of background activity and its inhibitory action is more evident in stroke-affected region of the brain. This evidence could suggests LD as more appropriate ASM in babies with stroke (15) because its more evident action in the affected hemisphere without inducing aEEG background pattern suppression.

It is very important to note that no major side effects directly related to the use of a specific ASMs were reported in the studies examined. This is probably partially due to the severity of the disease in some cases that often require intubation and profound sedation that can cover some potential side effects. Furthermore, there are lack of information on these aspects often reported concisely and in some cases the need of a polytherapy makes not easy to distinguish if a side effect is due to ASM or to other drugs (44).

Limits

The main limitation of the study is due to the heterogeneity of the criteria used in the several studies to evaluate the response to the ASMs and the lack of stratification in relation to severity based on the seizure burden. In most studies there were no information on the location and extension of the brain damage caused by the stroke and therefore a detailed analysis of the patients according to the severity of the stroke was not possible. Furthermore, the cohorts of the enrolled newborns are small and, although many cases of neonatal stroke are reported in the literature, their description was often incomplete especially in relation to the ASM used and its modality of use.

Conclusions

Our review shows that the use of ASMs that act throughout a gabaergic mechanism are inadequate in controlling seizures secondary to neonatal stroke in full-term newborns. Very effective appears, instead, the use of LD or LEV to treat these seizures with an apparent safer profile in short and long term. Bumetanide shows promising results, but they are to be confirmed by phase 3 studies.

In summary, our study highlighted how is still impossible to define what kind of ASM is more safe and more specific indicated to treat acute neonatal symptomatic seizures due to perinatal stroke. This suggest that further and more focused studies are still needed. Furthermore, complete information about the severity of the brain damage and the entity of the seizure burden should be better reported in the next studies to understand if the use of ASM can mitigate the brain injury due to the stroke and, above all, it can improve the outcome.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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