Review Article

Critical care of acute stroke

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In the last decade, there has been tremendous interest and growth in setting up ICUs and stroke centers across India. Because of changes in modern stroke therapy and advanced imaging techniques with software for remote reading in real-time available 24/7, there has been a monumental change in how stroke patients are cared for. From the availability of ICU trained physicians proficient in ventilator management to the readiness of neurosurgeons willing to perform emergency decompression in patients at risk for malignant cerebral swelling and brain herniation, the fate of critically ill stroke patients has drastically improved. [*J Indian Med Assoc* 2017; **115:** 66-70]

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The last few years have witnessed a rise in the number of neurologists and other physicians treating acute stroke patients with time-sensitive interventions such as intravenous thrombolysis and endovascular embolectomy in India. This paradigm shift is owed to the availability of high-quality CT scanners, a heightened awareness among physicians about the idea that "Time is Brain," the readiness of neurologists to administer thrombolytic therapy, and continuous progress in various facets of stroke care.

The high cost of acute stroke therapy also raises expectations. Physicians as well as caregivers tend to afford patients with extra care which perhaps is not routine in other stroke cases. In the last decade, there has been tremendous interest and growth in setting up ICUs and stroke centers across India to improve stroke outcomes and minimize complications. Because of changes in modern stroke therapy and advanced imaging techniques with software for remote reading in real-time available 24/7, there has been a monumental change in how stroke patients are cared for. From the availability of ICU trained physicians proficient in ventilator management to the readiness of neurosurgeons willing to perform emergency decompression in patients at risk for malignant cerebral swelling and brain herniation, the fate of critically ill stroke patients has drastically improved.

While the goal of thrombolytic therapy and embolectomy in ischemic stroke is to rapidly restore blood flow and minimize cerebral ischemia, the ICU team must consider several issues simultaneously. The most critical of these issues are optimization of cerebral blood flow and prevention of secondary brain injury. Paying close attention to seemingly mundane clinical decisions such as which sedative to choose for intubation, what target blood pressure to aim for,or how to detect and monitor neurologic deterioration can make a significant difference in improving stroke outcomes and minimizing complications.

Editorial Comments :
- **Early identification and management of cerebral edima improve outcome in stroke patients.**
- **Thyrombolysis in stroke patient should be done in properly indicated patients.**
- **Intensive care management and prophylaxis improve outcome.**
- **Antiquagulation therapy in acute ischemic stroke should be individualized.**

The purpose of this article is to address essential critical care issues related specifically to stroke patients. Acute thrombolysis/endovascular embolectomy, neuroimaging, experimental therapies, and clinical trials are beyond the scope of this article.

Who is Eligible for ICU Admission ?

Eligible patients are typically aheterogeneous and diverse group who presented withischemic stroke and received acute pharmacological or mechanical interventions to restore blood flow to the brain. However, it is well known that reversal of deficits or clinical improvement is not instantaneous regardless of treatment modality, and most of these patients require at least a short-term stay in the ICU for initial stabilization, detection, and management of potential complications. Most centers involved in the delivery of acute stroke interventions recognize the ICU setting as the standard of care.

Patients who have the potential to develop 'malignant' middle cerebral artery (MCA) syndrome would also benefit from frequent and serial neurologic monitoring in ICU. Patients with large hemisphere infarction are prone to develop cerebral edema and subsequent neurological deterioration eventually leading to coma.

Stroke patients requiring ICU admission are usually

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those who are unable to protect their airway due to decreased level of consciousness or due to a brainstemstroke diminishing cough and gag reflexes, therefore necessitating intubation. ICU admission is also warranted for BP monitoring post-thrombolysis or post-embolectomy. Additionally, stroke patients with significant cardiac issues (CHF/recent MI and arrhythmias), pulmonary or renal issues with the potential to cause hemodynamic or respiratory compromise should all be monitored in the ICU.

Intensive care is also essential in stroke patients with comorbidities like uncontrolled diabetes and metabolic abnormalities or patients who develop worsening of neurological status that may be associated with medical or neurological (eg. seizures/hemorrhagic transformation) complications.

Airway, Breathing and Circulation :

As with all critical care patients, attention to airway, breathing and circulation remain top priority. The anesthesiologist should always be apprised of patients with increased or potentially increased ICP as this may change their intubation protocol. For example, succinylcholine can increase ICP while standard rapid sequence techniques may decrease cerebral blood flow. In general, induction of anesthesia should be done with an agent that may have neuroprotective properties of ICP lowering effects, such as midazolam, etomidate or thiopental. Lidocaine can be used to suppress cough reflex, and a non-depolarizing agent such as Rocuronium or Vecuroniumis preferred for jaw relaxation if needed. Maintenance of adequate oxygenation and normocarbia are treatment goals. Supplemental oxygen is not necessary for non-hypoxic patients with mild or moderate strokes, and its role in patients with severe stroke in the absence of hypoxia is inconclusive.

Except for those patients who receive thrombolysis or thrombectomy, there are no specific treatment thresholds and permissive hypertension is tolerated in acute ischemic stroke unless there are signs of end organ dysfunction. Strict blood pressure management is critical, especially during the administration of thrombolytic therapy, and is possibly the most critical parameter to monitor once thrombolysis has started. In stroke patients who have received intravenous tissue plasminogen activator (IV tPA), intra-arterial tPA or endovascular thrombectomy, it is recommended to keep blood pressure less than 180/105 for the first 24 hours.1Intravenous labetalol is the drug of choice to reduce blood pressure to acceptable levels as it is short acting with a rapid onset and offset of action. Occasionally, one has to switch to another agent due to bradycardia or history of prior use of beta-blockers that might exacerbate its action. In the Western world, nicardipine is a good alternative, though not available routinely in India. Other medications that one might use are enalaprilat or hydralazine, but these are also not widely available. However, intravenous glyceryltrinitrate (GTN) might be a suitable alternative in these scenarios with a demonstrable titration effect. Lastly, one can use sodium nitroprusside if blood pressure is still uncontrolled or if the diastolic blood pressureexceeds 140 mm Hg.

In patients who have not received thrombolysis or endovascular thrombectomy, a reasonable treatment threshold would be systolic blood pressure >220 mm Hg or diastolic blood pressure 120 mm Hg. Blood pressure reduction by 15 percent is safe during the first 24 hours to avoid increasing the penumbra (area with decreased cerebral perfusion) surrounding the core infarct area. Some conditions such as myocardial ischemia, heart failure or aortic dissection may accompany acute stroke and may be exacerbated by arterial hypertension, and in such conditions, blood pressure targets vary on a case-by-case basis. The role of volume expansion, use of vasodilator, and induced hypertension have all been studied, but no trials to date have demonstrated clear efficacy in acute stroke. It remains an area of interest with the potential to provide widely applicable therapy in the setting of newer imaging studies such as MR perfusion and CT perfusion. Ongoing clinical trials are aiming to determine whether there is a benefit of induced hypertension in a select subgroup of acute ischemic stroke patients.

Management of Pain and Agitation :

Symptoms of pain, agitation, and delirium are fairly similar in all ICU patients, but stroke patientspresent unique challenges in the diagnosis of delirium, harmful effects to the brain,and monitoring for progression of the stroke. A greater understanding of discomfort and intensity of pain is important as pain can confound the neurological exam by precipitating agitation in an aphasic patient. Understanding the stroke syndrome and their potential complications such as hemorrhagic conversion, cerebral edema or seizure, is critical in selecting the safest strategy to manage pain and agitation. The gold standard for monitoring stroke patients is an inexpensive bedside neurological examination[2-5]. Sedating agents can mask critical exam findings and interfere with detection of early signs of neurological worsening. While it is imperative to minimize sedation to allow for frequent neurological examination, ensuring comfort is equally important as untreated pain can reduce cerebral blood flow[5]. The ideal sedative for use in acute stroke patients should have a rapid onset of action and an ultrashort half-life, reduce ICP, maintain CBF, and reduce metabolic demands. Propofol has many of these desired effects, except hypotension which can become a limiting factor. It is well-suited for use in acute stroke patients allowing for predictable wake-up tests, but longer use can increase serum triglycerides and cause prolonged waking. Benzodi-

azepines can increase the risk of delirium and are hence avoided in the acute stroke setting. Dexmedetomidine can control agitation and pain without depressing level of consciousness or respiratory drive[6-8]. The safety of this agent on brain function and particularly cerebral hemodynamics is not well studied. It is used as an adjunct to analgesics, for weaning heavy sedation.

The optimal profile of analgesic agents in the ICU are a short-half life and minimal sedative effects for preservation of neurological examination. Fentanyl and particularly remifentanil possess these characteristics, and minimally affect cerebral hemodynamics[9,10]. Combining acetaminophen and dexmedetomidine for their opioid sparing effects may also be a reasonable approach to pain management in ICU stroke patients.

Non-pharmacologic strategies to prevent agitation---such as early mobilization, frequent orientation to surrounding, time and situation, preservation of sleep/wake cycles-- all help avert and mitigate agitation.

Management of Cerebral Edema :

Patients with large hemisphere infarction are prone to develop cytotoxic edema, subsequent neurological deterioration, and eventually coma and other signs of brain herniation. Malignant MCA syndrome refers to a rapid clinical deterioration due to a space occupying cerebral edema following an MCA territory stroke (Fig 1). Upto 10 percent of large MCA stroke patients develop fatal brain edema, characterized by hemispheric signs(forced gaze deviation, visual field deficit, aphasia or neglect and hemiplegia), and historically mortality ranges from 50 to 80 percent[11,12]. These are patients with NIHSS greater than 20 in the dominant hemisphere and greater than 15 in the non-dominant hemisphere. Clinical features such as decreased mentation and neuroimaging suggestive of large vessel occlusion with large infarct core as defined by an infarct volume of 82 mL or greater by MRI diffusion-weighted imaging (DWI)predict development of a malignant swelling with 98 percent specificity and 52 percent sensitivity[13].

Early identification of patients prone to cerebral edema remains critical for improved functional outcomes and decreased mortality. Confounding factors such as sedation, metabolic derangements, and infection need to be addressed. Osmotic therapy is instituted in patients with clinical signs of cerebral edema as manifested mainly by decreased level of consciousness and/or nausea/vomiting with worsening neurological exam. In stroke, clinical examination is more useful than ICP monitoring for detecting increases in cerebral edema and tissue shifts that can lead to brain herniation[14]. Osmotic therapy helps by creating an osmotic gradient that pulls fluid out of neurons and the interstitium into the vasculature. Mannitol is the most

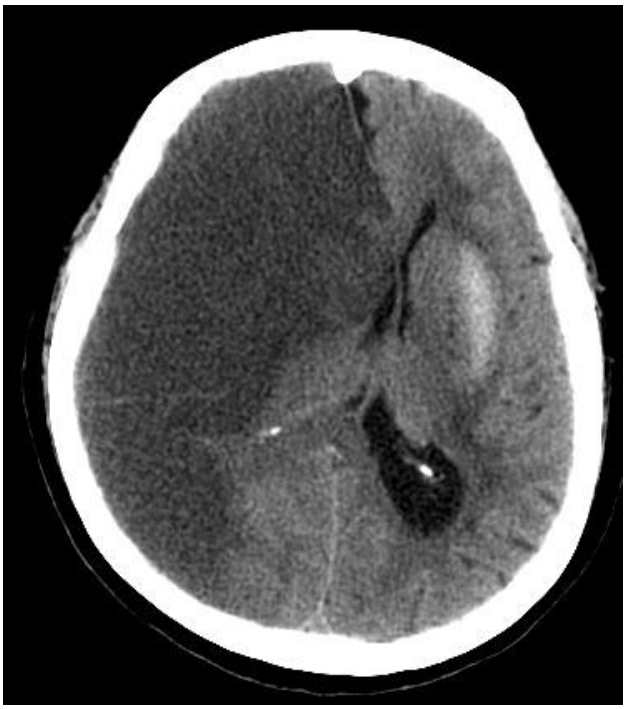

Fig 1 — 55-year-old woman presented with acute onset of dense L hemiparesis and gaze deviation (NIHSS=11), CTA showed a carotid T occlusion. She underwent a successful embolectomy at 5 hour from last seen normal. Six hours after her arrival to ICU, she became less responsive and was noted to have a non-reactive pupil on the right. A non-contrast head CT showed R MCA and ACA infarct with significant mass effect and subfalcineherniation

commonly used agent,although in cases where diuresis can be harmful, hypertonic saline can be used. Hypotension and hypovolemia can be complications of mannitol and thus it is important to use isotonic IV fluid replacement judiciously to maintain euvolemia.Serum osmolality can be checked to target administration of mannitol with the aim of maintaining serum osmolality less than 320 mOsm. In many settings in India, testing serum osmolality every six hoursmay not be feasible. In those cases, monitoring the neurological exam (level of consciousness and pupillary light reflex) and maintaining a slightly negative fluid status in patients with stable serum creatinine may be sufficient. A non-contrast head CT with worsening cerebral edema should be managed more aggressively and considered for decompressive craniectomy (DC). For patients in whom correction of medical issues and aggressive osmotic therapy fails, a scenario typical ofpatients with significant midline shift on neuroimaging, DC can be lifesaving[15]. A frank discussion with the family about the risk and benefits of DCshould be held, taking into consideration comorbidities. Using plain language and examples for describing disability helps set realistic expectations in terms of functional recovery. Long-term quality of life needs to be discussed with family members, specifically

in the elderly, before proceeding with DC.

Principles of management remain similar in posterior fossa infarcts as well as cerebellar hemorrhage. Prompt surgical decompression of the posterior fossa and placement of intraventricular catheter if hydrocephalus is present can be life saving and result in good neurological outcome. Lesions restricted to the cerebellum alone yield very good outcomes with significant reduction in morbidity.

ICU Prophylaxis :

DVT prophylaxis is a common and a preventable complication of stroke occurring in up to 0.6% stroke patients within one week and 2.5% within 3 months. Anti-DVT prophylaxis for these patients should comprise of intermittent pneumatic compression device, graduated stockings, or systemic anticoagulation along with early mobilization. Administration of Low Molecular Weight Heparin (LMWH) is preferred over unfractionated Heparin (UFH) though higher cost of LMWH should be taken into account in the Indian setting.Current AHA/ASA guidelines recommend the use of anticoagulation for immobilized patients to prevent DVT and possible intermittent pneumatic compression devices for patients who cannot receive anticoagulation[1].

Hyperthermia is associated with increased mortality and morbidity in stroke patients and a meta-analysis of six cohort studies found that acute ischemic stroke patients with a temperature ≥37.4ºC within the first 24 hours of stroke hospitalization had twice the mortality rate as compared to afebrile patients. The source of hyperthermia should be identified and treated and antipyretics should be administered to lower the temperature in hyperthermia patients with stroke. There is no role of prophylactic administration of antipyretics or antibiotics in afebrile acute stroke patients. The role of induced hypothermia in stroke is investigational and is not recommended in its present state of evidence.

Any stroke is a stressful situation and both hypoglycemia and hyperglycemia are common occurrences, especially in patients not receiving enteral feeding. Moreover, uncontrolled hyperglycemia may have an unfavorable bearing upon the treatment and outcome of acute ischemic stroke and should be monitored regularly. Intensive glucose control is associated with increased morbidity due to high incidence of hypoglycemia[16]. A glycemic level around 200mg/dl should be a reasonable target (and guidelines suggest glycemic protocols should target serum glucose levels of 140-180 mg/d). It is best to avoid oral hypoglycemic agents and long acting insulin preparations in the acute setting. If required, intravenous regular insulin should be the agent of choice.

Euvolemia should be maintained to achieve optimal cerebral perfusion pressure while taking special precaution in patients with cardiac or renal failure. Isotonic solutions like 0.9% saline are usually recommended since they are more evenly distributed into the extracellular space unlike hypotonic solutions (0.45% saline or 5% dextrose). Hypotonic solutions can exacerbate cerebral edema because of their distribution in intracellular space. Serum sodium should be maintained between 135-145 mEq/L. Packed red blood cell transfusion should be used to maintain hemoglobin levels above 7mg/dl. In patients who have elevated international normalized ratio (INR), warfarin should be discontinued and reversal with vitamin K should be considered to minimize the risk of hemorrhagic conversion. Early mobilization, dysphagia evaluation, and adequate nutrition protocols should be in place in all stroke patients.

Specific Issues :

ICH related to anticoagulant use : In patients with ICH secondary to warfarin-related coagulopathy, rapid correction of the INR is needed. Traditionally, fresh frozen plasma (FFP) and vitamin K have been used. Recently, prothrombin complex concentrate (PCC) and recombinant activator factor VIIIa(subject to availability) have emerged and may be faster and more effective. For patients with hemorrhages secondary to dabigatran, idarucizumab, a monoclonal antibody, is now available. Hemodialysis remains a more viable option in an Indian setting.

Hemorrhagic Conversion post IV tPA administration: Approximately 6% of patients have symptomatic intracranial hemorrhage (sICH) related to intravenous thrombolysis[17-19]. If the neurologic deterioration occurs while the IV tPA is still running, one must stop the infusion immediately and obtain a non contrast head CT scan to confirm hemorrhage accounting for the change in clinical exam. In case of sICH, a blood sample should be sent for testing type and cross, PT/PTT, platelet count and fibrinogen level. Depending on availability, transfusion of FFP (2 Units every 6 hours for 24 hours), cryoprecipitate (10-20 units) and platelets should be administered. If there isevidence of cerebral edema without hemorrhage on head CT, treatment along the management of cerebral edema (osmotic therapy/decompressivecraniectomy) needs to be initiated.

Seizures and Acute Stroke : Patients who have uncomplicated ischemic strokes irrespective of their thrombolysis status are not at increased risk of having seizures and should not be routinely given anti-epileptic medications. Stroke patients can have subclinical seizures causing depressed sensorium and must be kept in the differential of a patient with an unexplained coma in the absence of infection or electrolyte imbalance. In such cases, a bedside EEG can be high-yield in capturing electrographic seizure activity. Patients with clinical and electrographic

seizures should be treated with an antiepileptic medication, typically phenytoin.

Cardiac Arrhythmias and Stroke : The other frequently encountered cardiac condition in stroke patients is atrial fibrillation (AF). Rate controlled AF should not pose a serious clinical problem. However, in event of high grade AF with fast ventricular rate, intravenous amiodarone may have to be used with careful monitoring for the development of bradycardia.In older patients it is not unusual to witness both AF and bradycardia due to high prevalence of sick sinus syndrome in this group, and hence these patients should always be in a monitored setting in the acute aftermath of stroke.

Initiation of anticoagulation after acutestroke: The dilemma in treating patients with a cardioembolic stroke in the face of thrombolysis is in the decision to initiate anticoagulation. Whereas the NINDS guideline recommends starting patients with single antiplatelet drugs in the event of a thrombotic stroke after 24 hours, there seem to be no clear-cut guidelines for instituting anti-coagulation in patients with AF. Hence, treatment for such patients needs to be individualized. A patient with a large hemispheric stroke with or without hemorrhagic transformation may not be a suitable candidate to receive anticoagulation. However, patients with small strokes may be started on anticoagulant medications like heparin after 24 hours. Checking for left atrium clot may facilitate the decision-making. However, it should also be kept in mind that atransthoracic echo has limited predictive value and getting a transesophageal echo in an acute setting may be difficult.

Management of stroke patients, especially those who have just received thrombolytic therapy, poses unique challenges including careful consideration for admission to an ICU. With no clear guidelines for acute stroke care in a country like India, where resources are not uniformly available, managing such patients is challenging and mostly depends on resourcefulness and wisdom of the physician in charge. In this article, we have highlighted some commonly occurring clinical scenarios and made a case for creating evidence-based guidelines to standardize acute stroke care. Despite the diverse patient population and the vastly different work environments, understanding of the underlying pathophysiology, rapid detection, quick triaging, careful consideration and management of anticipated complications in the ICU can make a big difference in stroke outcome.

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